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Anxiety with Panic Disorder Linked to Chromosome 9q in Iceland

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The results of a genomewide scan for genes conferring susceptibility to anxiety disorders in the Icelandic population are described. The aim of the study was to locate genes that predispose to anxiety by utilizing the extensive genealogical records and the relative homogeneity of the Icelandic population. Participants were recruited in two stages: (1) Initial case-identification by a population screening for anxiety disorders, using the Stamm Screening Questionnaire, was followed by aggregation into extended families, with the help of our genealogy database; and (2) those who fulfilled the diagnostic and family aggregation criteria underwent a more detailed diagnostic workup based on the Composite International Diagnostic Interview. Screening for anxiety in close relatives also identified additional affected members within the families. After genotyping was performed with 976 microsatellite markers, affected-only linkage analysis was done, and allele-sharing LOD scores were calculated using the program Allegro. Linkage analysis of 25 extended families, in each of which at least one affected individual had panic disorder (PD), resulted in a LOD score of 4.18 at D9S271, on chromosome 9q31. The intermarker distance was 4.4 cM on average, whereas it was 1.5 cM in the linked region as additional markers were added to increase the information content. The linkage results may be relevant not only to PD but also to anxiety in general, since our linkage study included patients with other forms of anxiety.

Introduction

Anxiety disorders, often accompanied by depression, are health care problems of major concern worldwide (Murray 1996; Rice et al. 1998). Because of their high prevalence, early onset (usually midadolescence through the mid-20s), and chronic course, they cause as many disability days as do mood disorders (Andrews et al. 2001). The U.S. National Comorbidity Study showed the lifetime prevalences for panic disorder (PD [MIM 167870]) as 3.5/100, agoraphobia as 6.7/100, social phobia as 13.3/100, and generalized anxiety disorder (GAD) as 5.1/100 (Kendler 1994). The lifetime prevalences of these disorders in Iceland are within similar ranges (Lindal et al. 1993). The total lifetime prevalence of anxiety disorders is estimated to be 15%–18%, and anxiety disorders are more common among females. The treatment prevalence of anxiety disorders appears to be increasing (Skaer et al. 2000). Anxiety-disorder subtypes only rarely present alone, and comorbidity is almost the rule (Goldenberg et al. 1996). The most common comorbid conditions are other anxiety disorders, unipolar and bipolar mood disorders, and substance abuse (George et al. 1990; Hunt et al. 1995; Mineka 1998).

The etiology of anxiety disorders is complex, and etiological factors have been sought in the field of genetics, as well as in the environment (Hettema et al. 2001). It has been debated whether the anxiety disorders are etiologically distinct from each other or whether there are anxiety traits with shared etiological factors (Skre et al. 1993; Kendler et al. 1995; Muris et al. 2001*a;* Stewart et al. 2001). Results of family studies have consistently demonstrated that PD runs in families. Twin studies indicate that genetic variation contributes to this familiality, even though no specific susceptibility genes have been isolated (Finn and Smoller 2001). Irrational fears and phobias, as well as GAD, also appear to have a distinct genetic component, but environmental factors also play a role (Hettema et al. 2001; Kendler et al. 2001). The high comorbidity among the anxiety disorders and between anxiety and mood disorders suggests a unifying factor in their etiologies (Eley and Stevenson 1999). Whereas phobias—and, in particular, PD—are strongly familial, previous work clearly shows that individual clinical phenotypes do not run true within families; rather, the inheritance pattern strongly suggests that there exist genetic factors that are common among the different types of anxiety and perhaps even among their other comorbid conditions.

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The genetic basis of anxiety remains to be discovered. Numerous association studies have typically focused on genes involved in neurotransmission, such as receptors and transporters, as well as enzymes involved in synthesis or degradation of neurotransmitters (Mazzanti et al. 1998; Ohara et al. 1998; Nakamura et al. 1999; Sand et al. 2000; Hatton et al. 2001; Hamilton et al. 2002). Although most results provide no support for association or are inconclusive, there are some promising results, such as for the catechol-*O*-methyltransferase locus, on chromosome 22 (Hamilton et al. 2002). Linkage studies focusing on PD (Knowles et al. 1998; Crowe et al. 2001) have identified some regions of potential interest but so far have not yielded significant linkage. Although most of the work has focused on PD, there are some studies on a broader phenotype. For example, chromosome 13 has been implicated in a linkage study of a syndrome that includes PD and several medical disorders (Weissman et al. 2000); suggestive loci have been detected in a linkage study of PD and agoraphobia (Gelernter et al. 2001); and a polymorphic duplication on chromosome 15 has been identified as a susceptibility factor for PD, phobic disorders, and joint laxity (Gratacòs et al. 2001).

