Are there anxious genes?

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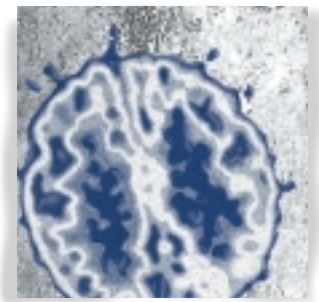

Anxiety comprises many clinical descriptions and phenotypes. A genetic predisposition to anxiety is undoubted; however, the nature and extent of that contribution is still unclear. Methods for the genetic analysis of such complex disorders is briefly reviewed, followed by a discussion of the comorbidity of anxiety with other psychiatric disorders and their possible common genetic etiology. Extensive genetic studies of the serotonin (5-hydroxytryptamine, 5-HT) transporter (5-HTT) gene have revealed how variation in gene expression can be correlated with anxiety phenotypes. Complete genome-wide linkage scans for panic disorder (PD) susceptibility genes have suggested a locus on chromosome arm 7p, and association studies have highlighted many candidate genes. A highly significant association between phobias, panic disorder, and a duplication at chromosomal region 15q24-26 is one of the most exciting findings to date. Emerging molecular genetic technologies and the use of increasingly sophisticated animal models of anxiety provide great promise for the future of the field.

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Anxiety is part of the normal human experience. We may speculate that it served human survival during evolution by enhancing preparedness and alertness. However, anxious manifestations are abnormal when they are exaggerated in excess of any objective danger that the individual is facing, when they induce psychological distress or physical ailments, or when they are self-aggravating in a vicious circle. As a subject of clinical diagnosis, anxiety may be chronic, for instance, in some types of personality disorder or in generalized anxiety disorder (GAD); in such cases, it is akin to a "trait." In other instances, anxiety is a short-lived, noncontinuous, discrete symptom, for example, in panic disorder (PD) or in acute stress; then it is a "state," rather than a trait. Anxiety comprises many phenotypes and clinical descriptions. It is routinely partitioned into disorders of general anxiety, panic, phobia, and in some classifications, obsessive-compulsive disorder (OCD); and the lifetime prevalence for the group of disorders has been estimated to be as high as 25%.[1] Even this classification does not go far to encompass the complexity of anxiety, and hence the arduousness of the task of getting at its biological root. The success to date has not been overwhelming; however, some recent studies have provided more hope than was in the past thought to be realistic. OCD is sometimes classified with anxiety (eg, in the *Diagnostic and Statistical Manual of Mental Disorders* [*DSM*]) and sometimes not (eg, in the *International Statistical Classification of Diseases, 10th Revision* [*ICD-10*]). Attempts to unravel the genetics of OCD are numerous and would be best served in a treatise of their own, and so will not be included in this review. Since many genetic studies on anxiety have been performed

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Selected abbreviations and acronyms

AR	*adenosine receptor*
DZ	*dizygotic*
GAD	*generalized anxiety disorder*
5-HT	*5-hydroxytryptamine (serotonin)*
5-HTT	*5-hydroxytryptamine transporter*
MZ	*monozygotic*
PD	*panic disorder*

on PD and, possibly as a direct result thereof, the most enlightening results to date have been found for PD, a proportionate amount of this review will concentrate on the findings in PD. The aim of this review is by no means to overstate the role of genetics in anxiety, rather to highlight the evidence that exists for the role of genetics in anxiety.

The term "complex trait" has been coined by geneticists to refer to any phenotype that does not exhibit classic mendelian recessive or dominant inheritance attributable to a single gene.[2] In general, complexities arise when the simple correspondence between genotype and phenotype breaks down, because either the same genotype can result in different phenotypes (due to the effects of chance, incomplete penetrance, environment, or interactions with other genes), or different genotypes can result in the same phenotype (eg, phenocopies, due to environmental or random causes). In fact, most traits of medical relevance, and particularly psychiatric disorders, do not follow simple mendelian inheritance. During the last decade, geneticists have taken up the challenge of the genetic dissection of complex traits.

