Minireview

Untangling genetic networks of panic, phobia, fear and anxiety

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Published: 28 July 2003

Genome ***Biology*** 2003, **4:**224

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2003/4/8/224

Abstract

As is the case for normal individual variation in anxiety levels, the conditions panic disorder, agoraphobia and other phobias have a significant genetic basis. Recent reports have started to untangle the genetic relationships between predispositions to anxiety and anxiety disorders.

"But if I am in an unfamiliar place, among a number of strange people, or people whom I feel to be strangers, then the whole room presses on my chest and I am unable to move, my whole personality seems virtually to get under their skins, and everything becomes hopeless."

Franz Kafka [1]

Anxiety, panic, and fear are natural responses to a hostile environment. Yet if inappropriately activated, these responses can wreak havoc. In extreme cases, people with anxiety disorders may be unable to leave home for fear of having a panic attack. Conversely, individuals vary in their baseline level of anxiety. In recent months, several reports on linkage studies have been published that identify loci involved in normal variation in anxiety and/or that predispose to several anxiety disorders. These studies suggest that there may be connections between anxiety disorders and normal variation in anxiety levels in humans and even in mice.

High levels of baseline anxiety are often associated with depression [2]. Feeling depressed, vulnerable, and anxious is summarized by the personality trait described as neuroticism, abbreviated N, a quantitative trait that can be determined for anyone using the NEO personality inventory (NEO-PI) [3]. People scoring high on the anxiety facet of neuroticism tend to endorse statements such as: "I often feel tense and jittery," "I often worry about things that might go wrong," or "I am easily worried." About 40% of individual variation in N is attributed to genes [4], and about 55% of the genetic vulnerability to N overlaps with that to depression [5].

In contrast to normal variation in baseline anxiety levels, individuals with anxiety disorders such as panic disorder, agoraphobia and specific phobias (formerly called simple phobias) are often severely handicapped by their fear. People with panic disorder experience unprovoked panic attacks with terrifying fear and physical signs of panic, such as increased heart rate, sweating and feeling choked. Agoraphobia is characterized by fear of being in public places and often co-exists with panic disorder, whereas specific phobias are characterized by intense, unreasonable fear of specific things (such as spiders, snakes or lightening) or situations (flying an airplane or having blood drawn). These are familial phenotypes in which first-degree relatives of those affected have a significantly increased risk relative to the general population risk. For panic disorder, the risk is 10-20-fold higher in first-degree relatives [6], compared to the general population incidence of about 2%. Phobias generally show about a three-fold increase in first-degree relatives [7], with a lifetime prevalence of any type of phobia in the general population of about 10% [8]. Family studies show that relatives usually have the same disorder as the proband (the affected individual who brought the family to the attention of researchers), except that relatives of probands with agoraphobia are also at increased risk for panic disorder [6]. Some therefore suggest that agoraphobia is a severe subtype of panic disorder, although this is not universally accepted

[6]. Twin studies suggest heritability of 44% for panic disorder [9], 39% for agoraphobia, and around 30% for anxiety disorder and specific phobias [10].

These disorders can segregate in large families and have a significant heritability. The genetics are complex, however, with a significant nongenetic contribution as well as partial overlaps in phenotypes, all of which make linkage analysis to identify genes a difficult endeavor. In spite of these difficulties, several risk loci for anxiety-related traits have recently been localized by linkage analysis [11-19]. While no specific gene has been identified, localization of the gene regions represents not just progress towards gene identification: it may help in outlining the etiology of the disorders. We are now starting to get an idea of which disorders may be distinct and which may overlap genetically.

QTL studies of anxiety traits in human and mice

Candidate genes that might affect anxiety in humans are many: dozens of genes when knocked-out show an increase in levels of anxiety in mice [20]. Most normal variation is, however, not likely to be due to null alleles. Thus, analysis of quantitative trait loci (QTLs), to study the variations in anxiety between normal mouse strains, may be a better model of normal human population variation. Many mouse QTLs related to anxiety have been published and reviewed recently [21]. But QTLs are often broad and cannot easily be narrowed down to small intervals or genes. Flint and coworkers have recently used heterogeneous stock (HS) mice to overcome this problem. HS mice are akin to a population - mice are mated to maximize heterogeneity, and each mouse is a genetically unique individual. But HS mice are derived from a small number of inbred strains, typically eight, so the number of different alleles is limited. Using two sets of HS mice, Talbot *et al*. [18] recently narrowed down several different mouse anxiety traits (conditioned fear, contextual fear and open-field exploration) to small, non-overlapping intervals on mouse chromosome 1, in a region previously implicated by other studies. These results suggest that there are several anxiety genes in close proximity, rather than one gene with pleiotropic effects.

