



Genetics and Mental Disorders

**Report of the National
Institute of Mental Health's
Genetics Workgroup**

National Institute of Mental Health
National Institutes of Health



Letter of Transmittal
from the NIMH
Genetics Workshop

Comments

TABLE OF CONTENTS

ACKNOWLEDGMENTS

PREFACE

EXECUTIVE SUMMARY

INTRODUCTION

MENTAL DISORDERS AND GENETICS: WHAT WE KNOW TODAY

- Mental Illness
- Models of Genetic Transmission
- The Tools of the Trade: Models for Locating Genes
- The Promise of Genetic Research

THE WORKGROUP'S DELIBERATIONS

- Overview
- Status of the NIMH Extramural Research Program
- Status of the NIMH Intramural Research Program

FINDINGS AND RECOMMENDATIONS

- Overview
- Findings of the Workgroup
- Creating and Analyzing Large, Well-documented Samples
- Fostering NIMH's Collaborations
- Recruiting and Retaining New Researchers
- Sponsoring Initiatives in the Molecular Genetics of Mental Disorders
- Category 1: Molecular Initiatives
- Category 2: Initiatives in Clinical and Epidemiological Research
- Addressing Administrative Issues
 - Extramural Research Program
 - Intramural Research Program

Establishing a Genetics Advisory Group

APPENDIX A: National Advisory Mental Health Council

APPENDIX B: NIMH Genetics Workgroup

APPENDIX C: Roster of Presenters

APPENDIX D: Data and Materials Sharing

APPENDIX E: Genetics Fact Sheets

Attention-Deficit Hyperactivity Disorder
Autism
Bipolar Disorder
Depression
Eating Disorders
Obsessive-Compulsive Disorder
Panic Disorder
Schizophrenia
Tourette's Syndrome
References

September 19, 1997

Steven E. Hyman, M.D.
Chairperson
National Advisory Mental Health Council
Director
National Institute of Mental Health
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Hyman:

We, the members of the National Institute of Mental Health's Genetics Workgroup, are pleased to forward our report to you and the National Advisory Mental Health Council.

Aided by the Institute's staff, grantees, and advocates, we have surveyed the field and the Institute's portfolio to identify significant opportunities to speed the search for the genes that influence mental disorders. The Workgroup determined that the Institute stands ready to capitalize on the rapid advances in molecular and statistical genetics. The tools that have been successful in detecting the genes that cause classical hereditary illnesses, such as Huntington's disease, are available for applications to more complex genetic diseases, such as mental disorders. Pairing these emerging advances with today's sophisticated diagnostic techniques offers unparalleled opportunities for revealing the biological components of mental disorders.

The Workgroup offers 22 recommendations to expedite the discovery process by creating and sharing unique resources, fostering new collaborations, and training more researchers.

We thank you and the Council for the opportunity to participate in this exciting endeavor.

Respectfully,

The Members of the Genetics Workgroup

ACKNOWLEDGMENTS

The NIMH Genetics Workgroup thanks the many individuals who contributed to this report. Appreciation is extended to each researcher, staff member, and advocate who met with or wrote to the Workgroup. Their comments expanded the Workgroup's deliberations conceptually and helped ensure the feasibility of the recommendations. A particular debt of gratitude is owed to Dr. Steven O. Moldin for his analyses of the literature and the NIMH research portfolio. The valuable editorial advice of Ms. Anne Rosenfeld, Ms. Joan Cole, Ms. Linda Hoffman, and Clarity Editing is gratefully acknowledged. The Workgroup highly valued the dedication of Ms. Susan Matthews, Ms. Valecia Parker, and Ms. Nancy Truszynski in ensuring its smooth functioning. The Workgroup also extends its gratitude to Ms. Catherine West for providing the artwork that enhances this report.

NIMH has obtained permission from Clea Simon and her publishers for use of her material. Further use or reproduction of this material is prohibited without specific permission of the copyright holder(s).

All other material in this report is in the public domain and may be used or reproduced without permission from NIMH. Citation of the source is appreciated.

PREFACE

Mental illnesses are common, serious brain disorders that affect our thinking, motivation, emotion, and social interactions. Because the illnesses are particularly difficult to model in animals, most research on the causes and treatments of them has occurred in clinical populations. Increasingly, these studies make use of evermore sophisticated brain imaging technologies and cognitive neuroscience. Such studies will advance our knowledge of brain function by yielding increasing detail on what goes awry in illness. Building on these accomplishments, the search for disease vulnerability genes is likely to yield the most important tools yet in our ongoing attempts to understand the brain in mental illness.

Identifying genes that may play a role in any complex disease - a formidable task in itself - is only a first step in understanding how a gene or genes affect an individual. Genes act by producing specific proteins that may contribute to a particular biological or behavioral trait. Every human carries between 80,000 and 100,000 genes; the products of these genes - acting together and in combination with the environment - enable every human characteristic. As the functions of genes in brain processes come to be better understood, researchers can begin to develop ways to intervene in processes that cause disease. Although such interventions can only be imagined today, NIMH already is investing in these strategies to lay the groundwork for tomorrow's discoveries. At the same time, vulnerability and "disease course-modifier" genes will provide extraordinary tools for both therapeutics and prevention research. For these reasons, NIMH is committed to the search for genes that create vulnerability to mental illness, affect the course of illness, and impact treatment.

The task ahead is daunting. It has become clear that the genetics of vulnerability to mental disorders is, in all cases, complex. We still do not know how many different genes might contribute to vulnerability for any specific mental disorder, nor do we know the nature of the nongenetic effects that convert vulnerability into illness. Yet, if NIMH is to succeed in its mission, the research we support must capitalize on the revolution that is occurring in genomic research and must take very seriously the complex genetics of mental disorders. Ultimately, understanding the pathophysiology that underlies discrete forms of mental disorder will lead to novel, increasingly specific treatments and, eventually, to prevention.

Toward this end, with the strong endorsement of the National Advisory Mental Health Council, I convened a Genetics Workgroup and charged them to help us to reorganize and prioritize our efforts. The Institute and the

field owe a debt of gratitude to the Workgroup Chair, Sam Barondes, M.D., and to the members of the Workgroup listed in Appendix B. They effectively concentrated diverse expertise in a thoughtful and creative manner. The report that follows illustrates the energy and alacrity with which they addressed the urgent scientific issues before us. I also am deeply appreciative of the efforts of the Workgroup Staff Director, Jane Steinberg, Ph.D., and of NIMH staff who participated in this important effort. I am particularly pleased that the authors have acknowledged the interests and needs of readers outside of the scientific community and have produced a concise, comprehensible report that presents a list of straightforward recommendations and achievable goals.

Despite the enormous scientific difficulties posed by complex genetic disorders, we can and must succeed. I believe this document will assist us significantly.

Steven E. Hyman, M.D.
Director, National Institute of Mental Health

EXECUTIVE SUMMARY

Molecular genetic approaches to understanding illness are changing the nature of medical research and practice in the United States. As the human genome is defined, the opportunity to determine genetic influences in mental disorders becomes a reality.

Although the National Institute of Mental Health (NIMH) has prepared well for this undertaking, much remains to be done. Rigorous diagnostic procedures are available for some mental disorders, but not all. Studies to identify the genes that influence the onset of mental disorders have been initiated, but too few are large enough to efficiently detect these genes. Dedicated investigators are working on various aspects of mental disorders, but more researchers with training in molecular and statistical genetics are required.

To build upon the field's strong beginning, Dr. Steven E. Hyman, NIMH Director, convened a workgroup of experts in clinical, basic, and statistical genetics to review the current status of this work and to provide advice on how to proceed. The NIMH Genetics Workgroup met over a 6-month period and reviewed the Institute's portfolio; consulted broadly with researchers, advocacy groups, and staff from NIMH and across the National Institutes of Health (NIH); and generated an action plan for directing NIMH's efforts. The Workgroup's recommendations follow.

Creating and Analyzing Large, Well-documented Samples

Recommendation 1: NIMH staff should draft a policy for the National Advisory Mental Health Council's consideration that provides for the sharing of genetic materials (i.e., DNA, diagnostic data, and genotypes) collected through NIMH's grants and cooperative agreements after a 12- to 18-month proprietary period. Staff members are encouraged to include all elements of the National Human Genome Research Institute/Department of Energy (NHGRI/DOE) policy on data sharing (see Appendix D).

Recommendation 2: NIMH should continue to provide a contract for maintaining cell lines from individuals with mental disorders and appropriate relatives, as well as for distributing DNA and all clinical data to qualified investigators.

Recommendation 3: NIMH should encourage consent procedures that describe and discuss the risks and benefits of DNA banking and clinical data sharing in genetic research.

Recommendation 4: NIMH should issue a request for applications (RFA) to conduct secondary analyses of clinical samples. The RFA should provide support for recoding diagnostic variables and for reanalysis. If the RFA proves successful, a program announcement should be established so that this very efficient and low-cost approach can continue.

Recommendation 5: NIMH should continue its support for core facilities such as NHGRI's Center for Inherited Disease Research (CIDR) to augment the available genotyping and analytic resources in academic research facilities.

Recommendation 6: RFAs and program announcements should explicitly allow international work and provide support for such shared undertakings when scientifically appropriate.

Recommendation 7: RFAs for future large-scale, coordinated efforts should call for self-selected teams of researchers.

☐ **Fostering NIMH Collaborations**

Recommendation 8: NIMH extramural staff should invite key clinical genetics staff across NIH to form a coordinating committee for complex disorders. Of particular interest would be discussions on joint efforts in training, software development, hardware, statistical models, ethical issues, and international alliances.

☐ **Recruiting and Retaining New Researchers**

Recommendation 9: NIMH should establish multidisciplinary institutional training grants at the pre and postdoctoral levels that provide education in clinical, statistical, and molecular genetics.

Recommendation 10: Two programs established by the National Heart, Lung, and Blood Institute (NHLBI) should be adapted for use at NIMH. First, the NHLBI Programs of Excellence in Molecular Biology should be modified for use by NIMH. This NIMH initiative should provide investigators with expertise in the genetics of mental disorders. Second, short-term training programs for new investigators or investigators seeking to redirect their career or broaden their skills should be established. Rather than a brief introduction to molecular genetics, the courses should offer intensive, hands-on training opportunities.

Recommendation 11: A new investigator's award should be created to provide entrance into the field without demanding long-term, high-risk projects for junior investigators and for established geneticists seeking to redirect their efforts into mental disorders. These grants, envisioned as 2-year awards at \$50,000 to \$100,000 a year, could be used, for instance, to analyze data sets in the repository. Other short-term projects should be considered as well.

☐ **Sponsoring Initiatives in the Molecular Genetics of Mental Disorders**

Recommendation 12: NIMH should issue RFAs for large-scale molecular genetics studies of schizophrenia, bipolar disorder, and early-onset depression.

Recommendation 13: NIMH should work with the NIH Autism Coordinating Committee to find methods for integrating ongoing studies and their samples.

Recommendation 14: A program announcement should solicit applications across all investigator-initiated research mechanisms for clinical, family, and epidemiological studies in the other mental disorders to develop the diagnostic tools and/or to better evaluate the role of genetics and the environment in contributing to the onset of these mental disorders.

☐ **Addressing Administrative Issues**

Extramural Research Program

Recommendation 15: The Workgroup supports the newly formed NIMH integrated genetics branch and recommends that it be headed by an established genetics researcher who can provide the leadership and creativity the NIMH extramural program warrants.

Recommendation 16: Applications on the genetics of mental disorders should be reviewed together with applications pertaining to other complex disorders in the new NIH Center for Scientific Review (CSR) structure. The eventual panels must include sufficient clinical, molecular, and statistical expertise.

Recommendation 17: The terms and conditions section of grant awards for genetic collection must specify a data-gathering plan and should be effectively monitored to ensure sufficient timely progress.

Intramural Research Program (IRP)

Recommendation 18: Appointing a permanent IRP Scientific Director who combines a very high level of scientific expertise with the vision to understand and appreciate the power of interdisciplinary research in mental disorders will advance NIMH's IRP genetics effort. Depending on the selection, additional genetics expertise and leadership may still be required at the IRP. Recruiting new leadership in genetics is critical to unifying and revitalizing the genetics program of the IRP.

Recommendation 19: Genetics research at the IRP should be consistent with the new mission statement.

Recommendation 20: Productive collaboration, including data and core resource sharing, should be expected and fostered across IRP laboratories and with NHGRI and NIMH extramural staff and investigators.

Recommendation 21: Reviews of the IRP laboratories must be expert and should promote the best genetics research by shaping the direction of and resources to the IRP genetics laboratories.

Establishing a Genetics Advisory Group

Recommendation 22: The Workgroup requests that an Advisory Group be established to consult on the implementation of this plan and its impact on the extramural and intramural programs of NIMH.

INTRODUCTION

Since its inception, the National Institute of Mental Health (NIMH) has recognized the importance of genetics in understanding mental disorders. From the earliest epidemiological studies to today's molecular approaches, the Institute has invested broadly in genetics research in hopes of discovering the interplay between genes and the environment in the predisposition to mental disorders. The clearest finding from this research is that there is no simple relationship between genes and mental disorders.

Single, causative genes, such as those resulting in sickle-cell anemia or Huntington's disease, do not explain how mental disorders affect one out of five Americans. Instead, researchers now believe that several susceptibility genes interact with each other and with environmental factors to influence the risk of developing a particular disorder. Finding the susceptibility genes amid multiple environmental factors is a formidable task, but not unique to mental disorders. Many diseases, such as asthma, hypertension, and diabetes, appear to have equally complex patterns of transmission. This labyrinth of genetic susceptibility and environmental factors poses a great challenge to geneticists. These gene hunters have responded to this challenge by developing increasingly powerful molecular and statistical tools. What seemed hopelessly complicated a few years ago is becoming solvable.

Recognizing this promise and the intensive work yet to come in molecular genetics, biotechnology, biostatistics, and informatics, Dr. Steven Hyman, NIMH Director, and the National Advisory Mental Health Council (Appendix A) formed a Council workgroup to explore new approaches and opportunities in this area. The membership of the NIMH Genetics Workgroup, which includes basic, clinical, and statistical geneticists, is presented in Appendix B. Dr. Hyman charged the Workgroup with considering how to invest NIMH resources selectively to speed the identification of the genes that influence mental disorders. The Workgroup was asked to provide a map for directing the research and infrastructure development that will be uniquely important to mental disorders. As part of this strategy, the Workgroup also considered how NIMH can best work with and build upon the efforts of other NIH institutes, private industry, and other key stakeholders. If all of these constituencies work together, the current opportunities for science will generate significant clinical advances for those living with mental disorders.

Though the Workgroup believes that the hunt for genes that influence susceptibility to mental disorders is critically

important, finding these genes is just one step toward improved clinical care. Advances in treatment will depend on understanding the ways in which these genes actually influence behavior and brain function. With this greater understanding, a new generation of treatments can be foreseen that will counteract the problems resulting from the susceptibility genes. Only then can the hopes and needs of individuals living with mental disorders and their families, so poignantly expressed in Clea Simon's personal story, be addressed (see *The Family Illness*).

The Family Illness

I had so many reasons not to think about schizophrenia, about the terror it caused me as a child. When I was six, I watched my brilliant brother change from an engaging 16-year-old to a zombie who stared into space for hours. Two years later, I saw my older sister turn cruel and loud, screaming for what seemed like hours. I was too young to know anything about schizophrenia, but I knew something was terribly wrong. Like many with this disease, neither my brother or sister could find satisfactory treatment, resulting in my brother's leaping off a cliff to his death and in the regular recurrence of my sister's psychotic rages.

Schizophrenia isn't the multiple personality of movie stereotype, but it is a horrible mental illness, causing aural hallucinations and provoking paranoid delusions that can make peculiar behavior seem normal to the sufferer. It often can be treated, but it isn't yet curable. And although public awareness of mental illness has come a long way in my lifetime, it's difficult not to feel cursed by the shadows it casts.

For much of my life, I have tried to believe that the madness was behind me. After all, my brother committed suicide 15 years ago, while I was still in college, and I've been out of touch with my sister for close to 20 years. They no longer inhabit my present life, but their illnesses haunt me like ghosts.

At this point in my life, that ghost has taken on a terrifying new shape. It haunts me now with the question: Would I have a child with schizophrenia? Talking with geneticists did not dispel my fears; in fact I soon learned that any children of mine would indeed have an increased risk of developing the illness that destroyed my siblings' lives. Although my fiancé has no relatives with schizophrenia, our kids would be as much as eight times more likely than the average person to have schizophrenia. But even for my children, schizophrenia is not a huge risk - their chances range from 3 to 8 percent. In the general population, schizophrenia occurs in one out of every hundred people. Several scientists told me that other considerations - such as the fact that both my siblings had schizophrenia - may increase the odds. Another factor could be the severity of my sibling's cases: Both became wildly, uncontrollably ill.

These odds are all the scientists can offer me. Unlike some other hereditary diseases, the genes for schizophrenia have not yet been isolated; there is no test. All we can provide are our family histories; all we can get in return are percentages.

If only the science were further along. Still, we try desperately to read our futures in the little information we have. The genetics of mental illness will be much better understood in 20 years, scientist say, but there isn't much chance of current research having practical applications within the next five years - when it would be useful to me. In the end, I have to face the fact that no one can tell me whether a child of mine would be healthy or ill.

And so the dilemma remains, particularly for people like me who carry the memories of our siblings at the same time that we feel the pressure of encroaching age. We cannot wait for research to provide the answers. We must make our peace - and our decisions -

with the knowledge at hand.

Clea Simon is an editor at the *Boston Globe*. This piece is adapted from her recently released book, *Mad House: Growing Up in the Shadow of Mentally Ill Siblings* (Doubleday), portions of which appeared in *The Washington Post*.

MENTAL DISORDERS AND GENETICS: WHAT WE KNOW TODAY

Mental Illness

Mental illnesses profoundly affect an individual's ability to think, feel, and act. They are also very common, affecting as many as one in five Americans over their lifetimes, irrespective of age, gender, or race. Four percent of the Nation's population lives with severe mental illnesses. The annual cost to the United States for treatment, social service and disability payments, lost productivity, and premature mortality is more than \$150 billion.¹ The diagnosis, treatment, and prevention of mental illnesses continue to be crucial to improving the quality of life for affected individuals, as well as to reduce health care costs.

Researchers and clinicians have worked for decades to reduce the suffering of those with these disabling disorders, and current treatments can alleviate symptoms for many. Unfortunately, none of these treatments offer sustained relief. Better treatments depend on discovering the causes of these disorders.

Although mental disorders were recognized as illnesses in the mid-18th century, suspicion and fear often overshadowed understanding. Gradually, trepidation has been replaced by knowledge as the fields of psychiatry, behavioral science, neuroscience, biology, and genetics have progressed. Through research conducted in each of these domains, a shared finding arises: the risk of developing an illness is increased if another family member is similarly affected, suggesting a strong hereditary component.

This finding of familial risk has been documented through twin studies, which use two types of twin pairs for exploring the role of inheritance. Identical or monozygotic twins come from the same fertilized egg and share 100 percent of their genes.² Fraternal or dizygotic twins come from two different fertilized eggs and share only 50 percent of their genes, just as any biological siblings would. To evaluate heritability, the rate of the disorder in monozygotic twins is compared with the rate in dizygotic twins. If the rate among monozygotic twins is significantly higher, then heredity is an important factor. For instance, in bipolar disorder, if one monozygotic twin is affected, then the other has a 60 to 80 percent chance of also having the disorder. In contrast, a dizygotic twin of an affected individual has only an 8 percent chance of having the disorder. Similarly, a monozygotic twin of a person with schizophrenia has a 46 percent chance of being affected, whereas a dizygotic twin has only a 14 percent chance of being affected.

Despite strong evidence for genetic susceptibility, no specific gene has been unambiguously identified for common forms of mental disorders. Many researchers believe that this is due, in part, to the critical role that the environment plays in modulating genetic susceptibility in mental disorders. Citing the twin studies above, researchers point out that monozygotic twins are not always concordant (i.e., do not share the disorder). Clearly, if twins with the same genes do not both have the disorder, there is strong evidence for the role of environmental factors.

Researchers may differ on their estimates of the amount that genes and the environment each contribute to the onset of mental disorders, but once a genetic component is reliably implicated, the search for the source and the location of the apparent genetic component underlying the mental disorder can begin. The estimate of the influence of environmental factors on the disorder provides an index of how difficult the search will be.

Models of Genetic Transmission

When people get sick, they want to know what disease they have and whether it can be treated. Their next question is often, "How did I get this disease?" Patients understand that knowing something about the causes of the illness can help their treatment and possibly prevent the spread of the disease. This intuitive link is the essence of medical research. The more learned about the natural course of the disease, the easier it is to test ideas about how the disease may be spread or cured. As ideas about treating the disorder are tested, the understanding of the disease becomes more sophisticated.

Genetic causes of certain diseases have been known for many years. The mutation in hemoglobin that leads to sickle-cell anemia was discovered more than 40 years ago. Many people are familiar with this kind of recessive genetic disorder, in which both parents pass along the affected form of the gene, resulting in the child's illness. More recently, investigators identified the gene for Huntington's disease, a serious disorder characterized by progressive deterioration of physical and mental functioning. Huntington's disease is caused by classic dominant transmission: people who receive just one affected gene from either parent develop the disease. These two types of transmission, in which dominant or recessive genes cause a disorder, are called "simple Mendelian models" because they are based on the rules of heredity codified by Gregor Mendel more than a century ago through his work with pea plants.

Most common medical diseases do not follow the rules of Mendelian inheritance. Instead, these complex disorders are influenced by multiple susceptibility genes, each of which contributes to the disorder. These genes may interact in complicated ways to increase or decrease susceptibility. The more genes necessary for a disorder, the harder it is to detect any one of them. This difficulty is magnified by the role of environmental factors.

Successfully tracking disease-related genes requires a population of individuals with the genetic variant and a means of identifying the genes in the population. Ideally, the definition of a disease should be clear enough so that all of the diagnosed individuals have relatively uniform symptoms, improving the chances for unambiguously identifying affected individuals for study. In sickle-cell anemia, for instance, experts and nonexperts can look through a microscope and see if the specific deformation of the blood cell - and therefore the disease - is present. For mental disorders, however, no clear biological test has been found. Further, investigators have had trouble discriminating specific forms of mental disorders, such as distinguishing someone experiencing depression as part of a depressive disorder from someone experiencing depression as part of bipolar disorder (also called manic-depressive disorder). Nonetheless, much progress has been made over the years, and researchers have developed procedures to permit the reliable and valid diagnosis of many mental disorders.

Understanding genetic influences on mental disorders and other complex diseases is further complicated by the fact that a given susceptibility gene may or may not result in the disorder. This ambiguity could be due to environmental influences or interactions with other genes. As an added complication, various combinations of genes may all lead to the same disorder.

Mental disorders will be considerably more difficult to understand than sickle-cell anemia and Huntington's disease. Such challenges are daunting, but with the tools and the talent available today, they are not insurmountable. The search for susceptibility genes in mental disorders will be exciting and potentially life-changing for many.

The Tools of the Trade: Models for Locating Genes

The human genome is the complete set of genetic instructions for an individual, one version from the mother and one from the father. Though the DNA from any two people is roughly 99.9 percent identical, the variation in this tenth of a percent is the source of human biological diversity. Inherited susceptibility to various diseases, which occurs when a particular form of the gene fails to give correct instructions for a trait or function, is one small part of this diversity. Researchers look for this unidentified gene by constructing finer and finer maps of known gene locations and functions or by comparing the DNA of affected and unaffected individuals.

The first phase of identifying a disease-related gene is the collection of diagnostic information and blood samples

from an appropriate set of affected individuals and their relatives. Typically, blood samples are drawn from family members, and the blood cells are transformed to preserve them. These transformed cells, called cell lines, can then be used to make DNA in unlimited quantities, allowing many researchers access to this resource. The art of this collection phase is in identifying appropriate families. Those in which affected individuals have very similar symptoms are preferable, since members of such a similar group are more likely to carry the same form of the gene than a symptomatically diverse family. At this stage, having valid and definitive criteria that accurately determine a particular diagnosis may make the difference between success and failure. The actual research designs selected in molecular genetics studies and the selected participants are closely allied, as indicated below:

- Linkage studies** are widely used to detect and locate genes that determine susceptibility to mental disorders. These studies are often based on the identification of large, densely affected families so that the inheritance patterns of known sections of DNA (called "markers") can be compared to the family's transmission of the disorder. If a known marker can be correlated with the presence or absence of the disorder, this finding narrows the location of the suspect gene. Great strides in linkage analysis, including laboratory and statistical methods, are increasing the power of this method and decreasing its cost.
- Linkage-disequilibrium studies** in isolated populations capitalize on the likelihood that the susceptibility genes for a particular disorder probably came from one or a few founding members. Whether the isolation is geographic or cultural, there are fewer individuals in the community's genealogies and therefore fewer variations of the disease genes within the population. This limited variation makes the search easier. In addition, the groups of markers that surround each of these susceptibility genes are likely to have the same limited variation, which further simplifies identification.
- Association studies** depend on the investigator hypothesizing that a specific gene or genes may influence the disorder. In this type of study, the investigator examines whether those people with the disorder have a different version of the gene than those without the disorder among related or unrelated individuals.

Pinpointing the likely genetic anomaly in linkage and linkage-disequilibrium studies occurs once an investigator narrows the search to a fairly small region in the genome. That "small" region, however, may still be large enough to contain DNA that codes for dozens of traits, and the investigator must now choose which parts of the region to study further. Because the NIH Human Genome Project is well on the way to identifying the location of all genes, this mapping of the human genome will greatly simplify the identification of possible susceptibility genes. Once the genes in a narrow DNA region are cataloged, they may each be tested and the susceptibility gene identified.

The Promise of Genetic Research

The discovery of specific gene forms related to mental disorders holds great promise for advancing diagnosis and treatment of the mental disorders. Genetic characterization of affected individuals will offer insight into molecular and biochemical subcategories of the disorder that clinicians may not be able to discern. This more accurate diagnosis can direct better tailoring of today's treatments and initiate new lines of treatment development targeted specifically to the contributing factor. Even if there are many factors required to fully understand complex mental disorders, interventions aimed at just one factor may be a successful prevention or treatment strategy.

Genetic identification will permit predictive screening for mental disorders to help affected individuals and their families prepare medically, emotionally, and financially and make helpful lifestyle changes. Predictive screening will greatly increase the feasibility of prevention studies, since interventions can be tailored for and provided to individuals at high risk of developing a given disorder.

THE WORKGROUP'S DELIBERATIONS

Overview

The Workgroup was charged by Dr. Hyman to advise the Institute on the opportunities for moving forward in understanding the genetics of mental disorders. To fulfill this charge (see Charge to the Workgroup), the Workgroup's initial deliberations focused on the Institute's current portfolio. Abstracts for every funded extramural genetics grant were reviewed, as were descriptions of the four intramural genetics laboratories. For a wider perspective, letters were mailed to all NIMH genetics grantees funded during fiscal year 1996, asking for advice on the pressing issues in molecular genetics. Advocacy groups and professional societies also were canvassed by mail. The Institute's extramural and intramural staff were invited to meet with the Workgroup to describe their programs, the activities they had undertaken, and their future goals. To more personally reach the community of researchers, senior and junior investigators were invited to meet with the Workgroup. Representatives of international collaborations, private industry, and other institutes also addressed the Workgroup. A list of speakers is presented in Appendix C. Finally, the Workgroup commissioned a summary of the published findings on the genetics of mental disorders by Dr. Steven Moldin, a member of NIMH's extramural staff.

Charge to the Workgroup

The Workgroup is charged with reviewing the Institute's extramural and intramural research portfolio and developmental activities in molecular genetics. Based on these findings and the Workgroup's broad understanding of the field, the Workgroup should make recommendations regarding future research initiatives by disorder, necessary infrastructure development, and administrative changes that the Institute should undertake to facilitate the search for the genes that influence mental disorders.

Status of the NIMH Extramural Research Program

The Workgroup began the extramural portfolio review by examining the Institute's holdings during fiscal year 1996. Although just a year's effort, this sampling contains work that was submitted, reviewed, and funded over the last 4 to 5 years. Given the rapidly developing field of molecular genetics, this retrospective assessment appeared sufficient.

Using a broad definition of genetics research (i.e., grants that involve genetic approaches or will have ramifications for understanding genetics), NIMH sponsored 318 grants for a total of \$81.8 million in fiscal year 1996. Using a narrow definition of genetics research (i.e., grants that involve genetic approaches), NIMH supported 173 grants involving genetic approaches to neuroscience, behavioral, and clinical phenomena for a total of \$44.5 million in fiscal year 1996. This amount is a sizable portion of the NIMH budget, approximately 10.1 percent of its non-AIDS 1996 extramural research budget of \$438.6 million. The portfolio was found to be diverse and promising. The breadth of the non-clinical research is an important investment that will serve the field well in developing new approaches for isolating susceptibility genes and in responding to the anticipated discovery of such genes.

The Workgroup focused its attention on the equally diverse clinical genetics portfolio. For this portion of the NIMH funded grants, the Workgroup also reviewed information culled by the NIMH staff regarding the 107 clinical genetics grants. This overview provided a summary of approaches, progress, opportunities, and needs. Of the 107 grants, 6 pertain to statistical model development and 7 to the analysis of existing data sets; 39 are new data collection efforts. Table 1 provides an overview of the disorder areas in which the new data collections are underway. In these new collection efforts, 52 percent are linkage studies, and 48 percent are association studies with or without a linkage component. The Workgroup also considered the populations under study, genotyping strategies,³ and statistical analysis plans.

Table 1
Disorders of interest

Disorder ^a	Frequency	%
Mood disorder	14.5 ^b	37
Schizophrenia	11	28
Childhood disorder	7.5 ^b	19
Alzheimer's disease	3	8
Anxiety disorder	3	8

^aMood disorder = bipolar or depressive disorder; childhood disorder = affective disorder, attention-deficit hyperactivity disorder (ADHD), or Tourette's syndrome; anxiety disorder = panic disorder or obsessive-compulsive disorder.

^bOne grant focused on two disorders.

The educational backgrounds of the principal investigators (PIs), as described in the grant applications, are summarized in Table 2. Grantees requested consultation from molecular or statistical geneticists in 77 and 69 percent of the grants, respectively.

Table 2
Background of principal investigators (n=39)

Background	Number	%
Ph.D. in genetics or related field; M.D. medical geneticist	9	23
Postdoctoral training in genetics	14	36
No degree or training in genetics	16	41

The Workgroup also reviewed the number of participants and families proposed for collection and the number currently collected. The figures for selected disorders appear in Table 3 and are based on data from the original grant applications and all available progress reports.

Table 3
Data collection

Disorder	Proposed Families	Families Collected	Individuals Collected	Affected Individuals Collected
Anxiety disorder	183	172	693	170
Childhood disorder	1,274	186	846	215
Mood disorder	560	325	4,977	880
Schizophrenia	1,095	719	5,155	1,700

NIMH undertook a special large-scale initiative in molecular genetics in 1989. The goal of the NIMH Genetics

Initiative,⁴ which was well ahead of its time, was to collect enough families to find the genes that influence the onset of selected mental disorders. The Initiative also enabled the establishment of a national repository of demographic, clinical, diagnostic, and genetic data from individuals with bipolar disorder, schizophrenia, or Alzheimer's disease to aid researchers in identifying factors responsible for these disorders.