The usual path taken to the elucidation of the genetic basis of psychiatric and other complex disorders is becoming fairly routine. Before undertaking studies aimed at genetic dissection, particularly at the molecular or DNA level, one would ideally like to infer as much as possible about the genetic basis of the trait on the basis of the pattern of disease incidence in families and populations. Hence, first we need evidence for a genetic component to anxiety. A genetic contribution to psychological traits and psychiatric disorders is not in doubt, but the nature and extent of that contribution is still unclear. Genetic epidemiology has assembled convincing evidence that anxiety and related disorders are influenced by genetic factors and that the genetic component is highly complex. While studies of the patterns of inheritance of personality indicate that various dimensions are likely to be influenced by many genes and quantitative traits, it also documents the significance of environmental factors. As the modes of inheritance of anxiety disorders are complex, it has been concluded that multiple genes of small effect, in interaction with each other and with nongenetic neurodevelopmental events, produce vulnerability to the disorder.

Segregation analysis involves fitting a general model to the inheritance pattern of a trait in pedigrees. The only opportunity to examine the expression of a human trait in a fixed genetic background comes from the study of monozygotic (MZ) twins.[3] The absolute risk to an MZ twin of an affected individual provides a direct estimate of penetrance for a given environment. Twin studies generally compare the similarity between identical (MZ) and fraternal (dizygotic [DZ]) twins. DZ twins share on average only half of their genes, as do normal sibs. A higher correlation between MZ than between DZ twins indicates a genetic influence on the trait under investigation. Twin studies of self-reported symptoms of anxiety, often called negative emotionality or neuroticism, consistently indicate that approximately 50% of the variance can be attributed to genetic factors.[4-6]

Tools of the trade

The methods available for the genetic dissection of complex traits, which will be referred to at various stages throughout this review, are linkage analysis, allele-sharing methods, association studies in human populations, and genetic analysis of large crosses in model organisms such as the mouse. For the purposes of this review, I will briefly summarize the methods; however, more detailed accounts abound in the literature.[2,6,7] Linkage analysis is a form of genetic mapping that is used to find the approximate chromosomal location of a putative gene. Linkage studies are based on the identification of large families with many affected members and one is required to specify a mode of inheritance for the disorder. The inheritance of the disorder in the family is then compared with the allelic inheritance of known sections of DNA known as polymorphic markers. The coinheritance, or linkage, of a particular marker allele with the presence or absence of the disorder allows one to define or narrow down the location of the suspected gene. Thus, linkage analysis allows one to find out where a gene is, without knowing what it is. A gene can then be isolated, based solely on its chromosomal location, without regard to its biochemical function, this being known as "positional cloning."[8]

In allele-sharing methods of analysis, one checks whether or not the inheritance pattern of a chromosomal region is consistent with random mendelian segregation. If not, patients and their affected relatives will inherit identical copies of DNA markers within that chromosomal region more often than expected by chance. Since allele-sharing methods are nonparametric (that is, they assume no model for the inheritance of the trait), they tend to be more robust than linkage analysis, particularly for complex disorders, for which the inheritance pattern is not clear. Association studies are case-control studies based on a comparison of unrelated affected and unaffected individuals from a population. An allele of a gene of interest is said to be associated with the trait if it occurs at a significantly higher frequency among affected compared with control individuals. Familial inheritance patterns are irrelevant to the method, however, the choice of the control group and its match to the patient group is vital to the study. Population associations between a genetic marker and a phenotypic trait can arise either from population stratification (ie, ethnic differences, and hence different allele frequencies between populations) or genetic transmission. A refinement of association studies is to use family trios (a patient and his or her parents) or sibling pairs, in an attempt to eliminate problems of population stratification. Association studies have most been applied to genes or DNA markers linked to genes proposed as candidates for a particular trait. Experimental crosses of mice and rats offer an ideal setting for the genetic dissection of mammalian physiology. With the opportunity to study hundreds of meioses from a single set of parents, the problem of genetic heterogeneity disappears, and far more complex genetic interactions can be probed than would be possible in human families. Animal studies relating to anxiety will be described in more detail in the final section of this review.

