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

National Advisory Mental Health Council

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APPENDIX B

NIMH Genetics Workgroup

NIMH Genetics Workgroup

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APPENDIX C

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Roster of Presenters[6]

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[6] The Workgroup appreciates the contribution of the above presenters in developing this report; however, inclusion in the above listing does not necessarily indicate endorsement of the Workgroup's recommendations.

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APPENDIX D

Data and Materials Sharing

high risk of 57% to offspring of ADHD probands has been found in one study [28]. Direct interview of second-degree male:female relatives yielded lifetime rates of 9:0 [27]. Evaluation by family history of second-degree relatives in Biederman et al.'s data set [25] showed that the prevalences of ADHD in aunts:uncles:grandmothers:grandfathers were 4:9:3:5 [29]. Three studies have specifically examined risks to ADHD in relatives of female ADHD probands [18,24,30,31]. The rates of ADHD to sibs of female probands vs. sibs of male probands were 35% vs. 23% [18], 9% vs. 33% [30], and 20 vs. 25% [24,31]. Finally, MZ probandwise concordance rate of 51% and 58% 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 of ADHD between 7% and 10%, the estimated recurrence risk ratios (λ_Rs) for type R relatives of an affected individual are as follows: λ_{MZ} = 3.3, λ_1 = 1.5 - 3.6, and λ_2 = 0.5 - 0.8. If second-degree [27,29] and first-degree [34] relatives are compared to their respective controls (one study [27] found a rate of 0% for ADHD in first-degree relatives), recurrence risk ratios are between 3 and 5 for second-degree relatives and between 3 and 5 for first-degree relatives.

Twin Studies: Two small twin studies found that 4/4 [35] and 3/3 [36] of MZ twins were concordant for ADHD. A larger twin study [33] reported respective MZ and DZ probandwise concordance rates of 51% and 33%, with a heritability estimate of 64%. In a subsequent re-analysis [37] the heritability of mother-reported activity levels was 75%. Respective MZ and DZ probandwise concordance rates of 81% and 29% for ADHD were found in a study of twins who also had reading disability, and heritability was estimated at 98%. A recent study yielded respective MZ and DZ concordance rates of 58% and 31%, with a heritability estimate of 79% [32]. The study of quantitative measures of hyperactivity, activity level, or inattentiveness in several twin samples have yielded estimates of heritability that ranged from 73% to 88% [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 among the natural parents of hyperactive boys when compared with controls [21,44,45].

Mode of Inheritance: Deutsch and colleagues found limited evidence for an incompletely penetrant autosomal dominant single major locus transmission in a small sample [46]. 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% of boys and 31% of girls with the ADHD gene would develop the disorder.

Molecular Genetic Studies: A population-based association study reported evidence of a association between ADHD and an allele at the dopamine D_2 receptor gene on 11q (P = 0.0003) [48], but this has not been replicated and was most likely an artifact of population stratification. The 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]. An association between ADHD and an allele at the dopamine D_4 receptor on 11p was found in a

population-based association study ($P \leq 0.01$) [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]: nine of the 24 were also diagnosed with ADHD. The relevance of this finding to most cases of ADHD is unclear.

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% 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 colobomahas been proposed as a genetic model for ADHD [54]. 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, no or abnormal 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

Adoption Studies: A small number of adopted-away children have been identified [92], but no adoption data have yet been published.

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]. It is unclear to what degree these disparate findings represent different genetic etiologies in different populations of families (locus heterogeneity). Estimates of broad heritability (additive gene effects and shared environment) were 91% - 93%, based on 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 evidence was not inconsistent with the involvement of 2 to perhaps 10 such loci [90]. In summary, the mode of transmission of autism remains unknown and is most likely complex. A subset of familial autism may be caused by a gene on the X chromosome, whereas other cases may be caused by multiple autosomal genes in epistatic interaction.

Molecular Genetic Studies: Several reports in the early 1980's 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]. A population-based association study found evidence for an association between autism and an X chromosome marker; however, the association was not significant after correcting for multiple testing [100]. Analysis of data from 38 multiplex families with autism led to 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 obtained with smaller values; a maximum lod score of 1.2 was obtained with λ_{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 the susceptibility to autism [102]. An association between autism and an allele at the HRAS gene on 11p has been reported in two small population-based association studies; however, in each the statistical evidence was weak (P = 0.05, after correction for multiple tests [103,104]; P = 0.04, no correction for multiple tests [105]). Another weak association (P = 0.03, no correction for multiple tests) was found between autism and the serotonin transporter gene on 17q in a family-based association study [106]. Finally, an association between autism and an extended HLA haplotype B44-SC30-DR4 on 6p has been reported in small samples [107,108]. These finding clearly require replication in other pedigrees.

