Genetic Studies of Panic Disorder: A Review

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Background: A review of the studies examining the genetic etiology of panic disorder shows the familial nature of the disorder and demonstrates that the etiology is greatly influenced by genetic factors. Strong evidence for vertical transmission in family studies led to molecular genetic studies, of which association designs appear promising, particularly when based on trait markers.

Data Sources: The MEDLINE and PsycLIT databases were searched for all reports published between 1966 and 2000 containing the keywords *panic, genetic, twin, adoption, linkage, association,* and *QTL.*

Conclusion: We conclude that the multifactorial nature of panic disorder requires a multidisciplinary approach to gain insight into the determinants of the phenotype and the interaction of environmental and genetic factors.

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The role of heredity as a predisposing factor for anxiety disorders was suggested in the late 19th century and has since been investigated in a large number of studies.[1,2] As early as 1895, Freud[3] noted that, in the majority of cases, anxiety neurosis could be explained by libidinal dysregulation, thought to result from frustration of normal sexual behavior. However, in cases without such an etiology, "a hereditary predisposition is usually easy to prove."[3(p113)] The role of hereditary factors in the genesis of neurosis (anxiety neurosis particularly) was subsequently described in 1937 by McInnes.[4] Cohen and White,[5] in their classic 1951 paper on anxiety neurosis, also stressed the high familial prevalence of the syndrome. Nevertheless, up to 25 years ago, etiologic explanations of anxiety disorders were dominated by psychodynamic and learning theory.[6]

Panic disorder is characterized by the occurrence of spontaneous panic attacks, defined as discrete episodes of intense fear or discomfort, together with vegetative complaints such as dyspnea, dizziness, tachycardia, sweating and paresthesias, and cognitive symptoms such as fear of losing control. Although the term *panic disorder* was formally introduced in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (1980) (DSM-III),[7] earlier variants of the disorder can be traced back in the literature at least to the 1860s.[8,9] However, these early accounts lack the clarity and detail of Freud's description of anxiety disorders, which have a fundamental and historical value similar to Kraepelin's classification of schizophrenia and mood disorders.[10] Anxiety neurosis was included in both DSM-I (1952)[11] and DSM-II (1968),[12] which faithfully adhered to Freud's clinical observations, although the reference to a sexual etiology was omitted in DSM-II. As is well-known, in DSM-III (1980)[7] the term *neurosis* was dropped and replaced by specific categories: anxiety neurosis was subdivided into panic disorder and generalized anxiety disorder (GAD). In DSM-III-R (1987),[13] diagnostic criteria for GAD were strengthened to increase clinical validity; also, agoraphobia was primarily considered a complication of panic disorder. In DSM-IV (1994),[14] the subdivision of anxiety disorders into phobias and anxiety states was retained; the latter category now includes panic disorder, GAD, obsessive-compulsive disorder, and posttraumatic and acute stress disorders.[14] Diagnostic criteria for panic attacks have remained largely unchanged, but the presence of psychological symptoms between successive attacks (such as chronic anxiety) is now required to diagnose panic disorder.[15]

Worldwide prevalence estimates of panic disorder are quite uniform: 1% to 3%.[16] Women are affected about twice as often as men.[2,17–19] Panic disorder is most common in the ages 30 to 44 years and is least often observed in the elderly. Panic attacks usually have their onset in young adulthood.[19,20]

Studies investigating the etiology of anxiety disorders such as panic disorder have focused on the possible role of environmental influences (common as well as individual specific) on the one hand and genetic factors on

the other hand. In contrast, Kendler[21,22] emphasized the interaction between genetic, environmental, and developmental influences during the life span in the etiology of psychiatric disorders, in which the pathogenic impact of many environmental risk factors is modulated by genotype. In this way, the identification of genetic factors may increase our understanding of the role of environmental risk factors.[22] Whereas the familial nature of panic disorder has been extensively documented and reviewed, the exact genetic mechanisms that might be involved have not yet been delineated.[1,23]

The influence of heredity on the development and transmission of psychiatric disorders can be investigated with the aid of several complementary study designs. These include

