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Linkage analysis of alternative anxiety phenotypes in multiply affected panic disorder families

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Abstract

Background—The choice of phenotype definitions for genetic studies of panic and phobic disorders is complicated by family, twin and neurobiological data indicating both distinct and shared risk factors as well as heterogeneity within categories. We previously reported a genome scan in 120 multiplex panic disorder (PD) families using a phenotype that closely adhered to the DSM IV PD definition. Here we extend this work by conducting exploratory linkage analyses in this same pedigree set using ten additional literature- based panic and phobia-related phenotypes that take into account aspects of these hypothesized complexities.

Methods—Multiply affected families (> 2 individuals with PD) were recruited from clinical and non-clinical sources, evaluated by clinician administered semi-structured interview and subsequent blind consensus best estimate procedure. Each phenotype was analyzed under dominant and recessive models using parametric 2-point (homogeneity and heterogeneity), multipoint, and non-parametric methods. Empirically based permutations were used to estimate model specific and global (across all phenotypes) p-values.

Results—The highest score was a 2-point lod (4.27, global $p < 0.08$) on chromosome 13 (D13S793, 76cM) for the phenotype “specific or social phobia” under a recessive model and conditions of homogeneity. There was minimal support for linkage to any of the remaining nine phenotypes.

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Conflict of Interest Disclosures

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Conclusions—Though interpretation of findings is limited by sample size and the large number of phenotypes and models analyzed these data suggest a region on chromosome 13 as a potential site for further exploration in relation to risk for specific and social phobias.

Keywords

panic; linkage; anxiety; specific phobia; social phobia; phenotype

Introduction

Panic disorder (PD) is a highly familial, genetically complex disorder with heritability estimated at between .3-.5. Family and twin study data indicate shared genetic risk factors among PD and other anxiety disorders, particularly phobias, [3, 4, 5] as well as heterogeneity within the category[4, 6, and 7]. We previously reported a genome scan of 120 multiplex families affected with PD. These initial analyses used a prospectively defined phenotype that closely adhered to the DSM IV definition of the disorder[1, 2]. Here we extend this work by conducting linkage analyses of additional panic and phobia-related phenotypes in the same dataset. Our initial phenotypic definitions are consistent with certain aspects of the twin, family study and psychobiological literature, but there are also compelling data supporting alternative approaches.

On the basis of the literature, particularly recent molecular genetic work, we chose ten panic-related phenotypes and conducted separate linkage analyses of each phenotype in our pedigree set. Table 1 summarizes these phenotypes and previous linkage analyses that have used these (or very similar) definitions. For ease of exposition we have classified the ten phenotypes into three broad categories: 1) composite phenotypes (i.e. phenotypes derived from hypotheses of shared genetic risk factors between PD and other disorders); 2) PD subtypes; and 3) phobias (specific and/or social) that segregate in these families with a high enough frequency to enable a separate linkage analysis.

Below we give a brief rationale for the choice of these phenotypes, organized in terms of these three broad categories. As the multiple testing problem constrains interpretation of these re-analyses, we consider this approach an exploratory (i.e. hypothesis -generating) tool.

Composite phenotypes

These phenotypes are derived from hypotheses of shared genetic risk factors between PD and other disorders. Each of the three is modeled on a phenotype for which suggestive evidence of linkage was found in a recent PD genome scan (Table 1)[8, 9, 10]. The broadest approach is taken by Thorgeirsson and colleagues,[8] who identified pedigrees through an individual with PD, but defined affectedness in relatives to include PD, social, specific or agoraphobia, generalized anxiety disorder (GAD), or somatoform pain. The narrower “PD or phobias” category was suggested by both twin study findings of overlap in the genetic risk factors for PD, social, specific and agoraphobia[11, 5] and a recent collaborative re-analysis of 19 pedigrees[12, 9]. This analysis, incorporating a “fuzzy clustering” approach, facilitates a fine-grained assessment of the interrelationships among the disorders using weighted likelihoods of affectedness of each family member for each of the three disorders. Early comorbid anxiety and the more restrictive phenotype (Diathesis or D-Type PD) tested here were defined by Smoller and colleagues, [10] based on results of longitudinal and family studies of the childhood temperament behavioral inhibition (BI). This phenotype includes individuals who have PD, *and* pre-pubertal onset of either the PD or another anxiety disorder.