IRP's New Mission Statement

The IRP conducts basic, clinical, and translational research to advance understanding of the causes, treatments, and prevention of mental disorders through the study of normal and abnormal brain function and behavior. The IRP supports outstanding research that, in part, complements extramural research activities and utilizes the special resources of the National Institutes of Health. The IRP provides an environment conducive to the training and development of clinical and basic scientists. The IRP fosters standards of excellence in the provision of clinical care to research subjects and in the translation of research into effective treatment. The IRP serves as a national resource in response to requests made by the Administration, members of Congress, and citizens' groups for information regarding mental illness.

Diagnosis, family history, and DNA samples were collected using identical procedures across multiple sites. The collecting researchers were given a 12-month proprietary period to analyze their data, at the end of which the data were made available to other qualified investigators. The repository contains information on 862 individuals with Alzheimer's disease, 432 with bipolar disorder, and 270 with schizophrenia.

These researchers founded a valuable resource that is in high demand. Requesting investigators receive a file of demographic and diagnostic variables necessary for genetic analysis, with accompanying documentation, access to DNA samples, a code manual listing additional clinical and demographic data, and pedigree drawings. NIMH supports the repository through a contract and by requesters' fees.

Status of the NIMH Intramural Research Program

The Intramural Research Program (IRP) just underwent a significant review, which is reported in *Finding the Balance: Report of the National Institute of Mental Health's Intramural Research Planning Committee (1997)*. The Committee strongly endorsed the role of the IRP and offered a new mission statement (see IRP's New Mission Statement). The report's 77 recommendations covered leadership, quality of science, training and mentoring, and clinical research as well as recruitment, retention, and retirement.

The Acting Director, Acting Deputy Director, and chiefs from each of the four IRP genetics laboratories briefed the Workgroup. This meeting occurred just as the IRP was beginning to implement the report's recommendations. Needless to say, this was a time of considerable flux, and the Workgroup was particularly appreciative of the IRP staff members' generosity in once again discussing their research programs. The Workgroup heard about each chief's approach to genetics, research plans, and collaborative activities. Written materials also were disseminated, which included selected publications, protocols, and strategy documents. These discussions and materials were enhanced by an overview from the IRP's Acting Director and Acting Deputy Director. In addition, NIMH budget staff provided overall figures for the Institute's IRP expenditures in this area. The Institute reports a total expenditure of \$15.7 million in fiscal year 1995 and \$10.3 million in fiscal year 1996 for the four separate genetics laboratories and any additional work in other laboratories with a secondary focus on genetics.

FINDINGS AND RECOMMENDATIONS

Overview

The Workgroup reviewed material submitted by NIMH staff, NIMH genetics grantees, advocacy groups, professional societies, private industry, and other NIH staff. To help integrate these ideas, speakers were invited to discuss specific issues. These deliberations and the Workgroup's own considerable experience provided the context for reviewing the Institute's portfolio and current progress in the molecular genetics of mental disorders. The Workgroup was not requested to consider the Institute's investment in other related domains, such as basic neuroscience and behavioral science, nor the more applied areas of clinical or epidemiological research. Nevertheless, the Workgroup endorses these areas as critical underpinnings to molecular genetic efforts. The Workgroup, therefore, was particularly interested in generating recommendations that would not significantly divert resources from these critical areas. The intent was to develop a series of recommendations on investing wisely.

The Workgroup synthesized its findings and generated six significant steps for furthering the field as follows:

- Creating and Analyzing Large, Well-documented Samples
- Fostering NIMH's Collaborations
- Recruiting and Retaining New Researchers
- Sponsoring Initiatives in the Molecular Genetics of Mental Disorders
- Addressing Administrative Issues
- Establishing a Genetics Advisory Group

Within each of the six categories, a set of concrete, executable recommendations is proposed. These recommendations are based on two assumptions. First, NIMH spends a significant portion of its budget on genetic approaches, and it is important to direct these resources into the most productive avenues for advancing the current understanding of complex disorders. Second, new forms of collaboration for both NIMH and its investigators will speed the search for susceptibility genes that influence mental disorders.

Findings of the Workgroup

Over the past 10 years, many researchers have attempted to detect and map susceptibility genes for the major mental disorders. Given the current understanding of complex genetic disorders, it has become clear that much larger numbers of affected individuals must be examined to detect and map these genes more unambiguously than originally thought. Since the efficiency of molecular genetic studies is rapidly increasing and their cost is decreasing, it is now opportune to establish the large-scale ventures necessary to meet the scientific requirements of these investigations. Such an effort will be enhanced by NIMH's significant experience in conducting coordinated, large-scale genetics studies. Of particular note is the previously described NIMH Genetics Initiative, which reflects many of the qualities that the Workgroup finds most promising. However, much remains to be done.

The Workgroup believes that the traditional methods and assumptions of NIMH staff and grantees will be of continued assistance in conducting genetic research but may not be sufficient for the large-scale efforts that many molecular approaches require. That is, the investigator-initiated project (often referred to by the NIH computer code R01) may not, by itself, accommodate the large ventures that molecular genetic studies of complex disorders will require. In this R01 approach, a principal investigator submits a research plan to collect a modest number of well-documented individuals or families with a given disorder in a specified geographic area. If the application is found to be meritorious through peer review, the Institute funds the grant for the new collection effort. NIMH has many grants of this type in its current portfolio, as do the other NIH institutes.

Although there are numerous investigator-initiated studies, some have not been able to recruit the necessary number of participants. Determining the necessary number is problematic because such estimates are specific to the underlying mode of genetic transmission, which is unknown. The more complex the transmission pattern, the

larger the study must be. Researchers who began collecting 10 years ago would have thought that 100 to 200 affected individuals and relatives would have been adequate. Now that multiple susceptibility genes are hypothesized, much larger samples than previously expected are necessary. If limited to an R01 grant approach, the investigator often seeks consecutive 5-year grants to accrue a large enough sample of affected individuals. These investigators then must analyze limited samples to justify their funding for the next grant period. As an alternative, or in addition to extending the project in time to achieve an adequate sample, an investigator could change the diagnostic criteria and permit a broader range of affected individuals into the sample. Although sample size is increased, the added variability makes the search more difficult.

Another difficulty facing investigators is that too few sites have all of the necessary staff and equipment to collect blood from well-diagnosed samples, transform and maintain cell lines, and genotype, analyze, and then identify genes. Many sites have one or more components, but they would benefit from access to additional infrastructure support to fully participate in the effort.

To speed the discovery process, NIMH must match the realities of complex disorders with feasible funding mechanisms and the establishment of infrastructure and training opportunities. Through its Genetics Initiative, NIMH has already assembled many of the critical elements for an efficient search. Policies, programs, and initiatives from across NIH offer additional opportunities for strengthening the Institute's strategy. What remains to be done is to expand and coordinate the necessary resources for a state-of-the-art molecular genetics initiative in the mental disorders.

Creating and Analyzing Large, Well-documented Samples

Clinically and genetically characterized families are a rare and valuable resource. To invest efficiently, NIMH should insist upon the timely sharing of clinical data and DNA materials obtained by grantees. That is, there should be a standing policy that taxpayer-supported samples be made available to qualified investigators in a timely manner. The Workgroup suggests that researchers and NIMH reassess current policies and procedures for sharing data and materials from grants and cooperative agreements.

In addition to the scientific and administrative considerations that are discussed in this section, the public health need must provide the context for reviewing these policies. The public health importance of sharing research materials is well expressed by John Shestack's story on the following page.

3:00 a.m.

Tonight I sit with my 6-month old son sleeping beside me, and I am uneasy. I am excited for the future that awaits him, but I am also afraid. I am the reluctant master of recurrence ratios, twin studies, lod scores, and odds. No formula can tell me - will he be whole, or will he be mysteriously broken like his brother? The brother who hardly seems to know he exists. Five years ago, my wife and I didn't know anything about autism. If we thought about it at all, we knocked on wood and thought it was something rare, something awful, and something that happened to other people.

Then we had a baby. I remember the day my son, Dov, was born. I held him in my arms and marveled at the continuity of life. How one day he would grow, go to school, get married, and have children. How one day he too would know the unbelievable happiness I was experiencing at that moment. My wife and I took Dov home to love and care for him.

When Dov was just over a year old, something began to go terribly wrong. He stopped answering to his name. He lost the few words he had. He no longer ran to greet us at the door. Instead, we would find him staring at specks of dust in the sunlight. In two months, our most precious gift vanished in front of our eyes. This is the special curse of autism. You have your child, and yet you

don't have him. You have a shell, a ghost of all the dreams and hopes you ever had. Every day is not a tragedy. There are good days. A ball is thrown, a word is learned, the bed is dry, or a hug is given freely. Once in a while, we clear all the insurance paperwork off the dining room table and eat dinner together. But there is never an easy day.

Now my wife and I know so much more about autism. Some studies suggest that it may affect up to 400,000 people in the United States. Though some individuals will make strides through early intervention, the vast majority will never marry, have a meaningful job, or live on their own. More than half will never learn to speak. Until very recently, there was little hope for people with autism. When we first learned that autism had a genetic component, we despaired. If autism is genetic, we thought, then it's hopeless. Now we understand that genetic research provides a pathway that can lead to understanding and to treatment. What might the next few years of research bring for children like Dov? We hope that biological research will provide new answers for autism. That is why my wife and I work to fund research in autism and to give this message of hope to hundreds of parents. We encourage them to participate in research.

But we also carry a message from the families to the scientists. It is this: you can't make it alone. Rapid progress is only possible if researchers work together. You may each have a piece of the puzzle, but the picture only emerges if you lay your piece down on the table for each other to see and build upon. Let everyone know what you know when you know it. Create strength by sharing your resources and findings. There are thousands of parents worrying at 3:00 a.m. and hoping for an answer.

Jonathan Shestack lives in Los Angeles where he recently produced the movie Air Force One. He and his wife, Portia Iversen, established Cure Autism Now, a non-profit organization.

Sharing high-quality materials will solve two of the field's biggest problems. First and foremost, collecting large enough samples for the detection of susceptibility genes becomes a possibility. Without the sharing of materials, it is difficult to see how peer review committees, institutional review boards, potential subjects, or funding agencies could support studies that have little chance of meeting their scientific aims in a reasonable time frame. The Workgroup sees the mandatory sharing of materials as one change that can sustain the feasibility of R01s by uniformly boosting their scientific potential.

Second, the availability of such a generative resource will attract additional molecular and statistical geneticists into the area of mental disorders. The Workgroup's survey of the portfolio indicates that more trained investigators in these areas are essential. The availability of rich clinical data and DNA will provide established geneticists with an attractive path into mental disorders research. New investigators also need rich materials, since years can pass before they can begin to accrue and then work on their own sample. Well-defined clinical samples will bring an infusion of new talent into the search for the genes that contribute to mental disorders.

The researchers who collect the diagnostic and DNA samples are entitled to recognition and incentives for their critical contribution. The Workgroup therefore recommends granting a proprietary period of 12 to 18 months during which the collecting investigators can make considerable progress on their own or with additional collaborators. But, in the end, the DNA samples and the clinical data must be shared with the scientific community.

NIMH has been a leader by making available the clinical data and DNA samples from the Genetics Initiative. Staff negotiated a reasonable proprietary period with investigators, and, after this period, the data were made available to other qualified investigators. Although this is a strong beginning, this sharing is limited to the clinical data and DNA from this particular set of grants. The Workgroup was impressed by the broader coverage in the procedures the National Human Genome Research Institute (NHGRI) and the Department of Energy (DOE) have jointly established (see Appendix D) for genomic research. Here, a policy was announced that states: (1) the specific time frame within which materials or results are to be shared; (2) the need for investigators to provide data

release and sharing plans in their grant application; (3) the review of the adequacy of the plan and its conformity with the policy by peer review; and (4) the incorporation of the investigator's plans into the terms and conditions of the awarded grant. The Workgroup appreciated both the concrete time limits announced in the NHGRI/DOE policy and the ability of review committees to permit any well-justified exception to these limits. Also significant is the clear monitoring role that staff members are to play in ensuring that the plans are executed.

The Workgroup recognizes that NIH policy on data rights is evolving and hopes that the NHGRI/DOE procedures are applicable to the NIMH case in genetics. If not, the issue of data sharing is so important that NIMH staff will need to explore contract options rather than grants or cooperative agreements. Contracts provide for the acquisition of materials that the Government then can distribute. The Government specifies exactly what the contractor should do, make, or deliver. Although contracts are a possibility, the Workgroup believes that the researchers' creativity and potential for capitalizing on serendipitous findings are diminished through this approach.

Recommendation 1: NIMH staff should draft a policy for the National Advisory Mental Health Council's consideration that provides for the sharing of genetic materials (i.e., DNA, diagnostic data, and genotypes) collected through NIMH's grants and cooperative agreements after a 12- to 18-month proprietary period. Staff members are encouraged to include all elements of the NHGRI/DOE policy on data sharing.

NIMH sets the pace in providing a self-supporting contract for maintaining cell lines and distributing the DNA and clinical diagnostic data. In this way, requestors' payment for the materials covers most of the costs of replenishing and distributing the DNA samples. Contracts such as this are a necessary vehicle for making full use of the shared data.

Recommendation 2: NIMH should continue to provide a contract for maintaining cell lines from individuals with mental disorders and appropriate relatives, as well as for distributing DNA and all clinical data to qualified investigators.

The data-sharing approach is predicated on informed consent from participants. Prospective participants in new genetic research projects must be asked if they will consent to having their anonymous materials shared with other qualified researchers. When ethicists have focused on the issue of data sharing, the discourse turns to privacy, individual rights, and the potential negative effects of such sharing. The Workgroup found that individuals with mental disorders and their families wanted to be assured of confidentiality but then wanted wide distribution of their anonymous samples for research.

Recommendation 3: NIMH should encourage consent procedures that describe and discuss the risks and benefits of DNA banking and clinical data sharing in genetic research.

Another opportunity for NIMH is the use of extant samples, in which NIMH has invested heavily. If valid diagnostic standards can be defined, these samples may be merged for re-analysis or reanalyzed after recoding diagnostic status.

Recommendation 4: NIMH should issue a request for applications (RFA) to conduct secondary analyses of clinical samples. The RFA should provide support for recoding diagnostic variables and for reanalysis. If the RFA proves successful, a program announcement should be established so that this very efficient and low-cost approach can continue.

Although there are centers in the United States and Europe capable of performing cost-efficient, large-volume genotyping called "high-through-put genotyping," the demand for such services may outpace these facilities. An answer to this potential rate-limiting problem is the broad availability of high-through-put genotyping, such as that soon to be available through NHGRI's Center for Inherited Disease Research (CIDR). In addition to offering capacity, such resources empower collecting researchers, who are the clinical and epidemiological experts, to expand their opportunities for carrying out such research and removing technical bottlenecks posed by genotyping. CIDR also provides expert consultation on study design and analysis.

Recommendation 5: NIMH should continue its support for core facilities such as CIDR to augment the available genotyping and analytic resources in academic research facilities.

Establishing well-identified, large samples will be facilitated by the establishment of international consortia. Finding ideal isolated populations will carry U.S. investigators around the world. NIMH should actively foster partnerships between American scientists and their counterparts in other countries. Partnership is the key word. In addition to establishing a full collaboration, productive international research requires a shared understanding of the materials that must be collected and their transportability, each country's patent laws, expectations regarding contributions to the local community, and publication rights.

Recommendation 6: *RFAs and program announcements should explicitly allow international work and provide support for such shared undertakings when scientifically appropriate.*

NIMH should reconsider the cooperative agreement process as well. The cooperative agreement is a grant that allows the Government's staff to provide substantial assistance through resources or collaboration. Through peer review, individual investigators are selected for participation and then asked to meet with the other awardees to design the eventual study. An alternative model was used by the National Heart, Lung, and Blood Institute (NHLBI) in its genetics program. Rather than having individual investigators or sites submit separate applications, the RFA called for teams of cooperating investigators across multiple sites to apply as a unified group. That way, the peer reviewers were able to assess the proposed research, the investigators knew with whom they would be working, and the methodology already was agreed upon within the team. This procedure seems much more likely to enable productive collaborations than the standard cooperative agreement approach or other types of RFA solicitations.

Recommendation 7: *RFAs for future large-scale, coordinated efforts should call for self-selected teams of researchers.*

Fostering NIMH Collaborations

Like the researchers, the NIMH extramural staff will need to work in collaborative groups. Rather than focusing on what the Institute can or cannot do with its allocation, NIMH staff members are encouraged to look for new alliances within NIH as well as with private industry, advocacy groups, and international consortia.

Many of the institutes at NIH are beginning to travel down this same road. NIMH is asked to seek out inter-institute collaborations on complex disorders. Each of these institutes will be investing in certain generic infrastructure activities that would be better integrated and financed if conducted in concert. A coordinating committee of key genetics staff from NIH should be convened to meet and discuss issues of genetics research and to exchange ideas.

Ideas for consideration by that committee are:

- All NIH communities could benefit from an NIH-wide training program in statistical analysis for molecular geneticists.
- The field still requires appropriate models and software for analysis. Efficient computer programs are needed that implement new analytic methods and provide the necessary power to handle both large family-size and multiple genetic markers. Because these tools will not be specific to a disorder and no individual institute is likely to pay for this entire effort, a joint RFA across NIH should be developed.
- New and revised NIH extramural policies could be reviewed to ensure applicability to genetics research.
-

As NIMH and other institutes move closer to finding causative and susceptibility genes, the consequences of these discoveries must be considered carefully. Resources such as NHGRI's Ethical, Legal and Social Implications program (ELSI) can assist in anticipating and considering ethical issues that might arise. For instance, as in other illnesses, when findings are first announced, individuals wish to make clinical decisions based on preliminary findings. There will be a sudden and significant need to train clinicians in genetic counseling. Additionally, issues concerning privacy and anticipated social implications are other areas of significant overlap. The institutes can build upon the experience from other disease entities via the ELSI program.

The ELSI program would gain much by learning about the specific needs of individuals with mental disorders. Individuals with mental disorders will be part of the audience for health care information regarding other illnesses with genetic components. Also, researchers in other areas will find that some individuals in their studies have a mental disorder. Of course, the large majority of individuals with a mental disorder do not require special protections, but some do. Learning about these considerations in the consent process and when to apply them will be quite helpful to researchers.

In addition to its NIH-wide activities, the coordinating committee should reach out to other communities invested in the outcome of complex genetics research:

- Private industry** is becoming an increasingly larger player in the field. Just as pharmaceutical companies have changed the way most clinical trials are conducted, similar financial forces are shaping genetics research. NIH staff should explore ways to advance the field through collaborations with business. Technology transfer opportunities can benefit private industry, NIH, and, ultimately, individuals with mental disorders and their families.
- Advocacy groups** provide opportunities for investigators to better understand how the results of their work may affect lives. Addressing these needs and concerns has multiple benefits. First, the research becomes more relevant to public health. Second, advocacy groups are interested in assisting with recruitment of participants. Third, new collaborations can be created, such as the jointly funded RFA supported by the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Diseases. Fourth, advocacy groups are eager for information from genetic studies. Providing results in lay language will benefit these individuals and help share the excitement of the science with the general public.
- International consortia for genetics research** should be fostered. Collaborating with these consortia can reduce the barriers to establishing unique resources across the globe.

Recommendation 8: *NIMH extramural staff should invite key clinical genetics staff across NIH to form a coordinating committee for complex disorders. Of particular interest would be discussions on joint efforts in training, software development, hardware, statistical models, ethical issues, and international alliances.*

Recruiting and Retaining New Researchers

The hunt for genes requires the coordinated effort of a large number of scientists with a good variety of skills. Genetic epidemiologists will likely be the key players during the phase of collecting genetic samples, since their expertise will result in the most consistent diagnostic categories being chosen, a critical element for success. Molecular geneticists have the expertise to generate the data that will be used to establish the linkage between DNA markers and the defective genes. Statisticians are required to analyze those data and to create new statistical tools to analyze very complex situations in which multiple defective genes may be interacting to produce a disease state. Interdisciplinary collaboration will be required to foster progress.

Too few researchers are studying the genetics of mental disorders, and even fewer are proficient in all the areas mentioned above. Complex disease genetics is a rapidly expanding field, and researchers of every type are in great demand by academia and industry. Providing an adequate community of geneticists committed to working on mental disorders will be an ongoing challenge for NIMH. The Workgroup recommends establishing the following programs to lower barriers to entering the field and to train new and established researchers.

Recommendation 9: *NIMH should establish multidisciplinary institutional training grants at the pre and postdoctoral levels that provide education in clinical, statistical, and molecular genetics.*

Recommendation 10: *Two programs established by NHLBI should be adapted for use at NIMH. First, the NHLBI Programs of Excellence in Molecular Biology should be modified for use by NIMH. This NIMH initiative should provide investigators with expertise in the genetics of mental disorders. Second, short-term training programs for new investigators or investigators seeking to redirect their career or broaden their skills should be established. Rather than a brief introduction to molecular genetics, the course should offer intensive, hands-on training opportunities.*

Recommendation 11: *A new investigator's award should be created to provide entrance into the field without demanding long-term, high-risk projects for junior investigators and for established geneticists seeking to redirect their efforts into mental disorders. These grants, envisioned as 2-year awards at \$50,000 to \$100,000 a year, could be used, for instance, to analyze data sets in the repository. Other short-term projects should be considered as well.*

Sponsoring Initiatives in the Molecular Genetics of Mental Disorders

The Workgroup also focused on what steps must be taken to understand the role, if any, of genetics in each of the mental disorders. The Workgroup found that the concept of readiness was a helpful index for making recommendations to the Institute. Depending on the existing empirical literature and diagnostic reliability, some disorders are clearly ready for large-scale molecular approaches while others require an investment in additional preliminary research.

Dr. Steven Moldin, Acting Chief of the NIMH Genetics Research Branch, summarized the research findings that the Workgroup surveyed (see Appendix E). These findings include a description of each disorder and technical summaries of the current genetics findings from human and animal studies. Based on these published findings, Dr. Moldin determined for each disorder the population prevalence and the risk of illness for different classes of relatives of an affected individual (see Table 4). The precision of these estimates varies widely, due to differences in methodologies, number of studies, and sample sizes. Table 4 includes recurrence risk ratios (lambdas, or λ_s), which are the risks to relatives of different degrees of genetic relationship divided by the disorder's lifetime prevalence (i.e., how frequently the disorder occurs in the population). The degree of genetic relationship is the amount of genes two individuals would be expected to share (i.e., identical twins, 100 percent; first-degree relatives such as fraternal twins, siblings, or parents, 50 percent; second-degree relatives such as grandparents, 25 percent). Each pattern of relative risks is an important characteristic of that illness that geneticists can use to discriminate among models of genetic transmission and to estimate the magnitude of genetic effects. Also, the geneticist used figures like these to estimate Clea Simon's chance of having a child with schizophrenia.

Table 4
Recurrence risk ratios

Disorder	Population Prevalence	Observed Recurrence Risk Ratios			
	(%)	λ_{mx}	λ_1	λ_2	λ_3
Category 1					
Autism ^a	0.02 - 0.05	1,460 - 3,650	84 - 210	0	0
Bipolar disorder	0.8	60	7	--	--
Schizophrenia	1	48	11	4.25	2
Category 2					
ADHD	7 - 10	6 - 8	2 - 4	0.5 - 0.8	--
Depression	5 - 17	1.5 - 2	1.1 - 1.6	--	--
Eating disorders					
Anorexia nervosa ^b	0.1	710	41	40	--
Bulimia nervosa ^{a,b}	1 - 3.5	8	2	--	--
Obsessive-compulsive					

disorder ^b	2	--	4.6	--	--
Panic disorder ^{a,b}	1.7 - 3.5	4	3.5 - 7	2.4 - 4.75	--
Tourette's syndrome	0.05	--	174	--	--

The precision of these estimates varies widely due to differences in methodologies, number of studies, and sample sizes. Definition of lambda (λ) subscripts: mz = monozygotic twins; 1 = first-degree relatives; 2 = second-degree relatives; 3 = third-degree relatives. ^aDizygotic concordance of 0 percent obtained in one or more twin studies. ^bMonozygotic concordance not greater than dizygotic concordance in one or more twin samples.

The disorders in Table 4 sort into two categories: (1) mental disorders that are ready for and require a large NIMH Genetics Initiative and (2) mental disorders that would benefit from nonmolecular genetic and/or epidemiological studies and smaller scale molecular approaches to better document their estimated heritability.

Category 1: Molecular Initiatives

Schizophrenia, bipolar disorder, and autism are ready for large-scale molecular approaches. Another disorder, a particular subtype of depression called early-onset depression, which begins before the age of 20 and tends to be recurrent and severe, should also be considered, although its empirical basis is not as strong as the other three. These disorders can be reliably diagnosed and for the first three recurrence risk ratios are sufficiently high. There is no recurrence risk ratio for early-onset depression because there is no published population prevalence estimate for this subtype of depressive disorder. This is why depression, as a whole, is not listed in category 1 but appears in category 2. Nonetheless, a clear preponderance of research literature indicates this subtype is reasonable to explore. Because autism has yet another important characteristic, recommendations pertaining to this disorder will be discussed separately, after the other three disorders.⁵

NIMH should develop coordinated molecular genetic initiatives in schizophrenia, bipolar disorder, and early-onset depression. These initiatives should be disorder-specific and reflect the Workgroup's recommendations from the previous sections. Whether the RFA calls for a cooperative agreement or another method for collaboration among teams of researchers, NIMH staff must ensure that new collections will either establish a sufficiently large sample or augment an existing sample. Review criteria should emphasize the rigorous definition of the disorder and the comparability of data across sites. Further, investigators should include a timetable designating the expected rate of progress to serve as a monitoring tool for the NIMH project officer when the noncompetitive renewal is considered.

The Workgroup thought that specifying a particular scientific approach was premature and leaves this to the investigators and the peer-review groups. Association, linkage, and linkage disequilibrium studies all should be solicited.

Recommendation 12: NIMH should issue RFAs for large-scale molecular genetics studies of schizophrenia, bipolar disorder, and early-onset depression.

Initiatives in autism need to be developed in a different manner. The heritability of autism is very high, but there is a significant problem that must be thoughtfully addressed. Families with several affected individuals are exceedingly uncommon. Sampling from these families must be accomplished in an integrated manner. Simply funding more investigators may result in this limited resource being divided up into multiple, small samples, none of which are sufficient. Thus, coordinated approaches among the current researchers are essential. Integration also is necessary because multiple institutes fund in the area of autism. NIMH is encouraged to collaborate with the other NIH institutes in the existing NIH Autism Coordinating Committee to ensure the most productive use of resources. Further, NIMH and the other institutes should provide the necessary extramural staffing and financial support to foster this collaboration. Once the integration is established, the feasibility of additional collection efforts should be assessed.

Recommendation 13: *NIMH should work with the NIH Autism Coordinating Committee to find methods for integrating ongoing studies and their samples.*

Category 2: Initiatives in Clinical and Epidemiological Research

The disorders listed in category 2 would greatly benefit from additional diagnostic development and/or from rigorous family, twin, and epidemiological studies. The standard R01 approach has been successful in this type of research; however, if teams from various sites worked together in establishing registries or diagnostic standards, the time frame could be greatly reduced and the comparability of data enhanced. Such collaborations could be established through an R10 approach, in which investigators from various sites apply as a team with a shared protocol. Collaborative efforts would be particularly important for the molecular studies that are currently underway or will begin in these disorder areas.

Recommendation 14: *A program announcement should solicit applications across all investigator-initiated research mechanisms for clinical, family, and epidemiological studies in the other mental disorders to develop diagnostic tools and/or to evaluate the role of genetics and environment in contributing to the onset of these mental disorders.*

Addressing Administrative Issues

The Workgroup was asked to comment on specific administrative issues in the Institute's extramural and intramural programs. The recommendations below are provided to facilitate the best extramural and intramural research. Again, the organizing principles of coordination and efficiently investing resources (e.g., personnel, time, and expertise) guide these recommendations.

Extramural Research Program

The organizational structure of the extramural research program is undergoing change. The Workgroup was pleased to provide advice in reshaping the extramural programs in genetics. Joining research on the genetics of mental disorders with basic genetics research is a particularly promising organizational change. The new branch will require a leader of considerable breadth and vision.

Recommendation 15: *The Workgroup supports the newly formed NIMH integrated genetics branch and recommends that it be headed by an established genetics researcher who can provide the leadership and creativity the NIMH extramural program warrants.*

The Workgroup appreciated the relocation of the review of NIMH's genetic applications to NIH's Center for Scientific Review (CSR) committees, where broad expertise exists in molecular and statistical genetics. The integration of NIMH peer review into CSR provides a unique opportunity for NIMH applications to receive the in-depth, multi-disciplinary expertise that is required for funding outstanding science. The Workgroup believes that applications concerning the genetics of mental disorders should be reviewed with other complex disorders in the new organizational structure.

Recommendation 16: *Applications on the genetics of mental disorders should be reviewed together with applications pertaining to other complex disorders in the new CSR structure. The eventual panels must include sufficient clinical, molecular, and statistical expertise.*

Both the Workgroup's review of the portfolio and observations from NIMH staff indicate a recurrent problem in meeting sampling projections. Although some of the Workgroup's previous recommendations are expected to

alleviate this difficulty, the "terms and conditions" of the grant award should include clear criteria for success for all grant activity. These benchmarks, which should be self-set, explicitly stated, and peer reviewed, should be part of the terms and conditions of grant awards so that the project officer can fairly monitor and allocate future (noncompetitive) funds based on progress toward the stated goals. This monitoring would include the data-sharing procedures as previously described.

Recommendation 17: *The terms and conditions section of grant awards for genetic collection must specify a data-gathering plan and should be effectively monitored to ensure sufficient timely progress.*

Intramural Research Program

The Workgroup's recommendations regarding IRP amplify those in *Finding the Balance: Report of the National Institute of Mental Health's Intramural Research Planning Committee*, particularly the statements on leadership, direction, staffing, review, and resource management.

Just as individual laboratories in the extramural community are unlikely to have the fiscal resources or clinical samples to solve these complex disorders, separate NIMH intramural laboratories face the same difficulties. Integration of efforts and sharing of facilities only can strengthen the program. Further, liaisons with extramural activities, already evidenced in some of the laboratories, should be encouraged. They hold particular promise for new ties between basic and clinical genetics, human and animal work, and connections across disorders. The Workgroup believes that these connections can be a unique feature of the IRP research and should be fostered. Quality research must be recognized and promoted by adhering to the highest standards of peer review in the site-visit teams and on the Board of Scientific Counselors. The review process should be taken seriously, and the recommendations for expanding and contracting research programs should be acted upon with dispatch and determination.

Recommendation 18: *Appointing a permanent IRP Scientific Director who combines a very high level of scientific expertise with the vision to understand and appreciate the power of interdisciplinary research in mental disorders will advance NIMH's IRP genetics effort. Depending on the selection, additional genetics expertise and leadership still may be required at IRP. Recruiting new leadership in genetics is critical to unifying and revitalizing the genetics program of the IRP.*

Recommendation 19: *Genetics research at the IRP should be consistent with the new mission statement.*

Recommendation 20: *Productive collaboration, including data and core resource sharing, should be expected and fostered across IRP laboratories and with NHGRI and NIMH extramural staff and investigators.*

Recommendation 21: *Reviews of the IRP laboratories must be expert and should promote the best genetics research by shaping the direction of and resources to the IRP genetics laboratories.*

Establishing a Genetics Advisory Group

The ideas and recommendations outlined here will require 3 to 5 years to initiate and 10 years to implement. Such long-term planning will also require constant evaluation since today's best insights may change as genetic loci are identified and as technology advances. With this in mind, the Workgroup suggests that the Institute establish a Genetics Advisory Group to ensure swift reaction to new developments and opportunities. The main tasks for this group will include reviewing concepts for RFAs and requests for proposals, identifying important trends, suggesting or reviewing ideas for work-shops and conferences, and monitoring the portfolio and the adequacy of data-sharing procedures. This group should include expertise from the many disciplines that contribute to human genetics. Further, an expert in technology development and transfer should be included. The new extramural genetics program will benefit from the Advisory Group's counsel, as will the intramural program.