1. Family studies,[23] in which the prevalence of a particular condition is assessed in biological relatives of probands with the disorder and compared with the prevalence in relatives of controls. Family studies, while useful in demonstrating that a condition is familial, cannot, however, reliably differentiate between genetic and environmental influences.
2. Twin studies,[24,25] in which the concordance rate for monozygotic (MZ) twins is compared with that for dizygotic (DZ) twins. If genetic factors are important, the rate of a particular disorder for MZ twins will be significantly higher than the rate for DZ twins.
3. Adoption studies,[26] in which the offspring of an affected parent, adopted and reared by unaffected parents, are compared with children raised by their affected biological parents. These studies are particularly helpful in delineating the impact of environmental factors on the development of the condition under study. Adoption studies in psychiatry are relatively rare,[26] and for panic disorder none has been published. Similarly, although in the well-known Minnesota study[27] twin adoption research has been performed, for panic disorder no such data exist.
4. Linkage studies,[28] in which DNA markers in the genome are examined to determine if they cosegregate with the disorder under study. If a locus conferring susceptibility for the disease is close to a marker locus, recombination between the 2 loci will be rare, and the 2 loci will cosegregate within families. A number of methods have been developed to detect linkage. These methods include classical linkage approaches that require large multigenerational families with many affected family members and sib-pair designs. Sib-pair designs in which extremely discordant or concordant pairs are used are especially powerful for studying quantitative traits.[29–31] Association studies in which candidate genes are explored use case-control designs or family-based association approaches such as triads of patients and their parents.

Each method has its strengths and weaknesses, and some are better suited for the study of complex disorders, which are influenced by multiple genes as well as multiple nongenetic factors.[32–34] In this article, an overview of genetic research (familial, twin, and recent molecular genetic studies) in panic disorder will be presented.

DATA SOURCES

The MEDLINE and PsycLIT databases were searched for all reports published between 1966 and 2000 containing the keywords *panic, genetic, twin, adoption, linkage, association,* and *QTL.*

FAMILY STUDIES

Increased rates of panic disorder have been reported among first-degree relatives of probands compared with relatives of controls (Table 1).[23,35–44] Reported lifetime morbidity risks for first-degree relatives of probands with panic disorder vary between 7.7% and 20.5%.[23,37–40,42,43] In the same vein, Noyes and colleagues,[37,42] using DSM-III criteria, reported that the risk of panic disorder for first-degree relatives of probands with agoraphobia was 7.7% to 8.3%. In studies that included control groups, the lifetime morbidity risk for panic disorder among control relatives ranged between 0% and 4.2%.[23,37,39,40,42,43]

Several studies have been completed that examined the relationship between panic disorder (with or without agoraphobia) and other anxiety disorders, GAD in particular. Skre et al.[44] found an increased prevalence of panic disorder among first-degree relatives of probands with GAD. However, Crowe et al.[40] did not observe such an increase and questioned the involvement of genetic factors in GAD. Results from the studies of Noyes et al.[38] suggest that anxiety disorders are genetically heterogeneous. Rather than representing a continuum, they may constitute distinct entities influenced by unique genetic factors.

Mode of Transmission

As stated earlier, family study data cannot prove the existence of genetic factors, but they can be used to examine whether the pattern of transmission observed within families is consistent with those predicted by specific genetic hypotheses. Several investigators have performed complex segregation analyses to examine specific hypotheses with regard to mode of inheritance. Pauls et al.[45] reported that the transmission of panic disorder was consistent with a pattern predicted by a highly penetrant auto-

Table 1. Family Studies[a]

Study	Date	Diagnostic Criteria	Interview Type	Probands, N	First-Degree Relatives, N	Morbidity Risks in First-Degree Relatives
Raskin et al[35]	1982	DSM-III	Semistructured	17 PD[b]	34[c]	29.3% parental anxiety
				16 GAD	32[c]	29.1% parental anxiety
Crowe et al[40]	1983	DSM-III	Structured	41 PD	278	17.3% for PD
				41 controls	262	1.8% for PD
Leckman et al[36]	1983	RDC	Not specified	56 MD	338	2.1% for PD, 10.7% for MD
				10 MD + AgPh	96	2.1% for PD, 11.5% for MD
				22 MD + PD	133	3.8% for PD, 19.6% for MD
				45 MD + GAD	243	0.4% for PD, 19.8% for MD
				82 controls	521	0% for PD, 5.6% for MD
Harris et al[37]	1983	DSM-III	Structured	20 AgPh	108	7.7% ± 2.5% for PD
				20 PD	101	20.5 ± 3.9% for PD
				20 controls	92	4.2% ± 2.1% for PD
Noyes et al[42]	1986	DSM-III	Structured	40 AgPh	256	8.3% for PD, 11.6% for AgPh
				40 PD	241	17.3% for PD, 1.9% for AgPh
				20 controls	113	4.2% for PD, 4.2% for AgPh
Noyes et al[38]	1992	DSM-III-R	SCID	41 GAD[b]	...	10% for GAD, 1.8% for PD[d]
				71 PD	...	3.8% for GAD, 11.8% for PD[d]
Weissman[23]	1993	RDC	SADS	30 PD	141	10.6% for PD, 8.1% for PD + MD
				77 PD + MD	442	4.7% for PD, 6.7% for PD + MD
				41 MD	209	1.1% for PD, 3.0 for PD + MD
				45 controls	255	0.7% for PD, 0.4% for PD + MD
Maier et al[43]	1993	DSM-III-R	SADS	21 PD	89	7.7% for PD
				19 PD + AgPh	85	8.2% for PD
				80 controls	309	2.3% for PD
Skre et al[44]	1994	DSM-III-R	SCID	33 anxiety disorder[b]	76	43% for anxiety disorder
				20 mood disorders	45	31% for anxiety disorder
				6 substance abuse	13	31% for anxiety disorder
Fyer et al[39]	1996	DSM-III-R	SADS	21 PD + SoPh	76	4% for SoPh, 9% for PD
				39 SoPh	162	15% for SoPh, 2% for PD
				58 PD	236	9% for SoPh, 10% for PD
				77 controls	380	6% for SoPh, 3% for PD