One way to undertake genetic studies of psychiatric illness is to find a classification that might relate more directly to the inheritance pattern. The ideal would be to find pedigrees in which the disorder segregates in a strictly mendelian fashion, as a recessive or dominant. Although these families may not be phenotypically typical of the disorder, there would be good chance of finding genetic linkage and the first step towards isolating an abnormal gene. This gene and its product may provide a clue as to the type of pathway or mechanism causing the disorder. Unfortunately, such families are not abundant. An alternative is to find other genetically determined features that predispose to psychiatric illness, for example, the deletion of chromosomal region 22q11 has been shown to be associated with an increased risk of developing a psychotic illness.[9] The recent findings of the duplication of part of chromosome 15 in patients with anxiety disorders,[10] described later in this review, has caused great excitement and hope for workers in the field.

Comorbidity of anxiety with other psychiatric disorders

The comorbidity of anxiety disorders with each other and with other psychiatric disorders,[11] particularly mood,[12] has been observed and accepted for many decades. It is known that patients with major depression invariably show either syndromal comorbidity of one or another anxiety disorder or clinically significant severity of anxiety symptoms.[13] Also, the efficacy of many major psychotropic drugs in the treatment of depression and a broad spectrum of anxiety disorders, eg, GAD, PD, social anxiety disorder, and posttraumatic stress disorder (PTSD), is well established. However, wherever possible, mood and anxiety have been separated and delineated into different disorders.

Evidence for a common genetic etiology for bipolar disorder and PD came from a family study[14] in which an unusually high prevalence of PD in 57 families with high rates of bipolar disorder was reported. Families at high risk of PD showed linkage to markers on the long arm of chromosome 18 (18q), whereas families of probands without PD did not. This led the authors to conclude that there may be a genetic subset of patients with bipolar disorder who had comorbid PD. These results were very recently extended and confirmed by the same group in an independent group of bipolar disorder families.[15] In the same recent issue of the *American Journal of Psychiatry*, Rotondo and colleagues[16] conducted a case-control association study of the genetic polymorphisms of three monoamine neurotransmitter system candidate genes, catechol-*O*-methyltransferase (COMT), serotonin (5-hydroxytryptamine or 5-HT) transporter (5-HTT), and tryptophan hydroxylase (TPH), in patients with bipolar disorder with and without lifetime PD. Remarkably, the patients with bipolar disorder without PD showed significantly higher frequencies of the COMT *Met158* and the short *5-HTTLPR* alleles and

genotypes. These results suggest that bipolar disorder with and without comorbid PD represent distinct genetic forms, although no single genetic model could be applied to the subset of families with PD. The boundaries between the bipolar/panic phenotype remain obscure, and the question arises as to whether the bipolar/panic phenotype includes individuals with panic attacks below the threshold for a diagnosis of PD.[15] Thus, it is still not clear whether panic vulnerability in families with a high prevalence of bipolar disorder is the result of general nongenetic activation of anxiety mechanisms, a specific, partially penetrant gene, or a combination of genes.[15]

GAD, which is usually classified under the anxiety spectrum disorders, is defined by excessive and uncontrollable worry about a number of life events or activities for at least 6 months, accompanied by at least three of the following six associated symptoms of negative effect or tension: restlessness, fatigability, concentration difficulties, irritability, muscle tension, and sleep disturbance.[17] Twin and family-based studies have indicated a clear genetic influence in GAD with a heritability of approximately 30%; however, Kendler et al[18,19] found that GAD-associated genetic factors were completely shared with depression, while environmental determinants seemed to be distinct. GAD is associated with high comorbidity rates for other psychiatric disorders, including PD, major depression, dysthymia, social phobia, and specific phobia.[20-24] This notion is consistent with recent models of emotional disorders that view anxiety and mood disorders as sharing common vulnerabilities, but differing on dimensions including, for instance, focus of attention or psychosocial liability.[25]