Animal Studies: No genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (e. g., knock-out and knock-in techniques) have been reported. Development of more robust animal models is needed. 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 YACs from a 2 Mb region from 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 the generation of these cognitive deficits.

Bipolar Disorder

Phenotype. Modern psychiatric nosology follows Leonhard's [110] suggestion to subdivide mood disorders into bipolar disorder--episodes of mania or both mania and depression occur -- and unipolar depressive disorder--only episodes of depression occur. Symptoms of mania include 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 include depressed mood, diminished interest or pleasure in activities, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, excessive guilt, inability to concentrate or act decisively, and recurrent thoughts of death or suicide. Inter-rater reliability is excellent (kappa = 0.83) [111]. Test-retest reliability over a 6 year period is moderate (kappa = 0.60) [112]. Several mental disorders have been proposed as alternate expressions of a bipolar genotype. These include variants of schizoaffective disorder, recurrent unipolar depression, and hypomania (bipolar II disorder) [113-115]. Important considerations regarding these "spectrum" disorders are that familial aggregation is not specific to bipolar disorder [116,117] (i.e., etiologic heterogeneity is likely), and inter-rater reliability is generally less than that for the diagnosis of bipolar disorder proper [111,118].

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

Family Studies. Data from over 40 family and twin studies spanning six decades consistently show that the risk to relatives of affected individuals is greater than the risk to relatives of normal controls [113,119,123-125]. The risks to both bipolar and unipolar depressive disorders are increased in the relatives of bipolar probands, while the first-degree relatives of unipolar depressive probands have a higher rate of unipolar depression only [125-130]. Assuming a lifetime risk of 1%, recurrence risk ratios (λ_Rs) for type R relatives of an affected individual as estimated from epidemiological, family and twin studies of bipolar disorder are as follows: λ_1 = 7, λ_{MZ} = 60 [131]. Reliable estimates are not available for more distantly related 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% to 80% and 0% to 8%, with heritability estimates ranging from 30% to 80%. The respective MZ and DZ probandwise concordance rates in the largest and most methodologically rigorous study [134] were 62% and 8%, with a heritability estimate of 59%.

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]. Segregation analyses provide limited support for major-locus transmission of bipolar disorder in some studies [115,138-140] but not others [141-143]. Familial risks for bipolar disorder are not consistent with single locus models [131,144]. None of the two-locus heterogeneity or epistatic models considered by Rice and Neuman [144] provided a good fit to observed data, but the epistatic models were closest. Multiplicative models involving three or more loci were more consistent [131]. A three-locus symmetric multiplicative model (each locus has an equal effect) offers a good fit to these data, with a locus-specific recurrence risk ratio = 2 [131]. 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 bipolar disorder.