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Panic disorder subtypes

Three PD subtypes (PD with agoraphobia [PD+A]; PD without agoraphobia [PD-A]; early-onset PD) have been the subject of considerable study, including work suggesting heritable differences. For example, Kendler et al[4] found both specific and shared (with PD and GAD) genetic contributions to agoraphobia; Noyes et al[6] found equal rates of panic attacks but increased rates of panic disorder with agoraphobia (PDA) among the relatives of probands with PDA when compared with relatives of PD probands. Early onset of PD (< 20 years), has been associated with increased severity, duration, and psychiatric comorbidity, and significantly higher rates of PD have been found in families of probands with early-onset PD when compared to families of probands with late-onset PD[13, 14, 15]. However, there are no molecular genetic data addressing the genetic basis of these observations, and the one family study that examined onset in relatives found no relationship between age of onset in the proband (< 20 years) and age of onset in an affected relative (i.e. early-onset probands did not have early-onset relatives)[13]. We chose to test two definitions of early-onset PD, the < 20 years and < 13 (i.e. pre-pubertal PD).

Specific and social phobia

Twin studies indicate a moderate genetic contribution to risk for both social and specific phobia, with heritability usually in the 0.3-0.6 range[16, 17, 18, 19, 20]. Linkage analyses in pedigree sets collected specifically to study phobias have not been reported. However, Gelernter and colleagues[21, 22] conducted linkage analyses in a set of panic disorder pedigrees, successively using each social and specific phobia (rather than panic disorder) as the "affected" phenotype (Table 1). We use the same strategy here in our collection of pedigrees collected for PD. In addition, as twin study data indicate some overlap between genetic risk factors for social and specific phobia, we include an additional composite phenotype: "social or specific phobia"[23, 5].

Methods

Sample

Recruitment and evaluation of this pedigree sample were previously described[1, 2]. The study was approved by the New York State Psychiatric Institute Institutional Review Board, and all subjects gave informed consent before participating. Briefly, we recruited families from clinical and non-clinical sources who at screening appeared to have at least three affected members willing to be interviewed and to give a blood sample for DNA. All available subjects were interviewed by specially trained clinicians using the SADS L-Anxiety Version (SADS-LA) [24, 25] which provides lifetime DSM III-R or IV diagnoses for most psychiatric disorders, as well as more detailed information about anxiety disorders. Interviewed individuals provided family history information about those relatives thought to have anxiety disorders. Interviewers wrote detailed narratives describing the development of psychiatric symptoms in the context of subject's social history[26]. Depending on phenotype prevalence, each analysis included between 51 and 120 pedigrees (Table 2).

Genotyping

Microsatellite genotyping was conducted at the Center for Inherited Disease Research (CIDR) following the standard CIDR protocol, with a marker set including 384 simple tandem repeats at an average spacing of 9cM, with no gaps greater than 20cM. Quality control procedures were previously described.[2]

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Diagnosis

PD diagnoses and age at onset were arrived at through a best estimate process[1] in which all available materials were independently reviewed by at least two senior clinicians and classified in one of six levels of panic disorder affectedness (definite, probable, possible, "any panic", unaffected, and unknown). We further defined three PD thresholds: Broad (definite, probable, possible, "any panic"), Intermediate (excludes "any panic"); and Narrow (definite or probable). All other diagnoses used to define the various phenotypes (e.g. social and specific phobia, agoraphobia, GAD) are the DSM III R or DSM IV diagnoses made by the clinical interviewer using the SADS-LA. Narratives and interview forms were reviewed by a PhD-level experienced research clinician for diagnostic validity, but a formal best estimate was not carried out for these diagnoses.