[a]Abbreviations: AgPh = agoraphobia, GAD = generalized anxiety disorder, MD = major depression, PD = panic disorder, RDC = Research Diagnostic Criteria (revised to make DSM-III or DSM-III-R diagnoses), SADS = Schedule for Affective Disorders and Schizophrenia, SCID = Structured Clinical Interview for DSM-III-R, SoPh = social phobia.
[b]No control group.
[c]Data derived only on parental history of anxiety.
[d]Data derived only on family history (parents and siblings).

somal dominant single major locus. These investigators did not examine patterns of transmission predicted by other genetic hypotheses. Later studies suggested that the mode of inheritance is more complex. Crowe et al.[40] tested both single locus models and multifactorial polygenic transmission models and could not exclude either. Vieland and colleagues[46,47] found that both a dominant and a recessive model provided an equally good fit in families of probands with panic disorder, while nongenetic transmission models could be rejected. Recently, Cavallini et al.[48] performed a complex segregation analysis on a sample of 165 families of panic disorder probands as well as on the subgroup of relatives of probands with CO_2 hypersensitivity. Their data, in line with those of Vieland et al.,[46,47] were compatible with a Mendelian model for the transmission of panic disorder, with a best fit for an "additive model": incomplete penetrance of genotypes with additional factors contributing to transmission and gene expression. Furthermore, they showd a difference between families of patients with normosensitive and hypersensitive reactions to CO_2 challenge, respectively, because a Mendelian model with a "dominant model" gave the best fit in families of patients with CO_2 hypersensitivity. In conclusion, family studies have provided ample evidence for vertical transmission of panic disorder; however, the mode of transmission (dominant or additive) has not been established from these data.

TWIN STUDIES

Before the introduction of DSM-III, a twin study by Slater and Shields[49] in anxiety neurosis had shown a considerable difference in concordance rates between MZ and DZ twins (41% vs. 4%). Since 1980, a number of twin studies have been reported that specifically examined the genetics of panic disorder (Table 2).[49–56] Concordance rates for MZ twins were at least 2.5 times higher than those for DZ twins, supporting the role of genetic factors in the etiology of panic disorder. In the same vein, Martin et al.[55] estimated that 33% of the variance of liability to panic symptoms (palpitations and feelings of panic) could be explained by genetic factors. It should be noted, however,

Table 2. Twin Studies[a]

Study	Date	Diagnostic Criteria	Interview Type	Twin Pairs, N	Diagnosis of Probands	Concordance Rate, % Monozygotic	Concordance Rate, % Dizygotic	Estimates of Heritability	Model of Best Fit
Torgersen[52]	1983	DSM-III	PSE	85	PD	31	0		
Kendler et al[53]	1986	None	Mailed questionnaire	3798	Symptoms of anxiety and depression	...	...	0.33–0.46	Additive genes and individual-specific environment
Martin et al[55]	1988	None	Mailed questionnaire	2903	Neuroticism with physical symptoms	...	...	0.33	Nonadditive genes
Skre et al[56]	1993	DSM-III-R	SCID	49	PD	42	17		
Kendler et al[54]	1993	DSM-III-R	SCID	1033	PD			0.32–0.46	Additive genes and individual-specific environment
Kendler et al[50]	1995	DSM-III-R	SCID	1030	Phobia	...	...	0.35* 0.63†	*Additive genes and †individual-specific environment
					GAD	...	...	0.32* 0.66†	
					PD	...	...	0.44* 0.55†	
					Bulimia	...	...	0.30* 0.29†	
					MD	...	...	0.41* 0.55†	
					Alcoholism	...	...	0.59* 0.37†	
Perna et al[51]	1997	DSM-IV	No	60	PD	73	0		
					SPA	57	43		