Molecular Genetic Studies: Studies are interpreted in regard to Lander and Kruglyak's thresholds for "suggestive" or "significant" linkage evidence [145]. Several reports by Mendlewicz and colleagues [146] produced sizeable lod scores linking bipolar disorder with color blindness and G6PD deficiency. Others have reported significant evidence for Xq linkage [147,148]. 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 5 Israeli families [151]; however, additional subsequent analysis in 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) was diminished to non-significance when pedigrees were extended and members re-evaluated [154]. Suggestive evidence was found for linkage to 18p [155,156]. Another report found suggestive evidence for linkage about 10 Mb away on 18p, and also found significant linkage evidence to another region about 48 Mb away on 18q; both findings were in 11 "paternally transmitting" pedigrees only (i.e., probands' fathers or uncles were affected) [157]. Analysis of the full data set [157] resulted in less than suggestive evidence for 18q linkage and suggestive evidence for 18p linkage. The interpretation of 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 linkage evidence in this sample [157] is highly dependent on which age correction is employed [160]. Suggestive evidence for a locus on 18q was obtained in association analyses [161]; however, the implicated region was over a 5 Mb region and other markers in-between provided evidence against linkage. This region implicated was at least 15 Mb away from the 18q region for which significant linkage evidence was reported previously [157]. Thus, an 80 Mb region encompassing most of both arms of chromosome 18 has been implicated. At least four non-replications of chromosome 18 linkage have been reported [162-165]. A lod score of 3.41 (genome-wide P value $\approx .04$) was found in 1 of 47 bipolar families for localization to 21q [166]; 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; unfortunately, the strongest evidence of linkage in Detera-Wadleigh et al.'s study [167] was to a region over 15 Mb away from that implicated earlier [166]. Three non-replications have been published [163,164,169]. Significant evidence for 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 linkages to 5p [171], 6p [172], 10q [173], 12q [174], 16p [175], and 22q [176]. Finally, anticipation has been reported [177], but this 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 linkage evidence to date is consistent with susceptibility loci on chromosomal regions 18p, 18q, and 21q; however, the methodological issues discussed above and the existence of nonreplication 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 currently indistinguishable. Suggestive evidence for 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% 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 include depressed mood, diminished interest or pleasure in activities, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, excessive guilt, inability to concentrate or act decisively, recurrent thoughts of death or suicide. Inter-rater reliability varies depending on the number of episodes and severity [111]: single severe depressive episode, kappa = 0.72; single mild depressive episode, kappa = 0.51; recurrent severe depressive disorder, kappa = 0.69; recurrent mild depressive disorder, kappa = 0.37. Reliability over a 6 year period was moderate (kappa = 0.61) [112]. Reliability over a one year period in a nonclinical population is much lower (kappa = 0.34) [181]. Rice and colleagues [112,118,182] formulated a clever approach to use multiple diagnostic assessments over time to model the relationship between clinical covariates and the probability of being a true case. Application to longitudinal data on unipolar depression showed that 96% of subjects initially diagnosed with depression who had 8 symptoms and a history of treatment also had a unipolar depressive diagnosis six years later [112].

Epidemiology. Older Swedish [183], Icelandic [184], and English [185] data are consistent in regard to morbid risks to men (9%-12%); there is less consistency in risks to women (12%-20%) [129]. Results from a national probability sample in the US showed that the lifetime prevalences of a major depressive episode were 13% in men and 21% in women [186]. A recent report of population-based epidemiologic studies using operational criteria and similar methods from 10 countries [121] found that the lifetime rate of major depression varied widely by site, with a range from 2% to 19%; 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% - 23%; men, 1% to 15%. Lifetime rates for the US population were 7% for women and 3% for men (5% overall). Klerman and Weissman [187] reviewed an extensive epidemiological literature and reported that several studies (including most large-scale studies of mood disorders in the US [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; an earlier age of onset in each cohort; an increase between 1960 and 1975 in the rates of depression for all ages; a persistent sex effect, with the risk of depression consistently 2-3 times higher among women than men across all adult ages; and the suggestion of a narrowing of the differential risk to men and women due to a greater increase among young men. Results on secular changes in rates of major depression from 9 cross-national sites showed a significant trend for increasing rates of major depression over time, in addition to an earlier age of onset for younger cohorts [191]. Analyses of data collected in a large sample of the US general population documented an increasing lifetime prevalence of depression in both men and women in more recent cohorts, with a male:female ratio averaged across cohorts of 1.8 [192]. Prevalence estimates ranged from 12% to 33%, depending on diagnostic criteria, in a large population-based study of female twins [193]. Likewise, estimates of lifetime prevalence derived from a large Swedish twin study ranged from 17% to 34% in women and from 8% to 19% in men 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 in lifetime risk to depression, but estimates of lifetime prevalence are highly variable. Three-fold differences averaged across men and women were

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 the generation of these cognitive deficits.