Anxiety as a behavioral trait

Anxiety-related traits are fundamental, enduring, and continuously distributed dimensions of normal human personality.[26,27] Attempts to dissect out anxiety-related personality traits, including fearfulness, emotional stability, and stress reactivity, and to measure their heritability, are possibly the most difficult and definitely amongst the most contentious. The analysis of genetic contributions to anxiety-related or aggressive behavior is both conceptually and methodologically difficult, so that consistent findings remain sparse. Mood, anxiety, emotion, and cognition are modulated by the serotonergic midbrain raphe system, and a dysregulation of 5-HTT expression might be important in the course of these disorders.[28] Transporter-facilitated uptake of 5-HT has been implicated in anxiety in human and animal models and is the site of action of widely used uptake-inhibiting antidepressant and antianxiety drugs. The 5-HTT terminates the synaptic actions of 5-HT by sodium-dependent reuptake of 5-HT into the presynaptic vesicles. Heils et al[29] isolated and cloned the 5´-regulatory region of the 5-HTT gene, *SLC6A4*, which is located on chromosomal region 17q12. Systematic screening for length variations and functional promotor analyses revealed a genetic polymorphism that shows allelic variation in transcriptional activity and protein expression.[30] The short variant of the polymorphism reduces the transcriptional efficiency of the 5-HTT gene promotor, resulting in decreased 5-HTT expression and 5-HT uptake in lymphoblasts. Extensive genetic studies of the 5-HTT gene have revealed how variation in gene expression can be correlated with anxiety phenotypes. Association studies in two independent population and family-based samples, totaling 505 individuals, revealed that the 5-HTT polymorphism accounts for 3% to 4% of total variation and 7% to 9% of inherited variance in anxiety-related personality traits in individuals as well as sibships.[31] Using three different personality assessment scales, the results showed that the *5-HTTLPR* influences a constellation of traits related to anxiety. Lesch et al[31] stressed that the associations reported by them represent only a small portion of the genetic contribution to anxiety-related personality traits, and that if other genes were hypothesized to contribute similar gene dosage effects to anxiety, approximately 10 to 15 genes might be predicted to be involved.

Panic disorder

Probably the most genetic studies of anxiety have been conducted on patients with PD. PD typically has its onset between late adolescence and the mid-30s, and is strikingly different from other types of anxiety in that the panic attacks are sudden, appear to be unprovoked, and are often disabling. The first attacks are frequently triggered by physical illnesses, psychosocial stress, or certain drug treatments or drugs of abuse that increase the activity of neural systems involved in fear responses. Panic attacks respond to a variety of antidepressant drugs, they can be precipitated pharmacologically by carbon dioxide (CO_2), caffeine, lactate, cholecystokinin tetrapeptide,[32] and serotonergic compounds[33]; and func-

tional imaging studies have identified neurological correlates of attacks.[34-36] All of these observations speak for a physiological vulnerability. Sensitivity to CO_2 and lactate may indicate a distinct genetic liability.[37-39] Candidate genes for association studies in PD have often been selected on the basis of the molecular mechanisms of drugs utilized in challenge tests, such as *m*-chlorophenylpiperazine (mCPP), a nonselective 5-HT_{2C} receptor agonist.[40] The enhancement of GABAergic (GABA, γ-aminobutyric acid) neurotransmission has been closely linked to antipanic drug efficacy.

Hettema et al[41] recently published the results of meta-analysis of selected epidemiological studies, in order to summarize and quantify the information gathered to date on the familial aggregation of anxiety disorders and the relative contributions of genetics and environment to their etiology. Five family studies of PD, all from clinical populations that met their inclusion criteria, were included in the meta-analysis. All five studies supported the familial aggregation of PD, with a significant association between PD in the probands and PD in first-degree relatives. The unadjusted aggregate risk based on 1356 total first-degree relatives of PD probands was 10%, compared with 2.1% in 1187 comparison relatives. Small twin studies of PD by Torgersen[42,43] have found concordance rates of 22% to 31% for MZ twins and 0% for DZ twins. In an enlarged sample, the same group, using *DSM-III-R* criteria, found concordance rates of 25% for MZ twins and 10% for DZ twins.[44] A large population-based twin study of PD in women found a 24% MZ concordance and 11% DZ concordance using a "narrow clinician's" diagnosis.[45] The estimate of narrow-sense (additive) heritability of PD using this diagnosis was 46%. This is similar to what has been observed for the other anxiety disorders. Interestingly, the subdivision of PD patients according to age of onset before or after 20 years of age led to remarkable differences in risk of 22% and 8%, respectively. This indicates a much stronger genetic component in early-onset PD as opposed to late-onset PD; a finding consistent with other complex disorders, for example, Alzheimer's disease and breast cancer, which are rendered genetically more homogeneous when focusing on early-onset cases.[46,47]