Testing specific candidate genes in humans can be done by simple association tests that ask the following: does the average N score depend significantly on the genotype? The first such study implicating a specific gene was by Lesch *et al*. [22], who found a common functional promoter variant in the serotonin transporter associated with neuroticism. Similarly, we recently identified a coding variant in brain-derived neurotrophic factor (BDNF) [23] associated with N - and this variant is also found associated with bipolar disorder [24], confirming the link between N and depression. Each of these genetic variants has only a small effect size, however, influencing just a few percent of the total variance.

A more systematic way to identify genetic variants affecting N is a whole-genome analysis. Recently Fullerton *et al*. [12] reported the first large-scale systematic linkage analysis of N. Over 80,000 individuals in over 20,000 sibships of at least two individuals were identified, contacted and administered the NEO-PI. Of these, over 600 sibships scoring at the extremes of the distribution - either both extremely high, both extremely low, or extremely discordant high-low - were selected for the genome scan. Five loci were identified with logarithm of odds (LOD) scores above 3.8, which corresponds to a genome-wide significance $p < 0.05$. Some loci acted only in females and others only in males, suggesting that gender needs to be considered in studies of anxiety. Interestingly, one of these loci maps to a region of 1q homologous to the region containing the QTLs found in mice on chromosome 1.

Linkage analysis of panic disorder and phobias

Five linkage studies have investigated panic disorder using whole-genome scans [11,13,15,16,19] and one scanned targeted regions [17]. These studies differed in their phenotypic classification, however, several started out with panic disorder probands but found a high incidence of generalized anxiety disorders, agoraphobia and specific phobias in the respective pedigrees. Thus, some of the etiology may overlap, and indeed, linkage analysis in some studies resulted in higher LOD scores when a more inclusive phenotype was used [17]. But other studies report higher LOD scores when families with distinct phenotypes were separate [13,15]. Comparing the loci found in different studies for the different chromosomes results in a complex picture that is summarized in Table 1. Some loci seem to be specific to fairly narrowly defined disorders, such as panic disorder on chromosomes 9q, 13q, and 22q, and phobias on distal 3q, whereas others suggest linkage to multiple forms of anxiety related to panic disorder, for example on 1q and 10q.

Many chromosomal regions show evidence for linkage to panic disorder and related phenotypes, and some of them have been confirmed in more than one study (Table 1). Three loci (1q, 7p, and 13q) are linked to both panic disorder and neuroticism but not agoraphobia or simple phobias. Three different studies found linkage of panic disorder to chromosome 1q [11,13,15] - but all map panic disorder distal to the 1q locus related to neuroticism and to the murine anxiety QTL discussed above. Two different study designs implicated the same region of chromosome 13q: an HLOD score (a LOD score under conditions of heterogeneity) of 3.57 was corroborated by multipoint analyses in 60 families segregating panic disorder and bladder/kidney conditions [15], suggesting that this locus includes genes involved in a pleiotropic syndrome. In addition, this region was also implicated by a large sibling study of neuroticism, at least in females [12]. Two studies also found linkage to 7p in panic disorder [11,16], which is also associated with neuroticism [12].

Table 1

Chromosomal regions implicated in panic disorder, phobias and anxiety traits

Phenotype	1q	3q	4q21	4q34	7p	8q	9q	10q	11p	12q	13q	14p	22q	Reference
Panic disorder (PD)	+++	+			+	++	++++			+	++++	+	++++	[13,15,16,19]
	+	+		+	++					++*				[11,17]
	++									++				[15,16]
Agoraphobia (AG)	-	++	+						++					[13]
		++++*												[13]
PD + AG									+			+		[13]
Specific Phobia	+	++		+		++		+	+			+++		[14]
		+++*												[14]
PD + anxiety	+		+				++	++		+				[17,19]
Neuroticism	++++			++++	++++					++++	++++			[12]
Mouse QTL†	++++									++++		++++	+++	[17,27]

*One family. †Human equivalents of mouse QTLs. The number of + signs indicates the approximate relative significance of the linkage.