Eating Disorders

Phenotype: Eating disorders usually begin in adolescence or early adulthood and are characterized by gross disturbances in eating behavior. The most common manifestations include 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 include recurrent episodes of binge eating, a lack of control over eating behavior during the eating binges, self-induced vomiting, use of laxatives or diuretics or strict dieting or fasting or vigorous exercise to prevent weight gain, and persistent overconcern with body shape and weight. Inter-rater 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 US population yielded a lifetime prevalence of 0.06% for AN [225]. Other population and archival studies estimate lifetime prevalence as ranging from 0.1% to 0.7% [226-230]. Prevalence estimates of AN in a female twin sample ranged from 0.5% to 3.7%, depending on the phenotypic definition [231]. The incidence of AN in men may be as low as 0.02% [232]. The rate of anorexia nervosa 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%; use of diagnostic interviews resulted in rates of about 1% - 2% [225]. Use of clinician interviews in several studies yielded a prevalence for BN of about 1% to 1.5% [234-238]. The most rigorous epidemiologic studies have reported rates ranging from 1.1% to 4.2% [230,239-241] for female subjects and from 0.1% to 0.5% for male subjects [230,237,241-245]. Classification of probable BN-like syndromes in women increased the lifetime prevalence in one study to 8% [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 for AN of 3.8% in the relatives of AN probands who also had a mood disorder, and a risk of 0% in AN probands without that co-occurring diagnosis [247]. Only one family study of AN could be identified that ascertained subjects through AN probands and employed structured interviewing for all relatives: the risk of AN was 4.1% in first-degree relatives of AN probands, vs. risks of 0% to relatives of affective disorder and mixed disorder probands [248]. The risk of AN to second-degree relatives was 4.0%. Respective risks for AN to relatives of depressed vs. nondepressed AN probands were 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% for BN in first-degree relatives of BN probands, vs. 3.5% in relatives of controls [249]. Other studies have reported a risk of 3.4% but without comparison to a control sample [250], a risk of 2.2% that was not significantly higher than the risk of 0% in controls [251], and a risk of 0% in relatives of BN probands [252]. The lifetime risk for BN among relatives of AN probands was not significantly different from the risks for BN in relatives of controls [248]. Using the above data, and assuming a lifetime rate for AN of 0.1%, risk to MZ twins of 71% (see below), risk to first-degree relatives of 4.1%, and a risk to second-degree relatives of 4.0%, the estimated recurrence risk ratios (λ_R) for type R relatives of an affected individual with

narrowly defined AN are as follows: λ_{MZ} = 710, λ_1 = 41, and λ_2 = 40; however, striking inconsistencies exist (e.g., one twin study found a greater DZ vs. MZ concordance rate [231]).

Using the above data, and assuming a lifetime rate for BN of 3.5%, risk to MZ twins of 23% (associated lifetime prevalence of 2.8% - see below), risk to first-degree relatives of 9.6%, the estimated recurrence risk ratios (λ_Rs) for type R relatives of an affected individual with BN are as follows: λ_{MZ} = 8, and λ_1 = 2; striking inconsistencies also exist (e.g., one family study found no evidence of familial aggregation [251], and one twin study found no differences in MZ:DZ concordance rates [149]).

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

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

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

Molecular Genetic Studies: Only one study could be located. 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 (e.g., 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 one's normal routine or functioning. Obsessions are recurrent and persistent ideas, thoughts, impulses, or images which the individual attempts to ignore or suppress. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession, in order to neutralize or prevent discomfort or some dreaded event. Inter-rater reliability for diagnosing OCD 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 5 US communities, and lifetime rates ranged from 1.9% to 3.3% [262]. The estimate of lifetime prevalence across all 5 sites was 1.8%, 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 re-interview by clinicians of a subset of the population [149].

Family Studies: Early studies of OCD that predated the use of operational criteria showed risks to first-degree relatives that ranged widely from 0.4% to 3.1% [264]; two studies found no increase in familial risk [265,266]. 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 range of risk was from 3% to 35% for narrowly defined OCD. Pooling age-corrected data across studies results in a lifetime risk of 9.21% in relative of OCD probands, and a lifetime risk of 2.2% 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% (range - 21% to 37%) in relatives of OCD probands and 15% in controls. Assuming a lifetime risk of 2% and not counting subthreshold OCD cases as affected, the recurrence risk ratio first-degree relatives is 4.6 (estimates are not available for other relative classes.)

Twin Studies: Sixty-three percent of MZ twins were concordant for OCD in anecdotal reports that did not include DZ twins [275]. The respective MZ and DZ pairwise concordance rates in one study were 33% and 7%, and the heritability was 68% [264]. Two other very small twin studies found no difference in MZ and DZ concordance rates [276,277]. Analysis of a quantitative trait of obsessionalism resulted in a heritability estimate of 47% [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; recessive vs. dominant transmission could not be distinguished.