Models for the mode of inheritance of PD remain highly speculative. Some segregation analyses have suggested the involvement of a major gene,[48,49] other studies have provided equal support for both recessive and dominant genetic models.[50,51] Two complete genome-wide linkage scans for PD liability genes have been published.[52,53] Knowles et al[52] genotyped up to 23 families with many affected individuals, with 540 microsatellite DNA markers. Since their previous studies had indicated that a large number of PD cases in the general population are likely to be phenocopies,[50,51] they included phenocopies, reduced penetrance, and "unaffected" individuals in their analysis. Six DNA markers, on chromosomal regions 1, 7, 17, 20p, and 20q (short and long chromosome arms, respectively) and X and Y gave promising lod scores (>1); however, no markers gave lod scores that exceeded the significant threshold of 3.3 suggested for declaring linkage to a complex trait in a genome scan.[7] In the more recent study of Crowe et al,[53] in which they genotyped 23 multiply affected families with a different set of 469 markers, the highest lod score obtained (2.23) was for a marker on the short arm of chromosome 7 (7p15), within the same region (within 10 cM) of one of the markers to which Knowles et al[52] had detected possible linkage. This replication of a previous finding adds importance to the result, and interesting candidate genes in this region have been highlighted. The corticotropin-releasing hormone receptor 2 locus maps between the two markers that showed possible linkage on 7p, and mouse knockouts for this gene have shown increased anxiety-related behaviors.[54] Similarly, the elastin gene is located within the region of possible linkage, and is also of interest because of the prevalence of joint hypermobility in patients with PD, which is discussed in a separate section below.

In addition to the linkage studies in PD, a number of candidate, or putative vulnerability, genes have been assessed in association studies. A role of monoamine neurotransmitters in the etiology of PD has been suggested by the observation that increased serotonergic neurotransmission provokes anxiety even up to the level of panic attacks in PD patients[33] and that decreased 5-HT uptake is found in patients with anxiety disorders.[55] Although it could be hypothesized that enhanced serotonergic neurotransmission in PD is due to increased 5-HT, no association with *5-HTTLPR*-dependent variation in 5-HTT expression and PD was detected in different populations.[56-58] Monoamine oxidase A (MAOA), an enzyme involved in the degradation of 5-HT and norepinephrine and thus positioned at the crossroads of two monoaminergic systems, is another plausible candidate gene.[25] A 30-bp repeat polymorphism was recently identified in the promotor region of the MAOA gene that

differentially modulates gene transcription.[59] Variation in the number of repeats in the MAOA polymorphic region showed allele-dependent transcriptional efficiency, with the effectiveness of the 3-repeat allele being two times less than alleles with longer repeats. An association study in two independent samples of 209 individuals revealed that longer alleles were significantly more frequent in female patients than controls. Considering that the inhibition of MAOA is clinically effective in the treatment of PD, particularly in women, these findings suggest that altered MAOA activity may be a gender-specific risk factor for PD.