Classification of individuals and families for linkage analyses

Phenotype definitions and criteria for including families are described in this section. In all analyses: 1) those individuals who did not meet the specific affected and unaffected criteria were classified as "unknown"; and 2) all 120 families were used unless otherwise specified. This set of 120 families is the same as was reported in our 2006 using article using a PD phenotype that closely adhered to the DSM IV definition.

Composite PD-related phenotypes—*Broad anxiety:* Individuals were included as "affected" if they met criteria for any of these anxiety disorders: Broad PD with or without agoraphobia, GAD, or social or specific phobia. "Unaffecteds" met our "PD unaffected" criteria *and* did not have any of the above listed anxiety disorders. *PD or phobias:* Affected was defined as having Broad PD or specific or social phobia, and unaffected, as meeting our "PD unaffected" criteria *and* not having social or specific phobia. *Early comorbid anxiety*: Affected was defined as: 1) Broad PD at or before age 13 years or 2) another anxiety disorder at or before age 13 *and* PD at any age. Individuals without PD were classified as unaffected.

PD subtypes—For each analysis, families with at least one person who met the affected criteria were included; unaffected was defined as our best estimate unaffected category. *Panic disorder without agoraphobia (PD-A):* Affected individuals met criteria for definite, probable or possible PD but *not* for agoraphobia. *Panic disorder with agoraphobia (PD+A):* Affected individuals met criteria for both any level of PD *and* agoraphobia. *Early onset PD:* We analyzed two definitions: ≤ 20 and ≤ 13 years. In each case affected individuals met the Broad PD criteria by the given age.

Phobic disorders—These three analyses followed the same format. Individuals were considered affected if they met the DSM IIIR or IV criteria for the phobic disorder studied; families with at least two persons with the phobia diagnosis were included in the analysis; and all persons without the diagnosis were classified as unaffected. Individuals were considered affected if they met criteria for social phobia in the first analysis, for specific phobia in the second analysis, and for *either* social or specific phobia in the third analysis.

Linkage analysis

Statistical procedures were the same as those in our primary report[2]. Each phenotype was analyzed under two genetic models (dominant and recessive), using both parametric (2-point, multipoint) and non-parametric methods. We performed 2-point parametric analyses twice, first using sex-averaged recombination fractions, then allowing for gender-specific recombination fractions. FASTLINK[27] and ANALYZE[28] were used for the 2-point analyses and GENEHUNTER[29], for the multipoint parametric and nonparametric calculations.

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Although we consider these analyses to be exploratory, it nevertheless seemed of interest to have a systematic evaluation of the relative significance of the linkage findings, though to do so required taking into account the large number of models and phenotypes examined. To this end, and given the computational intensity, we adopted a two-step permutation based approach. First we estimated empirical p-values *within* each phenotype using 100 randomized replicates. Then, for our best-supported scores, we estimated phenotype-specific and "global" (maximized across all models and phenotypes) p-values in 10,000 replicates created through bootstrap re-sampling. The randomized replicates of the data were generated by random assignment of genotypes to the founders within each family, while conditioning on the observed allele frequency and inter-marker distances in the data, and then matching individuals within families according to the observed pedigree structure using the program SIMULATE[30]. In this way, 100 randomized replicates of the data were generated and then analyzed for each of the genetic markers and models (dominant, recessive) considered in this study.[2] Model-specific p-values were estimated *within each phenotype* maximizing across genetic models and markers. This estimate is done by recording the number of times a maximum lod score from a replicate exceeds the maximum lod score from that of the observed data, and therefore corrects for the testing of multiple marker loci examined. Lod scores that achieved model specific $p < 0.05$ in this analysis were further evaluated as follows. First, 100 of the original replicates were used for bootstrap re-sampling 10,000 times. This new sample was then used to estimate both the model-specific and the global empirical p-values at the markers for which lods with $p < 0.05$ were achieved in the first stage analysis. These analyses were done using the same genetic models (i.e., in this case 2-point lods, under dominant and recessive models, but assuming homogeneity, see Table 2 below) that were used in the first-stage analysis of that marker. The global p-value was estimated by maximizing the lod scores across all genotypic-phenotypic models for each replicate, and then recording the number of times these maximized scores exceed the observed model-specific lod score per replicate. The global p-value accounts for all markers and models tested. Thus it accurately captures the experimental design of this study and provides a reliable measure for interpreting the findings.