Recommendation 22: *The Workgroup requests that an Advisory Group be established to consult on the implementation of this plan and its impact on the extramural and intramural programs of NIMH.*

APPENDIX A

National Advisory Mental Health Council

Chairperson

Steven E. Hyman, M.D.
Director
National Institute of Mental Health
Rockville, Maryland

Executive Secretary

Jane A. Steinberg, Ph.D.
Associate Director
National Institute of Mental Health
Rockville, Maryland

Members

Thomas Detre, M.D.
Senior Vice Chancellor For Health Sciences
University of Pittsburgh
Pittsburgh, Pennsylvania

Robert L. Johnson, M.D.
Professor
Department of Pediatrics
University of Medicine and Dentistry
of New Jersey
Newark, New Jersey

Apostolos Georgopoulos, M.D., Ph.D.
Professor, Department of Physiology, Neurology
and Psychiatry
University of Minnesota Medical School
Director, Brain Sciences Center
Veterans Affairs Medical Center
Minneapolis, Minnesota

Kathryn Cameron Porter
President
The Human Rights Alliance
Fairfax, Virginia

Ann M. Graybiel, Ph.D.
Walter A. Rosenblith Professor
Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology
Cambridge, Massachusetts

Richard H. Scheller, Ph.D.
Investigator, Howard Hughes
Medical Institute
Professor, Department of Molecular and Cellular
Physiology
Stanford University School of Medicine
Stanford, California

Michael F. Hogan, Ph.D.
Director
Ohio Department of Mental Health
Columbus, Ohio

James G. Townsel, Ph.D.
Professor
Department of Anatomy and Physiology
Meharry Medical College
Nashville, Tennessee

G. Richard Smith, Jr., M.D.
Professor
Director of Centers for Mental Healthcare
Research
Department of Psychiatry
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Myrna M. Weissman, Ph.D.
Professor
Department of Psychiatry
Chief, Department of Clinical and Genetic
Epidemiology
New York State Psychiatric Institute
Columbia University
New York, New York

Jos, Szapocznik, Ph.D.
Professor and Director
Center for Family Studies
Department of Psychiatry and Behavioral
Sciences
University of Miami School of Medicine

Miami, Florida

Ex Officio Members

National Institutes of Health
Harold E. Varmus, M.D.
Director
National Institutes of Health
Bethesda, Maryland

Department of Veterans Affairs
Thomas B. Horvath, M.D., F.R.A.C.P.
Chief Consultant for Mental Health
Veterans Health Administration
Department of Veterans Affairs
Washington, DC

Department of Defense
Robert A. Mays, Jr., Ph.D.
Colonel, U.S. Army
Deputy Chief of Staff
North Atlantic Regional Medical Command
and Walter Reed Army Medical Center
Washington, DC

Department of Health and Human Services
Donna E. Shalala, Ph.D.
Secretary
Department of Health and Human Services
Washington, DC

Liaison Representative

Center for Mental Health Services
Thomas H. Bornemann, Ed.D.
Deputy Director
Substance Abuse and Mental Health
Services Administration
Rockville, Maryland

Special Consultants

Thomas J. Coates, Ph.D.
Professor of Medicine and Epidemiology
Director, AIDS Research Institute and
Center for AIDS Prevention Studies
University of California, San Francisco
San Francisco, California

Kathy Cronkite
Mental Health Advocate
Austin, Texas

Mary Jane England, M.D.
President
Washington Business Group on Health
Washington, DC

Dale L. Johnson, Ph.D.
Professor
Psychology Department
University of Houston
Houston, Texas

Constance E. Lieber
President
National Alliance for Research on
Schizophrenia and Depression (NARSAD)
Great Neck, New York

A. John Rush, M.D.
Betty Jo Hay Professor
and Chair in Mental Health
Department of Psychiatry
University of Texas
Southwestern Medical Center
Dallas, Texas

Joseph S. Takahashi, Ph.D.
Investigator, Howard Hughes
Medical Institute
Walter and Mary E. Glass Professor
Department of Neurobiology and Physiology
Northwestern University
Evanston, Illinois

APPENDIX B

NIMH Genetics Workgroup

Chairperson

Samuel H. Barondes, M.D.
Jeanne and Sanford Robertson Professor of
Neurobiology and Psychiatry
University of California, San Francisco
San Francisco, California

Staff Director

Jane A. Steinberg, Ph.D.
Associate Director
National Institute of Mental Health
Rockville, Maryland

Members

Aravinda Chakravarti, Ph.D.
Professor of Genetics
Department of Genetics
Case Western Reserve University
Cleveland, Ohio

Theodore Reich, M.D.
Professor of Genetics and Psychiatry
Department of Psychiatry
Washington University School of Medicine
St. Louis, Missouri

Mary Claire King, Ph.D.
Professor of Medicine
Division of Medical Genetics
University of Washington
Seattle, Washington

Joseph Takahashi, Ph.D.
Investigator
Howard Hughes Medical Institute
Walter and Mary E. Glass Professor
Department of Neurobiology and Physiology
Northwestern University
Evanston, Illinois

Eric S. Lander, Ph.D.
Director
Whitehead Institute
Center for Genome Research
Massachusetts Institute of Technology
Cambridge, Massachusetts

Stephen T. Warren, Ph.D.
Investigator
Howard Hughes Medical Institute
Professor
Department of Biochemistry
Emory University
Atlanta, Georgia

Robert L. Nussbaum, M.D.
Chief
Laboratory of Genetics Disease Research
National Human Genome Research Institute
Bethesda, Maryland

APPENDIX C

Roster of Presenters

Extramural Community

Laura Bierut, M.D.
Washington University

Kay Redfield Jamison, Ph.D.
The Johns Hopkins School of Medicine

Linda Brzustowicz, M.D.
Center for Molecular and Behavioral Neuroscience
Rutgers University

Kenneth Kendler, M.D.
Medical College of Virginia

Lee Ducat
Human Biological Data Interchange

Michele LaBuda, Ph.D.
The Johns Hopkins University

Geoffrey Duyk, M.D., Ph.D.

Jacques Mallet, Ph.D. Laboratoire de Genetique
Moleculaire de la

Exelixis Pharmaceuticals, Inc.

Neurotransmission et des Processus
Neurodegeneratifs

Michael Escamilla, M.D.
University of California, San Francisco

Vishwajit Nimgaonkar, M.D., Ph.D.
University of Pittsburgh

Laurie Flynn
National Alliance for the Mentally Ill

Jonathan Shestack
Cure Autism Now (CAN)

NIMH and NIH Staff

Michael Brownstein, M.D., Ph.D.
Section on Genetics
Division of Intramural Research Programs

Stephen Foote, Ph.D.
Behavioral and Integrative Neuroscience Research
Branch
Division of Basic and Clinical Neuroscience Research

Jacqueline N. Crawley, Ph.D.
Experimental Therapeutics Branch
Division of Intramural Research Programs

Elliot Gershon, M.D.
Clinical Neurogenetics Branch
Division of Intramural Research Programs

Mary E. Farmer, M.D.
Genetics Research Branch
Division of Basic and Clinical Neuroscience
Research

Edward I. Ginns, M.D., Ph.D.
Clinical Neuroscience Branch
Division of Intramural Research Programs

Steven E. Hyman, M.D.
National Institute of Mental Health

Mary E. Oliveri, Ph.D.
Behavioral Science Research Branch
Division of Mental Disorders, Behavioral Research and
AIDS

Carl R. Merrill, M.D.
Laboratory of Biochemical Genetics
Division of Intramural Research Programs

David Shore, M.D.
Office of the Associate Director for Clinical Research

Stephen C. Mockrin, Ph.D.
National Heart, Lung, and Blood Institute

Brent Stanfield, Ph.D.
Division of Intramural Research Programs

Steven O. Moldin, Ph.D.
Genetics Research Branch
Division of Basic and Clinical Neuroscience
Research

Susan Swedo, M.D.
Division of Intramural Research Programs

Grayson S. Norquist, M.D., M.S.P.H.
Division of Services and Intervention Research

Steven J. Zalcman, M.D.
Molecular and Cellular Neuroscience Research Branch
Division of Basic and Clinical Neuroscience Research

APPENDIX D

Data and Materials Sharing

NIH-DOE Guidelines for Access to Mapping and Sequencing Data and Material Resources

The information and resources generated by the Human Genome Project have become substantial, and the interest in having access to them is widespread. It is therefore desirable to have a statement of philosophy concerning the sharing of these resources that can guide investigators who generate the resources as well as those who wish to use them.

A key issue for the Human Genome Project is how to promote and encourage the rapid sharing of material and data that are produced, especially information that has not yet been published or may never be published in its entirety. Such sharing is essential for progress toward the goals of the program and to avoid unnecessary duplication. It is also desirable to make the fruits of genome research available to the scientific community as a whole as soon as possible to expedite research in other areas.

Although it is the policy of the Human Genome Project to maximize outreach to the scientific community, it is also necessary to give investigators time to verify the accuracy of their data and to gain some scientific advantage from the effort they have invested. Furthermore, in order to assure that novel ideas and inventions are rapidly developed to the benefit of the public, intellectual property protection may be needed for some of the data and materials.

After extensive discussion with the community of genome researchers, the advisors of the NIH and DOE genome programs have determined that consensus is developing around the concept that a 6- month period from the time data or materials are generated to the time they are made available publicly is a reasonable maximum in almost all cases. More rapid sharing is encouraged.

Whenever possible, data should be deposited in public databases and materials in public repositories. Where appropriate repositories do not exist or are unable to accept the data or materials, investigators should accommodate requests to the extent possible.

The NIH and DOE genome programs have decided to require all applicants expecting to generate significant amounts of genome data and materials to describe in their application how and when they plan to make such data and materials available to the community. Grant solicitations will specify this requirement. These plans in each application will be reviewed in the course of peer review and by staff to assure they are reasonable and in conformity with program philosophy. If a grant is made, the applicant's sharing plans will become a condition of the award and compliance will be reviewed before continuation is provided. Investigators will be asked to address the issue in their progress reports.

APPENDIX E

Genetics Fact Sheets

Attention-Deficit Hyperactivity Disorder

Phenotype: Attention-deficit hyperactivity disorder (ADHD) has its onset in childhood and is characterized by developmentally inappropriate degrees of inattention, impulsiveness, and hyperactivity. Typical symptoms are fidgeting, difficulty remaining seated, distractibility, difficulty following through, impatience, inattentiveness, excessive talking with frequent interruption of others, and engaging in physically dangerous activities. These symptoms are expressed in the classroom or workplace, at home, and with peers, and conduct, depressive, and anxiety symptoms are often associated [1-5]. When data were obtained from both parents and children, test-retest reliabilities for symptom ratings and diagnosis were excellent ($\kappa = 0.8$) [6], but one methodological issue concerns whether teacher information is needed for a diagnosis [7, 8]. ADHD is difficult to establish in adulthood, since a childhood history is required, and some of its clinical features mimic those of the other disorders with which it frequently occurs [9]. Milberger and colleagues recently identified for use in genetic analysis a quantitative ADHD phenotype that combines data across diagnostic, cognitive, and demographic domains [10].

Epidemiology: In a large sample from the U.S. population, the prevalence of ADHD (male: female ratio) in school-age children was 6.7 percent (5.1:1) [2]. Depending on the use of adaptive functioning ratings to define definite maladjustment, prevalence estimates of 6.6 percent and 9.5 percent (with an unspecified higher rate in boys) were obtained in an epidemiologic survey of Puerto Rican children [11]. A large population-based epidemiologic study of U.S. children based on data obtained from both parents and children [6] used a structured instrument and yielded a prevalence estimate of 11.5 percent for the diagnosis of any disruptive disorder (ADHD, conduct disorder, or oppositional defiant disorder). A recent study of teacher-reported rates for ADHD defined by different

diagnostic criteria sets revealed rates of 7 percent to 11 percent, with a male:female ratio of 4-16:1-6 [12]. A 12-month prevalence of 0.3 percent in adults has been reported [9].

Family Studies: Several studies demonstrate that ADHD aggregates in families [13-15]. The rates in probands' sibs in three older studies [16-18] ranged from 17 percent to 41 percent, with respective rates in controls' sibs ranging from zero to 8 percent [16, 17]. Rates of childhood ADHD in parents of hyperactive probands in several older studies ranged from 15 percent to 44 percent for fathers and 4 percent to 38 percent for mothers [19-22], although one study found no evidence of an increased rate of childhood ADHD in parents of ADHD probands [23]. Large case-control studies using structured interviews reported rates of 25 percent [24] and 16 percent (for broadly defined ADHD, the rate was 25 percent [25]) in first-degree relatives of ADHD probands, with respective rates of 5 percent and 3 percent (broadly defined ADHD was 8 percent) among sibs of normal controls.

The rates of ADHD in fathers:mothers:sibs of ADHD probands in these two studies were 44:18:21 and 17:11:15 [14], and a 4-year follow-up showed a lifetime prevalence of 26 percent for ADHD in sibs [14, 26]. Another recent case-control study using structured interviews found lifetime rates of ADHD in fathers:mothers:male sibs:female sibs to be 12:6:21:0 [27]. Another study found a high risk of 57 percent for offspring of ADHD probands [28]. Direct interviews of second-degree male:female relatives yielded lifetime rates of 9:0 [27], and evaluation by family history of second-degree relatives in a study of Biederman and colleagues [25] showed that the prevalences of ADHD in aunts:uncles: grandmothers:grandfathers were 4:9:3:5 [29]. Four studies have specifically examined the risk of ADHD in relatives of female ADHD probands [18, 24, 30, 31]. The rates for sibs of female probands versus sibs of male probands were 35 percent and 23 percent [18], 9 percent and 33 percent [30], and 20 percent and 25 percent [24, 31]. Finally, monozygotic (MZ) probandwise concordance rates of 51 percent and 58 percent have been reported in two twin series [32, 33]. Using figures from the most methodologically rigorous and largest family and twin studies described above [25, 27, 32] and assuming a population prevalence between 7 percent and 10 percent for ADHD, the estimated recurrence risk ratios (λ_{R-s}) for type R relatives of someone with the disorder are as follows: $\lambda_{MZ} = 6-8$, $\lambda_1 = 2-4$, and $\lambda_2 = 0.5-0.8$. If second-degree [27, 29] and first-degree [25] relatives are compared with their respective controls (one study [27] found no ADHD in female siblings or female second-degree relatives), recurrence risk ratios are between 3 and 5 for first-degree relatives and about 3 for second-degree relatives.

Twin Studies: Two small twin studies found that 4 of 4 [34] and 3 of 3 [35] MZ twins were concordant for ADHD. A larger twin study [33] reported respective MZ and dizygotic (DZ) probandwise concordance rates of 51 percent and 33 percent, with a heritability estimate of 64 percent. In a subsequent reanalysis [36], the heritability of mother-reported activity levels was 75 percent. Respective MZ and DZ probandwise concordance rates of 79 percent and 32 percent for ADHD were found in a study of twins who also had a reading disability, and heritability was estimated at 98 percent [37]. One recent study yielded respective MZ and DZ concordance rates of 58 percent and 31 percent, with a heritability estimate of 79 percent [32]. Studies of quantitative measures of hyperactivity, activity level, or inattentiveness in several twin samples have yielded heritability estimates that ranged from 73 percent to 88 percent [38-42].

Adoption Studies: Increased rates of hyperactivity or a history of hyperactivity have been found among both adopted-away sibs of children with ADHD [43] and the biological parents of hyperactive boys compared with controls [21, 44, 45].

Mode of Inheritance: Deutsch and colleagues found limited evidence in a small sample [46] for an incompletely penetrant autosomal dominant single major locus transmission. A segregation analysis of a different data set [25] also resulted in statistical evidence -- including estimates of transmission parameters that were not significantly different from Mendelian expectations -- for an incompletely penetrant dominant or additive autosomal single major locus [47]. Low penetrance estimates predicted that only 46 percent of boys and 31 percent of girls with the ADHD gene would develop the disorder.

Molecular Genetic Studies: A population-based association study reported evidence of an association between ADHD and an allele at the dopamine D₂ receptor gene on 11q ($p = 0.0003$) [48], but this finding has not been replicated and was most likely an artifact of population stratification. The Transmission Disequilibrium Test (TDT) [49] was used in a family-based association study to identify an association between ADHD and a specific allele at the dopamine transporter locus on 5p ($p = 0.006$) [50]. Another population-based association study found an association between ADHD and an allele at the dopamine D₄ receptor on 11p ($p = 0.01$) [51]. Given that the numbers of other association tests conducted in these studies were not specified, the statistical meaning of the

results is unclear. Finally, a 3 Mb deletion within 22q has been reported in 24 of 26 patients with velo-cardio-facial syndrome [52]: 9 of the 24 also were diagnosed with ADHD, although the relevance of this finding to most cases of ADHD is unclear.

Animal Studies: A quantitative trait locus (QTL) for a hyperactivity phenotype (spontaneous activity, locomotor reactivity to a novel environment, and rearing in the open field) has been localized to rat chromosome 8 and explains 29 percent of the variance of an intercross between the Wistar-Kyoto and Wistar-Kyoto hyperactive strains [53]. The implicated region maps to mouse chromosome 9. The murine strain Coloboma has been proposed as a genetic model for ADHD [54] and a knockout mouse for the dopamine transporter gene (showing compromised dopamine transport) exhibited extreme hyperactivity [55].

Autism

Phenotype: Autism is a childhood disorder characterized by the following symptoms: qualitative impairments in social interaction (marked lack of awareness of the existence or feelings of others, no or abnormal seeking of comfort at times of distress, no or impaired imitation, abnormal or no social play, failure to develop peer friendships, lack of social or emotional reciprocity); qualitative impairments in verbal and nonverbal communication (no mode of communication, markedly abnormal nonverbal communication, absence of imaginative activity, marked abnormalities in speech production and in the form or content of speech, delay in or total lack of the development of spoken language, marked impairment in the ability to initiate or sustain a conversation); and a markedly restrictive repertoire of activities (stereotypic body movements, persistent occupation with parts of objects, distress over minimal changes in the environment, unreasonable insistence on precisely following routines, markedly restrictive range of interests).

About 66 percent to 75 percent of autistic subjects have full-scale IQ scores less than or equal to 70 [56, 57]. No evidence on test-retest or interrater diagnostic reliability is available. There is no consensus on the type and severity of symptoms or behaviors that should define the autistic phenotype in adults [58, 59].

In most family studies, cognitive disorders (including speech and language disorders) and abnormal social behaviors that are qualitatively similar to the defining features of autism -- but that extend beyond the current phenotypic definition -- significantly aggregate in the families of autistic probands [60-70]. However, other work suggests that there does not appear to be a highly variable autistic phenotype expressed in children who are relatives of autistic probands [71].

Epidemiology: Estimates of the lifetime prevalence of autism range from 0.7 in 10,000 to 5.6 in 10,000, with male:female ratios varying from 1.3:1 to 15.2:1 across 11 epidemiologic studies [72-82]. Prevalence appears to vary across age groups, from 0.4 in 10,000 (age range, 18-20 years) to 12.6 in 10,000 (age range, 7 - 9 years) [57]. Differences in prevalence rates across studies reflect differences in strategies and diagnostic criteria. Pooling data across the 11 studies yields a lifetime prevalence of 2 to 5 per 10,000, with a male:female ratio of about 3-4:1 [57, 83].

Family Studies: In nine family studies [61, 63, 64, 84-89], the risk to sibs of persons with autism ranged from 2.5 percent to 8.6 percent, with an average risk of 4.2 percent. One study [65] reported a probandwise concordance rate of 73 percent in MZ twins. Using these figures and assuming a lifetime risk between 0.02 percent and 0.05 percent, recurrence risk ratios (λ_{R^1}) for type R relatives of someone with the disorder are as follows: $\lambda_{SIB} = 84-210$, $\lambda_{MZ} = 1,460-3,650$. Pickles and colleagues [90] analyzed family history and twin data [65] and found no cases among second- and third-degree relatives of autistic probands.

Twin Studies: The MZ:DZ pairwise concordance rates in the four twin studies to date are as follows: 36:0 [64]; 96:24 [87]; 91:0 [91]; and 60:0 [65]. The pairwise concordance MZ:DZ rate across these four studies is 73:7. DZ concordance rates of zero are problematic. Broadening the criteria for affected status to include the following phenotypes led to increased MZ:DZ concordance rates: cognitive/ linguistic impairments, 82:10 [64]; cognitive disorders, 91:30 [91]; and cognitive and social abnormalities, 92:10 [65].

Adoption Studies: Although a small number of adopted-away children have been identified [92], no adoption data

have been published as yet.

Mode of Inheritance: Polygenic [89, 93], autosomal recessive [87], and X-linked [94, 95] models have been proposed for the familial transmission of autism, but none fully explains the empiric data. For example, single major locus autosomal transmission has been excluded in some families [89] and X-linked transmission in others [96] but the degree to which these disparate findings represent different genetic etiologies in different populations of families (locus heterogeneity) is unclear. Estimates of broad heritability (additive gene effects and shared environment) were 91 percent to 93 percent (base rate estimates of 1.75/10,000 and 10/10,000, respectively) [65]. Jorde and colleagues [89] estimated heritability to be 1 and concluded that the observed familial clustering was due to a combination of both polygenic and shared environmental effects. Latent class analysis of family history and twin data collected by Bailey and colleagues [65] excluded a single major gene model and supported the involvement of three multiplicative loci, although the evidence was not inconsistent with the involvement of 2 to perhaps as many as 10 such loci [90].

In summary, the mode of transmission of autism remains unknown and is most likely complex, with many cases caused by multiple genes of small relative effect in epistatic interaction.

Molecular Genetic Studies: Several reports in the early 1980s of an apparent association between autism and the fragile X syndrome were followed by conflicting results [97]. In recent molecular studies, no expansion of triplet repeats in the FMR-1, FRAXE, and FRAXF genes were observed [98, 99]. Although a population-based association study found evidence for an association between autism and an X chromosome marker, after correcting for multiple testing the association was not significant [100]. Analysis of data from 38 multiplex families with autism led to the exclusion of linkage across the entire X chromosome for a disease recurrence risk ratio to sibs (λ_{XS}) conferred by a specific susceptibility locus of 4 [101]. The ability to exclude an X-linked gene decreased with smaller λ_{XS} values, and some positive evidence was found with smaller values; a maximum lod score of 1.2 was obtained with $\lambda_{XS} = 1.5$.

Cook and colleagues recently described a pedigree in which two autistic siblings and their unaffected mother had a 15q11-q13 duplication and hypothesized that a maternally imprinted gene in this region may contribute to susceptibility to autism [102]. Two small population-based association studies have reported an association between autism and an allele on the HRAS gene on 11p; however, in each case the statistical evidence was weak ($p = 0.05$, after correction for multiple tests [103, 104]; $p = 0.04$, no correction for multiple tests [105]).

A family-based association study [106] found another weak association ($p = 0.03$, no correction for multiple tests) between autism and the serotonin transporter gene on 17q, and, finally, an association between autism and an extended human lymphocyte antigen haplotype B44-SC30-DR4 on 6p has been reported in small samples [107, 108]. These findings clearly require replication in other pedigrees.

Animal Studies: No genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (knock-out and knock-in techniques) have been reported. More robust animal models need to be developed. Given that cognitive deficits occur in autism, a recent study using Down syndrome as a model for complex trait analysis may have some relevance [109]. Transgenic mice containing yeast artificial chromosomes (YACs) from a 2 Mb region of human chromosomal region 21q22.2 were subjected to learning and behavioral assays. Two YACs caused specific defects in learning and memory, thereby implicating genes from at least two different genomic regions on chromosome 21 in generating these cognitive deficits.

Bipolar Disorder

Phenotype: Modern psychiatric nosology follows Leonhard's [110] suggestion to subdivide mood disorders into bipolar disorder -- where episodes of mania or both mania and depression occur -- and unipolar depressive disorder -- where episodes of depression alone occur. Symptoms of mania are expansive, elevated, or irritable mood; inflated self-esteem; grandiosity; decreased need for sleep; increased talkativeness; racing thoughts; distractibility; increased goal-directed activity; and excessive involvement in pleasurable activities with a high potential for painful consequences. Depressive symptoms consist of depressed mood, diminished interest or pleasure in activities, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy,

feelings of worthlessness or excessive guilt, inability to concentrate or act decisively, and recurrent thoughts of death or suicide. Interrater reliability is excellent ($\kappa = 0.83$) [111], and test-retest reliability over a 6-year period is moderate ($\kappa = 0.60$) [112]. Several mental disorders, including variants of schizoaffective disorder, recurrent unipolar depression, and hypomania (bipolar II disorder), have been proposed as alternate expressions of a bipolar genotype [113-115]. Regarding these "spectrum" disorders, it is important to note that familial aggregation is not specific to bipolar disorder [116, 117] (i.e., etiologic heterogeneity is likely) and that interrater reliability is generally less than for the diagnosis of bipolar disorder proper [111, 118].

Epidemiology: The age-corrected lifetime morbid risk of bipolar disorder in the United States is about 0.8 percent [119, 120]. A recent report of population-based epidemiologic studies used similar methods and found age-corrected lifetime risks that ranged from 0.3 percent to 1.5 percent, with equal risks to men and women in 10 countries as divergent as Lebanon and Korea [121]. It seems that lifetime rates of bipolar disorder may be increasing in more recently born cohorts [115], but this is not a universal finding [122].

Family Studies: Data from more than 40 family and twin studies spanning six decades consistently show that the risk to relatives of those with the disorder is greater than the risk to relatives of normal controls [113, 119, 123-125]. The risks for both bipolar and unipolar depressive disorders are higher in the relatives of bipolar probands, while the first-degree relatives of unipolar depressive probands have a higher rate of unipolar depression alone [125-130]. Assuming a lifetime risk of 1 percent, recurrence risk ratios (λ_{R_s}) for type R relatives as estimated from epidemiological, family, and twin studies of bipolar disorder are as follows: $\lambda_{1s} = 7$, $\lambda_{mz} = 60$ [131]. Reliable estimates are not available for more distant relatives.

Twin Studies: Four twin studies have specifically investigated the concordance for bipolar disorder [132-135], and the respective ranges for MZ and DZ probandwise concordance rates were 33 percent to 80 percent and zero to 8 percent, with heritability estimates ranging from 30 percent to 80 percent. The respective MZ and DZ probandwise concordance rates in the largest and most methodologically rigorous study [134] were 62 percent and 8 percent, with a heritability estimate of 59 percent.

Adoption Studies: Two adoption studies provide support for the involvement of genetic factors in the familial transmission of bipolar disorder [136, 137].

Mode of Inheritance: Some early pedigree analyses yielded evidence for vertical familial transmission, but results in general were not consistent with inheritance under a single major gene [125]. In some studies [115, 138-140], segregation analyses provide limited support for major locus transmission of bipolar disorder, but not in others [141-143]. Familial risks for bipolar disorder are not consistent with single locus models [131, 144], and none of the two-locus heterogeneity or epistatic models considered by Neuman and Rice [144] provided a good explanation for observed data, although the epistatic models were closest. Multiplicative models involving three or more loci are more consistent [131]. A three-locus symmetric multiplicative model (each locus has an equal effect) offers a good fit, with a locus-specific recurrence risk ratio of 2 [131].

In summary, the mode of inheritance is complex and likely involves multiple interacting genes. The number of susceptibility loci, the recurrence risk ratio conferred by each locus, and the degree of interlocus interaction are all unknown, but it is clear that a single major locus does not account for a large proportion of the familial aggregation of bipolar disorder.

Molecular Genetic Studies: Studies are interpreted on the basis of Lander and Kruglyak's thresholds for "suggestive" or "significant" evidence of linkage [145]. Several reports by Mendlewicz and colleagues [146] produced sizable lod scores linking bipolar disorder with color blindness and G6PD deficiency, while others [147, 148] have reported significant evidence for Xq linkage. However, methodological criticisms have been raised about many of the earlier studies, and multiple failures to replicate have been reported [125, 149, 150]. A lod score of 7.5 was obtained in a methodologically rigorous study of five Israeli families [151] but subsequent additional analysis of these families led to a diminution of the linkage evidence [152].

Linkage to 11p was reported in an analysis of Amish family data [153], but the lod score (4.9) diminished to nonsignificance when pedigrees were extended and members reevaluated [154]. Suggestive evidence was found for linkage to 18p [155, 156]. Another report found suggestive evidence of linkage about 10 Mb away on 18p and also found significant evidence of linkage to another region about 48 Mb away on 18q; both findings were in 11 paternally transmitting pedigrees only (probands' fathers or uncles were affected) [157]. Analysis of the full data

set [157] resulted in less than suggestive evidence of 18q linkage but suggestive evidence of 18p linkage. Interpreting these results is difficult, given that evidence has been presented for a maternal effect in the transmission of bipolar disorder in these [158] and other [159] families and given that evidence of linkage in this sample [157] is highly dependent on which age correction is employed [160].

Although suggestive evidence of a locus on 18q was obtained in association analyses [161], the implicated region was over a 5 Mb region and other markers in between provided evidence against linkage. The region implicated was at least 15 Mb away from the 18q region for which significant evidence of linkage was previously reported [157]. Thus, an 80 Mb region encompassing most of both arms of chromosome 18 has been implicated.

At least four nonreplications of chromosome 18 linkage have been reported [162-165]. A lod score of 3.41 (genome-wide p value 0.04) was found in 1 of 47 bipolar families for localization to 21q [166] and analysis of the entire sample resulted in suggestive evidence (lod score = 2.80). Suggestive [167] and less than suggestive [168] evidence has been reported in other samples, but, unfortunately, the strongest evidence of 21q linkage in Detera-Wadleigh and colleagues' study [167] was to a region more than 15 Mb away from that implicated earlier [166]. Also, three non-replications have been published [163, 164, 169].

Significant evidence of linkage to 4p was reported in a single pedigree [170], but a failure to replicate occurred in other pedigrees from the same population. Suggestive evidence has been reported for other linkages to 5p [171], 6p [172], 10q [173], 12q [174], 16p [175], and 22q [176]. Finally, anticipation has been reported [177], but this finding may reflect ascertainment bias [178]; a report of an association between trinucleotide repeat expansions and bipolar disorder [179] has not been followed by identification of a specific expanded gene [180].

In conclusion, no region identified as the location of a bipolar susceptibility locus has been convincingly replicated. The strongest evidence of linkage to date is consistent with susceptibility loci on chromosomal regions 18p, 18q, and 21q, but the methodological issues discussed above and the nonreplications demonstrate that these are clearly not confirmed, convincing findings. The inability to obtain more compelling evidence may have resulted because (1) genes on 18 and 21 confer susceptibility to bipolar disorder, but they have such a small relative effect on risk that a very large sample is required for detection; (2) genes on 18 and 21 confer susceptibility in a small number of families (failures to replicate reflect the confounding effects of genetic heterogeneity); or (3) the reported positive results are due to chance. Unfortunately, these three explanations are indistinguishable. Suggestive evidence of linkages to other autosomes (4, 5, 6, 10, 12, 16, 22) and the X chromosome is less compelling.

Animal Studies: A QTL for a hyperactivity phenotype (spontaneous activity, locomotor reactivity to a novel environment, and rearing in the open field) has been localized to rat chromosome 8 and explains 29 percent of the variance of an intercross between the Wistar-Kyoto and Wistar-Kyoto hyperactive strains [53]. The implicated region maps to mouse chromosome 9.