Caffeine, an adenosine receptor (AR) antagonist, induces panic attacks in patients with the disorder[60] and caffeine intoxication (*DSM-III-R*) resembles anxiety disorders. Adenosine analogues have depressant effects on respiratory function in the brainstem, and an impairment of depressant brainstem respiratory mechanisms are considered a central feature in PD.[61] These and other observations have led to the hypothesis that the effectiveness of adenosinergic neuromodulation in patients with PD may be impaired due to changes in receptor function. Four different human AR subtypes have thus far been identified, the A_1 and A_{2a} of which mediate the central nervous system effects of adenosine. Deckert et al[62] systematically searched for mutations in the A_1 and A_{2a} genes in patients with PD and, although only silent mutations or polymorphisms were found, a significant association between an A_{2a}AR polymorphism and PD was found. This polymorphism must not be directly involved in the etiology of PD, but may be in linkage disequilibrium with a true functional variant either in this or a nearby gene. Further evidence for involvement of ARs in anxiety has been provided in mouse models. Mice in which the A_{2a} or A_1 receptors had been disrupted or "knocked out" scored higher in anxiety tests, and male $A_{2a}R^{-/-}$ mice (homozygous $A_{2a}R$ knockout mice) were much more aggressive towards intruders.[63,64]

Phobias

Kendler et al[65] investigated the reliability and heritability of unreasonable fears and phobias in a population-based sample of 1942 female twins. Phobia was defined as the presence of a fear that the respondent recognized as unreasonable and that, in the judgment of the interviewer, objectively interfered with the respondent's life. Unreliability occurred both for subject recall of unreasonable fears and for interviewer assessment of which fears constituted phobias. When fears and phobias were examined together in a multiple threshold model, their results suggested that the resemblance between twins was due solely to genetic factors, with estimated total heritabilities, after correction for unreliability, of 43% to 67%, with the latter highest value for agoraphobia. These authors concluded that individual-specific environmental experiences play an important role in the development of phobias, while familial–environmental factors appear to be of little etiological significance. These "phobia-genic" experiences are, apparently, rarely shared with a cotwin.

Only few population-based association and linkage-disequilibrium studies have been conducted for phobias, with few really promising results, which therefore will not be listed in this review. However, very recently, possibly one of the most exciting genetic studies in anxiety to date has been reported by the group of Estivill,[10] who found an association between the duplication of part of chromosomal region 15q24-26 and irrational fears, or phobias. One of the major uncertainties of the study is the phenotypic classification of the patients; the authors apparently lump panic and phobic disorders together and do not include a detailed clinical description of the patients. For this reason, as well as the importance and hope that their findings provide for the field as a whole, the study deserves a section of its own.

The chromosome 15 connection

Among the biological variables studied in PD, joint laxity or joint hypermobility syndrome has yielded particularly interesting results. Joint laxity is a clinical condition characterized by an increased distensibility and hypermobility of joints. It has a female-to-male ratio of 3:1, a dominant pattern of inheritance, and a prevalence of 10% to 15%.[66] Joint laxity is a feature common to several hereditary diseases of the connective tissue, and has also been significantly associated with mitral valve prolapse,[67] but a specific joint laxity gene has not been identified. Strong associations between joint laxity, mitral valve prolapse, and anxiety disorders have been described.[68-71] On the basis of a case-control study in rheumatology patients,[68] it was reported that PD, agoraphobia, and simple phobia were four times more common in patients with joint laxity than in controls.[72] A second case-control study, carried out in psychiatric patients,

found that joint laxity was 16-times more common in patients with panic/agoraphobia than in controls.[73]