[a]Abbreviations: GAD = generalized anxiety disorder, MD = major depression, PD = panic disorder, PSE = present state examination, SCID = Structured Clinical Interview for DSM-III-R, SPA = sporadic panic attacks.

that the concordance rates for MZ twin pairs in these twin studies were always less than 1 and in most cases, 40% or lower. Thus, common and individual-specific environmental factors appear to be at least of equal importance in the etiology of panic disorder.[56] On the basis of clinician-made diagnoses, Kendler et al.[50,53,54] estimated the hereditary factor of liability to panic disorder to be about 40%. Familial environmental factors could not or could only weakly explain the development of symptoms,[50,53,55] but individual-specific environmental factors appeared to be of importance in the etiology of panic disorder.[52–55]

In their twin study, Perna et al.[51] compared the MZ/DZ ratio in panic disorder with that in sporadic panic attacks. Their results showed no significant difference in concordance rates between MZ and DZ twins in sporadic panic attacks, whereas a highly significant difference (73% vs. 0%) was found in panic disorder, implying that genetic factors may not be relevant in the etiology of sporadic panic attacks.

Several twin studies have also investigated GAD. Torgersen[52] reported an increased MZ/DZ ratio for all DSM-III anxiety disorders except GAD. In contrast, both Kendler et al.,[57] in their population-based twin study, and Skre et al.[56] concluded that there is a genetic contribution in the etiology of GAD, although no significant difference was found between the concordance ratios of MZ and DZ for GAD in either study. In conclusion, although twin studies have supported the hypothesis of the hereditary nature of panic disorder, the evidence for GAD is equivocal, suggesting etiologic differences between the two disorders. This notion is supported by data from Martin et al.,[55] which indicate that unique genetic influences exist for panic symptoms that do not affect other anxiety symptoms.

MOLECULAR GENETIC RESEARCH

Linkage Studies

Molecular genetic techniques allow the identification of highly polymorphic markers on nearly any chromosomal region. These markers can be examined to determine if linkage exists between a disease gene and a chromosomal region. This technique has become extremely successful for finding genes in autosomal dominant or recessive and X-linked disorders. However, linkage studies have not been very successful in helping to identify genes for psychiatric disorders: since most psychiatric disorders are presumed to be multifactorial, gene localization becomes increasingly difficult.[58]

Whereas it is highly likely that the genetic mechanisms underlying panic disorder are complex, results from early complex segregation analyses have suggested that the underlying genetic mechanisms might involve genes of major effect.[40,45] Thus, several linkage studies were undertaken. Crowe et al.[59] tested for linkage between panic disorder and 29 genetic markers in 26 families and found evidence suggestive of linkage with the alpha-haptoglobin locus on chromosome 16q22. Unfortunately, a replication study did not support the presence of a disease gene for panic disorder closely linked to this locus.[60]

Fyer and Weissmann[61] completed a first-pass genome scan for panic disorder, excluding linkage with circa 95% of the genetic length of the autosomes, for a homogeneous dominant model with reduced penetrance and with circa 60% for a homogeneous recessive model with reduced penetrance. These authors did, however, find evidence for linkage with a marker on chromosome 20p.[62]

In the same series of pedigrees, they examined the parent-of-origin effect, the pattern of maternal versus paternal transmission of panic disorder, and found a significant difference for the affected offspring of transmitting mothers (but not transmitting fathers) in the frequency of affected females compared with males greater than the expected 2:1 ratio.[17] Although these results have not yet been replicated, they suggest that the increased female/male ratio in panic disorder may be hereditary.

Other researchers have concentrated on candidate genes assumed to be pathogenetically relevant for panic disorder.