Molecular Genetic Studies: No significant associations have been detected between OCD and alleles of the serotonin transporter gene and the dopamine D2, D3, D4 and serotonin 2A receptor genes [280-283]. A recent population-based association study found some evidence for an association in men ($P = 0.002$), but not women, between OCD and an allele of the COMT gene on 22q [284].

Animal Studies: No genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (e.g., 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) has onset typically between late adolescence and the mid-30s. The hallmark of the disorder is the presence of recurrent and unexpected panic attacks, which are each characterized by a discrete period--lasting from minutes to hours--of intense fear or discomfort that accompanies several physiological symptoms. These include palpitations, accelerated heart rate, sweating, trembling or shaking, shortness of breath, choking sensations, chest pain, nausea, dizziness, fear of losing control, fear of dying, chills, or hot flashes. 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 inter-rater reliability of a PD diagnosis. PD, agoraphobia, and major depression significantly co-occur [258,286,287]. Panic 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 US population was 1.7%, with a female:male ratio of 2.3:1 [297,298]. However, another large multisite epidemiologic study of the US population using different diagnostic criteria and a structured interview found a two-fold increase in the lifetime rate (3.5%), 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 US population [286]. Epidemiologic data on PD from independently conducted community surveys in 10 countries revealed lifetime prevalences that ranged from 0.4% to 3.5%, 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% in for narrowly-defined PD in women was estimated from a large twin study [299]. 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 utilized structured interviews in direct interviews of relatives [301-306], and the risks to first-degree relatives of PD probands ranged from 4% to 17%. Exclusion of Heun and Maier's study [306], which only reported risks of PD without any other co-occurring mental disorder, results in a range from 8% to 17%. Risks to relatives of controls without mental illness in these studies ranged from 0.8% to 4.2%; thus, ratios of risk in relatives of probands vs. relatives of normal controls ranged from 3.4 to 14.7. Risks to PD of 4% [307] and 7% [308] were obtained in 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 risks of PD in PD probands with or without major depression were 9% and 16%, respectively [309]. A subsequent subdivision of PD probands according to age of onset before or after age 20 led to

dramatic differences in risks for PD in their relatives of 22% and 8%, respectively [310]. One study reported a lifetime risk of PD of 9.5% in second-degree relatives of PD probands [311]. Three studies reported family history rates of PD of 12% [312], 8% [313], and 12.5% [314]. Consideration of 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 in first-degree relatives of about 14%. Using this figure and those from the largest twin study [299], and assuming a population prevalence of 2% to 4% (or 5.7% for MZ twins [299]) the estimated recurrence risk ratios (λ_R(s)) for type R relatives of an affected individual are as follows: $\lambda_{MZ} = 4$, $\lambda_1 = 3.5 - 7$, and $\lambda_2 = 2.4 - 4.75$.

Twin Studies: Four twin studies have been conducted in which concordance rates for PD may be determined. 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]. A subsequent follow-up in one data set [277] using modern criteria 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 reported MZ:DZ probandwise concordance rates of 24:11, with respective heritability estimates of 35% and 46% for a narrow phenotype and a multiple threshold model [299].

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% to 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 AD in agoraphobia probands found no evidence for simple major gene models [314]. Analysis of family data with Class A logistic regression models [322] yielded evidence for vertical transmission and the effect of the sibship environment [323]. A segregation analysis of PD family data resulted in limited evidence for an incompletely penetrant dominant or recessive major gene [324]. Analyses of twin data on quantitative PD symptomatology measures found evidence for nonadditive genetic (dominant or epistasis) 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 (i.e., the same genetic factors are operating in the two sexes) additive genetic effects, dominant genetic factors, individual-specific environmental factors, a special twin environment only for women, 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 (< 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% and 46%, with no contribution from the shared environment [299]. In summary, the mode of transmission of PD remains unknown. Conflicting results may be attributable to methodological differences in family ascertainment, phenotype definition, diagnostic assessment, and data analytic approaches, but may represent true etiologic differences among families (locus heterogeneity). Based on 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 linkage evidence (lod = 2.3) was obtained at a protein marker on 16q [327,328]. 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 (e.g., knock-out and knock-in techniques) have been reported.