Depression

Phenotype: Depressive symptoms consist of depressed mood, diminished interest or pleasure in activities, insomnia or hypersomnia, psycho-motor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, inability to concentrate or act decisively, and recurrent thoughts of death or suicide. Interrater reliability varies depending on the number of episodes and their severity [111]: a single severe depressive episode, kappa = 0.72; a single mild depressive episode, kappa = 0.51; a recurrent severe depressive disorder, kappa = 0.69; and a recurrent mild depressive disorder, kappa = 0.37. Reliability over a 6-year period was moderate (kappa = 0.61) [112], but reliability over a 1-year period in a nonclinical population was much lower (kappa = 0.34) [181].

Rice and colleagues [112, 118, 182] formulated a clever approach to using multiple diagnostic assessments over time to model the relationship between clinical covariates and the probability of a true case. Application to longitudinal data on unipolar depression showed that 96 percent of subjects who were initially diagnosed with depression and had 8 symptoms plus a history of treatment also had a unipolar depressive diagnosis 6 years later [112].

Epidemiology: Older Swedish [183], Icelandic [184], and English [185] data are consistent with morbid risks to men (9% to 12%), but there is less consistency in risks to women (12% to 20%) [129]. Results from a U.S. national probability sample showed that the lifetime prevalence of a major depressive episode was 13 percent in men and 21 percent in women [186]. A recent report of population-based epidemiologic studies using operational criteria and similar methods [121] found that the lifetime rate of major depression in 10 countries varied widely by site, with a range from 2 percent to 19 percent; a higher risk to women, with a female:male ratio on the order of 2-3:1, was found in every country. Ranges of risk were as follows: women, 2 percent to 23 percent and men, 1 percent to 15 percent. Lifetime rates for the U.S. population were 7 percent for women and 3 percent for men (5 percent overall).

Klerman and Weissman [187] reviewed an extensive epidemiologic literature and reported that several studies, including most large-scale studies of mood disorders in the United States [183, 188-190]), suggest significant secular trends in rates of major depression: a progressive increase in rates in successive cohorts born after World War II with an earlier age at onset in each cohort; an increase in the rates of depression for all ages between 1960 and 1975; a persistent sex effect, with the risk of depression consistently 2 to 3 times higher among women than men across all adult ages; and the suggestion of a narrowing of the differential risk to men and women because of a greater increase among young men. Results on secular changes in rates of major depression from nine cross-national sites showed a significant trend for increasing rates over time, in addition to an earlier age at onset for younger cohorts [191]. Analyses of data collected in a large sample of the U.S. general population documented an increasing lifetime prevalence of depression in both men and women in more recent cohorts, with a male:female ratio across cohorts of 1.8 [192].

In a large population-based study of female twins [193], prevalence estimates ranged from 12 percent to 33 percent, depending on diagnostic criteria. Further, estimates of lifetime prevalence derived from a large Swedish twin study ranged from 17 percent to 34 percent in women and from 8 percent to 19 percent in men, again depending on the diagnostic criteria [194]. Overall, it is clear that a sex difference (male:female ratio) on the order of 2-3:1 exists for lifetime risk of depression, but estimates of lifetime prevalence are highly variable. Three-fold differences averaged across men and women were observed in two large epidemiologic studies of the U.S. population [121, 186]: Such discrepancies may reflect real population differences or methodological differences (that is, different structured interviews or diagnostic criteria).

Family Studies: Reviews of family studies conducted over the past three decades show that the range in age-adjusted risk of depression for first-degree relatives of a depressed proband is from 5 percent to 25 percent [125, 129]. Observed differences in reported familial risk for unipolar depression may be due to a variety of factors that make comparisons across studies difficult, such as differences in sample characteristics, methods of age correction, ascertainment schemes, and diagnostic procedures. Four studies comparing normal controls and high-risk relatives by similar case-finding and diagnostic methods show that unipolar depression aggregates in families and that the risk to relatives of depressive probands (11%-18%) is significantly greater than the risk to relatives of normal controls (0.7%-7%) [113, 123, 124, 195]. The first-degree relatives of depressive probands have a higher rate of depressive disorder but not of bipolar disorder [125-130].

It is difficult to determine which of the traditional subtyping strategies defines an etiologically homogeneous subgroup of patients with familial unipolar illness. The observation that multiple episodes of illness are associated with heritable depression was noted as early as 1936 [196], and several studies reviewed elsewhere [197] found an increased risk of depression among the relatives of probands with early versus late onset. Six family studies using modern diagnostic criteria have addressed this question [197-202]. In these studies, probands were subdivided according to age at onset or history of recurrent depression (or both). The greatest risk is to relatives of early-onset, recurrent depressive probands. In two of the studies [200, 202], the risk in relatives of such probands is over twice that of relatives of patients with late-onset recurrent depression. Three studies [197, 201, 202] provide evidence for the utility of an age-at-onset cutoff of 20, but the study by Bland and colleagues [200] supports the utility of higher cutoffs in some populations. The very high unadjusted rates in offspring (aged 6 to 23) of probands in the study by Weissman and colleagues [201] may reflect a cohort effect [183, 187-190] and is consistent with the high rates of familial depression found in relatives of prepubertal children with major depression [203].

Although variability in risks likely reflects methodological or procedural differences across studies, it appears that depression is more familial when probands are chosen on the basis of early-onset recurrent depression. It is difficult to estimate recurrence risk ratios for relative classes; estimates from a large population-based twin study yield a recurrence risk ratio for MZ twins between 1.5 and 1.9 and between 1.1 and 1.6 for DZ twins [193]. The

latter figure is not unlike a recurrence risk ratio for nontwin first-degree relatives, a ratio that can be approximated by using data from several family and epidemiologic studies [129]. No data on the population prevalence of early-onset, recurrent depression are available.

Twin Studies: The mean probandwise MZ concordance rate (40%) for unipolar depression is more than twice the corresponding DZ concordance rate (17%) obtained from six twin studies published in the past 45 years [133-135, 204-206]. Analysis of twins ascertained from hospital- and population-based registers showed respective MZ:DZ probandwise concordance rates of 35:20 and 50:29 for narrowly defined depression [194]. The corresponding MZ:DZ concordance rates for broadly defined depression in twins ascertained from hospital- and population-based registers in this study were 69:32 and 51:34.

A U.S.-based population study of twins yielded probandwise concordance rates that ranged from 23 percent to 49 percent in MZ twins and from 16 percent to 42 percent in DZ twins across nine different diagnostic definitions of depression [193]. The number of episodes and degree of impairment predicted increased the risk to the MZ co-twins of women with depression [207].

Adoption Studies: The results of three adoption studies on unipolar depression [136, 137, 208] are consistent with twin data in supporting the involvement of a genetic component in the etiology of unipolar depression. Data from a fourth study are not [209], but a methodological issue -- the reliance on case records for diagnostic data -- may explain the discrepancy.

Mode of Inheritance: Segregation analyses of unipolar depression have rejected single major locus inheritance without testing a multifactorial model [210-212] and failed to discriminate between single major locus and multifactorial transmission [213]. Another study rejected a multifactorial component and found limited evidence for single locus transmission [214]. Assuming population risks for hospital-based depression of 17 percent for women and 9 percent for men, heritabilities of 75 percent were estimated from a hospital-based twin sample [206]. There was no contribution from the shared family environment. Assuming a population risk of 21 percent for women and 13 percent for men resulted in a heritability estimate of 48 percent, with no shared environmental contribution. A heritability estimate of 79 percent, again with no contribution from the shared environment, was obtained in a twin study of depressive symptoms in adolescence [215]. Finally, heritabilities that ranged from 21 percent to 45 percent, with no contribution from the shared environment, were estimated in a population-based twin study of women [193]. Development and use of a caseness index [112] to increase diagnostic reliability in this sample resulted in an increased heritability estimate of 52 percent; explicit modeling of measurement error resulted in an even higher estimate of heritability at 71 percent [181]. In summary, the mode of inheritance for depression is complex, and transmission in most families does not follow simple Mendelian patterns. Multilocus genetic effects and not shared environmental ones appear to play a significant role in influencing the risk of disease; heritability estimates (like prevalence and risk of recurrence) are highly susceptible to changes in phenotypic definition. The potential involvement of epistatic multilocus transmission and locus heterogeneity have yet to be specified.

Molecular Genetic Studies: Anticipation has been reported in depression [216] but without an association between trinucleotide repeat expansions and the illness [217]. A report of an association between unipolar depression and a polymorphism in the human serotonin transporter gene on chromosome 17q [218] has been followed by two nonreplications [219, 220]. Also, a weak association between the dopamine D₄ receptor gene and depression has been found in one sample [221]; but no subsequent efforts to replicate this finding have been published.

Animal Studies: Several interesting animal models have been developed for symptomatic states of depression [119], but no genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (knock-out and knock-in techniques) have been reported. Given that learning and memory deficits occur in depression, a recent study using Down syndrome as a model for complex trait analysis may have some relevance [109]. Transgenic mice having YACs from a 2 Mb region of human chromosomal region 21q22.2 were subjected to learning and behavioral assays. Two YACs caused specific defects in learning and memory, thereby implicating genes from at least two different regions on chromosome 21 in the generation of these cognitive deficits.

Phenotype: Eating disorders usually begin in adolescence or early adulthood and are characterized by gross disturbances in eating behavior. The most common manifestations are anorexia nervosa (AN) and bulimia nervosa (BN). The essential features of AN are a refusal to maintain body weight over a minimal normal weight for age and height; intense fear of gaining weight or becoming fat even though one is underweight; a distorted body image; and amenorrhea in women. The essential features of BN are a persistent overconcern with body shape and weight, recurrent episodes of binge eating, a lack of control over eating behavior during the binges, self-induced vomiting, and the use of laxatives, diuretics, strict dieting or fasting, or vigorous exercise to prevent weight gain. Interrater reliability for eating disorders is excellent ($\kappa = 0.7$) [222]. AN, anxiety disorders, and major depression significantly co-occur [223, 224].

Epidemiology: A large epidemiologic study of the U.S. population yielded a lifetime prevalence of 0.06 percent for AN [225]. Other population and archival studies estimate lifetime prevalence as ranging from 0.1 percent to 0.7 percent [226-230]. Prevalence estimates of AN in a female twin sample ranged from 0.5 percent to 3.7 percent, depending on the phenotypic definition [231]. The incidence of AN in men may be as low as 0.02 percent [232], and the rate of AN in women may be increasing in some populations but not in others [233]. The mean prevalence of BN across self-report studies is about 10 percent, while the use of diagnostic interviews resulted in rates of about 1 percent to 2 percent [225]. Using clinician interviews in several studies yielded a prevalence of about 1 percent to 1.5 percent for BN [234-238]. The most rigorous epidemiologic studies have reported rates ranging from 1.1 percent to 4.2 percent for female subjects [230, 239-241] and from 0.1 percent to 0.5 percent for male subjects [230, 237, 241-245]. However, classification of probable BN-like syndromes in women increased the lifetime prevalence in one study to 8 percent [239].

Family Studies: Several family studies showed an increased rate of mood disorders among relatives of AN probands [246]. An early study showed a risk of 3.8 percent for AN in the relatives of AN probands who also had a mood disorder and a zero risk in AN probands without that co-occurring diagnosis [247]. Only one family study that ascertained subjects through AN probands and employed structured interviewing for all relatives could be identified: The risk of AN was 4.1 percent in first-degree relatives of AN probands, compared with zero for relatives of affective disorder and mixed disorder probands [248]. The risk of AN for second-degree relatives was 4.0 percent.

Respective risk of AN for relatives of depressed versus nondepressed AN probands was not significantly different (5.4% vs. 3.6%). Robust evidence for the familial aggregation of BN was found in one study, which reported a risk of 9.6 percent for first-degree relatives of BN probands, compared with 3.5 percent for relatives of controls [249]. Other studies have reported (a) a risk of 3.4 percent but without comparison to a control sample [250], (b) a risk of 2.2 percent that was not significantly higher than the zero in controls [251], and (c) a zero risk in relatives of BN probands [252]. The lifetime risk of BN among relatives of AN probands was not significantly different from the risk in the relatives of controls [248]. Using the above data and assuming a lifetime rate for AN of 0.1 percent, risk to MZ twins of 71 percent (see below), risk to first-degree relatives of 4.1 percent, and risk to second-degree relatives of 4.0 percent, the estimated recurrence risk ratios ($\lambda_{R's}$) for type R relatives of those with narrowly defined AN are as follows: $\lambda_{MZ} = 710$, $\lambda_1 = 41$, and $\lambda_2 = 40$; however, there are striking inconsistencies (one twin study [231] found a greater DZ vs. MZ concordance rate).

Using the above data and assuming a lifetime rate of 3.5 percent for BN, risk to MZ twins of 23 percent (associated lifetime prevalence of 2.8% -- see below), and a risk to first-degree relatives of 9.6 percent, the estimated recurrence risk ratios ($\lambda_{R's}$) for type R relatives of someone with BN are as follows: $\lambda_{MZ} = 8$ and $\lambda_1 = 2$. Striking inconsistencies also exist; two family studies found no evidence of familial aggregation [251, 252], and one twin study found no difference in MZ:DZ concordance rates [149].

Twin Studies: Although probandwise MZ:DZ concordance rates for AN were 71:10, with a heritability estimate of at least 80 percent [253, 254], higher DZ than MZ concordance rates for AN were observed in a large female twin sample [231]. Analysis of a quantitative measure of dieting, body dissatisfaction, and a drive for thinness derived from questionnaires on eating behaviors administered to a voluntary female twin sample resulted in respective heritabilities of 42 percent, 52 percent, and 44 percent [255]. Pairwise MZ:DZ concordance rates for BN in two twin samples were 33:0 [252] and 83:27 [256]. One study [239] reported probandwise MZ:DZ concordance rates of 23:9 for BN, with a heritability of 55 percent and a lifetime prevalence of 2.8 percent in women. MZ:DZ concordance rates of 36:38, with shared environment explaining over 80 percent of the variance, were observed in Holland and colleagues' expanded twin series [149].

Adoption Studies: No adoption data for AN or BN have been reported.

Mode of Inheritance: A heritability of 64 percent was derived by fitting the multifactorial model to AN family data [248]. This model provided the best fit for twin data, with estimates of BN's risk of heritability of 55 percent, with no contribution from the shared environment [239]. No formal segregation analyses have been conducted.

Molecular Genetic Studies: Only one study could be identified. Linkage and association tests failed to support a role of the β_3 adrenergic receptor gene in the etiology of AN [257].

Animal Studies: No genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (knock-out and knock-in techniques) have been reported.

Obsessive-Compulsive Disorder

Phenotype: Obsessive-compulsive disorder (OCD) usually begins in adolescence or early adulthood and is characterized by either obsessions or compulsions that cause marked distress and are time-consuming or significantly interfere with a person's normal routine or functioning. Obsessions are recurrent and persistent ideas, thoughts, impulses, or images that a person attempts to ignore or suppress. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession to neutralize or prevent discomfort or some dreaded event. Interrater reliability is excellent ($\kappa = 0.8$) [111]. OCD often co-occurs with other disorders like depression [258], anorexia nervosa [259], schizophrenia [260], and Tourette's syndrome [261].

Epidemiology: The prevalence of OCD was measured in five U.S. communities, and lifetime rates ranged from 1.9 percent to 3.3 percent [262]. The estimate of lifetime prevalence across all five sites was 1.8 percent, with no difference between men and women [263]. However, the diagnoses established by the lay raters in this project had disappointingly poor agreement with the result of a reinterview of a subset of the population by clinicians [149].

Family Studies: Although early studies of OCD that predated the use of operational criteria showed a risk to first-degree relatives that ranged widely from 0.4 percent to 3.1 percent [264], two studies found no increase in familial risk [265, 266]. Further, a higher risk to parents (5%) was observed in a study that used family history data to determine relatives' diagnoses [267]. Methodological shortcomings of this earlier research were addressed in seven subsequent family studies [268-274]. The risk ranged from 3 percent to 35 percent for narrowly defined OCD. Pooling age-corrected data across studies results in a lifetime risk of 9.21 percent for relatives of OCD probands and a lifetime risk of 2.2 percent in controls. Pooling age-corrected figures across two studies that used broader criteria and included subthreshold OCD cases as affected [269, 271] results in a lifetime risk of 28.1 percent (range 21% to 37%) in relatives of OCD probands and 15 percent in controls. Assuming a lifetime risk of 2 percent and not counting subthreshold OCD cases as affected, the recurrence risk ratio for first-degree relatives is 4.6 (estimates not available for other relative classes).

Twin Studies: In anecdotal reports that did not include DZ twins, 63 percent of MZ twins were concordant for OCD [275]. The respective MZ and DZ pairwise concordance rates in one study were 33 percent and 7 percent, and the heritability estimate was 68 percent [264]. Two other very small twin studies found no difference in MZ and DZ concordance rates [276, 277]. Analyzing a quantitative trait of obsessionality resulted in a heritability estimate of 47 percent [278].

Adoption Studies: No adoption data have been reported.

Mode of Inheritance: Nicolini and colleagues [279] performed segregation analyses on family data and found very limited evidence for an incompletely penetrant autosomal locus, but it was not possible to determine whether this was a dominant or recessive locus.

Molecular Genetic Studies: No significant associations between OCD and alleles of the serotonin transporter gene and the dopamine D_2 , D_3 , D_4 and the serotonin 2_A receptor genes have been detected [280-283]. A recent

population-based study found some evidence of an association between OCD and an allele of the COMT gene on 22q in men ($p = 0.002$), but not in women [284].

Animal Studies: No genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (knock-out and knock-in techniques) have been reported. Evidence for altered serotonergic functioning in fawn-hooded rats has been used to suggest that this strain may be a useful genetic model for OCD [285].

Panic Disorder

Phenotype: Panic disorder (PD) typically has its onset between late adolescence and the mid-30s. Its hallmark is the presence of recurrent and unexpected panic attacks, each of which is characterized by a discrete period -- lasting from minutes to hours -- of intense fear or discomfort accompanied by several physiological symptoms, including palpitations, accelerated heart rate, sweating, trembling or shaking, shortness of breath, choking sensations, chest pain, nausea, dizziness, chills, hot flashes or fear of losing control, or dying. Panic attacks are followed by persistent concerns about having additional attacks, worry about the implications of the attack or its consequences, and significant changes in behavior related to the attacks.

No studies have specifically addressed test-retest or interrater reliability of a PD diagnosis. PD, agoraphobia, and major depression significantly co-occur [258, 286, 287]. Attacks can be pharmacologically precipitated by carbon dioxide [288], caffeine [289], sodium lactate [290], and cholecystokinin tetrapeptide [291]. There is some evidence that hypersensitivity to the panic-inducing effects of carbon dioxide [292-294] and sodium lactate [295] may index genetic liability: At least one nonreplication has been reported for sodium lactate response [296].

Epidemiology: The lifetime rate of PD averaged across five sites of a large epidemiologic study of the U.S. population was 1.7 percent, with a female:male ratio of 2.3:1 [297, 298]. However, another large U.S. multisite epidemiologic study using different diagnostic criteria and a structured interview found a twofold increase in the lifetime rate (3.5 percent), with a female:male ratio of 5:2 [186]. These discrepancies in lifetime rates could reflect methodological differences or a period effect (from the 1980s through the 1990s) that resulted in increasing rates of PD in the U.S. population [286]. Epidemiologic data on PD from independently conducted community surveys in 10 countries revealed lifetime prevalences that ranged from 0.4 percent to 3.5 percent, with female:male ratios ranging from 0.2 to 1.9 [286]. Respective ranges of odds ratios for the co-occurrence of PD with agoraphobia and major depression ranged from 7.5 to 21.4 and from 3.8 to 20.1 [286]. A population prevalence of about 6 percent for narrowly defined PD in women was estimated from a large twin study [299], but a considerably higher prevalence estimate (14.1%) was obtained in a smaller twin sample [300].

Family Studies: Six case-control studies ascertained PD probands and used direct, structured interviews of relatives [301-306]; risks to first-degree relatives of PD probands ranged from 4 percent to 17 percent. Exclusion of Heun and Maier's study [306], which reported risks of PD alone without any other co-occurring mental disorder, results in a range from 8 percent to 17 percent. Risks to relatives of controls without mental illness in these studies ranged from 0.8 percent to 4.2 percent; thus, ratios of risk in relatives of probands versus relatives of normal controls ranged from 3.4 to 14.7. Risks of 4 percent [307] and 7 percent [308] were obtained for relatives of probands with PD and major depression who had been ascertained by virtue of having depression. Further analyses in the pedigrees initially collected by Weissman and colleagues [304] showed that the risk of PD in PD probands with or without major depression was 9 percent and 16 percent, respectively [309]. A subsequent subdivision of PD probands according to age at onset before or after age 20 led to dramatic differences in risk of 22 percent and 8 percent, respectively [310]. One study [311] reported a lifetime risk of 9.5 percent in second-degree relatives of PD probands, while three other studies reported family history rates of 12 percent [312], 8 percent [313], and 12.5 percent [314]. Familial patterns of aggregation suggest that PD and generalized anxiety [315], depression [308, 315-317], and agoraphobia [318] may co-occur but that they have different genetic etiologies.

In summary, averaging age-corrected data from the most methodologically rigorous studies [301-306] results in an estimate of risk for PD of about 14 percent in first-degree relatives. Using this figure and those from the largest twin study [299], and assuming a population prevalence of 2 percent to 4 percent (or 5.7% for MZ twins [299]), the estimated recurrence risk ratios ($\lambda_{R's}$) for type R relatives of someone with the disorder are as follows: $\lambda_{MZ} = 4$,

$\lambda_1 = 3.5-7$, and $\lambda_2 = 2.4-4.75$.

Twin Studies: Concordance rates for PD can be determined from four twin studies. Slater and Shields [319] studied twins with anxiety neurosis, a diagnosis that overlaps with the modern concept of PD. Respective probandwise MZ:DZ concordance rates were 41:4. Two other very small studies of PD reported MZ:DZ probandwise concordances of 31:0 [277] and 73:0 [300], and a subsequent follow-up using modern criteria for one data set [277] resulted in an MZ:DZ rate of 22:0 [320]. No significant differences between MZ and DZ concordance rates for PD or agoraphobia with PD were reported in a volunteer twin sample [276]. The largest twin study [299] reported MZ:DZ probandwise concordance rates of 24:11, with respective heritability estimates of 35 percent and 46 percent for a narrow phenotype and a multiple threshold model.

Adoption Studies: No adoption data for PD have been reported.

Mode of Inheritance: A family history study [311] yielded a morbid risk estimate of 9.5 percent for second-degree relatives of PD probands. The authors interpreted this as one-half the risk to first-degree relatives in four family studies (19%), which was about one-half the MZ probandwise concordance (41%) reported by Slater and Shields [319]. On this basis, they concluded that a single major gene was responsible for the familial aggregation of PD. An incompletely penetrant dominant major gene was consistent with one set of family data [321], but a major gene and multifactorial model could not be discriminated in another [302]. A family history study of PD in agoraphobia probands [314] found no evidence for simple major gene models.

Analysis of family data with class A logistic regression models [322] yielded evidence of vertical transmission and the effect of the sibship environment [323]. A segregation analysis of PD family data resulted in limited evidence of an incompletely penetrant dominant or recessive major gene [324], while analyses of twin data on quantitative PD symptomatology measures found evidence of nonadditive genetic (dominant or epistatic) and unique environmental effects, but no effect from the shared environment [325].

Model fitting in a large twin sample found evidence that the familial transmission of self-reported symptoms of panic-phobia was influenced by scalar sex-dependent (the same genetic factors are operating in the two sexes) additive genetic effects, dominant genetic factors, individual-specific environmental factors, a special twin environment for women only, and assortitive mating [326]. The best-fitting model predicted a substantially higher heritability in males (38%) than in females (16%). Shared environmental effects accounted for a small proportion of the variance in men (less than 1%) and a modest proportion (16%) in women.

Finally, application of the multifactorial single- and multiple threshold models to another population-based twin study in women resulted in heritability estimates between 35 percent and 46 percent, with no contribution from the shared environment [299].

In summary, PD's mode of transmission remains unknown. Conflicting results may be attributable to methodological differences in family ascertainment, phenotype definition, diagnostic assessment, and data analytic approaches, but they also may represent true etiologic differences among families (locus heterogeneity). According to these data, susceptibility to PD may be influenced by an incompletely penetrant major gene in some families and perhaps by multiple genes of unknown varying effect in others.

Molecular Genetic Studies: Suggestive evidence of linkage ($\text{lod} = 2.3$) was obtained at a protein marker on 16q [327, 328], but subsequent analyses in these and additional pedigrees failed to replicate the original result [329]. Linkage to numerous other markers over a substantial proportion of the genome has been excluded under various parametric models in different sets of pedigrees collected at the University of Iowa [327, 330-334].

Animal Studies: No genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (knock-out and knock-in techniques) have been reported.

Schizophrenia

Phenotype: Schizophrenia is defined by characteristic but nonspecific disturbances in the form and content of

thought, perception, emotion, sense of self, volition, social relationships, and psychomotor behavior. Interrater reliability is excellent ($\kappa = 0.76-0.82$), and test-retest reliability is good to excellent ($\kappa = 0.68-0.79$) [111, 335, 336]. Several mental disorders have been proposed as alternate expressions of a schizophrenia genotype, including schizotypal, paranoid, and schizoid personality disorders; nonaffective psychotic disorders (schizophreniform disorder, delusional or paranoid disorder, atypical psychosis); psychotic mood disorders; and variants of schizoaffective disorder [337-339]. It is important to note for these spectrum disorders that familial aggregation is not specific to schizophrenia [114-116, 340-343] (i.e., etiologic heterogeneity is likely) and that interrater reliability is generally less than that for the diagnosis of schizophrenia proper [111, 335, 336, 344]. Eye-tracking dysfunction [345, 346], neurophysiological deficits [347], and attentional deficits [348, 349] also have been proposed as traits genetically related to schizophrenia, but clear evidence is lacking. While multivariate analysis of such data can increase the power to detect linkage under a pleiotropy model [350, 351], the utility of these alternative phenotypes has not been fully realized.

Epidemiology: In a World Health Organization international study [352], the age-corrected lifetime morbid risk of narrowly defined schizophrenia is consistent worldwide at about 1 percent (range 0.7% to 1.4% across multiple sites as divergent as Chandigarh, India, and Moscow, Russia). Some studies [353-356] have reported a greater risk to men but others [357] have not; whether these discrepancies represent actual gender differences in some populations or methodological variation is unclear [358]. It seems that lifetime rates might be decreasing in more recently born cohorts [359, 360], but this is not a universal finding and may be a methodological artifact [361].

Family Studies: Data from over 40 family and twin studies spanning seven decades of research show consistently that risk to relatives of someone who has the disorder is greater than the risk to relatives of normal controls [362]. Recurrence risk ratios ($\lambda_{R's}$) for type R relatives as estimated from averaged morbid risks compiled from family and twin studies in European populations between 1920 and 1987 [363] are as follows: $\lambda_1 = 11$, $\lambda_{mx} = 48$, $\lambda_2 = 4.25$, and $\lambda_3 = 2$.

Twin Studies: In six twin studies published in the past 25 years [364], the median probandwise MZ concordance rate (46%) for schizophrenia is over three times the corresponding DZ concordance rate (14%). Comparable rates are found for MZ twins reared in different families [365, 366].

Adoption Studies: A combined analysis of adoption data collected in the city and county of Copenhagen, as well the remainder of Denmark, showed that the prevalence of chronic schizophrenia was significantly greater in biological relatives of adoptees with chronic schizophrenia than in the biological relatives of control adoptees [342, 367].

Mode of Inheritance: Model fitting using twin data from recent studies yielded a heritability of 89 percent, with no contribution from the common environment [368]. A model of somewhat lower heritability (74%), also without contribution from the common environment, provided the best statistical fit to the transmission of definite schizophrenia in an earlier analysis of twin and family data [369]. Non-genetic factors that influence the risk of schizophrenia are thus likely to be nonshared environmental effects (unique or idiosyncratic environmental events). A polygenic (multilocus) model has been consistently supported -- and a single major gene model consistently excluded -- in the quantitative analysis of actual and simulated schizophrenia family data [369-374].

Risk ratios for classes of relatives of schizophrenic probands in pooled Western European twin and family studies were consistent with the influence of two or three epistatic loci [375]. A four-locus multiplicative model (where each locus has an equal effect) offers a good fit for the recurrence risks presented above, with a locus-specific recurrence risk ratio of 1.8.

In summary, the mode of inheritance is complex and likely involves multiple genes in interaction. The number of susceptibility loci, the recurrence risk ratio conferred by each locus, and the degree of interlocus interaction all remain unknown. It is clear that a single major locus does not account for a large proportion of the familial aggregation of schizophrenia.

Molecular Genetic Studies: Only two studies have reported evidence of linkage meeting a genome-wide p value of 5 percent, corresponding to Lander and Kruglyak's threshold for significant evidence of linkage [145]. Although the first reported a linkage to 5q in British and Icelandic pedigrees [376], numerous nonreplications have been published, and a combined reanalysis of several data sets [377], among them the original report [376], excluded a susceptibility locus from 5q. Analyses of additional markers in a new sample of British and Icelandic families led to

exclusion of a linkage to 5q [378].

The second is a chromosome 6p linkage reported by Wang and colleagues [379]. However, correction for testing across multiple diagnostic and transmission models increased the genome-wide p value to between 0.05 and 0.07. Augmentation of the sample by 79 new pedigrees from the same population, which would be expected to increase evidence of linkage, actually resulted in *diminished* evidence [380] (a genome-wide p value of about 0.13, without adjustment for testing across multiple diagnostic and transmission models). Another study [381] found suggestive evidence for a linkage to 6p, but analyses of 713 families contributed by 14 research groups worldwide failed to find more than suggestive evidence of linkage to this region [382]. Nonreplications of 6p linkage have been reported as well [383-387].

An additional concern is that the markers implicated by the studies reporting suggestive evidence [379-381] lie within a very large chromosomal region (over 30 Mb). Wang and colleagues [388] conducted a family-based association study and found evidence for linkage disequilibrium between schizophrenia and a gene on 6p that causes spinocerebellar ataxia type 1. It is difficult to fully interpret the statistical meaning of their finding, but these results, if valid, substantially would narrow the candidate disease gene region on 6p.

Suggestive evidence for a linkage to 8p was found in two studies [389, 390], but less than suggestive evidence would be obtained if the results in one of them [390] were corrected for testing of multiple transmission and disease models. Analyses conducted in the collaborative sample of 713 families yielded only suggestive evidence for a linkage to 8p [382], and at least one study [391] has failed to find such a linkage.

The evidence for susceptibility loci on other chromosomes is less compelling. Linkage to 5q markers about 79 Mb from the region implicated previously [376] was suggestive in one study [392] and nearly suggestive in another [393], but at least one nonreplication has been reported [391]. Suggestive evidence has been found for a schizophrenia susceptibility locus on 22q [394], but again nonreplications have been reported [395, 396]. The results of a large post hoc analysis of multiple data sets, including the one in which suggestive evidence was obtained [394], failed to meet the criterion for suggestive evidence of linkage [397]. Less than suggestive evidence of linkage to 3p has been reported [389]; linkage to 3p was excluded in the large international collaborative study [382]. Less than suggestive evidence for a 9p linkage, as well as suggestive evidence for a 20p linkage, have been reported in two samples [391]. Several population-based association studies have implicated different candidate genes, but there are non-replications for each as well [398, 399]. Finally, anticipation has been reported [400], but it may represent ascertainment bias [178, 401, 402]. Reports of an association between trinucleotide repeat expansions and schizophrenia [179] have not been followed by identification of a specific expanded gene [180, 401, 403].