Here, we present the linkage results for 62 families altogether comprising 161 affected individuals, as determined on the basis of the broader phenotype of anxiety, and linkage results for a subset of 25 families (67 affected), each with at least one index case diagnosed as PD, in addition to individuals with other forms of anxiety. In defining the broader phenotype of anxiety, we decided to include the phobias, other anxiety disorders, GAD, and somatoform pain. The last two may be a debatable inclusion. GAD, typically classified with the anxiety disorders, has also been closely linked with depression. The distinction relies at least partly on the emphasis given common genetic versus environmental factors, as reviewed in two recent articles (Kessler 2000; Hunt 2002). In the total sample, of those with GAD, 41% are comorbid with PD, and 43% are comorbid with depressive disorders; 14% of those with GAD are comorbid with both PD and depressive disorders. Persistent somatoform pain has, as does GAD, a close relationship to both depression and anxiety (Von Korff et al. 1996); furthermore, Muris et al. (2001*b*) have found a close relationship between anxiety sensitivity and pain anxiety, which again may lead to chronic-pain complaints. In the present sample, persistent somatoform pain was highly comorbid with other anxiety disorders, and the average age at its onset (20.7 years) was in the same range as PD and the phobias. On the basis of this finding, we decided to include somatoform pain in our linkage analysis. The present study is based on a population sample, first screened for anxiety, then further classified with a more detailed diagnostic workup, and clustered into families by using a comprehensive genealogy database.

Material and Methods

Population Screening and Genealogy Work

The National Bioethics Committee and the Data Protection Commission of Iceland approved the study. The initial sample is based on a population screening for anxiety by mail. All person-identifying data were encrypted by the Data Protection Commission of Iceland, using a third-party encryption system developed by deCode Genetics (Gulcher et al. 2000). The Stamm Screening Questionnaire (SSQ), accompanied by a detailed description of the study, was mailed to a population sample of 9,992 randomly selected individuals, of 18–60 years of age. This questionnaire screens for lifetime occurrences of anxiety and mood disorders and is based on the Composite International Diagnostic Interview (CIDI) (Peters and Andrews 1995; Wittchen et al. 1996). The SSQ has 16 questions probing for the lifetime history of anxiety, mood, and addictive disorders. We relied on answers to five anxiety questions (appendix A); the PD question was the key one, added to which was the accumulated score of four other anxiety questions (GAD, social phobia, simple phobia, and agoraphobia). This formed the basis for our definition of an index case. Those who fulfilled the case-definition criteria for anxiety were clustered according to family relatedness, with the help of a population-wide genealogy database (Gulcher et al. 1998). The encrypted list of those meeting the SSQ criteria was analyzed through the genealogy database, using recursive algorithms to find all ancestors related to those on our encrypted list, given a number of generations. The cluster function then searched for ancestors common to any two or more members on the encrypted list, automatically generating extended pedigrees. For a family to be recruited for our linkage analysis, it needed to contain at least one proband scoring positively for panic attack and, in addition, positively for at least two of the four remaining anxiety questions (GAD and the three phobias). Individuals responding positively to one or two SSQ anxiety questions were also included if they were related to an index case subject as defined above.

The results of the search identified potential families that were defined by a genealogical relationship between affected family members within a distance of 5 meiotic events (i.e., first cousins, once removed). During the recruitment process, individuals from these families were invited to participate. Having signed informed consent forms, the participants underwent a further diagnostic evaluation based on the CIDI and donated a blood sample. The CIDI yields both *DSM-III-R* and *ICD-10* lifetime diagnoses. In our linkage

analysis, we combined the results of these two diagnostic systems such that each index case subject received one diagnosis for each disorder, and we did not separately analyze, for linkage, the data based on each diagnostic system. After the administration of the CIDI, each index case subject was asked to refer to the study any relative who possibly has an anxiety disorder. Relatives testing positive for anxiety by the SSQ were then invited to enter into the study as potential index case subjects and underwent the same procedures as the participants recruited through the initial SSQ survey. Blood samples were also collected from additional first-degree relatives, regardless of affected status, to ascertain to what extent the genetic make-up of an index case subject derives from each parent.