Schizophrenia

Phenotype: Schizophrenia is defined by characteristic but nonspecific disturbances in the form of thought, content of thought, perception, emotion, sense of self, volition, social relationships, and psychomotor behavior. Inter-rater 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. These include 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]. Important considerations regarding these "spectrum" disorders are that familial aggregation is not specific to schizophrenia [114-116,340-343] (i.e., etiologic heterogeneity is likely), and inter-rater 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] have also 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: The age-corrected lifetime morbid risk of narrowly defined schizophrenia is consistent world-wide at approximately 1% (range of 0.7% to 1.4% across multiple sites as divergent as Chandigarh, India and Moscow, Russia in the World Health Organization international study) [352]. A greater risk to men has been reported in some studies [353-356] but not others [357]; it is unclear whether these discrepancies represent actual gender differences in some populations, or methodological variation [358]. Lifetime rates may be decreasing in more recently born cohorts [359,360]; however, 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 consistently show that risk to relatives of affected individuals is greater than the risk to relatives of normal controls [362]. Recurrence risk ratios (λ_R(s)) for type R relatives of an affected individual as estimated from averaged morbid risks compiled from family and twin studies in European populations between 1920 and 1987 [363] are as follows: λ_1 = 11, λ_{MZ} = 48, λ_2 = 4.25, λ_3 = 2.

Twin Studies: The median probandwise MZ concordance rate (46%) for schizophrenia is approximately three times the corresponding dizygotic (DZ) concordance rate (14%) in six twin studies published in the last 25 years [364]. 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 as compared to the biologic relatives of control adoptees [342,367].

Mode of Inheritance: Model fitting using schizophrenia twin data from recent studies yielded a heritability of 89%, 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]. Nongenetic factors that influence risk to 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 to the recurrence risks presented above, with a locus-specific recurrence risk ratio = 1.8. In summary, the mode of inheritance is complex and likely involves multiple genes in interaction. The number of susceptibility loci, the disease 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 linkage evidence meeting a genome-wide P value of 5%, corresponding to Lander and Kruglyak's threshold for "significant" linkage evidence [145]. The first study reported linkage to 5q in British and Icelandic pedigrees [376]. However, numerous nonreplications have been published, and a combined re-analysis 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 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 linkage evidence, resulted in diminished evidence [380]. (a genome-wide P value of about 0.13, without adjustment for testing across multiple diagnostic and transmission models.) Suggestive evidence for linkage to 6p was found in another study [381]. Analyses of 713 families contributed by 14 research groups worldwide failed to find more than suggestive linkage evidence to this region [382]. Nonreplications of 6p linkage have been reported [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 if valid, these results would narrow substantially the candidate disease gene region on 6p. Suggestive evidence for linkage to 8p was found in two studies [389,390]; less than suggestive evidence would be obtained if the results in one [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 linkage to 8p [382]. At least one study has failed to find linkage to this region [391]. 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 non-replication has been reported [391]. Suggestive evidence has been found for a schizophrenia susceptibility locus on 22q [394], but 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 linkage evidence [397]. Less than suggestive evidence of linkage to 3p has been reported [398]. 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 [399]. Several population-based association studies have implicated different candidate genes, but nonreplications exist for each [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 linkage evidence to date support the existence of schizophrenia susceptibility loci on chromosomes 6 and 8; however, the magnitude of the statistical evidence and the existence of nonreplication demonstrate that these are clearly not confirmed, convincing findings [404]. The 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, 22) are less compelling.

Animal Studies No genetic studies using selectively bred, recombinant inbred, or transgenic animal strains and gene targeting (e.g., knock-out and knock-in techniques) have been reported. Development of more robust animal models is needed [406].

Tourette's Syndrome

Phenotype: Tourette's syndrome (TS) has onset before age 18 years and is characterized by the involuntary, sudden, rapid, recurrent, nonrhythmic, and stereotyped occurrence of both 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 to also include chronic motor or vocal tics (CT) and obsessive-compulsive disorder (OCD) [407-409], while others expand the phenotype even further to include attention-deficit hyperactivity disorder, panic disorder, 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 is available on test-retest or interrater diagnostic reliability.