In summary, the strongest evidence of linkage to date supports the existence of schizophrenia susceptibility loci on chromosomes 6 and 8, but the magnitude of the statistical evidence and the existence of nonreplication demonstrate that these are clearly not confirmed, convincing findings [404]. These inconsistent results may reflect the effects of small relative gene effects, genetic heterogeneity, or type I error [405]. Reported linkages to other chromosomes (3, 5, 9, 20, and 22) are less compelling.

Animal Studies: No genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (knock-out and knock-in techniques) have been reported. More robust animal models need to be developed [406].

Tourette's Syndrome

Phenotype: Tourette's syndrome (TS) has its onset before age 18 and is characterized by the involuntary, sudden, rapid, recurrent, nonrhythmic, and stereotyped occurrence of multiple motor and vocal tics. Tics typically involve the head and other parts of the body (torso, upper and lower limbs). Vocal tics include various sounds like clicks, grunts, barks, coughs, or words. Some investigators have expanded the phenotype also to include chronic motor or vocal tics (CT) and OCD [407-409], while others expand the phenotype even further to include ADHD, PD, conduct disorder, depression, dyslexia, stuttering, mania, obesity, and alcoholism [410]. Phenotypic definitions remain controversial and are an important consideration in the genetic analysis of TS [411-414]. No evidence on test-retest or interrater diagnostic reliability is available.

Epidemiology: Estimates of the prevalence (male:female ratio, if available) of TS in studies relying on identified treated cases were 0.046 in 10, 000 in Minnesota [415], 0.50 in 10, 000 (3.5:1) in North Dakota adults [416], and 5.2 in 10, 000 (9.3:1) in North Dakota juveniles [417]. School-based surveys [418] yield much higher estimates of 23.4 in 10, 000 (8:1). Community surveys have revealed prevalence rates of 2.9 in 10, 000 in Monroe County, NY [419], 0.7 in 10, 000 in New Zealand juveniles [420], and 4.3 in 10, 000 (1.6:1) in Israeli adolescents [421]. A population prevalence of 5 in 10, 000 therefore is commonly cited [422], and variability may represent methodological (including diagnostic) differences.

Family Studies: TS [423-430], CT [424, 431] and OCD [261, 427, 432-437] aggregate in the families of TS probands. While CT and OCD may be spectrum disorders that in some cases reflect a TS genotype, etiologic heterogeneity (including nongenetic causes) is likely [438]. Two early family studies that indirectly assessed first-degree relatives of TS probands in a national sample [423] and in consecutive clinical cases [424] found a recurrence risk of about 2 percent. A risk of 1.5 percent also was observed in relatives of twins assessed by telephone interviews [425], but subsequent studies that directly assessed relatives yielded much higher estimates. Risks of 18 percent [426], 21 percent [427], 27 percent [428], and 36 percent [429] for relatives of TS probands have been found in each of three large pedigrees. Including CT increased the recurrence risk to 46 percent [428], 30 percent [426], and 51 percent [429].

A family study in which all relatives were interviewed personally reported respective age-corrected risks of 8.7 percent for TS, 17.3 percent for CT, and 11.5 percent for OCD in first-degree relatives of TS probands, with no significant differences in the rates of these disorders in the relatives of male and female probands [430]. A nearly fivefold increase in risk for TS in males versus female relatives (15:3.4) and over a twofold difference in risk to OCD in female versus male relatives (15:7) of TS probands were observed [430]. Assuming a lifetime prevalence of 5 in 10, 000 and a lifetime recurrence risk of 8.7 percent for TS, the respective recurrence risk ratio for first-degree relatives is about 174.

Twin Studies: One twin study has been conducted, and the respective pairwise MZ and DZ concordance rates were 53 percent and 8 percent [425]. Twins were ascertained as pairs; thus, 50 probandwise concordance cannot be estimated.

Adoption Studies: No adoption data have been reported.

Mode of Inheritance: Segregation analysis of single pedigree or pedigree sets have supported transmission through an incompletely penetrant autosomal dominant major locus with variable sex- and age-specific penetrances [426-428, 439-442]. There is evidence of autosomal dominant transmission if the phenotype is defined as (a) TS only, (b) TS or CT, or (c) TS or CT or OCD [407, 426]. Two studies [440, 443] could not reject a multifactorial-polygenic model, and one [443] could not reject a mixed model of inheritance that combined an intermediate major locus and a small but non-negligible multifactorial background.

Evidence also has been found for semidominant or intermediate inheritance (higher penetrance in affected homozygotes than in heterozygotes) [443-445]. One possible explanation for discrepancies across studies is that dominant inheritance may have been falsely inferred because of the failure to account for assortitive mating [429, 446]. The rates of bilineality described previously appear greater than would be expected for a rare autosomal dominant disease. Modeling of assortitive mating in segregation analysis of TS [445] led to identification of a different model of major gene inheritance (intermediate or additive major locus) from that identified (dominant major locus) when random mating was assumed.

A recent study of nonbilineal pedigrees rejected pure multifactorial and single major locus models and found evidence of a mixed model of inheritance that combined an additive major locus with a multifactorial background [447]. It is unclear whether the multifactorial factor presents polygenic or shared additive environmental effects, but it did account for about 40 percent of the phenotypic variance.

In summary, the mode of inheritance for TS is likely complicated by locus heterogeneity and assortitive mating. Conflicting results may be attributable to methodological differences in family ascertainment, phenotypic definition, diagnostic assessment, and data analytic approaches, but they also may represent true differences among families. On the basis of these data, susceptibility to TS may be influenced by a major gene in some families and perhaps by multiple genes of small relative effect in others. The role of familial transmissible effects (environmental or additive genetic) is unclear.

Molecular Genetic Studies: The TS Genetic Consortium has pursued a total genomic search in 11 large families from the United States, Canada, the Netherlands, and Norway and tested over 600 genetic markers under the assumption of genetic homogeneity and incompletely penetrant autosomal dominant single major locus inheritance [448, 449]. Over 90 percent of the genome has been excluded [450]. Comings and colleagues [451] reported increased homozygosity for the D₃ receptor gene, but there has been at least one failure to replicate [452].

A role in linkage analysis has been excluded for several genes involved in catecholamine (D₁-D₅ receptors and DBH, DAT, TY, and TH genes) [453-457] and serotonin (5-HT_{1A} receptor, tryptophan oxygenase) [458] pathways, under incompletely penetrant autosomal dominant or intermediate major locus models. There have been several reports describing chromosomal abnormalities in single TS patients, including a 9p deletion [459], an 18q deletion [460], t(7;18) translocation [461], and a 46 XY, t(3;8) (p21.3 q24.1) balanced translocation [462-464]. Although a positive multipoint lod score of 2.9 was initially obtained on 3p in several pedigrees [462], subsequent analyses using improved map data and additional markers led the authors to conclude that this region was not involved in the etiology of TS [464]. A YAC spanning the translocation breakpoint at 18q22.3 in the TS proband carrying the balanced t(7;18) translocation [461] was identified; among the limited number of relatives in the family studied, no one without the translocation was diagnosed with TS [465]. Co-segregation of the translocation with TS of course could be coincidental, especially given that the frequency of a carrier of a balanced translocation in the population is about 1 in 1,000.

Finally, the TDT [49] was used in a family-based association study [466] to identify an association between a specific allele at the D₄ dopamine receptor locus and TS (p values varied from 0.004 to 0.001 across different disease definitions); linkage to this gene, albeit under restricted parametric assumptions, has been excluded in at least one large family [453]).

A recent report of earlier age at onset in maternally transmitted cases in a small number of families [467] led the authors to conclude that there could be a parent-of-origin effect on a putative TS gene. It was recommended that family data be re-examined separately for maternally and paternally transmitted cases. At least one failure to find a significant difference in age at onset between maternally and paternally transmitted TS cases was reported earlier [468].

Animal Studies: No relevant genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (knock-out and knock-in techniques) have been reported.

References

1. Faraone, S.V.; Biederman, J.; Chen, W.J.; Milberger, S.; Warburton, R.; and Tsuang, M.T. Genetic heterogeneity in attention-deficit hyperactivity disorder (ADHD): gender, psychiatric comorbidity, and maternal ADHD. *Journal of Abnormal Psychology*, 104:334-345, 1995.
2. Anderson, J.C.; Williams, S.; McGee, R.; and Silva, P.A. DSM-III disorders in pre-adolescent children. *Archives of General Psychiatry*, 44:69-76, 1987.
3. Biederman, J.; Newcorn, J.; and Sprich, S.E. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *American Journal of Psychiatry*, 148:564-577, 1991.
4. Caron, C. and Rutter, M. Comorbidity of child psychopathology: concepts, issues and research strategies. *Journal of Child Psychology and Psychiatry*, 32:1063-1080, 1991.
5. Biederman, J.; Faraone, S.; Milberger, S.; Guite, J.; Mick, E.; Chen, L.; Mennin, D.; Ouellette, C.; Moore, P.; Spencer, T.; Norman, D.; Wilens, T.; Kraus, I.; and Perrin, J. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. *Archives of General Psychiatry*, 53:437-446, 1996.
6. Shaffer, D.; Fisher, P.; Dulcan, M.K.; Davies, M.; Piacentini, J.; Schwab-Stone, M.E.; Lahey, B.B.; Bourdon, K.;

Jensen, P.S.; Bird, H.R.; Canino, G.; and Regier, D.A. The NIMH Diagnostic Interview Schedule for Children version 2.3 (DISC-2.3): description, acceptability, prevalence rates, and performance in the MECA study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35:865-877, 1996.

7. Biederman, J.; Keenan, K.; and Faraone, S.V. Parent based diagnosis of attention deficit disorder predicts a diagnosis based on teacher report. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29:698-701, 1990.
8. Biederman, J.; Faraone, S.V.; Milberger, S.; and Doyle, A. Diagnoses of attention-deficit hyperactivity disorder from parent reports predict diagnoses based on teacher reports. *Journal of the American Academy of Child and Adolescent Psychiatry*, 32:315-317, 1993.
9. Shaffer, D. Attention deficit hyperactivity disorder in adults. *American Journal of Psychiatry*, 151:633-638, 1994.
10. Milberger, S.; Faraone, S.V.; Biederman, J.; Testa, M.; and Tsuang, M.T. New phenotype definition of attention deficit hyperactivity disorder in relatives for genetic analyses. *American Journal of Medical Genetics*, 67:369-377, 1996.
11. Bird, H.R.; Canino, G.; Rubio-Stipec, M.; Gould, M.S.; Ribera, J.; Sesman, M.; Woodbury, M.; Huertas-Goldman, S.; Pagan, A.; Sanchez-Lacay, A.; and Moscoso, M. Estimates of the prevalence of childhood maladjustment in a community survey in Puerto Rico. *Archives of General Psychiatry*, 45:1120-1126, 1988.
12. Wolraich, M.L.; Hannah, J.N.; Pinnock, T.Y.; Baumgaertel, A.; and Brown, J. Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35:319-324, 1996.
13. Faraone, S. and Biederman, J. Is attention deficit hyperactivity disorder familial? *Harvard Rev Psychiatry*, 1:271-287, 1994.
14. Faraone, S.V. and Biederman, J. Genetics of attention-deficit hyperactivity disorder. *Child and Adolescent Clinics of North America*, 2:285-301, 1994.
15. Smalley, S.L. Behavioral genetics '97 genetic influences in childhood-onset psychiatric disorders: autism and attention-deficit/ hyperactivity disorder. *American Journal of Human Genetics*, 60:1276-1282, 1997.
16. Welner, Z.; Welner, A.; Stewart, M.; Palkes, H.; and Wish, E. A controlled study of siblings of hyperactive children. *Journal of Nervous and Mental Disease*, 165:110-117, 1977.
17. Manshadi, M.; Lippmann, S.; and O'Daniel, R.G. Alcohol abuse and attention deficit disorder. *Journal of Clinical Psychiatry*, 44:379-380, 1983.
18. Pauls, D.L.; Shaywitz, S.E.; and Kramer, P.L. Demonstration of vertical transmission of attention deficit disorder. *Annals of Neurology*, 14:363, 1983.
19. Morrison, J.R. and Stewart, M.A. A family study of the hyperactive child syndrome. *Biological Psychiatry*, 3:189-195, 1971.
20. Schachar, R. and Wachsmuth, R. Hyperactivity and parental psychopathology. *Journal of Child Psychology and Psychiatry*, 31:381-392, 1990.
21. Cantwell, D.P. Psychiatric illness in the families of hyperactive children. *Archives of General Psychiatry*, 27:414-417, 1972.
22. Frick, P.J.; Lahey, B.B.; Christ, M.G.; Loeber, R.; and Green, S. History of childhood behavior problems in biological relatives of boys with attention deficit hyperactivity disorder and conduct disorder. *Journal of Clinical Child Psychology*, 20:445-451, 1991.

23. Reeves, J.C.; Werry, J.S.; Elkind, G.S.; and Zimetkin, A. Attention deficit, conduct, oppositional, and anxiety disorders in children: II. Clinical characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry*, 26:144-155, 1987.
24. Biederman, J.; Faraone, S.V.; Keenan, K.; Knee, D.; and Tsuang, M.T. Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29:526-533, 1990.
25. Biederman, J.; Faraone, S.V.; and Keenan, K. Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder (ADHD): patterns of comorbidity in probands and relatives in psychiatrically and pediatrically referred samples. *Archives of General Psychiatry*, 49:728-738, 1992.
26. Faraone, S.V.; Biederman, J.; Mennin, D.; Gershon, J.; and Tsuang, M.T. A prospective four-year follow-up study of children at risk for ADHD: psychiatric, neuropsychological, and psychosocial outcome. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35:1449-1459, 1996.
27. Perrin, S. and Last, C.G. Relationship between ADHD and anxiety in boys: results from a family study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35:988-996, 1996.
28. Biederman, J.; Faraone, S.V.; Mick, E.; Spencer, T.; Wilen, T.; Kiely, K.; Guite, J.; Ablon, J.S.; Reed, E.; and Warburton, R. High risk for attention deficit hyperactivity disorder among children of parents with childhood onset of the disorder: a pilot study. *American Journal of Psychiatry*, 152:431-435, 1995.
29. Faraone, S.V.; Biederman, J.; and Milberger, S. An exploratory study of ADHD among second-degree relatives of ADHD children. *Biological Psychiatry*, 35:398-402, 1994.
30. Mannuzza, S. and Gittelman, R. The adolescent outcome of hyperactive girls. *Psychiatry Research*, 13:19-29, 1984.
31. Faraone, S.V.; Biederman, J.; Keenan, K.; and Tsuang, M.T. A family-genetic study of girls with DSM-III attention deficit disorder. *American Journal of Psychiatry*, 148:112-117, 1991.
32. Sherman, D.K.; McGue, M.K.; and Iacono, W.G. Twin concordance for attention deficit hyperactivity disorder: a comparison of teachers' and mothers' reports. *American Journal of Psychiatry*, 154:532-535, 1997.
33. Goodman, R. and Stevenson, J. A twin study of hyperactivity II: the aetiological role of genes, family relationships and perinatal adversity. *Journal of Child Psychology and Psychiatry*, 30:691-709, 1989.
34. Lopez, R.E. Hyperactivity in twins. *Canadian Psychiatric Association Journal*, 10:421-426, 1965.
35. Heffron, W.A.; Martin, C.A.; and Welsh, R.J. Attention deficit disorder in three pairs of monozygotic twins: a case report. *Journal of the American Academy of Child and Adolescent Psychiatry*, 23:299-301, 1984.
36. Stevenson, J. Evidence for a genetic etiology in hyperactivity in children. In: Fulker, D.W., Driscoll, P., Heston, L.L., Martin, N.G. and McGuire, T. eds: *Behavior genetics*. New York: Plenum Press, 1991. pp. 337-344.
37. Gillis, J.; Gilger, J.; Rennington, B.; and DeFries, J. Attention deficit disorder in reading-disabled twins: evidence for genetic etiology, *Journal of Abnormal Child Psychology*, 20:303-315, 1992.
38. Gjone, H.; Stevenson, J.; and Sundet, J.M. Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35:588-596, 1996.
39. Silberg, J.; Michael, R.; Joanne, M.; Hermine, M.; Hewitt, J.; Emily, S.; Pickles, A.; Loeber, R.; and Eaves, L. Genetic and environmental influences on the covariation between hyperactivity and conduct disturbance in juvenile twins. *Journal of Child Psychology and Psychiatry*, 37:803-816, 1996.

40. Thapar, A.; Hervas, A.; and McGuffin, P. Childhood hyperactivity scores are highly heritable and show sibling competition effects: twin study evidence. *Behavior Genetics*, 25:537-544, 1995.
41. Goodman, R. and Stevenson, J. A twin study of hyperactivity I: an examination of hyper-activity scores and categories derived from Rutter teacher and parent questionnaires. *Journal of Child Psychology and Psychiatry*, 30:671-689, 1989.
42. Willerman, L. Activity level of hyperactivity in twins. *Child Development*, 44:288-293, 1973.
43. Safer, D.J. A familial factor in minimal brain dysfunction. *Behavior Genetics*, 3:175-186, 1973.
44. Cantwell, D.P. Genetics of hyperactivity. *Journal of Child Psychology and Psychiatry*, 16:261-264, 1975.
45. Morrison, J.R. and Stewart, M.A. The psychiatric status of the legal families of adopted hyperactive children. *Archives of General Psychiatry*, 28:888-891, 1973.
46. Deutsch, C.K.; Matthyse, S.; Swanson, J.M.; and Farkas, L.G. Genetic latent structure analysis of dysmorphology in attention deficit disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29:189-194, 1990.
47. Faraone, S.V.; Biederman, J.; Chen, W.J.; Krifcher, B.; Keenan, K.; Moore, C.; Sprich, S.; and Tsuang, M. Segregation analysis of attention deficit hyperactivity disorder: evidence for single gene transmission. *Psychiatric Genetics*, 2:257-275, 1992.
48. Comings, D.E.; Comings, B.G.; Muhlman, D.; Dietz, G.; Shabahrani, B.; Tast, D.; Knell, E.; Kocsis, P.; Baumgarten, R.; Kovacs, B.W.; Levy, D.L.; Smith, M.; Borison, R.L.; Evans, D.D.; Klein, D.N.; MacMurray, J.; Tosk, J.M.; Sverd, J.; Gysin, R.; and Flanagan, S.D. The dopamine D₂ receptor locus as a modifying gene in neuropsychiatric disorders. *Journal of the American Medical Association*, 266:1793-1800, 1991.
49. Spielman, R.S.; McGinnis, R.E.; and Ewens, W.J. Transmission test for linkage disequilibrium: The insulin gene region and insulin-dependent diabetes mellitus (IDDM). *American Journal of Human Genetics*, 52:506-516, 1993.
50. Cook, E.H.; Stein, M.A.; Krasowski, M.D.; Cox, N.J.; Olkon, D.M.; Kieffer, J.E.; and Leventhal, B.L. Association of attention-deficit disorder and the dopamine transporter gene. *American Journal of Human Genetics*, 56:993-998, 1995.
51. LaHoste, G.J.; Swanson, J.M.; Wigal, S.B.; Glabe, C.; Wigal, T.; King, N.; and Kennedy, J.L. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. *Molecular Psychiatry*, 1:121-124, 1996.
52. Carlson, C.; Papolos, D.; Pandita, R.K.; Faedda, G.L.; Veit, S.; Goldberg, R.; Shprintzen, R.; Kucherlapati, R.; and Morrow, B. Molecular analysis of Velo-Cardio-Facial Syndrome patients with psychiatric disorders. *American Journal of Human Genetics*, 60:851-859, 1997.
53. Moisan, M.-P.; Courvoisier, H.; Bihoreau, M.-T.; Gauguier, D.; Hendley, E.D.; Lathrop, M.; James, M.R.; and Mormede, P. A major quantitative trait locus influences hyperactivity in the WKHA rat. *Nature Genetics*, 14:471-473, 1996.
54. Hess, E.J.; Rogan, P.K.; Domoto, M.; Tinker, D.E.; Ladda, R.L.; and Ramer, J.C. Absence of linkage of apparently single gene mediated ADHD with the human syntenic region of the mouse mutant coloboma. *American Journal of Medical Genetics*, 60:573-579, 1995.
55. Giros, B.; Jaber, M.; Jones, S.R.; Wightman, R.M.; and Caron, M.G. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature*, 379:606-612, 1996.

56. Rutter, M. Language, cognition and autism. In: Katzman, R. ed: *Congenital and Acquired Cognitive Disorders*. New York, NY: Raven Press, 1979. pp. 247-264.
57. Smalley, S.L.; Asarnow, R.F.; and Spence, M.A. Autism and genetics: a decade of research. *Archives of General Psychiatry*, 45:953-961, 1988.
58. Bailey, A.; Phillips, W.; and Rutter, M. Autism: towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *Journal of Child Psychology and Psychiatry*, 37:89-126, 1996.
59. Happe, F. and Frith, U. The neuropsychology of autism. *Brain*, 119:1377-1400, 1996.
60. Bolton, P. and Rutter, M. Genetic influences in autism. *International Review of Psychiatry*, 2:67-80, 1990.
61. Bolton, P.; MacDonald, H.; Pickles, A.; Rios, P.; Goode, S.; Crowson, M.; Bailey, A.; and Rutter, M. A case-control family history study of autism. *Journal of Child Psychology and Psychiatry*, 35:877-900, 1994.
62. Rutter, M.; Bailey, A.; Bolton, P. and LeCouteur, A. Autism: syndrome definition and possible genetic mechanisms. In: Plomin, R. and McClearn, G.E. eds: *Nature, Nurture, and Psychology*. Washington, DC: American Psychological Association Press, 1993. pp. 269-284.
63. August, G.J.; Stewart, M.A.; and Tsai, L. The incidence of cognitive disabilities in the siblings of autistic children. *British Journal of Psychiatry*, 138:416-422, 1981.
64. Folstein, S. and Rutter, M. Infantile autism: a genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry*, 18:297-321, 1977.
65. Bailey, A.; LeCouteur, A.; Gottesman, I.I.; Bolton, P.; Simonof, E.; Yuzda, E.; and Rutter, M. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychological Medicine*, 25:63-77, 1995.
66. Wolff, S.; Narayan, S.; and Moyes, B. Personality characteristics of parents of autistic children. *Journal of Child Psychology and Psychiatry*, 29:143-153, 1988.
67. Landa, R.; Piven, J.; Wzorek, M.; Gayle, J.; Chase, G.; and Folstein, S. Social language use in parents of autistic individuals. *Psychological Medicine*, 22:245-254, 1992.
68. Piven, J.; Wzorek, M.; Landa, R.; Lainhart, J.; Bolton, P.; Chase, G.A.; and Folstein, S. Personality characteristics of parents of autistic individuals. *Psychological Medicine*, 24:783-795, 1994.
69. Le Couteur, A.; Bailey, A.; Goode, S.; Pickles, A.; Robertson, S.; Gottesman, I.I.; and Rutter, M. A broader phenotype of autism: the clinical spectrum in twins. *Journal of Child Psychology and Psychiatry*, 37:785-801, 1996.
70. Piven, J.; Palmer, P.; Jacobi, D.; Childress, D.; and Arndt, S. Broader autism phenotype: evidence from a family history study of multiple-incidence autism families. *American Journal of Psychiatry*, 154:185-190, 1997.
71. Spiker, D.; Lotspeich, L.; Kraemer, H.C.; Hallmayer, J.; McMahan, W.; Peterson, P.B.; Nicholas, P.; Pingree, C.; Wiese-Slater, S.; Chiotti, C.; Wong, D.L.; Dimiceli, S.; Ritvo, E.; Cavalli-Sforza, L.L.; and Ciaranello, R.D. Genetics of autism: characteristics of affected and unaffected children from 37 multiplex families. *American Journal of Medical Genetics*, 54:27-35, 1994.
72. Steffenburg, S. and Gillberg, C. Autism and autistic-like conditions in Swedish rural and urban areas: a population study. *British Journal of Psychiatry*, 149:81-87, 1986.
73. Steinhausen, H.C.; Gobel, D.; Breinlinger, M.; and Wohlleben, B. A community survey of infantile autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, 25:186-189, 1986.

74. Gillberg, C. Infantile autism and other childhood psychoses in a Swedish urban region: epidemiological aspects. *Journal of Child Psychology and Psychiatry*, 25:35-43, 1984.
75. McCarthy, P.; Fitzgerald, M.; and Smith, M.A. Prevalence of childhood autism in Ireland. *Irish Medical Journal*, 77:129-130, 1984.
76. Bohman, M.; Bohman, I.L.; Bjorck, P.O. and Sjöholm, E. Childhood psychosis in a northern Swedish county: some preliminary findings from an epidemiological survey. In: Schmidt, M.H. and Remschmidt, H. eds: *Epidemiological Approaches in Child Psychiatry II*. Stuttgart, Germany: Georg Thieme Verlag, 1983. pp. 164-173.
77. Hoshino, Y.; Kumashiro, H.; Yashima, Y.; Tachibana, R.; and Watanabe, M. The epidemiological study of autism in Fukushima-ken. *Folia Psychiatrica Neurologica of Japan*, 36:115-124, 1982.
78. Wing, L.; Yeates, S.R.; Brierley, L.M.; and Gould, J. The prevalence of early childhood autism: comparison of administrative and epidemiological studies. *Psychological Medicine*, 6:89-100, 1976.
79. Brask, H.H. A prevalence investigation of childhood psychoses. In: Anonymous *Nordic Symposium on the Comprehensive Care of the Psychotic Child*. Oslo, Norway: Barnepsykiatrisk Forening-Norge, 1972. pp. 145-153.
80. Treffert, D.A. Epidemiology of infantile autism. *Archives of General Psychiatry*, 22:431-438, 1970.
81. Lotter, V. Epidemiology of autistic conditions in young children: I. prevalence. *Social Psychiatry*, 1:124-137, 1966.
82. Bryson, S.; Clark, B.; and Smith, T. First report of a Canadian epidemiological study of autistic syndromes. *Journal of Child Psychology and Psychiatry*, 29:433-445, 1988.
83. Lord, C.; Schopler, E.; and Rebecki, D. Sex differences in autism. *Journal of Autism and Developmental Disorders*, 12:317-330, 1982.
84. Baird, T.D. and August, G.J. Familial heterogeneity in infantile autism. *Journal of Autism and Developmental Disorders*, 15:315-321, 1985.
85. Deykin, E.Y. and MacMahon, B. Pregnancy, delivery, and neonatal complications among autistic children. *American Journal of Diseases of Children*, 134:860-864, 1980.
86. Minton, J.; Campbell, M.; Green, W.H.; Jennings, S.; and Samit, C. Cognitive assessment of siblings of autistic children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 21:256-261, 1982.
87. Ritvo, E.R.; Freeman, B.J.; Mason-Brothers, A.; Mo, A.; and Ritvo, A.M. Concordance of the syndrome of autism in 40 pairs of afflicted twins. *American Journal of Psychiatry*, 142:74-77, 1985.
88. Ritvo, E.R.; Jorde, L.B.; Mason-Brothers, A.; Freeman, B.J.; Pingree, C.; Jones, M.B.; McMahon, W.M.; Peterson, P.B.; Jenson, W.R.; and Mo, A. The UCLA-University of Utah Epidemiologic Survey of Autism: recurrence risk estimates and genetic counseling. *American Journal of Psychiatry*, 146:1032-1036, 1989.
89. Jorde, L.B.; Hasstedt, S.J.; Ritvo, E.R.; Mason-Brothers, A.; Freeman, B.J.; Pingree, C.; McMahon, W.M.; Peterson, B.; Jenson, W.R.; and Mo, A. Complex segregation analysis of autism. *American Journal of Human Genetics*, 49:932-938, 1991.
90. Pickles, A.; Bolton, P.; MacDonald, H.; Bailey, A.; Le Couteur, A.; Sim, C.-H.; and Rutter, M. Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: a twin and family study of autism. *American Journal of Human Genetics*, 57:717-726, 1995.
91. Steffenburg, S.; Gillberg, C.; Hellgren, L.; Andersson, L.; Gillberg, I.C.; Jakobsson, G.; and Bohman, M. A twin study of autism in Denmark, Finland, Iceland, Norway, and Sweden. *Journal of Child Psychology and Psychiatry*,

30:405-416, 1989.

92. LeCouteur, A. The role of genetics in the aetiology of autism, including findings on the links with the fragile-X syndrome. In: Wing, L. ed: *Aspects of Autism: Biological Research*. Washington, DC: National Autistic Society, 1988. pp. 38-52.
93. Tsai, L.; Stewart, M.A.; and August, G. Implications of sex differences in the familial transmission of infantile autism. *Journal of Autism and Developmental Disorders*, 11:165-173, 1981.
94. Gurling, H. Candidate genes and favored loci: strategies for molecular genetic research into schizophrenia, manic depression, autism, alcoholism, and Alzheimer disease. *Psychiatric Developments*, 4:289-309, 1986.
95. Szatmari, P. and Jones, M.B. IQ and the genetics of autism. *Journal of Child Psychology and Psychiatry*, 32:897-908, 1991.
96. Hallmayer, J.; Spiker, D.; Lotspeich, L.; McMahon, W.M.; Petersen, P.B.; Nicholas, P.; Pingree, C.; and Ciaranello, R.D. Male-to-male transmission in extended pedigrees with multiple cases of autism. *American Journal of Medical Genetics*, 67:13-18, 1996.
97. Cohen, I.L.; Sudhalter, V.; Pfadt, A.; Jenkins, E.C.; Brown, W.T.; and Vietze, P.M. Why are autism and the fragile-X syndrome associated? *American Journal of Human Genetics*, 48:195-202, 1991.
98. Holden, J.J.A.; Wing, M.; Chailfoux, M.; Julien-Inalsingh, C.; Schutz, C.; Robinson, P.; Szatmari, P.; and White, B.N. Lack of expansion of triplet repeats in the *FMR1*, *FRAXE*, and *FRAXF* loci in male multiplex families with autism and pervasive developmental disorders. *American Journal of Medical Genetics*, 64:399-403, 1996.
99. Vincent, J.B.; Konecki, D.S.; Munstermann, E.; Bolton, P.; Poustka, A.; and Gurling, H.M.D. Point mutation analysis of the *FMR-1* gene in autism. *Molecular Psychiatry*, 1:227-231, 1997.
100. Petit, E.; Herault, J.; Raynaud, M.; Cherpi, C.; Perrot, A.; Barthelemy, C.; Lelord, G.; and Muh, J.P. X chromosome and infantile autism. *Biological Psychiatry*, 40:457-464, 1996.
101. Hallmayer, J.; Hebert, J.M.; Spiker, D.; Lotspeich, L.; McMahon, W.M.; Petersen, B.; Nicholas, P.; Pingree, C.; Lin, A.A.; Cavalli-Sforza, L.L.; Risch, N.J.; and Ciaranello, R.D. Autism and the X chromosome: multipoint sib-pair analysis. *Archives of General Psychiatry*, 53:985-989, 1996.
102. Cook, E.H.; Lindgren, V.; Leventhal, B.L.; Courchesne, R.; Lincoln, A.; Shulman, C.; Lord, C.; and Courchesne, E. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *American Journal of Human Genetics*, 60:928-934, 1997.
103. Herault, J.; Martineau, J.; Petit, E.; Perrot, A.; Sauvage, D.; and Barthelemy, C. Genetic markers in autism: association study on short arm of chromosome 11. *Journal of Autism and Developmental Disorders*, 24:233-236, 1994.
104. Herault, J.; Perrot, A.; Barthelemy, C.; Buchler, M.; Cherpi, C.; Leboyer, M.; Sauvage, D.; Lelord, G.; Mallet, J.; and Muh, J. Possible association of c-Harvey-Ras-1 (HRAS-1) marker with autism. *Psychiatry Research*, 46:261-267, 1993.
105. Comings, D.E.; Wu, S.; Chiu, C.; Muhleman, D.; and Sverd, J. Studies of the c-Harvey-Ras gene in psychiatric disorders. *Psychiatry Research*, 63:25-32, 1996.
106. Cook, E.H.; Courchesne, R.; Lord, C.; Cox, N.J.; Yan, S.; Lincoln, A.; Haas, R.; Courchesne, E.; and Leventhal, B.L. Evidence of linkage between the serotonin transporter and autistic disorder. *Molecular Psychiatry*, 2:247-250, 1997.
107. Warren, R.P.; Singh, V.K.; Averett, R.E.; Odell, J.D.; Maciulis, A.; Burger, R.A.; and Daniels, W.W.