Microsatellite Markers and Genotyping

We genotyped 353 individuals (161 affected and 192 relatives) in 62 families, and we used a marker set, developed at deCode Genetics, that contains markers from the ABI Linkage Marker (version 2) screening and intercalating sets, as well as 500 custom-made markers. The set uses 976 fluorescently labeled primers with an initial genomewide average spacing of 3.8 cM. The set has been extensively tested for multiplex PCR results. PCR amplifications were set up, run, and pooled on Gilson Cyberlab robots. The reaction volume was 5 μl, and, for each PCR, 20 ng of genomic DNA was amplified in the presence of 2 pmol of each primer, 0.25 U Ampli*Taq* Gold, 0.2 mM dNTPs, and 2.5 mM $MgCl_2$ (buffer was supplied by the manufacturer, Applera). Cycling conditions were as follows: 95°C for 10 min, followed by 37 cycles of 94°C for 15 s, annealing for 30 s at 55°C, and 1 min extension at 72°C. The PCR products were supplemented with the internal size standard, and the pools were separated and detected on 3700 Sequencers by using Genescan (version 3.0) peak-calling software (Applera). The genotypes for a total of 867 markers from the genomewide set were used for the linkage analysis, resulting in an average intermarker distance of 4.4 cM. Alleles were automatically called using DAC, an allele-calling program developed at deCode Genetics (Fjalldal et al. 2001), and the program DecodeGT was used to fractionate called genotypes, according to quality, and to edit when necessary (Pálsson et al. 1999).

Statistical Methods for Linkage Analysis

To evaluate linkage, we used multipoint, affected-only allele-sharing methods. The program Allegro (Gudbjartsson et al. 2000) was used for the calculation of NPL and LOD scores. We employed the S^{pairs} scoring function (Whittemore and Halpern 1994; Kruglyak et al. 1996) and the exponential allele-sharing model (Kong and Cox 1997) to generate the relevant test statistics. Family scores were combined to obtain an overall score, using a weighting scheme that, on the log scale, is halfway between weighting the families equally (Kruglyak et al. 1996) and weighting the affected pairs equally, with the resulting weighting scheme being equal to the geometric mean of the two schemes. This scheme gives weights similar to those proposed by Weeks and Lange (1988) as an extension of the scheme that Hodge (1984) designed for sibships.

In addition to requiring the pointwise P value to be $<2 \times 10^{-5}$ (Lander and Kruglyak 1995), we consider the linkage results to be significant only if the information content in the region is $\geqslant 85\%$. Information content is calculated as follows. On the basis of the exponential model described by Kong and Cox (1997), the actual LOD score is obtained, in part, by maximizing the likelihood with respect to a scalar parameter, δ, that measures the amount of excess identity-by-descent sharing among affected relatives, with $\delta = 0$ corresponding to the null hypothesis. A corresponding, "predicted" LOD score can be calculated by considering the hypothetical situation in which the information is complete but the maximum-likelihood estimate of δ remains the same. This predicted LOD score is, in general, larger than the actual LOD score, and the information content is defined as the ratio of the actual LOD score to the predicted LOD score. Note that, when this definition is used, information content can be applied even to a locus with no excess sharing by allowing the maximum-likelihood estimate of δ to be negative. The singularity that occurs at $\delta = 0$, leading to division by 0, is resolved by the application of L'Hopital's rule. This information measure, implemented in Allegro, was introduced and studied in detail by Nicolae (1999), who demonstrated that it is asymptotically equivalent to a classic measure of information, as described by Dempster et al. (1977). This measure has the property that it lies between 0, if the marker genotypes are completely uninformative, and 1, if the genotypes determine the exact amount of allele sharing by descent among the affected relatives. The marker order and positions used in linkage analysis are from our high-resolution genetic map (Kong et al. 2002).