γ-Aminobutyric acid (GABA) is one of the most important presynaptic and postsynaptic inhibitory neurotransmitters in the human brain. Anxiolytic drugs such as benzodiazepines are known to change the $GABA_A$ receptor conformation; moreover, in a positron emission tomography study using a labeled benzodiazepine-receptor ligand, benzodiazepine binding sites were found to be reduced in panic disorder.[63] In view of the possible relevance of the $GABA_A$ receptor for the pathogenesis of panic disorder, a linkage study[64] of 5 pedigrees was undertaken in which linkage to the gene coding for this receptor was examined. No evidence for linkage was observed. Also, the results of a later study[65] from the same group that tested 8 of 13 subunits in the $GABA_A$ receptor gene failed to prove linkage. Similar negative results were reported for the association between panic disorder and 5 adrenergic receptor loci[66] and a candidate gene coding for pro-opiomelanocortin,[67] which is involved in synthesis of corticotropin. Finally, although selective serotonin reuptake inhibitors have been highly successful in the treatment of panic disorder, no linkage was found between panic disorder and functional polymorphism in the promoter region (preceding chromosomal region) of the gene coding for the serotonin transporter protein.[68]

In conclusion, linkage research in panic disorder has yielded mostly negative results. This may point to a multifactorial transmission mode of panic disorder, although methodological issues may have been responsible as well.[61]

Quantitative Trait Loci

Complex traits such as panic disorder could involve a number of additive genes, each with relatively small effect.[69] Methods have been developed that allow the identification of quantitative trait loci (QTLs). QTLs are genes that may be neither necessary nor sufficient in the etiology of the trait,[32] but do account for some of the phenotypic variance for the condition observed in the population. Large numbers of families are needed to detect linkage between a QTL and a marker, especially if the variance of the QTL is low relative to the total phenotypic variance of the trait.[33,70] Increased statistical power can be achieved in different ways, e.g., the use of a sib-pair approach instead of large pedigrees,[33,69] selective genotyping of extreme phenotypes,[31] interval mapping,[71] and statistically decreasing environmental variance by using an estimate of an individual's genotypic value at a QTL.[70,72] Sib-pair linkage designs are more robust than traditional pedigree studies, because they do not depend on a priori assumptions about mode of inheritance.[32,33,69] This robustness, however, comes at the cost of a decrease in statistical power. Sib-pair linkage designs are based on the hypothesis that under linkage to a marker locus or QTL, differences between siblings in their phenotypes will decrease in accordance with greater similarity at the marker locus.[32] Kruglyak et al.[73] propose a unified approach for both parametric and nonparametric methods for linkage analysis. At the present time, this approach has limited applicability for the study of panic disorder and other psychiatric disorders, because it is best suited for those conditions in which the trait being studied is quantitative. As most studies of panic disorder rely on categorical diagnoses, either much larger samples will be necessary to achieve adequate statistical power, or different assessment methods will need to be employed that will allow a quantification of the trait. Sib-pair collection strategies for complex diseases are described by McCarthy et al.[74]

Association Studies

For disorders of unknown mode of transmission in which several loci may be involved, an alternative or complementary strategy is to search for allelic association. In association studies, the frequency of marker genotypes in a sample of patients is compared with the frequency in a control sample. Although linkage studies remain the strategy of choice for detecting genes of moderate-to-large effects, allelic association studies may be more useful for detecting genes of small effects.[30,32,58] A considerable disadvantage of association studies is the high probability of false-positive results. As there is a large number of potential candidate loci and a low a priori probability that a given candidate locus will in fact be trait relevant, many tests are performed, increasing the risk of type II errors. Also, a case-control design increases the probability that false-positive results will be obtained because of population stratification.[75] Population stratification results from cases and controls that are not perfectly matched for ethnicity. Although there are safeguards that can be employed, this caveat needs to be kept in mind when evaluating association studies.

Family-based association studies with parental control groups may overcome the problem of stratification of qualitative traits. For mapping qualitative trait loci, Fulker et al.[76] described the advantages of the combined linkage and association tests for quantitative traits in sib pairs. Such a design consists of simultaneous testing for linkage, using so-called multipoint identity by descent information, and association, using a decomposition of

the mean phenotype into allelic effects between and within families. Sib-pair covariances are modeled for tests of linkage. Partitioning the mean effect of a locus into a between- and within-sibship component controls for spurious associations due to population stratification and admixture. A test of the within–sib-pair association parameter yields a robust test of association while controlling for stratification. If this parameter is significantly different from zero, a true association has been found.

For panic disorder, a number of association studies have been published. As was described for linkage research, association studies have focused on genetic loci coding for proteins incorporated in neurotransmitter systems assumed to be relevant for panic disorder. These include serotonergic, cholecystokinergic, and noradrenergic systems. With regard to the serotonergic system, neither linkage nor association techniques have been able to prove a relationship between functional promoter polymorphism of the serotonin transporter and panic disorder.[68,77] The *Drosophila* white gene is involved in the cellular uptake of tryptophan, the precursor of the neurotransmitter serotonin. Polymorphisms in its human homologue gene, mapped on chromosome 21q22.3, have been identified. Associations were found between these polymorphisms and mood disorders as well as panic disorder in males.[78] Han et al.[79] screened 93% of the coding region of the tryptophan gene by polymerase chain reaction single-strand conformation polymorphism in several psychiatric populations in which serotonin dysfunction has been implicated. No association was found.