Epidemiology: Estimates of the population prevalence (male:female ratio, if available) of TS in studies relying on identified treated cases were 0.046/10,000 in Minnesota [415], 0.50/10,000 (3.5:1) in North Dakota adults [416], and 5.2/10,000 (9.3:1) in North Dakota juveniles [417]. School-based surveys yield much higher estimates, i.e., 23.4/10,000 (8:1) [418]. Community surveys have revealed prevalence rates of 2.9/10,000 in Monroe County, NY [419], 0.7/10,000 in New Zealand juveniles [420], and 4.3/10,000 (1.6:1) in Israeli adolescents [421]. A population prevalence of 5/10,000 is commonly cited [422]. Variability in prevalence estimates 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]. Early family studies that indirectly assessed first-degree relatives of TS probands in a national sample [423] and in consecutive clinical cases [424] each found a recurrence risk of about 2%. Likewise, a risk of 1.5% was observed in relatives of twins assessed via telephone interviews [425]. Subsequent studies that directly assessed relatives yielded much higher estimates. Risks of 18% [426], 21% [427], 27% [428], and 36% [429] to relatives of TS probands have been found in each of three large pedigrees. Inclusion of CT increased the recurrence risk to 46% [428], 30% [426], and 51% [429]. A family study in which all relatives were personally interviewed reported respective age-corrected risks to TS, CT, and OCD of 8.7%, 17.3%, and 11.5% 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]. Nearly a five-fold increase in risk for TS in males vs. female relatives (15:3.4) and over a two-fold difference in risk to OCD in female vs. male relatives (15:7) of TS probands was observed [430]. Assuming a lifetime prevalence of 5/10,000, and a lifetime recurrence risk of between 8.7% and 27% for TS, the respective recurrence risk ratio for first-degree relatives is between 174 and 540.

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

Adoption Studies No adoption data have been reported.

Mode of Inheritance Segregation analysis of single pedigrees 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]. Evidence for autosomal dominant transmission was obtained if the phenotype was defined as TS only, TS or CT, or TS or CT or OCD [407,426]. Two studies could not reject a multifactorial-polygenic model [440,443], and one could not reject a mixed model of inheritance that combined an intermediate major locus and a small but non-negligible multifactorial background [443]. Evidence has also 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 assuming random mating (dominant major locus). A recent study of nonbilineal pedigrees rejected pure multifactorial and single major locus models, and found evidence for a mixed model of inheritance that combined an additive major locus with a multifactorial background [447]. It is unclear if the multifactorial factor presents polygenic or shared additive environmental effects, but it did account for about 40% of the phenotypic variance. In summary, the mode of inheritance of TS is likely complicated by locus heterogeneity and assortitive mating. Conflicting results may be attributable to methodological differences in family ascertainment, phenotype definition, diagnostic assessment, and data analytic approaches, but may represent true differences among families. Based on these data, susceptibility to TS may be influenced by an incompletely penetrant autosomal major gene in some families, and perhaps by multiple genes of varying effect and perhaps shared environmental effects in others.

Molecular Genetic Studies The TS Genetic Consortium has pursued a total genomic search in 11 large families from the US, Canada, the Netherlands, and Norway and tested over 600 genetic markers under the assumptions of genetic homogeneity and incompletely penetrant autosomal dominant single major locus inheritance [448,449]. Over 90% of the genome has been excluded [450]. Comings et al. [451] reported increased homozygosity for the D3 receptor gene, but there has been at least one failure to replicate [452]. A role has been excluded in linkage analysis for several genes involved in catecholamine (D1-D5 receptors, DBH, DAT, TY, and TH genes) [453-457] and serotonin (5HT1A 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. These include a 9p deletion [459], 18q deletion [460], t(7;18) translocation [461], and a 46 XY, t(3:8) (p21.3 q24.1) balanced translocation [462-464]. A positive multipoint lod score of 2.9 was initially obtained on 3p in several pedigrees [462]; however, subsequent analyses using improved map data and additional markers led the authors to conclude that this region is 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 was identified; among the limited number of relatives in the family studied, no one without the translocation was diagnosed with TS [465].

Cosegregation of the translocation with TS could of course be coincidental, especially given that the frequency of a carrier of a balanced translocation in the population is about 1/1,000. Finally, the TDT [49] was used in a family-based association study to identify an association between a specific allele at the D4 dopamine receptor locus and TS (values varied from 0.004 to 0.001 across different disease definitions) [466]; 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 led the authors to conclude that there could be a parent of origin effect on a putative TS gene [467]. A recommendation was made to re-examine family data 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 had been reported earlier [468].

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

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