Immunogenetic studies in autism and related disorders. *Molecular and Chemical Neuropathology*, 28:77-81, 1996.

108. Daniels, W.W.; Warren, R.P.; Odell, J.D.; Maciulis, A.; Burger, R.A.; Warren, W.L.; and Torres, A.R. Increased frequency of the extended or ancestral haplotype B44BSC30BDR4 in autism. *Biological Psychiatry*, 32:120-123, 1995.

109. Smith, D.J.; Stevens, M.E.; Sudanagunta, S.P.; Bronson, R.T.; Makhinson, M.; Watabe, A.M.; O'Dell, T.J.; Fung, J.; Weier, H.-U.G.; Cheng, J.-F.; and Rubin, E.M. Functional screening of 2 Mb of human chromosome 21q22.2 in transgenic mice implicates *minibrain* in learning defects associated with Down syndrome. *Nature Genetics*, 16:28-36, 1997.

110. Leonhard K: *Aufteilung der Endopen psychosen*, Berlin, Akademik Verlag; 1959.

111. Regier, D.A.; Kaelber, C.T.; Roper, M.T.; Rae, D.S.; and Sartorius, N. The ICD-10 clinical field trial for mental and behavioral disorders: results in Canada and the United States. *American Journal of Psychiatry*, 151:1340-1350, 1994.

112. Rice, J.P.; Rochberg, N.; Endicott, J.; Lavori, P.W.; and Miller, C. Stability of psychiatric diagnoses: An application to the affective disorders. *Archives of General Psychiatry*, 49:824-830, 1992.

113. Gershon, E.S.; Hamovit, J.H.; Guroff, J.J.; Dibble, E.; Leckman, J.F.; Sceery, W.; Targum, S.D.; Nurnberger, J.I.; Goldin, L.R.; and Bunney, W.E. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Archives of General Psychiatry*, 39:1157-1167, 1982.

114. Gershon, E.S.; DeLisi, L.E.; Hamovit, J.; Nurnberger, J.I.; Maxwell, M.E.; Schreiber, J.; Dauphanais, D.; Dingman, C.W.; and Guroff, J.J. A controlled family study of chronic psychoses: schizophrenia and schizoaffective disorder. *Archives of General Psychiatry*, 45:328-336, 1988.

115. Rice, J.P.; Reich, T.; Andreasen, N.C.; Endicott, J.; Van Eerdewegh, M.; Fishman, R.; Hirschfeld, R.M.A.; and Klerman, G.L. The familial transmission of bipolar illness. *Archives of General Psychiatry*, 44:441-447, 1987.

116. Kendler, K.S.; McGuire, M.; Gruenberg, A.; Spellman, M.; O'Hare, A.; and Walsh, D. The Roscommon Family Study: II. the risk of nonschizophrenic nonaffective psychoses in relatives. *Archives of General Psychiatry*, 50:645-652, 1993.

117. Maier, W.; Lichtermann, D.; Minges, J.; Hallmayer, J.; Heun, R.; Benkert, O.; and Levinson, D. Continuity and discontinuity of affective disorders and schizophrenia. *Archives of General Psychiatry*, 50:871-883, 1993.

118. Rice, J.P.; McDonald-Scott, P.; Endicott, J.; Coryell, W.; Grove, W.M.; Keller, M.B.; and Altis, D. The stability of diagnosis with an application to Bipolar II disorder. *Psychiatry Research*, 19:285-296, 1986.

119. Goodwin FK, Jamison KR: *Manic-Depressive Illness*, New York, NY, Oxford University Press; 1990.

120. Weissman, M.M.; Bruce, M.L.; Leaf, P.J.; Florio, L.P. and Holzer, C. Affective Disorders. In: Robins, L.N. and Regier, D.A. eds: *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*. New York, NY: Free Press, 1991. pp. 53-80.

121. Weissman, M.M.; Bland, R.C.; Canino, G.J.; Faravelli, C.; Greenwald, S.; Hwu, H.-G.; Joyce, P.R.; Karam, E.G.; Lee, C.-K.; Lellouch, J.; Lepine, J.-P.; Newman, S.C.; Rubio-Stipec, M.; Wells, J.E.; Wickramaratne, P.J.; Wittchen, H.-U.; and Yeh, E.-K. Cross-national epidemiology of major depression and bipolar disorder. *Journal of the American Medical Association*, 276:293-299, 1996.

122. Pauls, D.L.; Morton, L.A.; and Egeland, J.A. Risks of affective illness among first-degree relatives of bipolar I Old-Order Amish probands. *Archives of General Psychiatry*, 49:703-708, 1992.

123. Winokur, G.; Tsuang, M.T.; and Crowe, R.R. The Iowa 500: Affective disorder in relatives of manic and depressive patients. *American Journal of Psychiatry*, 139:209-212, 1982.
124. Weissman, M.M.; Gershon, E.S.; Kidd, K.K.; Prusoff, B.A.; Leckman, J.F.; Dibble, E.; Hamovit, J.; Thompson, D.; Pauls, D.L.; and Guroff, J.L. Psychiatric disorders in the relatives of probands with affective disorders. *Archives of General Psychiatry*, 41:13-21, 1984.
125. Tsuang MT, Faraone SV: *The Genetics of Mood Disorders*, Baltimore, MD, John Hopkins University Press; 1990.
126. Reich, T.; Cloninger, C.R.; Suarez, B.K. and Rice, J.P. Genetics of the affective psychoses. In: Wing, L. and Wing, J.K. eds: *Handbook of Psychiatry, Volume 3, Psychoses of Uncertain Aetiology*. Cambridge: Cambridge University Press, 1982. pp. 147-159.
127. McGuffin, P. and Katz, R. Nature, nurture, and affective disorder. In: Deakin, J.F.W. ed: *The Biology of Affective Disorders*. London: Gaskell Press, Royal College of Psychiatrists, 1986. pp. 26-52.
128. McGuffin, P. and Katz, R. The genetics of depression and manic-depressive disorder. *British Journal of Psychiatry*, 155:294-304, 1989.
129. Moldin, S.O.; Reich, T.; and Rice, J.P. Current perspectives on the genetics of unipolar depression. *Behavior Genetics*, 21:211-242, 1991.
130. Moldin, S.O. and Reich, T. The genetic analysis of depression: Future directions. *Clinical Neuroscience*, 1:139-145, 1993.
131. Craddock, N.; Khodel, V.; Van Eerdewegh, P.; and Reich, T. Mathematical limits of multilocus models: the genetic transmission of bipolar disorder. *American Journal of Human Genetics*, 57:690-702, 1995.
132. Kringlen E: *Heredity and Environment in the Functional Psychoses*, Oslo, Norway, Universitetsforlaget; 1967.
133. Allen, M.G.; Cohen, S.; Pollin, W.; and Greenspan, S.I. Affective illness in veteran twins: A diagnostic review. *American Journal of Psychiatry*, 131:1234-1239, 1974.
134. Bertelsen, A.; Harvald, B.; and Hauge, M.A. A Danish twin study of manic-depressive disorders. *British Journal of Psychiatry*, 130:330-351, 1977.
135. Torgersen, S. Genetic factors in moderately severe and mild affective disorders. *Archives of General Psychiatry*, 43:222-226, 1986.
136. Mendlewicz, J. and Rainer, J.D. Adoption study supporting genetic transmission in manic-depressive illness. *Nature*, 268:326-329, 1977.
137. Wender, P.H.; Kety, S.S.; Rosenthal, D.; Schulsinger, F.; Ortmann, J.; and Lunde, I. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Archives of General Psychiatry*, 43:923-929, 1986.
138. Crowe, R.R. and Smouse, P.E. The genetic implications of age-dependent penetrance in manic-depressive illness. *Journal of Psychiatric Research*, 13:273-285, 1977.
139. Spence, M.A.; Flodman, P.L.; Sadovnick, A.D.; Bailey-Wilson, J.E.; Ameli, H.; and Remick, R.A. Bipolar disorder: evidence for a major locus. *American Journal of Medical Genetics*, 60:370-376, 1995.
140. Pauls, D.L.; Bailey, J.N.; Carter, A.S.; Allen, C.R.; and Egeland, J.A. Complex segregation analyses of old order Amish families ascertained through bipolar I individuals. *American Journal of Medical Genetics*, 60:290-297,

1995.

141. Bucher, K.D.; Elston, R.C.; Green, R.; Whybrow, P.; Helzer, J.; Reich, T.; Clayton, P.; and Winokar, G. The transmission of manic depressive illness: II. segregation analysis of three sets of family data. *Journal of Psychiatric Research*, 16:65-78, 1981.
142. Goldin, L.R.; Gershon, E.S.; Targum, S.D.; Sparkes, R.S.; and McGinnis, M. Segregation and linkage analyses in families of patients with bipolar, unipolar, and schizoaffective mood disorders. *American Journal of Human Genetics*, 35:274-287, 1983.
143. Sham, P.C.; Morton, N.E.; and Rice, J.P. Segregation analysis of the NIMH Collaborative study: family data on bipolar disorder. *Psychiatric Genetics*, 2:175-184, 1991.
144. Neuman, R.J. and Rice, J.P. Two-locus models of disease. *Genetic Epidemiology*, 9:347-365, 1992.
145. Lander, E.S. and Kruglyak, L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nature Genetics*, 11:241-247, 1995.
146. Mendlewicz, J.; Simon, P.; Sevy, S.; Charon, F.; Brocas, H.; Legros, S.; and Vassart, G. Polymorphic DNA markers on X chromosome and manic depression. *Lancet*, 1:1230-1231, 1987.
147. Lucotte, G. and Landoulsi, A. Manic depressive illness is linked to factor IX in a French pedigree. *Annales de Genetique*, 35:93-95, 1992.
148. Pekkarinen, P.; Terwilliger, J.; Bredbacka, P.-E.; Lonnqvist, J.; and Peltonen, L. Evidence of a predisposing locus to bipolar disorder on Xq24-q27.1 in an extended Finnish pedigree. *Genome Research*, 5:105-115, 1995.
149. McGuffin P, Owen MJ, O'Donovan MC, Thapar A, Gottesman II: *Seminars in Psychiatric Genetics*, London, England, Royal College of Psychiatrists; 1994.
150. Risch, N. and Botstein, D. A manic depressive history. *Nature Genetics*, 12:351-353, 1996.
151. Baron, M.; Risch, N.J.; Hamburger, R.; Mandell, B.; Kushner, S.; Newman, M.; Drumer, D.; and Belmaker, R.H. Genetic linkage between X-chromosome markers and bipolar affective illness. *Nature*, 326:389-392, 1987.
152. Baron, M.; Freimer, N.F.; Risch, N.; Lerer, B.; Alexander, J.R.; Straub, R.E.; Asokan, S.; Das, K.; Peterson, A.; and Amos, J. Diminished support for linkage between manic depressive illness and X-chromosome markers in three Israeli pedigrees. *Nature Genetics*, 3:49-55, 1993.
153. Egeland, J.A.; Gerhard, D.S.; Pauls, D.L.; Sussex, J.N.; Kidd, K.K.; Allen, C.R.; Hostetter, A.M.; and Housman, D.E. Bipolar affective disorders linked to DNA markers on chromosome 11. *Nature*, 325:783-787, 1987.
154. Kelsoe, J.R.; Ginns, E.I.; Egeland, J.A.; Gerhard, D.S.; Goldstein, A.M.; Bale, S.J.; Pauls, D.L.; Long, R.T.; Kidd, K.K.; Conte, G.; Housman, D.E.; and Paul, S.M. Re-evaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. *Nature*, 342:238-243, 1989.
155. Berrettini, W.H.; Ferraro, T.N.; Goldin, L.R.; Weeks, D.E.; Detera-Wadleigh, S.; Nurnberger, J.I., Jr.; and Gershon, E.S. Chromosome 18 DNA markers and manic-depressive illness: evidence for a susceptibility gene. *Proceedings of the National Academy of Sciences of the USA*, 91:5918-5921, 1994.
156. Berrettini, W.H.; Ferraro, T.N.; Goldin, L.R.; Detera-Wadleigh, S.D.; Choi, H.; Muniec, D.; Guroff, J.J.; Kazuba, D.M.; Nurnberger, J.I.; Hsieh, W.-T.; Hoehe, M.R.; and Gershon, E.S. A linkage study of bipolar illness. *Archives of General Psychiatry*, 54:27-35, 1997.

157. Stine, O.C.; Xu, J.; Koskela, R.; McMahon, F.J.; Gschwend, M.; Friddle, C.; Clark, C.D.; McInnis, M.G.; Simpson, S.G.; and Breschel, T.S. Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. *American Journal of Human Genetics*, 57:1384-1394, 1995.
158. McMahon, F.J.; Stine, O.C.; Meyers, D.A.; Simpson, S.G.; and DePaulo, J.R. Patterns of maternal transmission in bipolar affective disorder. *American Journal of Human Genetics*, 56:1277-1286, 1995.
159. Gershon, E.S.; Badner, J.A.; Detera-Wadleigh, S.D.; Ferraro, T.N.; and Berrettini, W.H. Maternal inheritance and chromosome 18 allele sharing in unilineal bipolar illness pedigrees. *American Journal of Medical Genetics*, 67:202-207, 1996.
160. Cleves, M.A.; Dawson, D.V.; Elston, R.C.; and Schnell, A.H. A new test for linkage applied to bipolar disorder and marker D18S41. *Genetic Epidemiology*, 14:581-586, 1997.
161. Freimer, N.B.; Reus, V.I.; Escamilla, M.A.; McInnes, A.; Spesny, M.; Leon, P.; Service, S.K.; Smith, L.B.; Silva, S.; Rojas, E.; Gallegos, A.; Meza, L.; Fournier, E.; Baharloo, S.; Blankenship, K.; Tyler, D.J.; Batki, S.; Vinogradov, S.; Weissenbach, J.; Barondes, S.H.; and Sandkuijl, L.A. Genetic mapping using haplotype, association and linkage methods suggests a locus for severe bipolar disorder (BPI) at 18q22-q23. *Nature Genetics*, 12:436-441, 1996.
162. Coon, H.; Hoff, M.; Holik, J.; Hadley, J.; Fang, N.; Reimherr, F.; Wender, P.; and Byerley, W. Analysis of chromosome 18 DNA markers in multiplex pedigrees with manic depression. *Biological Psychiatry*, 39:689-696, 1996.
163. LaBuda, M.C.; Maldonado, M.; Marshall, D.; Otten, K.; and Gerhard, D.S. A follow-up report of a genome search for affective disorder predisposition loci in the Old Order Amish. *American Journal of Human Genetics*, 59:1343-1362, 1996.
164. Detera-Wadleigh, S.D.; Badner, J.A.; Yoshikawa, T.; Sanders, A.R.; Goldin, L.R.; Turner, G.; Rollins, D.Y.; Moses, T.; Guroff, J.J.; Kazuba, D.; Maxwell, M.E.; Edenberg, H.J.; Foroud, T.; Lahiri, D.; Nurnberger, J.I.; Stine, O.C.; McMahon, F.; Meyers, D.A.; MacKinnon, D.; Simpson, S.; McInnis, M.; DePaulo, J.R.; Rice, J.P.; Goate, A.; Reich, T.; Blehar, M.C.; and Gershon, E.S. Initial genome scan of the NIMH Genetics Initiative bipolar I pedigrees: chromosomes 4, 7, 9, 18, 19, 20, and 21q. *American Journal of Medical Genetics*, 74:254-262, 1997.
165. De Bruyn, A.; Souery, D.; Mendelbaum, K.; Mendlewicz, J.; and Van Broeckhoven, C. Linkage analysis of families with bipolar illness and chromosome 18 markers. *Biological Psychiatry*, 39:679-688, 1996.
166. Straub, R.E.; Lehner, T.; Luo, Y.; Loth, J.E.; Shao, W.; Sharpe, L.; Alexander, J.R.; Das, K.; Simon, R.; and Fieve, R.R. A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. *Nature Genetics*, 8:291-296, 1994.
167. Detera-Wadleigh, S.; Badner, J.A.; Goldin, L.R.; Berrettini, W.; Sanders, A.R.; Rollins, D.Y.; Turner, G.; Moses, T.; Haerian, H.; Muniec, D.; Nurnberger, J.I.; and Gershon, E.S. Affected-sib-pair analyses reveal support of prior evidence for a susceptibility locus for bipolar disorder, on 21q. *American Journal of Human Genetics*, 58:1279-1285, 1996.
168. Gurling, H.; Smyth, C.; Kalsi, G.; Moloney, E.; Rifkin, L.; O'Neill, J.; Murphy, P.; Curtis, D.; Petursson, H.; and Brynjolfsson, J. Linkage findings for bipolar disorder. *Nature Genetics*, 10:8-9, 1995.
169. Byerley, W.; Holik, J.; Hoff, M.; and Coon, H. Search for a gene predisposing to manic-depression on chromosome 21. *American Journal of Medical Genetics*, 60:231-233, 1995.
170. Blackwood, D.H.R.; He, L.; Morris, S.W.; McLean, A.; Whitton, C.; Thomson, M.; Walker, M.T.; Woodburn, K.; Sharp, C.M.; Wright, A.F.; Shibasaki, Y.; St.Clair, D.M.; Porteous, D.J.; and Muir, W.J. A locus for bipolar affective disorder on chromosome 4p. *Nature Genetics*, 12:427-430, 1996.
171. Kelsoe, J.R.; Sadovnick, A.D.; Kristbjarnarson, H.; Bergesch, P.; Mroczkowski-Parker, Z.; Drennan, M.;

Rapaport, M.H.; Flodman, P.; Spence, M.A.; and Remick, R.A. Possible locus for bipolar disorder near the dopamine transporter on chromosome 5. *American Journal of Medical Genetics*, 67:533-540, 1996.

172. Ginns, E.I.; Ott, J.; Egeland, J.A.; Allen, C.R.; Fann, C.S.J.; Pauls, D.L.; Weissenbach, J.; Carulli, J.P.; Falls, K.M.; Keith, T.P.; and Paul, S.M. A genome-wide search for chromosomal loci linked to bipolar affective disorder in the Old Order Amish. *Nature Genetics*, 12:431-435, 1996.

173. Rice, J.P.; Goate, A.; Williams, J.T.; Bierut, L.; Dorr, D.; Wu, W.; Shears, S.; Gopalakrishnan, G.; Edenberg, H.J.; Foroud, T.; Nurnberger, J.T.; Gershon, E.S.; Detera-Wadleigh, S.D.; Goldin, L.R.; Guroff, J.J.; McMahon, F.J.; Simpson, S.; MacKinnon, D.; McInnis, M.; Stine, O.C.; DePaulo, J.R.; Blehar, M.C.; and Reich, T. Initial genome scan of the NIMH Genetics Initiative bipolar I pedigrees: chromosomes 1, 6, 8, 10, and 12. *American Journal of Medical Genetics*, 74:247-253, 1997.

174. Craddock, N.; Owen, M.; Burge, S.; Kurian, B.; Thomas, P.; and McGuffin, P. Familial cosegregation of major affective disorder and Darier's disease (keratosis follicularis). *British Journal of Psychiatry*, 164:355-358, 1994.

175. Ewald, H.; Mors, O.; Flint, T.; Koed, K.; Eiberg, H.; and Kruse, T.A. A possible locus for manic depressive illness on chromosome 16p13. *Psychiatric Genetics*, 5:71-81, 1995.

176. Lachman, H.M.; Kelsoe, J.R.; Remick, R.A.; Sadovnick, A.D.; Rapaport, M.H.; Lin, M.; Pazur, B.A.; Roe, A.M.A.; Saito, T.; and Papolos, D.F. Linkage studies suggest a possible locus for bipolar disorder near the velo-cardio-facial syndrome region on chromosome 22. *American Journal of Medical Genetics*, 74:121-128, 1997.

177. McInnis, M.G.; McMahon, F.J.; Chase, G.A.; Simpson, S.G.; Ross, C.A.; and DePaulo, J.R. Anticipation in bipolar affective disorder. *American Journal of Human Genetics*, 53:385-390, 1993.

178. Hodge, S. and Wickramaratne, P. Statistical pitfalls in detecting age-of-onset anticipation: the role of correlation in studying anticipation and detecting ascertainment bias. *Psychiatric Genetics*, 5:43-47, 1995.

179. O'Donovan, M.C.; Guy, C.; Craddock, N.; Bowen, T.; McKoen, P.; Machedo, A.; Maier, W.; Wildenauer, W.; Aschauer, H.N.; Sorbi, S.; Feldman, E.; Mynett-Johnson, L.; Claffey, E.; Nacmias, B.; Valente, J.; Dourado, A.; Grassi, E.; Lenzinger, E.; Heiden, A.M.; Moorhead, S.; Harrison, D.; Williams, J.; McGuffin, P.; and Owen, M.J. Confirmation of association between expanded CAG/CTG repeats and both schizophrenia and bipolar disorder. *Psychological Medicine*, 26:1145-1153, 1996.

180. Sasaki, T.; Billett, E.; Petronis, A.; Ying, D.; Parsons, T.; Macciardi, F.M.; Meltzer, H.Y.; Lieberman, J.; Joffe, R.T.; Ross, C.A.; McInnis, M.G.; Li, S.H.; and Kennedy, J.L. Psychosis and genes with trinucleotide repeat polymorphism. *Human Genetics*, 97:244-246, 1996.

181. Kendler, K.S.; Neale, M.C.; Kessler, R.C.; Heath, A.C.; and Eaves, L.J. The lifetime history of major depression in women: reliability of diagnosis and heritability. *Archives of General Psychiatry*, 50:863-870, 1993.

182. Rice, J.P.; Endicott, J.; Knesevich, M.A.; and Rochberg, N. The estimation of diagnostic sensitivity using stability data: An application to major depressive disorder. *Journal of Psychiatric Research*, 21:337-345, 1987.

183. Hagnell, O.; Lanke, J.; Rorsman, B.; and Ojesjo, L. Are we entering an age of melan-choly? Depressive illnesses in a prospective epidemiological study over 25 years: The Lundby Study, Sweden. *Psychological Medicine*, 12:279-289, 1982.

184. Helgason, T. Epidemiological investigations concerning affective disorders. In: Schou, M. and Stromgren, E. eds: *Origin, Prevention, and Treatment of Affective Disorders*. New York: Academic Press, 1979. pp. 241-255.

185. Sturt, E.; Kumakura, N.; and Der, G. How depressing life is - life-long morbidity risk for depressive disorder in the general population. *Journal of Affective Disorders*, 7:109-122, 1984.

186. Kessler, R.C.; McGonagle, K.A.; Zhao, S.; Nelson, C.B.; Hughes, M.; Eshleman, S.; Wittchen, H.; and

- Kendler, K.S. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Archives of General Psychiatry*, 51:8-19, 1994.
187. Klerman, G.L. and Weissman, M.M. Increasing rates of depression. *Journal of the American Medical Association*, 261:2229-2235, 1989.
188. Klerman, G.L.; Lavori, P.W.; Rice, J.P.; Reich, T.; Endicott, J.; Andreasen, N.C.; Keller, M.B.; and Hirschfeld, R.M.A. Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. *Archives of General Psychiatry*, 42:689-693, 1985.
189. Lavori, P.W.; Klerman, G.L.; Keller, M.B.; Reich, T.; Rice, J.P.; and Endicott, J. Age-period-cohort analysis of secular trends in onset of major depression: Findings in siblings of patients with major affective disorder. *Journal of Psychiatric Research*, 21:23-35, 1987.
190. Gershon, E.S.; Hamovit, J.H.; Guroff, J.J.; and Nurnberger, J.I. Birth-cohort changes in manic and depressive disorders in relatives of bipolar and schizoaffective patients. *Archives of General Psychiatry*, 44:314-319, 1987.
191. Cross-National Collaborative Group The changing rate of major depression: cross-national comparisons. *Journal of the American Medical Association*, 268:3098-3105, 1992.
192. Kessler, R.C.; McGonagle, K.A.; Nelson, C.B.; Hughes, M.; Swartz, M.; and Blazer, D.G. Sex and depression in the National Comorbidity Survey. II: cohort effects. *Journal of Affective Disorders*, 30:15-26, 1994.
193. Kendler, K.S.; Neale, M.C.; Kessler, R.C.; Heath, A.C.; and Eaves, L.J. A population-based twin study of major depression in women: The impact of varying definitions of illness. *Archives of General Psychiatry*, 49:257-266, 1992.
194. Kendler, K.S.; Pedersen, N.; Johnson, L.; Neale, M.C.; and Mathe, A.A. A pilot Swedish twin study of affective illness, including hospital- and population-ascertained subsamples. *Archives of General Psychiatry*, 50:699-706, 1993.
195. Gershon, E.S.; Mark, A.; Cohen, N.; Belizon, N.; Baron, M.; and Knobe, K.E. Transmitted factors in the morbid risk of affective disorders: A controlled study. *Journal of Psychiatric Research*, 12:283-299, 1975.
196. Slater, E. The inheritance of manic-depressive insanity. *Proceeding of the Royal Society of Medicine*, 29:981-990, 1936.
197. Weissman, M.M.; Wickramaratne, P.; Merikangas, K.R.; Leckman, J.F.; Prusoff, B.A.; Caruso, K.A.; Kidd, K.K.; and Gammon, D. Onset of major depression in early adulthood. *Archives of General Psychiatry*, 41:1136-1143, 1984.
198. Winokur, G.; Cadoret, R.; Baker, M.; and Dorzab, J. Depression spectrum disease versus pure depressive disease: Some further data. *British Journal of Psychiatry*, 127:75-77, 1975.
199. Mendlewicz, J. and Baron, M. Morbidity risks in subtypes of unipolar depressive illness: Differences between early and late onset forms. *British Journal of Psychiatry*, 139:463-466, 1981.
200. Bland, R.C.; Newman, S.C.; and Orn, H. Recurrent and nonrecurrent depression. *Archives of General Psychiatry*, 43:1085-1089, 1986.
201. Weissman, M.M.; Warner, V.; Wickramaratne, P.; and Prusoff, B.A. Early-onset major depression in parents and their children. *Journal of Affective Disorders*, 15:269-277, 1988.
202. Kupfer, D.J.; Frank, E.; Carpenter, L.L.; and Neiswanger, K. Family history in recurrent depression. *Journal of Affective Disorders*, 17:113-119, 1989.

203. Puig-Antich, J.; Goetz, D.; Davies, M.; Kaplan, T.; Davies, S.; Ostrow, L.; Asnis, L.; Twomey, J.; Iyengar, S.; and Ryan, N.D. A controlled family history study of prepubertal major depressive disorder. *Archives of General Psychiatry*, 46:406-418, 1989.
204. Kallmann F: *Heredity in Health and Mental Disorder*, New York, W.W. Norton; 1953.
205. Slater E: *Psychotic and Neurotic Illness in Twins (Medical Research Council Special Report Series No. 278)*, London, Her Majesty's Stationery Office; 1953.
206. McGuffin, P.; Katz, R.; Watkins, S.; and Rutherford, J. A hospital-based twin register of the heritability of DSM-IV unipolar depression. *Archives of General Psychiatry*, 53:129-136, 1996.
207. Kendler, K.S.; Neale, M.C.; Kessler, R.C.; Heath, A.C.; and Eaves, L.J. The clinical characteristics of major depression as indices of the familial risk to illness. *British Journal of Psychiatry*, 165:66-72, 1994.
208. Cadoret, R. Evidence for genetic inheritance of primary affective disorder in adoptees. *American Journal of Psychiatry*, 133:463-466, 1978.
209. Von Knorring, A.L.; Cloninger, C.R.; Bohman, M.; and Sigvardsson, S. An adoption study of depressive disorders and substance abuse. *Archives of General Psychiatry*, 40:943-950, 1983.
210. Crowe, R.R.; Namboodiri, K.K.; Ashby, H.B.; and Elston, R.C. Segregation analysis and linkage analysis of a large kindred of unipolar depression. *Neuropsychobiology*, 7:20-25, 1981.
211. Goldin, L.R.; Gershon, E.S.; Targum, S.D.; Sparkes, R.S.; and McGinniss, M. Segregation and linkage analyses in families of patients with bipolar, unipolar, and schizoaffective mood disorders. *Journal of Human Genetics*, 35:274-287, 1983.
212. Tsuang, M.T.; Bucher, K.D.; Fleming, J.A.; and Faraone, S.V. Transmission of affective disorders: An application of segregation analysis to blind family study data. *Journal of Psychiatric Research*, 19:23-29, 1985.
213. Cox, N.J.; Reich, T.; Rice, J.P.; Elston, R.C.; Schober, J.; and Keats, B.J. Segregation and linkage analyses of bipolar and major depressive illness in multigenerational pedigrees. *Journal of Psychiatric Research*, 23:109-123, 1989.
214. Price, R.A.; Kidd, K.K.; and Weissman, M.M. Early onset (under age 30 years) and panic disorder as markers for etiologic homogeneity in major depression. *Archives of General Psychiatry*, 44:434-440, 1987.
215. Thapar, A. and McGuffin, P. A twin study of depressive symptoms in childhood. *British Journal of Psychiatry*, 165:259-265, 1994.
216. Engstrom, C.; Thornlund, A.; Johansson, E.; Langstrom, M.; Chotai, J.; Adolfsson, R.; and Nylander, P. Anticipation in unipolar affective disorder. *Journal of Affective Disorders*, 35:31-40, 1995.
217. Oruc, L.; Lindblad, K.; Verheyen, G.R.; Ahlberg, S.; Jakovljevic, M.; Ivezic, S.; Raeymaekers, P.; Van Broeckhoven, C.; and Schalling, M. CAG repeat expansions in bipolar and unipolar disorders. *American Journal of Human Genetics*, 60:730-732, 1997.
218. Ogilvie, A.D.; Battersby, S.; Bubb, V.J.; Fink, G.; Harmar, A.J.; Goodwin, G.M.; and Smith, D.C.A. Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet*, 347:731-733, 1996.
219. Kunugi, H.; Tatsumi, M.; Sakai, T.; Hattori, M.; and Nanko, S. Serotonin transporter gene polymorphism and affective disorder. *Lancet*, 347:1340, 1996.
220. Stober, G.; Heils, A.; and Lesch, K.P. Serotonin transporter gene polymorphism and affective disorder.

Lancet, 347:1340-1341, 1996.

221. Manki, H.; Kanba, S.; Muramatsu, T.; Higuchi, S.; Suzuki, E.; Matsushita, S.; Ono, Y.; Chiba, H.; Shintani, F.; Nakamura, M.; Yagi, G.; and Asai, M. Dopamine D2, D3 and D4 receptor and transporter gene polymorphisms and mood disorders. *Journal of Affective Disorders*, 40:7-13, 1996.

222. American Psychiatric Association: *DSM-III: Diagnostic and Statistical Manual of Mental Disorders, 3rd ed*, Washington, The Association; 1980.