Results

Table 2 gives the maximum lod scores and the number of families/subjects included in the analysis for each of our ten phenotypes. The maximum lod scores for each of the ten phenotypes under any model are shown in Table 2. The highest score (lod = 4.27) was a 2-point lod on chromosome 13 (D13S793, 76cM) for the phenotype "specific or social phobia" under a recessive model and conditions of homogeneity. For that analysis, a model-specific p-value was estimated at 0.01 using our initial 100 replicates. In the second permutation analysis, using the 10,000 bootstrapped replicates, we estimated the model-specific p-value at 0.002 and the global $p < 0.08$. However, multipoint and NPL scores for "specific or social phobia" under the same model were modest (1.13 and 1.05 respectively). At this same location and under the same genetic model, the specific phobia phenotype on its own also achieved a model-specific lod with p-value less than 0.03 in the initial 100 replicate analyses. However, in the larger bootstrapped permutation sample the model-specific p was higher (0.07), and the global $p = 0.846$. The only other phenotype that achieved a lod score with accompanying p-values less than 0.10 was early-onset PD defined as onset before age 13 years. For this phenotype a 2-point mode-specific lod of 2.69 ($p = 0.06$) was found using the 100 replicates on chromosome 20 at marker D20S480, under a recessive model and conditions of homogeneity. The corresponding model-specific and global p-values in the 10,000 replicate analyses under the same genetic model were 0.07 and 0.90 respectively. We did not replicate results of previous scans. For each phenotype, maximum lod scores were < 1.0 (data not shown) at the highest scoring locations in this earlier work (Table 1).

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Discussion

These exploratory re-analyses provide suggestive evidence for a susceptibility locus for a "social or specific phobia" phenotype on chromosome 13q within families also affected by PD. In this sample there was minimal support for linkage to any of the remaining nine phenotypes.

Though we consider the "specific or social phobia" findings on chromosome 13q of interest for further prospective study, we also emphasize their significant limitations. These include: moderate sample size; the large number of phenotypic, genetic and statistical models analyzed; and the lack of convergent support from our nonparametric and multipoint analyses; though, the latter may simply represent a loss of power due to GENEHUNTER's trimming of samples (a necessity in analysis of complex pedigrees) rather than divergent evidence from multipoint and 2-point methods. To our knowledge the only previous molecular genetic studies of the specific or social phobia phenotypes are the reports by Gelernter and colleagues, [21, 22] on which we modeled our phobia analyses. As shown in Table 1, the regions of their maximum lod scores were on chromosomes 14 and 16 respectively. Lod scores at these sites in our data set were < 1.0 for all three phobia phenotypes under all models. Gelernter and colleagues[21, 22] did not report data on the combined phobia phenotype.

The 10 Mb interval surrounding our peak (D13S793 at 76cM) includes over 30 genes. Though none of these genes has been previously associated with PD, several are intriguing candidates, as they are involved in aspects of neural development or function (e.g., FGF14, NALCN). However, as there is little knowledge of the etiology of phobias at the molecular level [32] it is difficult to construct specific hypotheses. In addition, though the genes that investigators discover for complex diseases are not necessarily those that anyone had predicted ahead of time would be involved in those diseases[33], we are not aware of data supporting any mechanism that would particularly link phobias to any of these processes. Interestingly, a small genome-wide association study of PD initially reported an association to a DNA variant just 1.4Mb from D13S793 ($p = 3\times10^{-7}$), but the finding was not replicated in an enlarged sample.[34, 35]