Results

Population Survey and Family Data

Valid responses were sent in by 2,792 respondents. There were no large differences in terms of age, sex, or urban/rural domicile between respondents and nonrespondents. A total of 1,783 individuals, or 64%, gave a positive answer to one or more of the five SSQ anxiety items used. Because the response rate was 28%, the results of the survey can by no means be interpreted as a measure of population prevalence; instead, they most

Table 1

Characteristics of the Members of the Families with Anxiety or PD

	Results for Families with	
Diagnosis	Anxiety (62 Families)	PD (25 Families)
PD	29 (18)	29 (43)
GAD	53 (33)	28 (42)
Agoraphobia	40 (25)	23 (34)
Social phobia	81 (50)	38 (56)
Simple phobia	54 (33)	26 (39)
Other anxiety	27 (17)	14 (21)
Persistent somatoform pain	76 (47)	26 (39)
Average no. of anxiety disorders	2.2	2.7
Dysthymia	30 (19)	20 (30)
Depression	83 (52)	45 (67)
Average age at interview	40.6 years	38.8 years
Male:female ratio	1:2.9	1:7.4

Note.—Except as otherwise indicated, data are given as no. (%).

likely represent a cohort biased toward those affected with anxiety. Analysis of those who fulfilled our case-definition criteria for anxiety through the genealogy database revealed that a total of 490 positive respondents were clustered in 73 families consisting of at least two members.

As a result of the population survey, we were able to identify and focus our initial sample collection on the families most likely to carry the highest load of PD. However, although the SSQ questionnaire is a sensitive tool, it does not yield specific diagnoses. After the CIDI, many of the families turned out to have no members with *DSM-III-R* or *ICD-10* PD, although approximately two-thirds of the potential index case subjects received one or more CIDI anxiety diagnoses. Diagnostic congruence between *ICD-10* and *DSM-III-R* varied. The *DSM-III-R* was more likely to produce phobia diagnoses, whereas the *ICD-10* produced a higher number of depressive disorders. We found this to be an acceptable false-positive rate, and we have now expanded our sample collection to include, in a similar manner, both GAD and the phobias. Currently, 1,040 CIDIs have been administered, resulting in anxiety diagnoses in 646 individuals.

For the present study, a total of 161 affected individuals within 62 families were identified. We also analyzed linkage for a part of the linkage cohort—namely, 25 families centered on individuals with PD. Each of these families included an index case subject with a *DSM-III-R* or *ICD-*

Table 2

Characteristics of the Members of the 25 Families with PD

	Results for Family Members	
Diagnosis	With PD	Without PD
PD	29	
Anxiety disorders without PD:		38
Subclinical PD	0	12 (32)
GAD	16 (55)	12 (32)
Agoraphobia	16 (55)	7 (18)
Social phobia	19 (66)	19 (50)
Simple phobia	14 (48)	12 (32)
Other anxiety	8 (28)	6 (16)
Persistent somatoform pain	12 (41)	14 (37)
Average no. of anxiety disorders:		
Including PD and subclinical PD	3.9	2.2
Excluding PD and subclinical PD	2.9	1.9
Dysthymia	10 (35)	10 (26)
Depression	20 (70)	25 (66)
Average age at interview	35.1 years	41.7 years
Male:female ratio	1:6.3	1:8.5
Age at onset of PD	18.1 years	

Note.—Except as otherwise indicated, data are given as no. (%).

Table 3

Results of Genomewide Scans for PD and Anxiety

Chromosome	Maximum Allele-Sharing LOD Score, for Families with		Position (Kosambi cM)	Range, for Loci with LOD ⩾ 1.0 (cM)	Peak Marker(s)
	Anxiety (62 Families)	PD (25 Families)			
3	1.24		52.6	43–54	D3S1266, D3S3547
3		1.81	54.6	41–57	D3S3547
3		1.08	106.6	100–107	D3S3653, D3S3508
4	1.37		100.2	74–101	D4S423
8	1.26		61.6	56–64	D8S532, D8S531
9	2.00		104.1	93–111	D9S1690
9		4.18[a]	105.6	79–113	D9S1690, D9S271
10	1.19		144.6	140–146	D10S1230
15		1.11	112.7	108–119	D15S157
18	1.09		32.4	28–35	D18S464
18		1.06	103.9	98–q-ter	D18S469
X		1.47	141.1	122–157	DXS1062

[a] Additional markers were genotyped in the linkage region on chromosome 9q, with a resulting average intermarker distance of 1.5 cM (information content ⩾85%).

10 diagnosis of PD and relatives with any anxiety disorder at a genealogical distance of ⩽5 meiotic events. Table 1 details some characteristics of both sets of families and the distribution of diagnoses.