Cholecystokinin (CCK) is a neuropeptide present in the gastrointestinal tract and cerebral cortex, where it acts as a neurotransmitter. Both the tetrapeptide and pentapeptide forms (CCK-4 and pentagastrin) are known to induce panic attacks in patients with panic disorder at a lower dose than in normal controls. The hypothesis that a mutation in the gene that codes for the CCK_B receptor could increase the affinity of the receptor for CCK and predispose one to panic disorder has been the starting point of various association studies. Kato et al.[80] investigated the CCK_B receptor gene as a candidate gene for panic disorder, but the mutation found was neither associated with nor linked to the illness. A more recent analysis of the CCK gene from the same group[81] revealed a point mutation of the promoter region in 33% of 48 patients with panic disorder, compared with 16% of controls. Kennedy et al.[82] could not replicate this association.

Garvey et al.[83] reported that serum levels of the enzyme *N*-acetyl-β-glucosaminidase, believed to be a marker for serotonergic activity, were higher in panic disorder patients with a CCK mutation than in patients without such a mutation. The authors interpreted these findings as evidence for 2 panic disorder subtypes, characterized by cholecystokinergic and serotonergic dysregulation, respectively.

Two studies, both by Deckert and coworkers,[84,85] have investigated genetic aspects of noradrenergic function. In one study,[84] these authors showed a significant increase of functionally active monoamine oxidase A gene promoter alleles (3a, 4, or 5) in female patients with panic disorder as compared with controls. No significant differences were found between male patients and controls. Although not yet replicated, these results are of interest in view of the reported clinical efficacy of monoamine oxidase inhibitors in the treatment of panic disorder.[86] Caffeine, an adenosine receptor antagonist, is able to induce panic attacks in panic disorder patients, possibly by blocking adenosine-mediated inhibition of norepinephrine release. This finding suggests that dysregulation of the adenosine system may be involved in the etiology of panic disorder. Results by Deckert et al.[85] showed linkage between the A_{2a} adenosine receptor gene and panic disorder, whereas they failed to provide evidence for an involvement of the A_1 adenosine receptor gene.

Finally, panic disorder as well as other anxiety disorders have recently been found to be significantly associated with low voltage electroencephalogram (EEG) characteristics.[87] A gene responsible for about one third of the cases of low voltage EEG was genetically mapped to 20q13.2-q13.3.[88] In the same chromosomal region, the gene for neuronal nicotinic acetylcholine receptor α4 subunit (CHRNA4) has been located. Steinlein et al.[89] investigated the association between CHRNA4 polymorphisms and panic disorder, but no significant differences in the allele frequencies were noted.

Thus, in contrast to linkage studies, association studies have yielded some promising results in investigating the genetic background of panic disorder, supporting a multifactorial mode of inheritance.

COMORBIDITY

The above reviewed findings for panic disorder are not unlike those for other psychiatric disorders—substantial evidence suggests that genetic factors are important for the manifestation of the condition, but the exact mode of transmission is still unclear. One possible explanation is that our understanding of the inherited phenotype is still incomplete, diagnostic refinements in successive editions of the DSM notwithstanding. Epidemiologic and clinical studies have shown a high frequency of comorbidity in panic disorder, especially for GAD and major depressive disorder (MDD). As noted by Rutter,[58] a full insight in the etiology of a disorder may not be achieved by investigating only "pure" cases, because these may represent an atypical minority subgroup. Neale and Kendler[90] developed several models for comorbidity between multifactorial disorders and stated, "Perhaps the most fundamental issues are at the nosological level: are 2 disorders distinct, or do they reflect an arbitrary division of a single syn-

drome? Conversely, might persons comorbid for disorder A and B actually have a third disorder independent from A and B?"[p935] As we have seen, the division of anxiety neurosis in panic disorder and GAD has received support from family and twin studies. However, 2 other syndromes often antedate and coexist, respectively, with the disorder: separation anxiety disorder and MDD.

Panic Disorder and Childhood Separation Anxiety Disorder

Klein[91] hypothesized an etiologic relationship between early separation anxiety and adult panic disorder. The finding that imipramine-responsive adult agoraphobic states were historically linked to a childhood history of separation anxiety led to a trial of imipramine in a childhood population with school phobia. A double-blind, placebo-controlled study of children with school phobia[92] supported Klein's hypothesis: imipramine was found to be significantly superior to placebo. However, subsequent research by the same group[93] failed to replicate previous findings of imipramine efficacy.