Of note, our previous study reported linkage between this same region on chromosome 13 (76cM, D13S793, 2 point HLOD = 3.57) and a potentially pleiotropic PD syndrome[31, 7] characterized by aggregation of PD and several medical disorders (renal/bladder problems, thyroid disease, migraines and other serious headaches, mitral valve prolapse) within a subset (N = 60) of our original120-family PD pedigree set. Given the available data it is not possible to determine whether this convergence reflects pleiotropy (i.e. phobias are also part of this previously identified syndrome) or two independent findings within the same region. The maximum scores for the "syndrome" and our phobia phenotype did occur under different genetic models (dominant and recessive, respectively). The 2-point lod score for "social or specific phobia" at D13S793 under a dominant model was 1.1. In addition, when we used a combined phenotype (affected = "syndrome" or "social or specific phobia") in a post hoc analysis within the 60 original syndrome families[7], the 2-point lod scores at D13S793 were considerably lower than those found using the original syndrome phenotype and did not provide substantial evidence for linkage (recessive model, homogeneity 0.45, heterogeneity 0.80; dominant model, homogeneity 0.83, heterogeneity 1.1). However, though these observations are consistent with independence they do not address the possibility of genetic heterogeneity within our specific/social phobia cases, or indirect influence of multiple interacting genes. Therefore pleiotropy cannot be ruled out.

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The possibility of a genetic variant that confers risk for either social or specific phobia (e.g. "phobia proneness") is consistent with previous genetic epidemiological data, though in some studies the best-fitting models suggest that social phobia has a closer relationship to PD or generalized anxiety than to specific phobia. For example, structural modeling analyses in the Virginia Twin Registry[23, 5] indicated two major additive genetic factors that contribute to anxiety disorders. Of these, one contributes roughly half the liability for situational and animal phobias and 15% of the liability for social phobia. The second factor contributes about 30% of the liability for social phobia, but only 10% for each type of specific phobia. Similarly, a Norwegian population-based twin/family study of irrational fears indicated that a genetic factor common to all irrational fears contributed 20% of the liability for animal and situational fears, but only 1% of liability for social fears[36].

Given the current experience in psychiatric genetics we do not find our failure to replicate previous work surprising.[37, 38] The most likely explanation is moderate sample size. Although our dataset is larger than most of those used to generate the original signals, none of the panic-related linkage samples described here would be expected to have sufficient power to detect linkage for genes contributing the small increases in liability that seem to characterize complex disorders.[39] In addition to our moderate sample sizes and significance levels (with their accompanying risk of false positives in the context of a study of genetically complex disorders), we also note: cross-study differences in diagnostic conventions and populations (e.g. Thorgierssen's population based vs our volunteer sample[8]); inaccuracies inherent in our attempt to retrospectively match diagnostic criteria for certain phenotypes (e.g. D type, broad anxiety) and the absence of analyses considering comorbid conditions (e.g. major depression, substance and alcohol abuse). In some cases [10,12] the analytic strategies and model parameters we used were almost identical to those in the previous reports or differed only in ways [21] unlikely to have a large effect on outcome[40]. However, in the case of the studies by Kaabi et al [9] and Thorgierssen[8] there were significant analytic differences that must be taken into account in evaluating our results.

In summary, we conducted exploratory linkage analyses of ten panic/phobia related phenotypes suggested by the literature in a previously analyzed panic pedigree set. We did not replicate any of the findings of previous investigators using similar phenotypes in panic disorder pedigrees. The analysis of a combined phobia phenotype (specific or social phobia) suggests a region on chromosome 13 as a potential site for further exploration in relation to risk for these disorders.

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TABLE 1

Panic disorder related phenotypes with maximum lod score locations in published linkage studies

Phenotype Category	Phenotypes analyzed in this report	Previous studies using same or similar phenotype[1]			
		Investigator	**Location**	**Max Lod**	**p**
Panic related phenotypes from previous PD genome scans	Broad Anxiety (any anxiety or somatoform disorder in families identified thru PD proband)	Thorgeirsson et al, (2003)[2]	D9S271 (105.6cM)	Lod =4.18	.05 (genome-wide)
	PD or Phobias (PD, social, specific or agoraphobia)	Kaabi et al (2006)[3] (Gelernter pedigrees)	D4S413 (158cM)	Lod>4	.0006 (empirical)
	Early co-morbid anxiety (PD and either PD or other anxiety at <13yrs	Smoller et al, (2001)[4]	D1S1678 (218cM) D10S587(147cM)	NPL=2.05 Lod =2.38	.035 --
PD subtypes	PD/Agoraphobia	Gelernter et al (2001)	D3S1279(167M)	NPL=2.75	.005
	PD/No Agoraphobia	NONE			
	Early onset PD (< 20 yrs)	NONE			
	Childhood onset PD (<13 yrs)	NONE			
Phobias segregating in PD pedigrees	Specific phobia	Gelernter et al. (2003)	D14S75 (37cM) Chr 14 (35cM)	Lod =3.17 Zlr =3.93	-- .00005
	Social phobia	Gelernter et al. (2004)	Chr 16 (62cM) Chr 16 (71cM)	Zlr =3.41 Lod =2.22	.0003 ---
	Specific or social phobia	NONE			