Before embarking on a linkage study in seven extended families each with many members affected with panic/phobic disorders and joint laxity, who all came from a small village near Barcelona, Spain, Estivill's group performed a cytogenetic study in 10 patients,[10] in order to exclude chromosomal rearrangements in their patients. A putative alteration on chromosome 15 was identified, consisting of a slight difference in size between the chromosome homologs, together with a different G-banding pattern at 15q24-26 in some metaphases. Further molecular analysis of this chromosome region using fluorescent in situ hybridization (FISH) revealed an interstitial duplication at 15q24-26 (named *DUP25*). FISH analysis of all available samples found the duplication in 72% of patients. They then analyzed the *DUP25* in three control groups and detected it in 6% of samples. The authors then went on to look for the duplication in a set of 70 unrelated patients with phobias and found it in 68 subjects. This degree of association is one of the strongest reported for a psychiatric disorder and a genetic polymorphism. There are, however, many questions that require further clarity, and which additional studies may answer. For example, what is surprising is the broad clinical classification of the anxiety disorders in the patients with the *DUP25*. From the description of the patients, one could assume that there is a common genetic predisposition to all types of phobia, which other studies do not support. The other surprising finding was the complete lack of linkage between the phenotype and DNA markers that flank or are contained within the duplication. Gratacòs et al[10] explain this to be a result of the nonmendelian segregation of the duplication within families, since the segregation of the duplication in families is far from simple. Cases of de novo duplication, reversion from duplicated to nonduplicated chromosomes, and the apparent conversion from one form of the duplication to another were all observed within families. The duplication also exhibits mosaicism, in that it is not present in all cells analyzed. The authors propose that the mechanism by which the 15q24-26 duplication leads to panic and phobic disorders and joint laxity is probably through a dosage effect, with the overexpression of one or several genes present in the duplicated region; however, we will have to await further studies to shed more light on this association.

Animal models of anxiety

A complementary approach to genetic studies of anxiety and related disorders in humans involves the investigation of genes and their protein products implicated in the brain neurocircuitry of fear and anxiety in animal models. Anxiety is one of the psychiatric syndromes best suited to analogy with animal states. It is well understood that fear, escape, or avoidance behavior, and panic-like responses are ubiquitous throughout animal phylogeny, and as Gorman et al[74] have posited, it takes relatively little intuition to recognize that a rodent that avoids entering a cage in which adverse stimulus has been presented in the past, emulates a phobic patient avoiding a situation that has previously elicited a panic attack. However, as the same authors caution,[74] the analogy of panic attacks to animal fear and avoidance responses "is to be sure, imperfect." Most animal models of anxiety states involve conditioning, and it is not at all clear that PD or any other anxiety disorder except PTSD involves prior exposure to any aversive stimulus. Nevertheless, there are many aspects of conditioned fear in animals that make the analogy with human phenotypes (eg, panic attacks) irresistible, and thus validate the pursuit of genetic studies in model animals.

The mouse has long been regarded as an optimal model system for mammalian genetics. High-resolution genetic maps, large sets of highly polymorphic markers, and the availability of inbred strains of genetically identical mice can now be combined with transgenic and gene-targeting technologies that permit the direct manipulation of the mouse genome. The availability of inbred strains eliminates trait variation due to differences in genetic background, and the ability to sample multiple, essentially identical individuals permits assessment of subtle interstrain differences in the expression of complex traits. At the same time, the number of valid and reliable mouse behavioral testing paradigms is rapidly expanding and these can be used to assess many aspects of behavioral capability.

A number of studies have now indicated that quantitative trait loci on specific chromosomes are associated with heightened emotionality and with fear-conditioning in rodents. For example, Flint et al[75] showed that three loci on mouse chromosomes 1, 12, and 15 were associated with decreased activity and increased defecation in a novel environment. They concluded that these loci were responsible for heightened "emotionality" and

speculated that the genetic basis of emotionality is similar in other species, and may underlie the psychological trait of susceptibility to anxiety in humans. In two studies,[76,77] quantitative trait loci on several chromosomes were found to be associated with contextual fear conditioning in rodents, and chromosome 1 was implicated in both studies. The fact that loci on chromosome 1 have been highlighted in three studies working on such different measures of the same trait is encouraging.[78] On the basis of the increasing evidence that genetic variability in expression and function of proteins that regulate brain neurotransmitter systems (eg, receptors, ion channels, transporters, and enzymes) is associated with complex behavioral traits, research is also emphasizing the molecular psychobiological basis of anxiety-related behavior in rodents, and increasingly in nonhuman primates.[25]

Conclusion

Anxiety disorders belong to the category of complex diseases for which intense research efforts are focused on the identification of genetic susceptibility factors. Emerging tools and technologies for genetic analysis will provide the groundwork for an advanced stage of gene identification and functional studies in anxiety and related disorders. More than 1.4 million single nucleotide polymorphisms (SNPs) have been identified in the human genome. This collection should allow the initiation of genome-wide linkage disequilibrium mapping of genes influencing anxiety in the human population.