Table 2 shows some characteristics of the affected members of the 25 families with PD, for those individuals with and without PD. The distribution of anxiety and depression diagnoses clearly shows that comorbidity was the rule, rather than the exception. The average age at the time of interview was higher in those family members who did receive a diagnosis of PD. This should have given them a chance to develop more psychopathology, particularly in the range of depressive illnesses, but analysis of comorbidity reveals that this is not the case. The prevalence in females is higher (male:female ratio 1:7.4) in these families than in our total sample (male:female ratio 1:2.9), both in those affected with PD and those affected with other anxiety disorders only. This is an interesting observation, but, because the numbers are small, we refrain from drawing any conclusion from this.

The average number of anxiety diagnoses, even when PD is excluded, is higher in the group with PD as compared to family members without PD. This applies to all the anxiety disorders, with the difference being most marked in agoraphobia. Thus, having PD increases the risk of additional anxiety comorbidity. The mood-disorder prevalence in these families is similar for those with and without PD, but the rate is much higher than that in the general population, as indicated by the lifetime prevalence of depression in Iceland, which has been estimated at 11% (Lindal and Stefansson 1991). The trend is clear—namely, having one anxiety disorder, particularly having PD, leads to a high risk of developing other anxiety and mood disorders.

Linkage Analysis

Only those with *DSM-III-R* or *ICD-10* anxiety diagnoses are considered to be affected in the linkage analysis, and the remaining family members are considered to have "unknown" affected status for linkage analysis. The diagnoses leading to affected status are given in table B1 (see appendix B). As has been explained above (see the "Material and Methods" section), the families were constructed on the basis of a genealogical distance of 5 meiotic events, and, therefore, each member was related to at least one other affected member at that or a lower distance. However, the distance between some pairs was higher, and such pairs were also included in the linkage analysis. The positions of all the loci with LOD scores ⩾1.0 in the linkage analysis using the framework markers are shown in table 3, for both sets of families. The analysis for the broad phenotype of anxiety revealed a suggestive locus (LOD = 2.00) at D9S1690 (104.1 cM) and several regions with LOD scores of 1.0–2.0 (table 3).

Figure 1 shows the LOD scores from the genomewide scan for the families with PD. The 25 families with PD have two to five affected members and they provide 60 different affected relative pairs with an average genealogical distance of 3.6 meiotic events. Of the affected relative pairs, only three involve two patients with PD, and the remaining pairs have one member with PD (41 pairs) or neither member with PD (16 pairs). Six regions achieved allele-sharing LOD scores >1.0, and the highest LOD score was 3.89, on