In a more targeted approach, focusing on a single extended pedigree and only on regions syntenic to suggested QTLs in mice, linkage was obtained for panic disorder combined with agoraphobia to 12q13 [17]. In addition, an HLOD score peak on 12q22 - possibly another locus - was obtained for families segregating panic disorder and bladder/kidney conditions [15]. Fullerton and colleagues' [12] study of discordant and concordant siblings found their highest LOD score of 4.7 for a QTL for neuroticism in this region. In a linkage study of 25 Icelandic extended pedigrees, linkage to chromosome 9q31 was found with a highly significant allele-scanning LOD score of 4.18 [19]. If the phenotype is broadened to include anxiety and an additional 37 pedigrees are included, the LOD score goes down to 2.0, suggesting that 9q31 harbors a locus that is fairly specific for panic disorder. Two independent studies in non-Icelandic Caucasians [11,15] showed LOD scores between 1 and 2 for panic disorder in a region about 30 centiMorgans distal to 9q31.

Modest LOD scores for panic disorder on chromosome 3q were reported in two studies [11,13]. One of these studies, a genome scan of families segregating panic disorder, agoraphobia, specific phobias and other anxiety disorders, also identified a region on chromosome 14p as linked to panic disorder and agoraphobia [13] as well as to specific phobias [14]. If a narrow phenotype of exclusively agoraphobia was considered, the linkage peak on 3q moved to a more distal location, but this result was dominated by a single family that showed no linkage to 14p. Removal of this family from the genome-scan analysis for specific phobias increased the LOD score for 14p in the remaining families. Thus, by careful attention to phenotypes, the differential contribution of 14p, predominantly to phobias, and 3q, predominantly to agoraphobia but also panic disorder, could be dissected in spite of some overlap. These linkage studies suggest that agoraphobia and specific phobias may have different etiologies, a conclusion that is consistent with epidemiological data [6]. Moreover, in mouse one of five QTLs for open-field activity, an anxiety-related trait, mapped to a region homologous to 14p [25].

Finally, linkage of a chromosome 22q marker, but not multipoint linkage, was reported in the same families segregating panic disorder and bladder/kidney conditions that showed linkage to 13q [15]. In addition, association was reported between panic disorder and a haplotype around a candidate gene on 22q12, catechol-O-methyltransferase (COMT), which may have a biological role in anxiety [26]. A mouse QTL for transition from dark to light, an anxiety-related phenotype, has been mapped to a mouse chromosome 15 region homologous in part to human 22q13 [27], but the map position is too broad to conclude with certainty that the mouse QTL is syntenic with human 22q.

How many phenotypes?

The high comorbidity of multiple anxiety disorders within the same individuals and between individuals in the same pedigree presents a particular challenge for genetics. Are some of these disorders extremes of a dimensional trait, do they share some susceptibility genes, or are they completely different phenotypes with some degree of overlap? There is some agreement between epidemiological and genetic linkage data to suggest that panic disorder and agoraphobia are related to each other but distinct from specific phobias. But there seem to be genes that increase risk only for specific disorders, as well as genes that broadly increase the risk for anxiety disorders. Some (see [6]) argue strongly that dimensional traits such as neuroticism should be incorporated into the diagnostic criteria for genetic studies. The fact that all five QTLs for neuroticism identified in the large population study [12] also map near anxiety disorder loci strongly supports this

approach. The focus on extremes in this QTL study may have introduced a bias towards anxiety disorders, however. On the other hand, some studies have been quite successful by focusing on rare subtypes such as panic disorder associated with bladder and renal abnormalities [15]. Estivill and colleagues [28] used a similar narrow subtype approach, and found many patients with panic disorder and hyperextendable joints to have a somatic chromosome 15 abnormality.

A final question to consider is whether linkage to the same region always implies the same gene. Although a number of related phenotypes may map to the same chromosomal interval, these regions are often large and may harbor more than one susceptibility locus. This is exemplified by the mouse study in which several anxiety-related QTLs mapped to the same region of chromosome 1 but were later shown by fine mapping to map to more than one locus [18]. Thus, while it is tempting to conclude that some loci are associated with more generalized anxiety whereas others are more specific and linked to only one disorder, we have to be careful: some of the 'reproducible' linkage regions may contain more than one gene, and others will be false positives. Nevertheless, enormous progress has been made in the past year. Careful ascertainment and recording of all relevant phenotypes will be necessary to allow linkage and association analysis with both narrowly and more broadly defined traits and disorders, and will probably be essential if we are to succeed with the next step, the identification of the genes involved in these complex and disabling disorders.

Acknowledgements

We thank the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Nancy Pritzker Neuropsychiatric Disorders Consortium, and the NIMH grant 5P50MH60398 for support of our research on depression and anxiety, Hans-Gerd Koch (University of Wuppertal, Germany) for the Kafka citation and Michael Hortsch for critical reading.

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