[1] Differences between phenotype as defined in published report and phenotypes used in our analyses are given in the footnotes below

[2] Thorgeirsson et al. included as affected: PD, GAD, social or specific phobia, somatoform disorder or subthreshold somatoform pain. We did not have data on the subthreshold somatoform syndrome. In addition we had only 4 cases of somatoform so our criteria or measurement methods most likely differed from theirs.

[3] Kaabi et al. used a fuzzy cluster method that gives weighted values to each diagnosis, here we include individuals as affected if they have any one of the three disorders, giving equal weight to each and ignoring comorbidity.

[4] Smoller et al. required onset of anxiety in childhood, PD and persistence of anxiety disorder into adulthood. As only lifetime diagnoses were coded, in some cases the latter criterion could not be confirmed. Subjects in our analyses were considered affected if they met the first two criteria.

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Table 2

Linkage analyses of panic-related phenotypes: maximum lod scores

Phenotype Category	Phenotype	Current study sample size		Current Study: Maximum Lod[3]			
		Number of Families	Individuals Genotyped (Affected/All)	Chrom	Marker (cM)	Model	Lod Score[1]
Composite PD-related phenotypes based on previous scans[2]	*Broad anxiety* (PD, GAD, Soc, Spec, somatoform)	120	869/992	2	D2S125 (261)	Dominant Sex-dif, Hetlod	2.64
	PD or phobias (PD, specific social, or agoraphobia) [3]	120	861/992	2	D2S125 (261)	Dominant Sex-dif, Hetlod	2.52
	Early comorbid anxiety (PD & anxiety disorder <13 years)	120	247992	2	D2S1788 (56)	Recessive Sex dif, Hetlod	1.96
Panic Disorder Subtypes	PD no Agoraphobia	112	379/916	16	N/A (141)	Dominant MP, Hetlod	*2.76*†
	PD with Agoraphobia	92	271/824	7	D7S821 (109)	Recessive Sex-dif, Hetlod	2.67
	Early onset PD (≤20)	91	213/767	4	D4S2361 (93)	Dominant 2 point, Hetlod	2.29
	Early onset PD (≤13)	51	81/734	20	D20S480 (80)	Recessive 2point, Homlod	2.69†
Anxiety Disorders Segregating in PD pedigrees	Specific Phobia	69	247/644	13	D13S793 (76)	Recessive 2point, Homlod	**2.77**$^{*\#}$
	Social Phobia	61	213/609	7	D7S1799 (114)	Dominant 2pint, Hetlod	2.28
	Specific or Social Phobia	93	386/816	13	D13S793 (76)	Recessive 2point, Homlod	**4.27**$^{**\Psi}$

[1] Significance: Model specific p values (see text, data analysis)

† p=0.1;

* p≤.05;

** p≤.01.

"Global" p values:

$^{\Psi}$ p=.076;

$^{\#}$ p=0.9

[2] Modified respectively from Thorgeirsson et al, 2004; Kaabi et al, 2006; and Smoller et al, 2001.

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[3] Abbreviations: Chrom = chromosome; cM=centimorgans, Hetlod = lod calculated under assumption of heterogeneity; Homlod = lod calculated under assumption of homogeneity; MP= multipoint, N/A = not apply; sex-dif = calculated will allowance for gender distinction in recombination fraction.