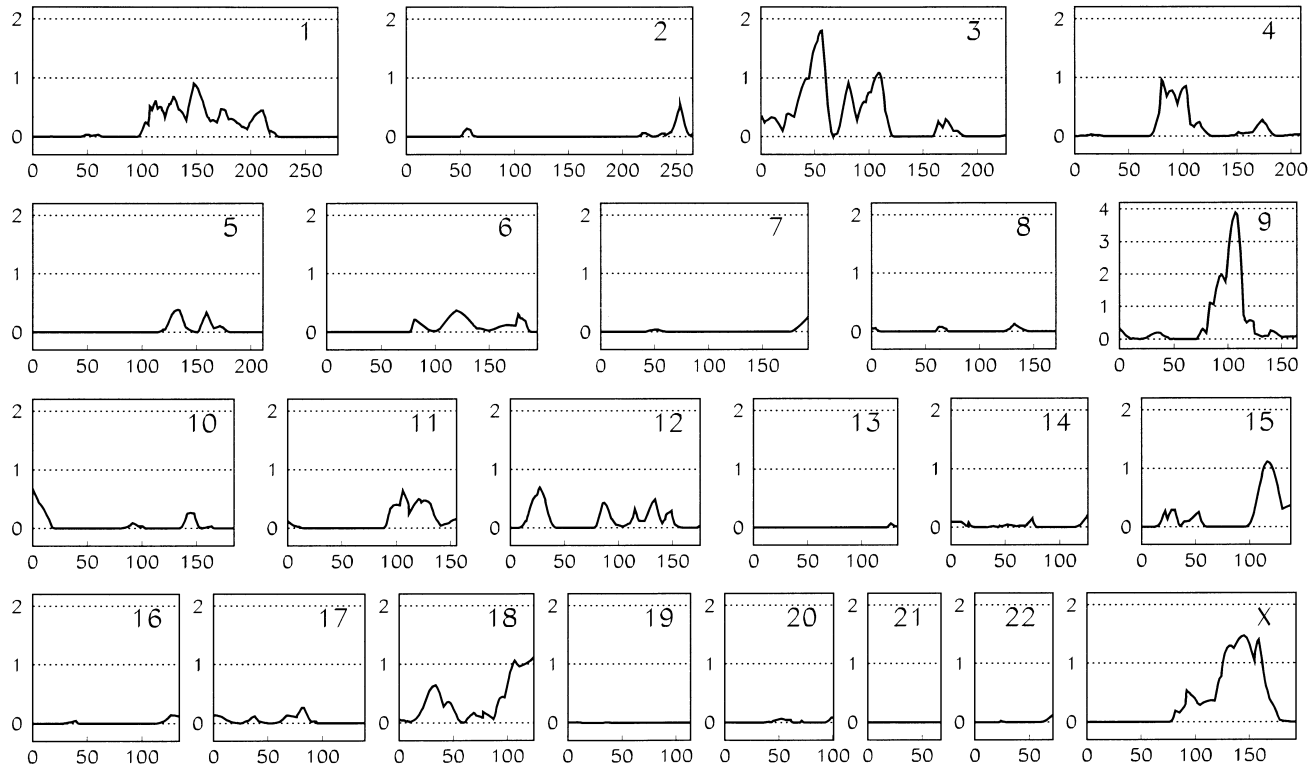

Figure 1 Results of genomewide linkage analysis of 25 families (67 affected members), using a multiplexed framework set of 976 markers. The genotypes of 867 markers were used for analysis, resulting in an average intermarker distance of 4.4 cM. The multipoint allele-sharing LOD score is shown on the *Y*-axis, and the distance (in Kosambi cM) from the p-terminus of each chromosome is shown on the *X*-axis.

chromosome 9 (104.1 cM). We genotyped additional markers in this locus, to bring the information content to 85%. The resulting average intermarker distance was 1.5 cM. Figure 2 depicts the resulting LOD scores on chromosome 9. Linkage analysis using genotypes for the high-density map resulted in a LOD-score maximum of 4.18, at 105.6 cM (D9S271), with an information content of 85%. Although the locus is fairly wide (the LOD score is >1.0 in the region between 79 and 113 cM), the curve is somewhat asymmetric, and the LOD score drops rapidly distal to its maximum. The pointwise *P* value for the locus was 6×10^{-6}, which corresponds to a genomewide adjusted *P* value <.05 (Lander and Kruglyak 1995). The correction for multiple testing is small, since only two complete scans were performed, and the adjusted *P* value remains <.05. No single family is responsible for the LOD score, and 14 of the 25 families have more sharing than had been expected on the basis of their familial relationship alone, at D9S271. Correspondingly, of the 62 families with anxiety, 30 have excess sharing at D9S1690. No other region had LOD scores reaching suggestive levels, but additional regions with maximum LOD scores near 1.0 were observed on five chromosomes: X, 3, 4, 15, and 18 (see fig. 1 and table 3).

Discussion

We have detected linkage of PD and anxiety to chromosome 9q31, with a LOD score of 4.18, in Icelandic families centered on probands with PD. The linked region has a suggestive LOD score of 2.0 in a larger set of families defined by the broader phenotype of anxiety. Although the linkage appears to be strong, the finding should be questioned until it has been replicated, both in additional families from the present study in Iceland and in other populations. The families with PD were collected in an effort whose focus was PD, but more than half of the affected family members had other forms of anxiety without a diagnosis of PD. Whereas all the affected members of these families are related to a proband with PD, only 3 of the 60 affected relative pairs in the linkage analysis involve pairs in which both individuals received a diagnosis of PD. Furthermore, most of the affected members diagnosed with PD have also received other anxiety diagnoses. It is therefore just as likely that