A number of other studies have also suggested a relationship between panic disorder and separation anxiety in childhood. Battaglia et al.[94] reported a significantly higher rate of childhood separation anxiety among patients with panic disorder when compared with controls. These investigators concluded that separation anxiety disorder was an individual predictor of early-onset panic disorder, which was found to be associated with a stronger genetic component. The latter finding was corroborated by Goldstein et al.,[95] who compared adult first-degree relatives of probands with panic disorder onset before or after 20 years of age and found a 17-fold and 6-fold increased risk, respectively, to develop panic disorder compared with controls. Ayuso et al.[96] also reported an increased frequency of separation anxiety disorder among patients with panic disorder when compared with controls. The presence of separation anxiety disorder in childhood was, however, not found to be significantly correlated to the severity of panic disorder in adults. Finally, studies by Silove et al.[97–99] also supported the developmental link between early separation anxiety and panic disorder. It should be noted, however, that panic disorder patients meet criteria for other childhood anxiety disorders more frequently than controls as well; conversely, separation anxiety disorder may also predispose to other adult anxiety disorders such as GAD.[35,100,101] The occurrence of "true" panic attacks in preadolescent children has long been the subject of controversy.[102] Moreau and Weissman[103] concluded in their review on panic in children and adolescents that strong evidence exists for the occurrence of childhood panic attacks with symptoms that are similar to those found in adults and qualitatively distinct from those in separation anxiety disorder.

In conclusion, separation anxiety disorder is not a specific precursor of panic disorder; consequently, in DSM-IV the relationship between separation anxiety and panic disorder has received less emphasis. Final conclusions concerning the frequency of panic attacks in children must await prospective, longitudinal, epidemiologic, and genetic research.[103–105]

Panic Disorder and MDD

Panic disorder and depression have often been found to be associated,[20,23,36,106–112] although findings have sometimes been inconsistent. Weissman et al.[113] reported an increased risk for both anxious and depressive symptoms among offspring of anxious and depressed parents. However, later results[23] suggested that the transmission of panic disorder and MDD was independent, although there was substantial co-occurrence of these disorders in affected individuals. In contrast, a twin study suggested that MDD with comorbid anxiety is genetically related to MDD but not to other anxiety disorders.[107] Thus, genetic factors appear to be more important in mixed cases than in cases of MDD alone, suggesting a partially shared common diathesis. Findings of Leckman et al.[36] were consistent with these results. Relatives of probands with depression and anxiety were more than twice as likely to have anxious and depressive symptoms than the relatives of probands with depression only. Maier et al.,[114] in their family study, compared 4 proband groups (panic disorder, unipolar depression, comorbid panic disorder and unipolar depression, and healthy controls) and found only a modest overlap of familial components, suggesting that the comorbidity between panic disorder and MDD is largely due to nonfamilial factors. These investigators[43] concluded that in addition to MDD, etiologic factors underlying panic disorder may also overlap with those of alcoholism. However, these findings were not supported in a family study by Goldstein et al.,[110] who did not find evidence for a common genetic etiology of panic disorder and other psychiatric disorders. It should be noted that a shared genetic contribution for GAD and MDD has been reported as well,[109] although the development of either MDD or GAD was suggested to be the result of individual environmental factors. Thus, these genetic factors appear to be largely nonspecific.[108,109]

In conclusion, genetic data with regard to panic disorder and MDD have been inconsistent, although there is some evidence for a shared diathesis for comorbid anxiety and depression.

DEFINITION OF PHENOTYPE: TRAIT MARKERS

As illustrated by the work on comorbidity, it has been debated whether the concept of panic disorder should include comorbid depression and/or generalized anxiety, or preexisting separation anxiety. One of the most basic problems in genetic research of psychiatric disorders is the defi-

nition of the phenotype.[90,115–117] Although the use of empirically derived, uniform criteria in DSM-III and its successors has improved diagnostic reliability, this does not imply syndromal validity, let alone etiologic specificity.[26,58] Family, adoption, and twin studies may still have much to contribute in refining our understanding of inherited phenotypes, which in turn will benefit molecular genetic research. In addition, longitudinal studies need to be undertaken to investigate phenotype changes over development.