223. Katz, J.L. Eating disorder and affective disorder: relatives or merely chance acquaintances? *Comprehensive Psychiatry*, 28:220-228, 1987.

224. Halmi, K.; Eckert, E.; Marchi, P.; Sampugnaro, V.; Apple, R.; and Cohen, J. Comorbidity of psychiatric diagnoses in anorexia nervosa. *Archives of General Psychiatry*, 48:712-718, 1991.

225. Fairburn, C.G. and Beglin, S.J. Studies of the epidemiology of bulimia nervosa. *American Journal of Psychiatry*, 147:401-408, 1990.

226. Szmukler, G.; McCane, C.; McCrone, L.; and Hunter, D. Anorexia nervosa: a psychiatric case register study from Aberdeen. *Psychological Medicine*, 16:49-58, 1986.

227. Crisp, A.H.; Palmer, R.L.; and Kalucy, R.S. How common is anorexia nervosa: a prevalence study. *British Journal of Psychiatry*, 128:549-554, 1976.

228. Cullberg, J. and Engstrom-Lindberg, M. Prevalence and incidence of eating disorders in a suburban population. *Acta Psychiatrica Scandinavica*, 78:314-319, 1988.

229. Lucas, A.R.; Beard, C.M.; O'Fallon, W.M.; and Kurland, L.T. Anorexia nervosa in Rochester, Minnesota: a 45 year study. *Mayo Clinic Proceedings*, 63:433-442, 1988.

230. Whitaker, A.; Johnson, J.; Shaffer, D.; Rapoport, J.L.; Kalikow, K.; Walsh, B.T.; Davies, M.; Braiman, S.; and Dolinsky, A. Uncommon troubles in young people: prevalence estimates of selected psychiatric disorders in a nonreferred adolescent population. *Archives of General Psychiatry*, 47:487-496, 1990.

231. Walters, E.E. and Kendler, K.S. Anorexia nervosa and anorexic-like syndromes in a population-based female twin sample. *American Journal of Psychiatry*, 152:64-71, 1995.

232. Lucas, A.R.; Beard, C.M.; O'Fallon, W.M.; and Kurland, L.T. 50-year trends in the incidence of anorexia nervosa in Rochester, Minn: a population-based study. *American Journal of Psychiatry*, 148:917-922, 1991.

233. Eagles, J.M.; Johnston, M.I.; Hunter, D.; Lobban, M.; and Millar, H.R. Increasing incidence of anorexia nervosa in the female population of Northeast Scotland. *American Journal of Psychiatry*, 152:1266-1271, 1995.

234. Drewnowski, A.; Yee, D.K.; and Krahan, D.D. Bulimia in college women: incidence and recovery rates. *American Journal of Psychiatry*, 145:753-755, 1988.

235. Rand, C.S.W. and Kuldau, J.M. Eating patterns in normal weight individuals: bulimia, restrained eating and the night eating syndrome. *International Journal of Eating Disorders*, 5:75-84, 1986.

236. Johnson-Sabine, E.; Wood, K.; Patton, G.; Mann, A.; and Wakeling, A. Abnormal eating attitudes in London schoolgirls - a prospective epidemiological study: factors associated with abnormal response on screening questionnaires. *Psychological Medicine*, 18:615-622, 1988.

237. Schotte, D.E. and Stunkard, A.J. Bulimia vs. bulimic behaviors on a college campus. *JAMA*, 258:1213-1215, 1987.

238. King, M.B. Eating disorders in general practice. *British Medical Journal*, 293:1412-1414, 1986.
239. Kendler, K.S.; MacLean, C.; Neale, M.; Kessler, R.; Heath, A.; and Eaves, L. The genetic epidemiology of bulimia nervosa. *American Journal of Psychiatry*, 148:1627-1637, 1991.
240. Bushnell, J.A.; Wells, J.E.; Hornblow, A.R.; Oakley Browne, M.A.; and Joyce, P. Prevalence of three bulimia syndromes in the general population. *Psychological Medicine*, 20:671-680, 1990.
241. Garfinkel, P.E.; Lin, E.; Goering, P.; Spegg, C.; Goldbloom, D.S.; Kennedy, S.; Kaplan, A.S.; and Woodside, D.B. Bulimia nervosa in a Canadian community sample: prevalence and comparison of subgroups. *American Journal of Psychiatry*, 152:1052-1058, 1995.
242. Drewnowski, A.; Hopkins, S.A.; and Kessler, R.C. The prevalence of bulimia nervosa in the U.S. college student population. *American Journal of Public Health*, 78:1322-1325, 1988.
243. King, M.B. Eating disorders in a general practice population: prevalence characteristics and follow-up at 12 to 18 months. *Psychological Medicine Monographs*, 14:1-34, 1989.
244. Striegel-Moore, R.H.; Silberstein, L.R.; Frensch, P.; and Rodin, J. A prospective study of disordered eating among college students. *International Journal of Eating Disorders*, 8:499-509, 1989.
245. Timmerman, M.G.; Wells, L.A.; and Chen, S. Bulimia nervosa and associated alcohol abuse among secondary school students. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29:118-122, 1990.
246. Hebebrand, J. and Remschmidt, H. Anorexia nervosa viewed as an extreme weight condition: genetic implications. *Human Genetics*, 95:1-11, 1995.
247. Gershon, E.S.; Schreiber, J.L.; Hamovit, J.R.; Dibble, E.D.; Kaye, W.; Nurnberger, J.I.; Anderson, A.E.; and Ebert, M. Clinical findings in patients with anorexia nervosa and affective illness in their relatives. *American Journal of Psychiatry*, 141:1419-1422, 1984.
248. Strober, M.; Lampert, C.; Morrell, W.; Burroughs, J.; and Jacobs, C. A controlled family study of anorexia nervosa: evidence of familial aggregation and lack of shared transmission with affective disorders. *International Journal of Eating Disorders*, 9:239-253, 1990.
249. Kasset, J.A.; Gershon, E.S.; Maxwell, M.E.; Guroff, J.J.; Kazuba, D.M.; Smith, A.L.; Brandt, H.A.; and Jimerson, D.C. Psychiatric disorders in the first-degree relatives of probands with bulimia nervosa. *American Journal of Psychiatry*, 146:1468-1471, 1989.
250. Hudson, J.I.; Pope, H.G.; Jonas, J.M.; and Yurgelun-Todd, D. Phenomenologic relationship of eating disorders to major affective disorder. *Psychiatry Research*, 9:345-354, 1983.
251. Hudson, J.I.; Pope, H.G.; Jonas, J.M.; Yurgelun-Todd, D.; and Frankenburg, F.R. A controlled family history study of bulimia. *Psychological Medicine*, 17:883-890, 1987.
252. Logue, C.M.; Crowe, R.R.; and Bean, J.A. A family study of anorexia nervosa and bulimia. *Comprehensive Psychiatry*, 30:179-188, 1989.
253. Holland, A.J.; Sicotte, N.; and Treasure, J. Anorexia nervosa: evidence for a genetic basis. *Journal of Psychosomatic Research*, 32:561-571, 1988.
254. Holland, A.J.; Hall, A.; Murray, R.; Russell, G.F.M.; and Crisp, A.H. Anorexia nervosa: a study of 34 twin pairs and one set of triplets. *British Journal of Psychiatry*, 145:414-419, 1984.
255. Rutherford, J.; McGuffin, P.; Katz, R.J.; and Murray, R.M. Genetic influences on eating attitudes in a normal

female twin population. *Psychological Medicine*, 23:425-436, 1993.

256. Fichter, M.M. and Noegel, R. Concordance for bulimia nervosa in twins. *International Journal of Eating Disorders*, 9:255-263, 1990.

257. Hinney, A.; Lentes, K.; Rosenkranz, K.; Barth, N.; Roth, H.; Ziegler, A.; Hennighausen, K.; Coners, H.; Wurmser, H.; Jacob, K.; Romer, G.; Winnikes, U.; Mayer, H.; Herzog, W.; Lehmkuhl, G.; Poustka, F.; Schmidt, M.H.; Blum, W.F.; Pirke, K.M.; Schafer, H.; Grzeschik, K.; Remschmidt, H.; and Hebebrand, J. β_3 Adrenergic-receptor allele distributions in children, adolescents and young adults with obesity, underweight or anorexia nervosa. *International Journal of Obesity*, 21:224-230, 1997.

258. Boyd, J.H.; Burke, J.D.; Guenberg, E.; Holzer, C.E.; Rae, D.S.; George, L.K.; Karno, M.; Stoltzman, R.; McEvoy, L.; and Nestadt, G. Exclusion criteria of DSM III: a study of co-occurrence of hierarchy-free syndromes. *Archives of General Psychiatry*, 41:983-989, 1984.

259. Kasviskis, Y.G.; Tsakiris, F.; Marks, I.M.; Basoglu, M.; and Noshirvani, H.F. Past history of anorexia nervosa in women with obsessive compulsive disorder. *International Journal of Eating Disorders*, 5:1069-1075, 1986.

260. Fenton, W.S. and McGlashan, T.H. The prognostic significance of obsessive-compulsive symptoms in schizophrenia. *American Journal of Psychiatry*, 143:437-441, 1986.

261. Pauls, D.L.; Towbin, K.E.; Leckman, J.F.; Zahner, G.E.P.; and Cohen, D.J. Gilles de la Tourette syndrome and obsessive-compulsive disorder: evidence supporting a genetic relationship. *Archives of General Psychiatry*, 43:1180-1182, 1986.

262. Karno, M.; Golding, J.M.; Sorenson, S.B.; and Burnam, M.A. The epidemiology of obsessive-compulsive disorder in five U.S. communities. *Archives of General Psychiatry*, 45:1094-1099, 1988.

263. Karno, M. and Golding, J.M. Obsessive compulsive disorder. In: Robins, L.N. and Regier, D.A. eds: *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*. New York, NY: Free Press, 1991. pp. 204-219.

264. Carey, G. and Gottesman, I.I. Twin and family studies of anxiety, phobic and obsessive disorders. In: Klein, D.F. and Rabkin, J. eds: *Anxiety: new research and changing concepts*. New York: Raven Press, 1981. pp. 117-136.

265. Insel, T.R.; Hoover, C.; and Murphy, D.L. Parents of patients with obsessive-compulsive disorder. *Psychological Medicine*, 13:807-811, 1983.

266. McKeon, P. and Murray, R. Familial aspects of obsessive-compulsive neurosis. *British Journal of Psychiatry*, 151:528-534, 1987.

267. Rasmussen, S.A. and Tsuang, M.T. Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. *American Journal of Psychiatry*, 143:317-322, 1986.

268. Pauls, D.L.; Alsobrook II, J.P.; Goodman, W.; Rasmussen, S.; and Leckman, J.F. A family study of obsessive-compulsive disorder. *American Journal of Psychiatry*, 152:76-84, 1995.

269. Lenane, M.C.; Swedo, S.E.; Leonard, H.; Pauls, D.L.; Sceery, W.; and Rapoport, J.L. Psychiatric disorders in first degree relatives of children and adolescents with obsessive compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29:407-412, 1990.

270. Sciuto, G.; Pasquale, L.; and Bellodi, L. Obsessive compulsive disorder and mood disorders: a family study. *American Journal of Medical Genetics*, 60:475-479, 1995.

271. Black, D.W.; Noyes, R.; Goldstein, R.B.; and Blum, N. A family study of obsessive-compulsive disorder.

Archives of General Psychiatry, 49:362-368, 1992.

272. Leonard, H.L.; Lenane, M.C.; Swedo, S.E.; Rettew, D.C.; Gershon, E.S.; and Rapoport, J.L. Tics and tourette's disorder: a 2- to 7-year follow-up of 54 obsessive-compulsive children. *American Journal of Psychiatry*, 149:1244-1251, 1992.
273. Riddle, M.A.; Scahill, L.; King, R.; Hardin, M.T.; Towbin, K.E.; Ort, S.I.; Leckman, J.F.; and Cohen, D.J. Obsessive compulsive disorder in children and adolescents: phenomenology and family history. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29:766-772, 1990.
274. Bellodi, L.; Sciuto, G.; Diaferia, G.; Roncجي, P.; and Smeraldi, E. Psychiatric disorders in the families of patients with obsessive-compulsive disorder. *Psychiatry Research*, 42:111-120, 1992.
275. Rasmussen, S.A. Genetic studies of obsessive-compulsive disorder. *Annals of Clinical Psychiatry*, 5:241-248, 1993.
276. Andrews, G.; Stewart, G.; Allen, R.; and Henderson, A.S. The genetics of six neurotic disorders: a twin study. *Journal of Affective Disorders*, 19:23-29, 1990.
277. Torgersen, S. Genetic factors in anxiety disorders. *Archives of General Psychiatry*, 40:1085-1089, 1983.
278. Clifford, C.A.; Murray, R.M.; and Rulker, D.W. Genetic and environmental influences on obsessional traits and symptoms. *Psychological Medicine*, 14:791-800, 1984.
279. Nicolini, H.; Hanna, G.; Baxter, L.; Schwartz, J.; and Weissbacker, K. Segregation analysis of obsessive compulsive and associated disorders: preliminary results. *Ursus Medicus*, 1:25-28, 1991.
280. Nicolini, H.; Cruz, C.; Camarena, B.; Orozco, B.; Kennedy, J.L.; King, N.; Weissbecker, K.; de la Fuente, J.R.; and Sidenberg, D. DRD2, DRD3 and 5HT2A receptor genes polymorphisms in obsessive-compulsive disorder. *Molecular Psychiatry*, 1:461-465, 1996.
281. Altemus, M.; Murphy, D.L.; Greenberg, B.; and Lesch, K.P. Intact coding region of the serotonin transporter gene in obsessive-compulsive disorder. *American Journal of Medical Genetics*, 67:409-411, 1996.
282. Di Bella, D.; Catalano, M.; Balling, U.; Smeraldi, E.; and Lesch, K. Systematic screening for mutations in the coding region of the human serotonin transporter (5BHTT) gene using PCR and DGGE. *American Journal of Medical Genetics*, 67:541-545, 1996.
283. Di Bella, D.; Catalano, M.; Cichon, S.; and Nothen, M.M. Association study of a null mutation in the dopamine D4 receptor gene in Italian patients with obsessive-compulsive disorder, bipolar mood disorder and schizophrenia. *Psychiatric Genetics*, 6:119-121, 1996.
284. Karayiorgou, M.; Altemus, M.; Galke, B.L.; Goldman, D.; Murphy, D.L.; Ott, J.; and Gogos, J.A. Genotype determining low catechol-O-methyltransferase activity as a risk factor for obsessive-compulsive disorder. *Proceedings of the National Academy of Sciences of the USA*, 94:4572-4575, 1997.
285. Aulakh, C.S.; Tolliver, T.; Wozniak, K.M.; Hill, J.L.; and Murphy, D.L. Functional and biochemical evidence for altered serotonergic function in the fawn-hooded rat strain. *Pharmacology Biochemistry and Behavior*, 49:615-620, 1994.
286. Weissman, M.M.; Bland, R.C.; Canino, G.J.; Faravelli, C.; Greenwald, S.; Hwu, H.; Joyce, P.R.; Karam, E.G.; Lee, C.; Lellouch, J.; Lepine, J.; Newman, S.C.; Oakley-Browne, M.A.; Rubio-Stipec, M.; Wells, J.E.; Wickramaratne, P.J.; Wittchen, H.; and Yeh, E. The cross-national epidemiology of panic disorder. *Archives of General Psychiatry*, 54:305-309, 1997.
287. Wittchen, H.U.; Essau, C.A.; and Krieg, J.-C. Anxiety disorders: similarities and differences of comorbidity in

treated and untreated groups. *British Journal of Psychiatry*, 159:23-33, 1991.

288. Gorman, J.M.; Askanazi, J.; Liebowitz, M.R.; Flyer, A.J.; Stein, J.; Kinney, J.; and Klein, D.F. Response to hyperventilation in a group of patients with panic disorder. *American Journal of Psychiatry*, 141:857-861, 1984.

289. Charney, D.S.; Heninger, G.R.; and Jatlow, P.I. Increased anxiogenic effects of caffeine in panic disorder. *Archives of General Psychiatry*, 42:233-243, 1985.

290. Pitts, F.N. and McClure, J.N. Lactate metabolism in anxiety neurosis. *New England Journal of Medicine*, 277:1329-1336, 1967.

291. Bradwejn, J.; Koszycki, D.; and Shriqui, C. Enhanced sensitivity of cholecystokinin-tetrapeptide in panic disorder: clinical and behavioral findings. *Archives of General Psychiatry*, 48:603-607, 1991.

292. Perna, G.; Cocchi, S.; Bertani, A.; Arancio, C.; and Bellodi, L. Sensitivity to 35 percent CO₂ in healthy first-degree relatives of patients with panic disorder. *American Journal of Psychiatry*, 152:623-625, 1995.

293. Giampaolo, P.; Gabriele, A.; Caldirola, D.; and Bellodi, L. Hypersensitivity to inhalation of carbon dioxide and panic attacks. *Psychiatry Research*, 57:267-273, 1995.

294. Perna, G.; Bertani, A.; Caldirola, D.; and Bellodi, L. Family history of panic disorder and hypersensitivity to CO₂ in patients with panic disorder. *American Journal of Psychiatry*, 153:1060-1064, 1996.

295. Balon, R.; Jordan, M.; Pohl, R.; and Yeragani, V.K. Family history of anxiety disorders in control subjects with lactate-induced panic attacks. *American Journal of Psychiatry*, 146:1304-1306, 1989.

296. Reschke, A.H.; Mannuzza, S.; Chapman, T.F.; Lipsitz, J.D.; Liebowitz, M.R.; Gorman, J.M.; Klein, D.F.; and Fyer, A.J. Sodium lactate response and familial risk for panic disorder. *American Journal of Psychiatry*, 152:277-279, 1995.

297. Eaton, W.W.; Kessler, R.C.; Wittchen, H.U.; and Magee, W.J. Panic and panic disorder in the United States. *American Journal of Psychiatry*, 151:413-420, 1994.

298. Eaton, W.W.; Dryman, A. and Weissman, M.M. Panic and phobia. In: Robins, L.N. and Regier, D.A. eds: *Psychiatric disorders in America*. New York: The Free Press, 1991. pp. 155-179.

299. Kendler, K.S.; Neale, M.C.; Kessler, R.C.; Heath, A.C.; and Eaves, L.J. Panic disorder in women: a population-based twin study. *Psychological Medicine*, 23:397-406, 1993.

300. Perna, G.; Caldirola, D.; Arancio, C.; and Bellodi, L. Panic attacks: a twin study. *Psychiatry Research*, 66:69-71, 1997.

301. Maier, W.; Lichtermann, D.; Minges, J.; Oehrlein, A.; and Franke, P. A controlled family study in panic disorder. *Journal of Psychiatric Research*, 27:79-87, 1993.

302. Crowe, R.R.; Noyes, R.; Pauls, D.L.; and Slymen, D. A family study of panic disorder. *Archives of General Psychiatry*, 40:1065-1069, 1983.

303. Noyes, R.; Crowe, R.R.; Harris, E.L.; Hamra, B.J.; McChesney, C.M.; and Chaudhry, D.R. Relationship between panic disorder and agoraphobia. *Archives of General Psychiatry*, 43:227-232, 1986.

304. Weissman, M.M.; Wickramaratne, P.; Adams, P.B.; Lish, J.D.; Horwath, E.; Charney, D.; Woods, S.W.; Leeman, E.; and Frosch, E. The relationship between panic disorder and major depression. *Archives of General Psychiatry*, 50:767-780, 1993.

305. Mendlewicz, J.; Papadimitriou, G.; and Wilmotte, J. Family study of panic disorder: comparison with generalized anxiety disorder, major depression, and normal subjects. *Psychiatric Genetics*, 3:73-78, 1993.
306. Heun, R. and Maier, W. Relation of schizophrenia and panic disorder: evidence from a controlled family study. *American Journal of Medical Genetics*, 60:127-132, 1995.
307. Leckman, J.F.; Weissman, M.M.; Merikangas, K.R.; Pauls, D.L.; and Prusoff, B.A. Panic disorder and major depression. *Archives of General Psychiatry*, 40:1055-1060, 1983.
308. Coryell, W.; Endicott, J.; Andreasen, N.C.; Keller, M.B.; Clayton, P.J.; Hirschfeld, R.M.A.; Scheftner, W.A.; and Winokur, G. Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. *American Journal of Psychiatry*, 145:293-300, 1988.
309. Goldstein, R.B.; Weissman, M.M.; Adams, P.B.; Horwath, E.; Lish, J.D.; Charney, D.; Woods, S.W.; Sobin, C.; and Wickramaratne, P.J. Psychiatric disorders in relatives of probands with panic disorder and/or major depression. *Archives of General Psychiatry*, 51:383-394, 1994.
310. Goldstein, R.B.; Wickramaratne, P.J.; Horwath, E.; and Weissman, M.M. Familial aggregation and phenomenology of "early"-onset (at or before age 20 years) panic disorder. *Archives of General Psychiatry*, 54:271-278, 1997.
311. Pauls, D.L.; Noyes, R.; and Crowe, R.R. The familial prevalence in second-degree relatives of patients with anxiety neurosis (panic disorder). *Journal of Affective Disorders*, 1:279-285, 1979.
312. Hopper, J.L.; Judd, F.K.; Derrick, P.L.; and Burrows, G.D. A family study of panic disorder. *Genetic Epidemiology*, 4:33-41, 1987.
313. Battaglia, M.; Bertella, S.; Politi, E.; Bernardeschi, L.; Perna, G.; Gabriele, A.; and Bellodi, L. Age at onset of panic disorder: influence of familial liability to the disease and of childhood separation anxiety disorder. *American Journal of Psychiatry*, 152:1362-1364, 1995.
314. Moran, C. and Andrews, G. The familial occurrence of agoraphobia. *British Journal of Psychiatry*, 146:262-267, 1985.
315. Weissman, M.M. Family genetic studies of panic disorder. *Journal of Psychiatric Research*, 27:69-78, 1993.
316. Maier, W.; Minges, J.; and Lichtermann, D. The familial relationship between panic disorder and unipolar depression. *Journal of Psychiatric Research*, 29:375-388, 1995.
317. Woodman, C.L. and Crowe, R.R. The genetics of panic disorder. In: Asnis, G.M. and van Praag, H.M. eds: *Panic Disorder: Clinical, Biological, and Treatment Aspects*. New York: John Wiley & Sons, Inc. 1995. pp. 66-79.
318. Weissman, M.M. Panic and generalized anxiety: are they separate disorders? *Journal of Psychiatric Research*, 24:157-162, 1990.
319. Slater, E. and Shields, J. Genetic aspects of anxiety. In: Lader, M.H. ed: *Studies of anxiety*. London: Royal Medico Psychological Association, 1969. pp. 62-71.
320. Torgersen, S. Comorbidity of major depression and anxiety disorders in twin pairs. *American Journal of Psychiatry*, 147:1199-1202, 1990.
321. Pauls, D.L.; Bucher, K.D.; Crowe, R.R.; and Noyes, R. A genetic study of panic disorder pedigrees. *American Journal of Human Genetics*, 32:639-644, 1980.
322. Bonney, G.E. Regressive models for familial disease and other binary traits. *Biometrics*, 42:611-625, 1986.

323. Hopper, J.L.; Judd, F.K.; Derrick, P.L.; Macaskill, G.T.; and Burrows, G.D. A family study of panic disorder: reanalysis using a regressive logistic model that incorporates a sibship environment. *Genetic Epidemiology*, 7:151-161, 1990.
324. Vieland, J.E.; Hodge, S.E.; Lish, J.D.; Adams, P.; and Weissman, M.M. Segregation analysis of panic disorder. *Psychiatric Genetics*, 3:63-71, 1993.
325. Martin, N.G.; Jardine, R.; Andrews, G.; and Heath, A.C. Anxiety disorders and neuroticism: are there genetic factors specific to panic? *Acta Psychiatrica Scandinavica*, 77:698-706, 1988.
326. Kendler, K.S.; Walters, E.E.; Truett, K.R.; Heath, A.C.; Neale, M.C.; Martin, N.G.; and Eaves, L.J. A twin-family study of self-report symptoms of panic-phobia and somatization. *Behavior Genetics*, 25:499-515, 1995.
327. Crowe, R.R.; Noyes, R.; Wilson, A.F.; Elston, R.C.; and Ward, L.J. A linkage study of panic disorder. *Archives of General Psychiatry*, 44:933-937, 1987.
328. Crowe, R.R. Panic disorder: genetic considerations. *Journal of Psychiatric Research*, 24:129-134, 1990.
329. Crowe, R.R.; Noyes, R.; Samuelson, S.; Wesner, R.; and Wilson, R. Close linkage between panic disorder and α -haptoglobin excluded in 10 families. *Archives of General Psychiatry*, 47:377-380, 1990.
330. Kato, T.; Wang, Z.W.; Zoega, T.; and Crowe, R.R. Missense mutation of the cholecystokinin B receptor gene: lack of association with panic disorder. *American Journal of Medical Genetics*, 67:401-405, 1996.
331. Crowe, R.R.; Noyes, R.; and Persico, A.M. Pro-opiomelanocortin (POMC) gene excluded as a cause of panic disorder in a large family. *Journal of Affective Disorders*, 12:23-27, 1987.
332. Wang, Z.W.; Crowe, R.R.; and Noyes, R. Adrenergic receptor genes as candidate genes for panic disorder: a linkage study. *American Journal of Psychiatry*, 149:470-474, 1992.
333. Mutchler, K.; Crowe, R.R.; Noyes, R.; and Wesner, R.W. Exclusion of the tyrosine hydroxylase gene in 14 panic disorder pedigrees. *American Journal of Psychiatry*, 147:1367-1369, 1990.
334. Crowe, R.R. The Iowa linkage study of panic disorder. In: Gershon, E.S. and Cloninger, C.R. eds: *Genetic approaches to mental disorders*. Washington, DC: American Psychopathological Association Series, 1994. pp. 291-309.
335. Andreasen, N.C. Symptoms, signs, and diagnosis of schizophrenia. *Lancet*, 346:477-481, 1995.
336. Flaum, M.; Amador, X.; Gorman, J., et al. The DSM-IV field trial for schizophrenia and other psychotic disorders. In: Widiger, T.A., Frances, A.J., Pincus, H.A., First, M.B., Ross, R. and Davis, W. eds: *DSM-IV Sourcebook, Volume 4*. Washington, DC: American Psychiatric Association, 1997.
337. Weeks, D.E.; Brzustowicz, L.; Squires-Wheeler, E.; Cornblatt, B.A.; Lehner, T.; Stefanovich, M.; Bassett, A.; Gilliam, T.C.; Ott, J.; and Erlenmeyer-Kimling, L. Report of a workshop on genetic linkage studies in schizophrenia. *Schizophrenia Bulletin*, 16:673-686, 1990.
338. Kendler, K.S.; O'Neill, F.A.; Burke, J.; Murphy, B.; Duke, F.; Straub, R.E.; Shinkwin, R.; Ni Nuallain, M.; MacLean, C.J.; and Walsh, D. Irish Study of High-Density Schizophrenia Families: field methods and power to detect linkage. *American Journal of Medical Genetics*, 67:179-190, 1996.
339. Kendler, K.S.; McGuire, M.; Gruenberg, A.; O'Hare, A.; Spellman, M.; and Walsh, D. The Roscommon Family Study: III. Schizophrenia-related personality disorders in relatives. *Archives of General Psychiatry*, 50:781-788, 1993.

340. Baron, M.; Gruen, R.; Asnis, L.; and Kane, J. Schizoaffective illness, schizophrenia, and affective disorders: Morbidity risk and genetic transmission. *Acta Psychiatrica Scandinavica*, 65:253-262, 1982.
341. Kendler, K.S.; Masterson, C.; and Davis, K.L. Psychiatric illness in first-degree relatives of patients with paranoid psychosis, schizophrenia, and medical illness. *British Journal of Psychiatry*, 147:524-531, 1985.
342. Kety, S.S.; Wender, P.H.; Jacobsen, B.; Ingraham, L.J.; Jansson, L.; Faber, B.; and Kinney, D.K. Mental illness in the biological and adoptive relatives of schizophrenic adoptees. Replication of the Copenhagen Study in the rest of Denmark. *Archives of General Psychiatry*, 51:442-455, 1994.
343. Erlenmeyer-Kimling, L.; Squires-Wheeler, E.; Adamo, U.H.; Bassett, A.S.; Cornblatt, B.A.; Kestenbaum, C.J.; Rock, D.; Roberts, S.A.; and Gottesman, I.I. The New York High-Risk Project: psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. *Archives of General Psychiatry*, 52:857-865, 1995.
344. Zimmerman, M. Diagnosing personality disorders: a review of issues and research methods. *Archives of General Psychiatry*, 51:225-245, 1994.
345. Matthyse, S.; Holzman, P.S.; and Lange, K. The genetic transmission of schizophrenia. *Journal of Psychiatric Research*, 20:57-76, 1986.
346. Arolt, V.; Lencer, R.; Nolte, A.; Muller-Myhsok, B.; Purmann, S.; Schurmann, M.; Leutelt, J.; Pinnow, M.; and Schwinger, E. Eye tracking dysfunction is a putative phenotypic susceptibility marker of schizophrenia and maps to a locus on chromosome 6p in families with multiple occurrence of the disease. *American Journal of Medical Genetics*, 67:564-579, 1996.
347. Freedman, R.; Coon, H.; Myles-Worsley, M.; Orr-Urtreger, A.; Olincy, A.; Davis, A.; Polymeropoulos, M.; Holik, J.; Hopkins, J.; Hoff, M.; Rosenthal, J.; Waldo, M.C.; Reimherr, F.; Wender, P.; Yaw, J.; Young, D.A.; Breese, C.R.; Adams, C.; Patterson, D.; Adler, L.E.; Kruglyak, L.; Leonard, S.; and Byerley, W. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proceedings of the National Academy of Sciences of the USA*, 94:587-592, 1997.
348. Cornblatt, B.A. and Keilp, J.G. Impaired attention, genetics, and the pathophysiology of schizophrenia. *Schizophrenia Bulletin*, 20:31-46, 1994.
349. Moldin, S.O. Indicators of liability to schizophrenia: perspectives from genetic epidemiology. *Schizophrenia Bulletin*, 20:169-184, 1994.
350. Moldin, S.O. and Van Eerdewegh, P. Multivariate genetic analysis of oligogenic disease. *Genetic Epidemiology*, 12:801-806, 1995.
351. Moldin, S.O. Detection and replication of linkage to a complex human disease. *Genetic Epidemiology*, 14:1023-1028, 1997.
352. Jablensky, A.; Sartorius, N.; Ernberg, G.; Anker, M.; Korten, A.; Cooper, J.E.; Day, R.; and Bertelsen, A. Schizophrenia: manifestations, incidence and course in different cultures. a World Health Organization ten-country study. *Psychological Medicine Monographs*, 20:1-97, 1992.
353. Odegaard, O. Hospitalized psychosis in Norway. Time trends 1926-1965. *Social Psychiatry*, 6:53-78, 1971.
354. Munk-Jorgensen, P. First-admission rates and marital status of schizophrenics. *Acta Psychiatrica Scandinavica*, 75:62-68, 1987.
355. Ni Nuallain, M.; O'Hare, A.; and Walsh, D. Incidence of schizophrenia in Ireland. *Psychological Medicine*, 17:943-948, 1987.