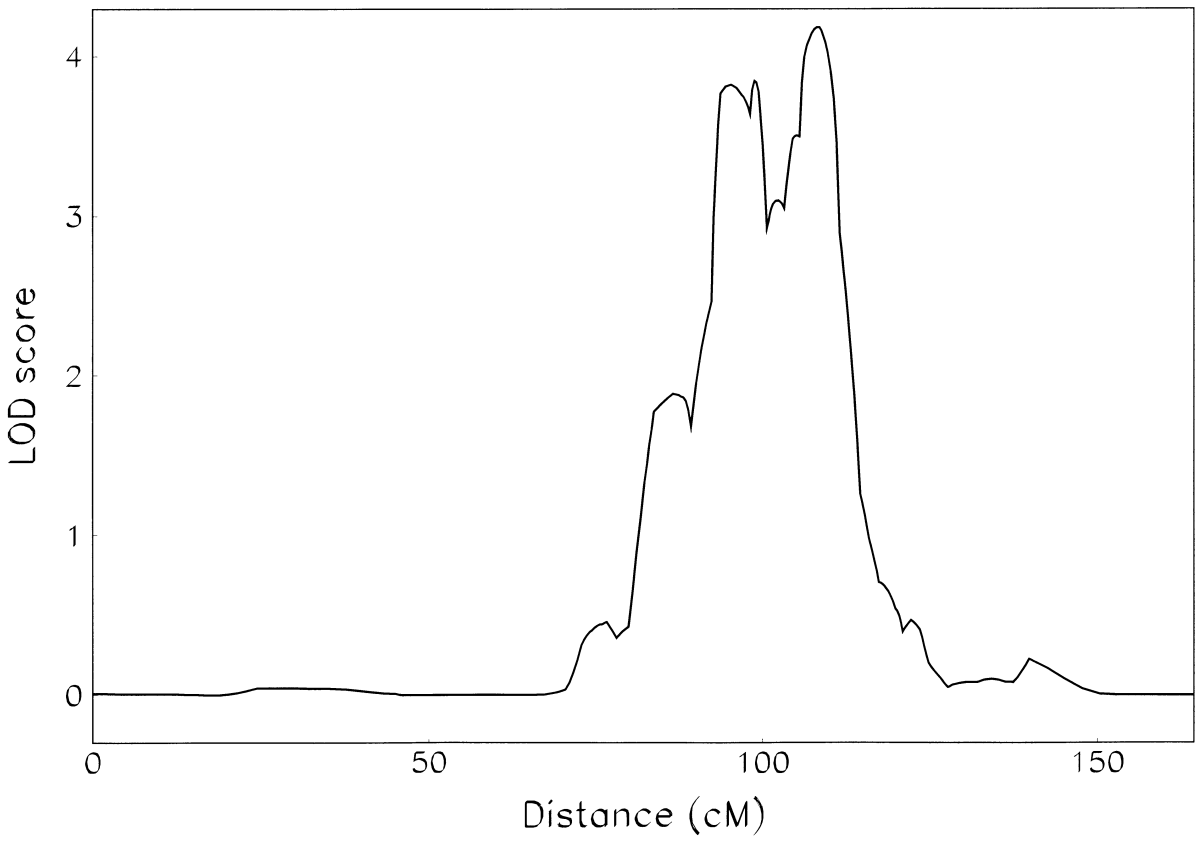

Figure 2 Multipoint allele-sharing LOD scores for chromosome 9, using a higher-resolution map. With an average intermarker distance of 1.5 cM in the linked region, a multipoint LOD score of 4.18 was detected at marker D9S271 (105.6 cM). The multipoint allele-sharing LOD score is shown on the *Y*-axis, and the distance (in Kosambi cM) from the p-terminus is shown on the *X*-axis.

the linkage results are due to a gene that plays a role in susceptibility to anxiety in general, rather than to PD only. However, although 38 affected members did not receive a diagnosis of PD, some may have experienced symptoms of PD or may develop PD later in life. The families were collected on the basis of the SSQ question relating to PD, and, of the 38 without PD, 12 (32%) reported symptoms of PD without fulfilling all the criteria for diagnosis of PD by *ICD-10* or *DSM-III-R*.