The duplication of part of chromosome 15 is probably a major genetic factor of susceptibility for panic and phobic disorders, and its identification may have important implications for psychiatry and health. If the findings of Gratacòs et al[10] are confirmed, and the duplication is shown to segregate in a nonmendelian fashion, it then suggests another line of investigation for complex disorders. Large-scale chromosomal rearrangements are common enough in pericentromeric regions for cytogeneticists to ignore size variation as an irrelevant polymorphism; however, in the future they will perhaps be assigned greater importance. Complex repeat regions at the ends of chromosomes also show size variation, involving hundreds of kilobases of DNA, some of which may contain functional genes.[79,80]

What holds great promise for the future is the increasing development of techniques that alter or inactivate gene expression. Whereas in the past, genes could be inactivated (knocked out) from the embryological stage throughout the life span of the animal, conditional mutants allow the regulation of expression of a particular gene by switching it on or off.[81,82] Thus, one can refine experiments to a much greater degree by the timing of the expression of a particular gene. With the achievement of the sequencing of the human genome, and the active development of techniques for large-scale molecular genetic analysis of the genome, there is now hope for the identification of the contribution of particular genes to the development of these disorders. Eventually, the nature of the gene products might provide the clues to novel treatment options. ❑

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¿ Hay genes para la ansiedad ?

La ansiedad incluye diversas descripciones clínicas y fenotipos. No cabe duda de que existe una predisposición genética para la ansiedad; sin embargo, aun no está aclarada la naturaleza y el alcance de esta contribución. En este artículo se revisan brevemente los métodos para el análisis genético de estos complejos trastornos y a continuación se discute la comorbilidad de la ansiedad con otros trastornos psiquiátricos y su posible etiología genética común. Existen numerosos estudios genéticos sobre el gen transportador de serotonina (5-hidroxitriptamina, 5-HT) que han revelado cómo la variación en la expresión genética se puede relacionar con los fenotipos de la ansiedad. Completos mapeos a lo largo del genoma de los enlaces de los genes de susceptibilidad para el trastorno de pánico (TP) han sugerido un sitio en el brazo corto del cromosoma 7 (7p) y estudios de asociación han puesto de relieve muchos genes candidato. Uno de los hallazgos más atractivos a la fecha lo constituye la asociación altamente significativa entre fobias, trastorno de pánico y una duplicación en la región cromosómica 15q24-26. Las tecnologías emergentes de genética molecular y el empleo de modelos animales de ansiedad altamente sofisticados prometen un gran futuro en este campo.

Existe-t-il des gènes de l'anxiété ?

L'anxiété comprend un grand nombre de descriptions cliniques et de phénotypes. Une prédisposition génétique à l'anxiété est indéniable, dont la nature et l'ampleur, toutefois, sont encore incertaines. Les méthodes pour l'analyse génétique de ces troubles complexes sont brièvement passées en revue, suivies par une discussion sur la comorbidité de l'anxiété avec d'autres pathologies psychiatriques et leur possible étiologie génétique commune. De vastes études génétiques sur le gène du transporteur (5-HTT) de la sérotonine (5-hydroxytryptamine, 5-HT) ont révélé l'existence d'une corrélation entre les variations de l'expression de ce gène et les phénotypes de l'anxiété. Des explorations complètes de tout le génome à la recherche de liaisons pour les gènes de la sensibilité au trouble panique (TP) ont montré un locus sur le bras du chromosome 7p et des études d'association ont mis en avant de nombreux gènes candidats. Un des faits les plus passionnants à noter a été la découverte d'une association hautement significative entre la phobie, le trouble panique et une duplication de la région chromosomique 15q24-26. Les technologies de génétique moléculaire émergentes et l'utilisation de modèles animaux de l'anxiété de plus en plus sophistiqués permettent les plus grands espoirs pour l'avenir de ce domaine.

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