A related issue concerns the use of categorical versus dimensional criteria. Most genetic research in panic disorder has relied on categorical definitions; however, in research designed to assess the contribution of specific genetic factors, continuous and multidimensional measurements are needed.[118] To maximize the likelihood of identifying genetic factors that influence anxiety disorders, a genetic nosology is necessary,[115,116] taking in account non-Mendelian inheritance: the possibility of phenocopies, variable expressivity, and incomplete penetrance.

In addition, investigation of possible trait markers—biological or psychological—may contribute to a more etiologically based definition of the disorder. As noted earlier, a large number of biological markers for panic disorder have been proposed, mostly based on results from challenge studies, implicating noradrenergic, serotonergic, GABAergic, and cholecystokinergic neurotransmitter systems,[119] while others have proposed a dysregulation of the hypothalamic-pituitary-adrenal axis.[105,120] Finally, CO_2 hypersensitivity has been suggested to be a "trait" marker of panic disorder, representing an underlying vulnerability.[121] This trait was explained by Papp et al.[122] to be due to an inherently unstable autonomic nervous system, while Klein[123] proposed a "false suffocation alarm." Although a single biological theory accounting for all challenge data does not yet exist, this CO_2 hypersensitivity model represents the most comprehensive hypothesis so far and has generated extensive research. In support of Klein's theory, Horwath et al.[124] in their family study reported a specific genetic contribution to respiratory symptoms in panic disorder.[48,122,125–130] In the same vein, Bellodi et al.[125] found a significantly higher concordance for 35% CO_2-induced panic attacks among MZ than DZ twins (55.6% vs. 12.5%). Finally, Perna et al.,[127] in their sample of family history data of 203 patients with panic disorder, found a significantly higher genetic risk in patients with a positive response to 35% CO_2 challenge than in nonresponding patients, supporting the notion that hypersensitivity to CO_2 is associated with a subtype of panic disorder with a greater familial loading.

Apart from biological markers, psychological traits may also be characteristic for panic disorder, particularly fear of anxiety-related symptoms as measured with the Body Sensations Questionnaire[131] or the Anxiety Sensitivity Index.[132] Recently, Stein et al.[133] in their twin study showed that the concordance rate for anxiety sensitivity was greater in MZ than in DZ twins, suggesting that cognitive risk factors for panic disorder may have a hereditary component.

CONCLUSION

Genetic factors are important in the expression of panic disorder. Increased morbidity risks have been shown in family studies, a finding that has generally been confirmed in twin studies, despite methodological differences between individual studies such as evolving diagnostic criteria. Still, it is possible that increased consistency in study design due to collaboration between different research groups may contribute to a better understanding of the etiologic mechanisms involved.[134]

Although results from family studies indicate a multifactorial mode of inheritance, the specific genetic mechanisms involved are not yet known. Early linkage studies based on single-gene models have yielded negative results, whereas association studies with candidate genes implicating various neurotransmitter systems have been somewhat more successful. However, these data clearly need further empirical confirmation. Studies on comorbidity have indicated that separation anxiety is not a specific precursor of panic disorder, although childhood anxiety disorders may be associated with early-onset panic disorder, which may have a stronger hereditary component. GAD is probably not related genetically to panic disorder, although there is some evidence for a shared diathesis for comorbid anxiety/depression. Finally, the use of quantifiable traits (biological or psychological) for molecular genetic research is promising, as witnessed by the family and twin studies using carbon dioxide hypersensitivity or anxiety sensitivity as illness markers.

Notwithstanding the exciting developments in recent genetic research, environmental factors have to be kept in mind, as demonstrated by the MZ concordance rate found in twin studies: an integration of genetic and environmental epidemiologic strategies is essential.[21] This might be achieved in twin adoption studies, for example, or by documenting both psychologically developmental and neurobiological processes in future research.[135]

Until now, no longitudinal family or twin studies have been carried out.[58] Prospective longitudinal research from childhood into adulthood may provide further insight into the complexity of interactions between genetic and environmental factors and changes during development.[136] Genes can modify the vulnerability of an individual to the disease-predisposing effects of the environment ("genetic control of sensitivity to the environment"). On the other hand, gene expression may be variable over the life cycle, with genes switching "on" and "off."[21,25] Assuming that interactions between genes and the environment are not static, longitudinal strategies are of importance. Apart

from the need for longitudinal research to gain insight into the pathogenesis of psychiatric disorders, Kendler[22] also stressed the necessity of multidisciplinary collaboration of clinical psychiatry, molecular genetics, statistical genetics, and epidemiology. Thus, a longitudinal sib-pair study, including quantitative as well as qualitative measures, is a promising possibility in future research of panic disorder.

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