Previous genomewide scans have focused on PD, with the exception of one study on PD and agoraphobia (Gelernter et al. 2001). Several loci have been reported, but, to our knowledge, none has reached genomewide significance. A region on chromosome 7p has been implicated twice (Knowles et al. 1998; Crowe et al. 2001), with parametric LOD scores near 2, but the nonparametric LOD score for this region was 0 in the present study. The same holds true for most loci that have previously been reported, but three regions with LOD scores near 1.0 in the present study have been described elsewhere: The peak on chromosome 4 has a LOD-score maximum at 78 cM, and the region (75–105 cM) overlaps with that reported by Gelernter et al. (2001) for agoraphobia. The region on Xq, with a LOD score of 1.47, also overlaps with a region reported by Gelernter et al. (2001) for PD, agoraphobia, and both phenotypes combined. The third region, on chromosome 15q, with a LOD score of 1.0, is just telomeric to the position of DUP25, a recently identified duplication that is associated with PD, phobias, and joint laxity in a Spanish population (Gratacòs et al. 2001).

Although LOD scores <2.0 are far from significant in a genomewide linkage scan, it is possible that some of them represent true anxiety-susceptibility loci, particularly when the regions have been indicated in other studies. That we have detected three such regions in addition to the strong linkage to chromosome 9q may reflect an underlying genetic heterogeneity of anxiety disorders. Interestingly, the overlapping regions are from previous studies involving not only PD but also other forms of anxiety.

Although it is most likely that the linkage is due to a gene that renders susceptibility to multiple forms of

anxiety, alternative explanations are possible. It is, for example, possible that the linkage is specific to conditions related to PD. If this were the case, the phenotype involved would not be PD as defined by the *ICD-10* or *DSM-III-R* systems; rather, it would comprise particular symptoms related to PD, such as the occurrence of a panic attack. The material that we have so far analyzed does not grant enough power to extensively fractionate the phenotypes for analysis, and, because of the high comorbidity among the anxiety disorders, their relative contributions to the linkage cannot be estimated. The same holds true for depression, and, formally, it cannot be ruled out that the linkage is to depression and related conditions, since both depression and GAD are enriched in the families with PD. We are, however, in the process of collecting and genotyping additional families with PD, as well as families found on the basis of answers to the SSQ questions relating to GAD and the phobias. We hope to be able to address the issue of subphenotypes after the analysis of linkage in these families. The analysis of phenotypes of the individuals so far identified clearly shows a high level of comorbidity among the different anxiety disorders and shows that families in which anxiety subtypes are segregating separately are rarely observed. These observations may reflect variable expressivity of each underlying anxiety gene within the same family, as is seen for numerous Mendelian disorders. In conclusion, the most reasonable explanation of our results is that the subtypes of anxiety are all complex disorders sharing some but not necessarily all susceptibility genes and that the locus at chromosome 9q31 most likely harbors a susceptibility gene for both PD and other forms of anxiety.

Acknowledgments

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Appendix A

Stamm Screening Questionnaire (SSQ)

Following are English translations of the five anxiety questions used following our population screening for anxiety when defining cases for the genealogy analysis. The SSQ was translated from German to Icelandic and was then back-translated; the English translation is ours and has not been back-translated.

- Panic attacks.—Have you ever had an anxiety attack, sometimes called "panic attack" or "fear," during which you suddenly were overwhelmed by feelings of intense fear, sadness, or uptightness?
- Generalized anxiety disorder.—Have you ever during your lifetime experienced a period of one month or longer during most of which you felt anxious, tense, or filled with worries?
- Social phobia.—Have you ever suffered from unreasonable intense fear in social situations, such as talking to others, to do certain things in the presence of others, or to be the center of attention?
- Agoraphobia.—Have you ever suffered from unreasonable intense fear when using public transportation, going shopping, waiting in line, or being in public places?
- Simple phobias.—Have there ever been periods of time during which you suffered from unreasonable intense fear of other situations (closed spaces) or things (heights, bad weather, animals)?

Appendix B

Table B1

***ICD-10* and *DSM-III-R* Codes Used in the Assignment of Affected Status**

Disorder	Code(s)	
	ICD-10	*DSM-III-R*
Panic disorder	F40.01, F41.00, F41.01	300.01, 300.21
Anxiety:		
Generalized anxiety disorder	F41.10, F41.11, F41.2	300.02
Agoraphobia	F40.00, F40.01	300.21, 300.22
Social phobia	F40.1	300.23
Simple phobia	F40.2	300.29
Other anxiety disorder	F41.8, F44	300.1, 300.6–8
Somatoform pain	F45.4	307.8
Depression	F32, F33	296.3, 296.4

Electronic-Database Information

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PD)

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