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Panic Disorder, Social Anxiety Disorder, and a possible medical syndrome previously linked to Chromosome 13

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Abstract

Background—Several studies have identified increased medical problems among individuals with panic disorder (PD). We previously found that specific conditions— interstitial cystitis (IC), mitral valve prolapse (MVP), migraines, and thyroid disorders— aggregated non-randomly among panic families (we called this the “PD syndrome”), and that families with and without the syndrome were genetically distinguishable on chromosome 13. We present data from a new case-control study that replicates and extends the syndrome phenotype clinically.

Method—Probands with a definite diagnosis and family history of PD (N= 219), social anxiety disorder (SAD; 199), or both (173), and 102 controls with no personal/family history of anxiety, were interviewed using the SADS-LA diagnostic instrument. Medical history was obtained via medical checklist and the family history screen; IC symptoms were assessed using criteria developed by the National Institute for Diabetes and Digestive and Kidney Diseases. Subjects and interviewers were unaware of the syndrome hypothesis; final best-estimate diagnoses were blind to syndrome data.

Results—Probands with PD or SAD, as compared to controls, were five or more times as likely to report IC symptoms, and twice as likely to report MVP and migraines (other genitourinary and cardiovascular problems were not elevated). First-degree relatives of probands with PD or SAD were also at increased risk for IC, MVP, thyroid problems and headaches, regardless of whether the proband reported the same condition.

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Conclusion—These findings are consistent with previous data supporting a PD syndrome, and further suggest that this syndrome may include other anxiety disorders well.

Keywords

panic disorder; social anxiety disorder/social phobia; interstitial cystitis; mitral valve prolapse; migraines; headaches; chromosome 13

Introduction

Panic disorder (PD) is a complex anxiety disorder characterized by recurrent episodes of sudden and uncontrollable fear, accompanied by cardio-respiratory (e.g., shortness of breath, chest pain, palpitations), gastrointestinal (nausea, abdominal distress), neurological (dizziness, trembling), and other autonomic responses. PD has a lifetime prevalence of approximately 1-3%, with mean age at onset in early adulthood, and is more common among women than men. Heritability estimates from twin studies range as high as 49%, suggesting a significant genetic role.(1-3)

Previous clinical and epidemiological studies have identified disproportionately high lifetime rates of cardiovascular/cerebrovascular, gastrointestinal, genitourinary, and other general medical problems in individuals with PD.(4-7) However, these studies had focused primarily on individual medical conditions rather than clusters within individuals or families. In the course of a genetic study of multiplex families with PD,(8,9) we observed that some medical problems— particularly those associated with the bladder, thyroid, and cardiovascular system (notably, mitral valve prolapse)- tended to aggregate non-randomly in some families but not others. We hypothesized that the subgroup of panic families who had these medical conditions (which we called “the syndrome”) may be genetically distinct from those that did not. Indeed, linkage analyses following reclassifications of families based on the presence or absence of the syndrome revealed a strong peak (logarithm of odds [lod] score, 4.2) on chromosome 13q (marker D13S779), suggesting that these seemingly diverse medical symptoms may be attributable to common genetic mechanisms (a phenomenon known as pleiotropy(10)). These findings were subsequently replicated in a larger study of 587 individuals in 60 multiplex pedigrees (including the original 34 families)(11) that also identified a syndrome-related linkage peak on chromosome 13q (lod score 3.57, on marker D13S793).

The strongest linkage evidence in the genetic studies was for the kidney and bladder problems (lod scores > 4), but it was unclear at the time what these symptoms represented. When reviewed *post hoc* by an urologist, these problems appeared suggestive of interstitial cystitis (IC) (also referred to as painful bladder syndrome [PBS]), a chronic and debilitating syndrome characterized by a frequent or urgent need to urinate, and pain and discomfort on bladder filling, which are not accounted for by a urinary tract infection.(12) IC has a low lifetime prevalence (< 0.5%), and like PD, is more common among women, although with a later onset age at around 40 years.(13) Also consistent with the syndrome, IC is frequently accompanied by neurological, gastro-intestinal, and musculoskeletal distress,(13-15) and data from twin studies allude to possible genetic underpinnings.(16,17) A large genetic study of IC is currently underway.