356. Kendler, K.S. and Walsh, D. Gender and schizophrenia: results of an epidemiologically-based family study. *British Journal of Psychiatry*, 167:184-192, 1995.
357. Hambrecht, M.; Riecher-Rossler, A.; Fatkenheuer, B.; Louza, M.R.; and Häfner, H. Higher morbidity risk for schizophrenia in males: fact or fiction? *Comprehensive Psychiatry*, 35:39-49, 1994.
358. Hambrecht, M.; Maurer, K.; and Häfner, H. Evidence for a gender bias in epidemiological studies of schizophrenia. *Schizophrenia Research*, 8:223-231, 1992.
359. Takei, N.; Lewis, G.; Sham, P.C.; and Murray, R.M. Age-period-cohort analysis of the incidence of schizophrenia in Scotland. *Psychological Medicine*, 26:963-973, 1996.
360. Waddington, J.L. and Youssef, H.A. Evidence for a gender-specific decline in the rate of schizophrenia in rural Ireland over a 50-year period. *British Journal of Psychiatry*, 164:171-176, 1994.
361. Kendell, R.E.; Malcolm, D.E.; and Adams, W. The problem of detecting changes in the incidence of schizophrenia. *British Journal of Psychiatry*, 162:212-218, 1993.
362. Kendler, K.S. and Diehl, S.R. Schizophrenia: genetics. In: Kaplan, H.I. and Sadock, B.J. eds: *Comprehensive Textbook of Psychiatry, VI*. Baltimore, MD: Williams & Wilkins, 1995. pp. 942-957.
363. Gottesman II: *Schizophrenia Genesis: The Origins of Madness*, New York, W.H. Freeman & Company; 1991.
364. Prescott, C.A. and Gottesman, I.I. Genetically mediated vulnerability to schizophrenia. *Psychiatric Clinics of North America*, 16:245-267, 1993.
365. Gottesman, I.I. Schizophrenia epigenesis: past, present, and future. *Acta Psychiatr Scand Suppl*, 384:26-33, 1994.
366. Torrey EF, Bowler AE, Taylor EH, Gottesman II: *Schizophrenia and Manic-Depressive Disorder: The Biological Roots of Mental Illness as Revealed by the Landmark Study of Identical Twins*, New York, NY, BasicBooks; 1994.
367. Kendler, K.S.; Gruenberg, A.M.; and Kinney, D.K. Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. *Archives of General Psychiatry*, 51:456-468, 1994.
368. McGuffin, P.; Asherson, P.; Owen, M.; and Farmer, A. The strength of the genetic effect: is there room for an environmental influence in the aetiology of schizophrenia? *British Journal of Psychiatry*, 164:593-599, 1994.
369. McGue, M.; Gottesman, I.I.; and Rao, D.C. The transmission of schizophrenia under a multifactorial threshold model. *American Journal of Human Genetics*, 35:1161-1178, 1983.
370. Gottesman, I.I. and Shields, J. A polygenic theory of schizophrenia. *Proceedings of the National Academy of Sciences of the USA*, 58:199-205, 1967.
371. Rao, D.C.; Morton, N.E.; Gottesman, I.I.; and Lew, R. Path analysis of qualitative data on pairs of relatives: Application to schizophrenia. *Human Heredity*, 31:325-333, 1981.
372. O'Rourke, D.H.; Gottesman, I.I.; Suarez, B.K.; Rice, J.P.; and Reich, T. Refutation of the general single locus model for the etiology of schizophrenia. *American Journal of Human Genetics*, 34:630-649, 1982.
373. McGue, M. and Gottesman, I.I. Genetic linkage in schizophrenia: perspectives from genetic epidemiology. *Schizophrenia Bulletin*, 15:453-464, 1989.

374. McGue, M.; Gottesman, I.I.; and Rao, D.C. Resolving genetic models for the transmission of schizophrenia. *Genetic Epidemiology*, 2:99-110, 1985.
375. Risch, N.J. Linkage strategies for genetically complex traits: I. multilocus models. *American Journal of Human Genetics*, 46:222-228, 1990.
376. Sherrington, R.; Brynjolfsson, J.; Petursson, H.; Potter, M.; Dudleston, K.; Barraclough, B.; Wasmuth, J.; Dobbs, M.; and Gurling, H.M.D. Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature*, 336:164-167, 1988.
377. McGuffin, P.; Sargeant, M.; Hetti, G.; Tidmarsh, S.; Whatley, S.; and Marchbanks, R.M. Exclusion of a schizophrenia susceptibility gene from the chromosome 5q11-q13 region. New data and a reanalysis of previous reports. *American Journal of Human Genetics*, 47:524-535, 1990.
378. Gurling, H. and Sharma, T. Genetic linkage analysis and clinical approaches to the resolution of heterogeneity in the schizophrenias. In: Gershon, E.S. and Cloninger, C.R. eds: *Genetic Approaches to Mental Disorders*. Washington, DC: American Psychiatric Press, 1994. pp. 231-251.
379. Wang, S.; Sun, C.E.; Walczak, C.A.; Ziegler, J.S.; Kipps, B.R.; Goldin, L.R.; and Diehl, S.R. Evidence for a susceptibility locus for schizophrenia on chromosome 6pter-p22. *Nature Genetics*, 10:41-46, 1995.
380. Straub, R.E.; MacLean, C.J.; O'Neill, F.A.; Burke, J.; Murphy, B.; Duke, F.; Shinkwin, R.; Webb, B.T.; Zhang, J.; Walsh, D.; and Kendler, K.S. A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogeneity. *Nature Genetics*, 11:287-293, 1995.
381. Schwab, S.G.; Albus, M.; Hallmayer, J.; Honig, S.; Borrmann, M.; Lichtermann, D.; Ebstein, R.P.; Ackenheil, M.; Lerer, B.; and Risch, N. Evaluation of a susceptibility gene for schizophrenia on chromosome 6p by multipoint affected sib-pair linkage analysis. *Nature Genetics*, 11:325-327, 1995.
382. Schizophrenia Linkage Collaborative Group for Chromosomes 3 6 and 8 Additional support for schizophrenia linkage on chromosomes 6 and 8: a multicenter study. *American Journal of Medical Genetics*, 67:580-594, 1996.
383. Gurling, H.; Kalsi, G.; Chen, A.H.-S.; Green, M.; Butler, R.; Read, T.; Murphy, P.; Curtis, D.; Sharma, T.; and Petursson, H. Schizophrenia susceptibility and chromosome 6p24-22. *Nature Genetics*, 11:234-235, 1995.
384. Mowry, B.J.; Nancarrow, D.J.; Lennon, D.P.; Sandkuijl, L.A.; Crowe, R.R.; Silverman, J.M.; Mohs, R.C.; Siever, L.J.; Endicott, J.; and Sharpe, L. Schizophrenia susceptibility and chromosome 6p24-22. *Nature Genetics*, 11:233-234, 1995.
385. Garner, C.; Kelly, M.; Cardon, L.; Joslyn, G.; Carey, A.; LeDuc, C.; Lichter, J.; Harris, T.; Loftus, J.; Shields, G.; Comazzi, M.; Vita, A.; Smith, A.M.; Dann, J.; Crow, T.J.; and DeLisi, L.E. Linkage analyses of schizophrenia to chromosome 6p24-22: an attempt to replicate. *American Journal of Medical Genetics*, 67:595-610, 1996.
386. Riley, B.P.; Rajagopalan, S.; Mogudi-Carter, M.; Jenkins, T.; and Williamson, R. No evidence for linkage of chromosome 6p markers to schizophrenia in Southern African Bantu-speaking families. *Psychiatric Genetics*, 6:41-49, 1996.
387. Daniels, J.K.; Spurlock, G.; Williams, N.M.; Cardno, A.G.; Jones, L.A.; Murphy, K.C.; Asherson, P.; Holmans, P.; Fenton, I.; McGuffin, P.; and Owen, M.J. Linkage study of chromosome 6p in sib-pairs with schizophrenia. *American Journal of Medical Genetics*, 74:319-323, 1997.
388. Wang, S.; Detera-Wadleigh, S.; Coon, H.; Sun, C.-E.; Goldin, L.R.; Duffy, D.L.; Byerley, W.F.; Gershon, E.S.; and Diehl, S.R. Evidence of linkage disequilibrium between schizophrenia and the SCA1 CAG repeat on chromosome 6p23. *American Journal of Human Genetics*, 59:731-736, 1996.
389. Pulver, A.E.; Lasseter, V.K.; Kasch, L.; Wolyniec, P.; Nestadt, G.; Blouin, J.L.; Kimberland, M.; Babb, R.; Vourlis, S.; and Chen, H. Schizophrenia: a genome scan targets chromosomes 3p and 8p as potential sites of

susceptibility genes. *American Journal of Medical Genetics*, 60:252-260, 1995.

390. Kendler, K.S.; MacLean, C.J.; O'Neill, A.; Burke, J.; Murphy, B.; Duke, F.; Shinkwin, R.; Easter, S.M.; Webb, B.T.; Zhang, J.; Walsh, D.; and Straub, R.E. Evidence for a schizophrenia vulnerability locus on chromosome 8p in the Irish Study of High-Density Schizophrenia Families. *American Journal of Psychiatry*, 153:1534-1540, 1996.

391. Moises, H.W.; Yang, L.; Kristbjarnarson, H.; Wiese, C.; Byerley, W.; Macciardi, F.; Arolt, V.; Blackwood, D.; Liu, X.; Sjogren, B.; Aschauer, H.N.; Hwu, H.-G.; Jang, K.; Livesley, W.J.; Kennedy, J.L.; Zoega, T.; Ivarsson, O.; Bui, M.-T.; Yu, M.-H.; Havsteen, B.; Commenges, D.; Weissenbach, J.; Schwinger, E.; Gottesman, I.I.; Pakstis, A.J.; Wetterberg, L.; Kidd, K.K.; and Helgason, T. An international two-stage genome-wide search for schizophrenia susceptibility genes. *Nature Genetics*, 11:321-324, 1995.

392. Straub, R.E.; MacLean, C.J.; O'Neill, F.A.; Walsh, D.; and Kendler, K.S. Support for a possible schizophrenia vulnerability locus in region 5q22-31 in Irish families. *Molecular Psychiatry*, 2:148-155, 1997.

393. Schwab, S.G.; Eckstein, G.N.; Hallmayer, J.; Lerer, B.; Albus, M.; Borrmann, M.; Lichtermann, D.; Ertl, M.A.; Maier, W.; and Wildenauer, D.B. Evidence suggestive of a locus on chromosome 5q31 contributing to susceptibility for schizophrenia in German and Israeli families by multipoint affected sib-pair linkage analysis. *Molecular Psychiatry*, 2:156-160, 1997.

394. Coon, H.; Holik, J.; Hoff, M.; Reimherr, F.; Wender, P.; Myles-Worsley, M.; Waldo, M.; Freedman, R.; and Byerley, W. Analysis of chromosome 22 markers in nine schizophrenia pedigrees. *American Journal of Medical Genetics*, 54:72-79, 1994.

395. Kalsi, G.; Brynjolfsson, J.; Butler, R.; Sherrington, R.; Curtis, D.; Sigmundsson, T.; Read, T.; Murphy, P.; Sharma, T.; and Petursson, H. Linkage analysis of chromosome 22q12-13 in a United Kingdom/Icelandic sample of 23 multiplex schizophrenia families. *American Journal of Medical Genetics*, 60:298-301, 1995.

396. Riley, B.; Mogudi-Carter, M.; Jenkins, T.; and Williamson, R. No evidence for linkage of chromosome 22 markers to schizophrenia in Southern African Bantu-speaking families. *American Journal of Medical Genetics*, 67:515-522, 1996.

397. Gill, M.; Vallada, H.; Collier, D.; Sham, P.; Holmans, P.; Murray, R.; McGuffin, P.; Nanko, S.; Owen, M.; Antonarakis, S.; Housman, D.; Kazazian, H.; Nestadt, G.; Pulver, A.E.; Straub, R.E.; MacLean, C.J.; Walsh, D.; Kendler, K.S.; DeLisi, L.; Polymeropoulos, M.; Coon, H.; Byerley, W.; Lofthouse, R.; Gershon, E.; Goldin, L.; Crow, T.; Freedman, R.; Laurent, C.; Boodeau-Pean, S.; d'Amato, T.; Jay, M.; Campion, D.; Mallet, J.; Wildenauer, D.B.; Lerer, B.; Albus, M.; Ackenheil, M.; Ebstein, R.P.; Hallmayer, J.; Maier, W.; Gurling, H.; Curtis, D.; Kalsi, G.; Brynjolfsson, J.; Sigmundson, T.; Petursson, H.; Blackwood, D.; Muir, W.; St.Clair, D.; He, L.; Maguire, S.; Moises, H.W.; Hwu, H.-G.; Yang, L.; Wiese, C.; Tao, L.; Liu, X.; Kristbjarnarson, H.; Levinson, D.F.; Mowry, B.J.; Donis-Keller, H.; Hayward, N.K.; Crowe, R.R.; Silverman, J.M.; Nancarrow, D.J.; and Read, C.M. A combined analysis of D22S278 marker alleles in affected sib-pairs: support for a susceptibility locus for schizophrenia at chromosome 22q12. *American Journal of Medical Genetics*, 67:40-45, 1996.

398. Kidd, K.K. Associations of disease with genetic markers: *Deja vu* all over again. *American Journal of Medical Genetics*, 48:71-73, 1993.

399. Crowe, R.R. Candidate genes in psychiatry: an epidemiological perspective. *American Journal of Medical Genetics*, 48:74-77, 1993.

400. Bassett, A.S. and Honer, W.G. Evidence for anticipation in schizophrenia. *American Journal of Human Genetics*, 54:864-870, 1994.

401. Petronis, A.; Bassett, A.S.; Honer, W.G.; Vincent, W.G.; Tatuch, Y.; Sasaki, T.; Ying, D.-J.; Klempan, T.A.; and Kennedy, J.L. Search for unstable DNA in schizophrenia families with evidence for genetic anticipation. *American Journal of Human Genetics*, 59:905-911, 1996.

402. Bassett, A.S. and Husted, J. Anticipation or ascertainment bias in schizophrenia? Penrose's familial mental

illness sample. *American Journal of Human Genetics*, 60:630-637, 1997.

403. Bowen, T.; Guy, C.; Speight, G.; Jones, L.; Cardno, A.; Murphy, K.; McGuffin, P.; Owen, M.J.; and O'Donovan, M.C. Expansion of 50 CAG/CTG repeats excluded in schizophrenia by application of a highly efficient approach using repeat expansion detection and a PCR screening set. *American Journal of Human Genetics*, 59:912-917, 1996.

404. Moldin, S.O. and Gottesman, I.I. Genes, experience, and chance in schizophrenia: positioning for the 21st century. *Schizophrenia Bulletin*, 23:547-561, 1997.

405. Moldin, S.O. The maddening hunt for madness genes. *Nature Genetics*, 17:127-129, 1997.

406. Barondes, S.H.; Alberts, B.M.; Andreasen, N.C.; Bargmann, C.; Benes, F.; Goldman-Rakic, P.; Gottesman, I.I.; Hienemann, S.F.; Jones, E.G.; Kirschner, M.; Lewis, D.; Raff, M.; Roses, A.; Rubenstein, J.; Snyder, S.; Watson, S.J.; Weinberger, D.R.; and Yolken, R.H. Workshop on schizophrenia. *Proceedings of the National Academy of Sciences of the USA*, 94:1612-1614, 1997.

407. Pauls, D.L. and Leckman, J.F. The inheritance of Gilles de la Tourette's syndrome and associated behaviors: evidence for autosomal dominant transmission. *New England Journal of Medicine*, 315:993-997, 1986.

408. Kurlan, R. Tourette's syndrome: current concepts. *Neurology*, 39:1625-1630, 1989.

409. Santangelo, S.; Pauls, D.L.; Lavori, P.W.; Goldstein, J.M.; Faraone, S.V.; and Tsuang, M.T. Assessing risk for the Tourette spectrum of disorders among first-degree relatives of probands with Tourette syndrome. *American Journal of Medical Genetics*, 67:107-116, 1996.

410. Comings, D.E. Tourette syndrome: a hereditary neuropsychiatric spectrum disorder. *Annals of Clinical Psychiatry*, 6:235-247, 1994.

411. Pauls, D.L.; Leckman, J.F.; and Cohen, D.J. Familial relationship between Gilles de la Tourette's syndrome, attention deficit disorder, learning disabilities, speech disorders, and stuttering. *Journal of the American Academy of Child and Adolescent Psychiatry*, 32:1044-1050, 1993.

412. Pauls, D.L.; Leckman, J.F.; and Cohen, D.J. Evidence against a genetic relationship between Tourette's syndrome and anxiety, depression, panic, and phobic disorders. *British Journal of Psychiatry*, 164:215-221, 1994.

413. Heutink, P.; van de Watering, B.J.M.; Pakstis, A.J.; Kurlan, R.; Sandor, P.; Oostra, B.A.; and Sandkuijl, L.A. Linkage studies on Gilles de la Tourette syndrome: what is the strategy of choice? *American Journal of Human Genetics*, 57:465-473, 1995.

414. Patel, P.I. Invited editorial: quest for the elusive genetic basis of Tourette syndrome. *American Journal of Human Genetics*, 59:980-982, 1996.

415. Lucas, A.R.; Beard, C.M.; Rajput, A.H. and Kurland, L.T. Tourette syndrome in Rochester, Minnesota, 1968-1979. In: Friedhoff, A.J. and Chase, T.N. eds: *Gilles de la Tourette Syndrome*. New York, NY: Raven Press, 1982. pp. 267-269.

416. Burd, L.; Kerbeshian, J.; Wikenheiser, M.; and Fisher, W. Prevalence of Gilles de la Tourette's syndrome in North Dakota adults. *American Journal of Psychiatry*, 143:787-788, 1986.

417. Burd, L.; Kerbeshian, J.; Wikenheiser, M.; and Fisher, W. Prevalence of Gilles de la Tourette syndrome in North Dakota school-age children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 25:552-553, 1986.

418. Comings, D.E.; Himes, J.A.; and Comings, B.G. An epidemiologic study of Tourette's syndrome in a single school district. *Journal of Clinical Psychiatry*, 51:463-469, 1990.

419. Caine, E.D.; McBride, M.C.; Chiverton, P.; Bamford, K.A.; Rediess, S.; and Shiao, J. Tourette's syndrome in Monroe County school children. *Neurology*, 38:472-475, 1988.
420. Robertson, M.M.; Verrill, M.; Mercer, M.; James, B.; and Pauls, D.L. Tourette's syndrome in New Zealand: a postal survey. *British Journal of Psychiatry*, 164:263-266, 1994.
421. Apter, A.; Pauls, D.L.; Bleich, A.; Zohar, A.H.; Kron, S.; Ratzoni, G.; Dycian, A.; Kotler, M.; Weizman, A.; and Gadot, N. An epidemiological study of Gilles de la Tourette's syndrome in Israel. *Archives of General Psychiatry*, 50:734-738, 1993.
422. Bruun, R.D. Gilles de la Tourette syndrome: an overview of clinical experience. *Journal of the American Academy of Child and Adolescent Psychiatry*, 23:126-133, 1984.
423. Kidd, K.K.; Prusoff, B.A.; and Cohen, D.J. The familial pattern of Tourette syndrome. *Archives of General Psychiatry*, 37:1336-1339, 1980.
424. Pauls, D.L.; Cohen, D.J.; Heimbuch, R.C.; Detlor, J.; and Kidd, K.K. The familial pattern and transmission of Tourette syndrome and multiple tics. *Annals of Human Genetics*, 38:1091-1093, 1981.
425. Price, R.A.; Kidd, K.K.; Cohen, D.J.; Pauls, D.L.; and Leckman, J.F. A twin study of Tourette syndrome. *Archives of General Psychiatry*, 42:815-820, 1985.
426. Eapen, V.; Pauls, D.L.; and Robertson, M.M. Evidence for autosomal dominant transmission in Tourette's syndrome: United Kingdom Cohort Study. *British Journal of Psychiatry*, 162:593-596, 1993.
427. Robertson, M.M. and Gourdie, A. Familial Tourette's syndrome in a large British pedigree. Associated psychopathology, severity, and potential for linkage analysis. *British Journal of Psychiatry*, 156:515-521, 1990.
428. Curtis, D.; Robertson, M.M.; and Gurling, H.M.D. Autosomal dominant gene transmission in a large kindred with Gilles de la Tourette syndrome. *British Journal of Psychiatry*, 160:845-849, 1992.
429. McMahon, W.M.; van de Wetering, B.J.M.; Filloux, F.; Betit, K.; Coon, H.; and Leppert, M. Bilineal transmission and phenotypic variation of Tourette's disorder in a large pedigree. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35:672-680, 1996.
430. Pauls, D.L.; Raymond, C.L.; Stevenson, J.M.; and Leckman, J.F. A family study of Gilles de la Tourette syndrome. *American Journal of Human Genetics*, 48:154-163, 1991.
431. Robertson, M.M. The Gilles de la Tourette syndrome: the current status. *British Journal of Psychiatry*, 154:147-169, 1989.
432. Fernando, S.J.M. Gilles de la Tourette's syndrome: a report on four cases and a review of published case reports. *British Journal of Psychiatry*, 113:607-617, 1967.
433. Frankel, N.; Cummings, J.L.; and Robertson, M.M. Obsessions and compulsions in Gilles de la Tourette's syndrome. *Neurology*, 36:378-382, 1986.
434. Montgomery, M.A.; Clayton, P.J. and Friedhoff, A.J. Psychiatric illness in Tourette syndrome and first degree relatives. In: Chase, T.N. and Friedhoff, A.J. eds: *Gilles de la Tourette Syndrome*. New York, NY: Raven Press, 1982. pp. 335-339.
435. Nee, L.E.; Polinsky, R.J. and Ebert, M.H. Tourette syndrome: clinical and family studies. In: Chase, T.N. and Friedhoff, A.J. eds: *Gilles de la Tourette Syndrome*. New York, NY: Raven Press, 1982. pp. 291-295.
436. Robertson, M.M.; Trimble, M.R.; and Lees, A.J. The psychopathology of the Gilles de la Tourette syndrome: a phenomenological analysis. *British Journal of Psychiatry*, 152:383-390, 1988.

437. Yaryura Tobias, J.A.; Neziroglu, F.; and Howard, S. Clinical aspects of Gilles de la Tourette syndrome. *Orthomolecular Psychiatry*, 10:263-268, 1981.
438. Palumbo, D.; Maughan, A.; and Kurlan, R. Hypothesis III: Tourette's syndrome is only one of several causes of a developmental basal ganglia syndrome. *Archives of Neurology*, 54:475-483, 1997.
439. Baron, M.; Shapiro, E.; and Shapiro, A. Genetic analysis of Tourette syndrome suggesting a major gene effect. *American Journal of Human Genetics*, 33:767-775, 1981.
440. Kidd, K.K. and Pauls, D.L. The familial pattern of Tourette syndrome. In: Chase, T.N. and Friedhoff, A.J. eds: *Gilles de la Tourette Syndrome*. New York, NY: Raven Press, 1982. pp. 243-249.
441. Price, R.A.; Pauls, D.L.; Kruger, S.D.; and Caine, E.D. Family data support a dominant major gene for Tourette syndrome. *Psychiatry Research*, 24:251-261, 1987.
442. Pauls, D.L.; Pakstis, A.J.; Kurlan, R.; Kidd, K.K.; Leckman, J.F.; Cohen, D.J.; Kidd, J.R.; Como, P.; and Sparkes, R. Segregation and linkage analyses of Tourette's syndrome and related disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29:195-203, 1990.
443. Comings, D.E.; Comings, B.G.; and Devor, E.J. Detection of a major gene for Gilles de la Tourette syndrome. *American Journal of Human Genetics*, 36:586-600, 1984.
444. Devor, E.J. Complex segregation analysis of Gilles de la Tourette syndrome: further evidence for a major locus mode of transmission. *American Journal of Human Genetics*, 36:704-709, 1984.
445. Hasstedt, S.J.; Leppert, M.; Filloux, F.; van de Wetering, B.J.M.; and McMahon, W.M. Intermediate inheritance of Tourette syndrome, assuming assortative mating. *American Journal of Human Genetics*, 57:682-689, 1995.
446. Kurlan, R.; Eapen, V.; Stern, J.; McDermott, M.P.; and Robertson, M.M. Bilineal transmission in Tourette's syndrome families. *Neurology*, 44:2336-2342, 1994.
447. Walkup, J.T.; LaBuda, M.C.; Singer, H.S.; Brown, J.; Riddle, M.A.; and Hurko, O. Family study and segregation analysis of Tourette syndrome: evidence for a mixed model of inheritance. *American Journal of Human Genetics*, 59:684-693, 1996.
448. Pakstis, A.J.; Heutink, P.; Pauls, D.L.; Kurlan, R.; van de Wetering, B.J.M.; Leckman, J.F.; Sandkuyl, L.A.; Kidd, J.R.; Breedveld, G.J.; Castiglione, C.M.; Weber, J.; Sparkes, R.S.; Cohen, D.J.; Kidd, K.K.; and Oostra, B.A. Progress in the search for genetic linkage with Tourette syndrome: an exclusion map covering more than 50 percent of the autosomal genome. *American Journal of Human Genetics*, 48:281-294, 1991.
449. Heutink, P.; Breedveld, G.J.; Niermeijer, M.F.; van de Wetering, B.J.M. and Oostra, B.A. Progress in gene localization. In: Kurlan, R. ed: *The Handbook of Tourette's Syndrome and Associated Tic and Behavioral Disorders*. New York, NY: Marcel Dekker, 1993. pp. 317-335.
450. van de Wetering, B.J.M. and Heutink, P. The genetics of the Gilles de la Tourette syndrome: a review. *Journal of Laboratory and Clinical Medicine*, 121:638-645, 1993.
451. Comings, D.E.; Muhleman, D.; and Dietz, G. Association between Tourette's syndrome and homozygosity at the dopamine D3 receptor gene. *Lancet*, 341:906, 1993.
452. Brett, P.M.; Robertson, M.M.; Gurling, H.M.D.; and Curtis, D. Failure to find linkage and increased homozygosity for the dopamine D3 receptor gene in Tourette's syndrome. *Lancet*, 341:1225, 1993.
453. Brett, P.M.; Curtis, D.; Robertson, M.M.; and Gurling, H.M.D. The genetic susceptibility to Gilles de la Tourette syndrome in a large multiple affected British kindred: linkage analysis excludes as role for the genes

coding for dopamine D1, D2, D3, D4, D5 receptors, dopamine beta hydroxylase, tyrosinase, and tyrosine hydroxylase. *Biological Psychiatry*, 37:533-540, 1995.

454. Devor, E.J.; Grandy, D.K.; and Civelli, O. Genetic linkage is excluded for the D2 dopamine receptor (λ -HD2G1) and flanking loci on chromosome 11q22-q23 in Tourette syndrome. *Human Heredity*, 40:105-108, 1990.

455. Gelernter, J.; Pakstis, A.J.; and Pauls, D.L. Tourette syndrome is not linked to D2 dopamine receptor. *Archives of General Psychiatry*, 47:1073-1077, 1990.

456. Barr, C.L.; Wigg, K.G.; Zovko, E.; Sandor, P.; and Tsui, L.-C. Linkage study of the dopamine D₅ receptor gene and Gilles de la Tourette syndrome. *American Journal of Medical Genetics*, 74:58-61, 1997.

457. Gelernter, J.; Vandenbergh, D.; Kruger, S.D.; Pauls, D.L.; Kurlan, R.; Pakstis, A.J.; Kidd, K.K.; and Uhl, G. The dopamine transporter protein gene (SLC6A3): primary linkage mapping and linkage studies in Tourette syndrome. *Genomics*, 30:459-463, 1995.

458. Brett, P.M.; Curtis, D.; Robertson, M.M.; and Gurling, H.M.D. Exclusion of the 5BHT1A serotonin neuroreceptor and tryptophan oxygenase genes in a large British kindred multiply affected with touretts's syndrome, chronic motor tics, and obsessive-compulsive behavior. *American Journal of Psychiatry*, 152:437-440, 1995.

459. Taylor, L.D.; Krizman, D.B.; and Jankovic, J. 9p monosomy in a patient with Gilles de la Tourette syndrome. *Neurology*, 41:1513-1515, 1991.

460. Donnai, D. Gene location in Tourette syndrome. *Lancet*, 14:627, 1987.

461. Comings, D.E.; Comings, B.G.; Dietz, G., et al. Evidence that the Tourette syndrome gene is at 18-22.1. In: Vogel, F. and Sperling, K. eds: *Human Genetics: Proceedings of the 7th International Congress of Human Genetics*. Berlin, Germany: Springer, 1986. pp. 620.

462. Brett, P.M.; Curtis, D.; Gourdie, A.; Schneiden, V.; Jackson, G.; Holmes, D.; Robertson, M.M.; and Gurling, H.M.D. Possible linkage of Tourette syndrome to markers on the short arm of chromosome 3 (C3p21-14). *Lancet*, Oct. 27:1076, 1990.

463. Brett, P.M.; Curtis, D.; and Melmer, G. Linkage analysis in a large pedigree multiply affected with Gilles de la Tourette syndrome. *Psychiatric Genetics*, 2:26, 1991.

464. Brett, P.M.; Curtis, D.; Robertson, M.M.; Dahilitz, M.; and Gurling, H.M.D. Linkage analysis and exclusion of regions of chromosomes 3 and 8 in Gilles de la Tourette syndrome following the identification of a balanced reciprocal translocation 46 XY, t(3:8)(p21.3-24.1) in a case of Tourette syndrome. *Psychiatric Genetics*, 6:99-105, 1996.

465. Boghosian-Sell, L.; Comings, D.E.; and Overhauser, J. Tourette syndrome in a pedigree with a 7;18 translocation: identification of a YAC spanning the translocation breakpoint at 18-22.3. *American Journal of Human Genetics*, 59:999-1005, 1996.

466. Grice, D.E.; Leckman, J.F.; Pauls, D.L.; Kurlan, R.; Kidd, K.K.; Pakstis, A.J.; Chang, F.M.; Buxbaum, J.D.; Cohen, D.J.; and Gelernter, J. Linkage disequilibrium between an allele at the dopamine D4 receptor locus and Tourette syndrome, by the transmission-disequilibrium test. *American Journal of Human Genetics*, 59:644-652, 1996.

467. Eapen, V.; O'Neill, J.; Gurling, H.M.D.; and Robertson, M.M. Sex of parent transmission effect in Tourette's syndrome: evidence for earlier age at onset in maternally transmitted cases suggests a genomic imprinting effect. *Neurology*, 48:934-937, 1997.

468. Furtado, S. and Suchowersky, O. Investigation of the potential role of genetic imprinting in Gilles de la

Tourette syndrome. *American Journal of Medical Genetics*, 51:51-54, 1994.

¹ Disease-Specific Estimates of Direct and Indirect Costs of Illness and NIH Support, Report to Congress. Appendix: "Mental Disorders" (Dept. Of Health and Human Services, NIH, 1995).

² A gene is the basic unit of heredity, and it consists of a specific bit of deoxyribonucleic acid (DNA) that contains the instructions for influencing a specific trait or function. Genes have multiple forms, called alleles. So, technically, what distinguishes monozygotic twins is that they share 100 percent of their alleles; but, throughout this report, the term genes will be used for simplicity.

³ Identification of the exact gene forms, or alleles, in an individual's genome.

⁴ Please visit the NIMH Human Genetics Initiative Website at <http://www-grb.nimh.nih.gov/gi.html> for further information.

⁵ Readers will note that Alzheimer's disease is not included on this list, even though the NIMH Human Genetics Initiative included this severe disorder. Because Alzheimer's disease is effectively supported by other institutes, the Workgroup believes that NIMH funds should be directed at other mental disorders.