To follow up on the bladder findings, we designed a case-control study to assess panic and other syndrome conditions blindly among clinical IC cases that were well-documented by urologists using urodynamics and/or cystoscopy with bladder distention.(18) Consistent with the previous studies, patients with IC (as compared to non-IC urological controls) had a four-fold higher lifetime prevalence of PD and a two-fold higher prevalence of any of the

syndrome conditions. Furthermore, first-degree relatives of probands with IC were also significantly more likely to have PD, thyroid disorder, and urologic problems than those of controls, regardless of whether the proband had the same medical condition.

We present data on the possible “chromosome 13 syndrome” in a new case-control study of panic disorder (PD) and social anxiety disorder (SAD; termed interchangeably in the DSM-IV as social phobia). SAD, which is characterized by significant and persistent fear of performance and social situations, is one of the most prevalent psychiatric disorders (prevalence of the full disorder ranges from 3–4%, with mean age of onset in the early teens(19)). Akin to PD, it is also more common among women, with some evidence for genetic susceptibility.(20–22) This paper is a follow-up of our original findings in this new sample to determine replication and specificity for PD. The sample includes a new proband group— SAD, as well as a “pure” control group with no lifetime psychiatric disorder or family history of anxiety. IC symptoms are assessed using screening criteria developed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for genetic studies.

We test the hypotheses that 1) probands with PD would have higher rates of IC, MVP, migraines or chronic headaches and thyroid problems (i.e., the syndrome medical conditions) than control probands free of any personal or family history of psychiatric diagnoses; and 2) first-degree relatives of probands with PD would have higher odds of the syndrome conditions compared to relatives of control probands, and this association would hold true regardless of whether or not the probands had the same conditions themselves. We also test the above hypotheses for probands with SAD to determine specificity of the syndrome.

Materials & Methods

Inclusion/Exclusion Criteria

Probands were required to be aged 18 - 65 at the time of assessment, and to have a definite DSM-IV(23) diagnosis of panic disorder (PD), social anxiety disorder (SAD), or both. Because earlier age of onset has been shown to be associated with increased familial aggregation and greater longitudinal severity, (24) we required first onset by age 30. Probands with a history of bipolar disorder, schizophrenia, or anti-social personality, were excluded *a priori*, as were those for whom a medical or neurological disorder, or use of a substance, was judged to be the cause of the anxiety symptoms. PD could be manifest with or without agoraphobia. For SAD, evidence of generalized phobia(25) was required. Finally, in order to maximize the likelihood of capturing familial forms of the disorders, probands were also required to report a family history of anxiety in at least one first-degree relative; however, we also included 16 (2%) probands whose family history was either uncertain or present only in a second-degree relative. Controls were required to have no evidence of any psychiatric disorder over their lifetime, with exceptions for minor depressive disorder, bereavement, adjustment disorders, or substance abuse (but not dependence) in adolescence, college, or the military, as well as no history of any anxiety symptoms in any first- or second-degree relative. Because panic disorder typically onsets in early adulthood, and social phobia in early teens, (19,26) controls were also required to be at least 30 years old at the time of assessment to minimize the possibility of capturing those who were still at risk for developing these disorders.

Recruitment

The study was conducted between May 2004 and December 2006. Subjects were recruited from across the United States via community-based mailings or media articles and websites

describing the study. All procedures were approved by the New York State Psychiatric Institute's Institutional Review Board. All eligible subjects gave written consent prior to participation, and were remunerated \$75 following completion of the study. Subjects were not aware of the syndrome hypothesis. Of 794 subjects interviewed, 101 (13%) met one or more exclusion criteria. The remaining eligible population included 219 subjects with a definite diagnosis of PD only, 199 with definite SAD only, 173 with definite PD and definite SAD, and 102 normal controls. Sixty-eight percent of PD probands had agoraphobia as well; however, because neither the presence of agoraphobia, nor the temporal sequence (i.e., whether panic symptoms preceded agoraphobic ones, or vice versa) impacted any findings, PD probands were grouped together. Ten probands with definite PD also had a possible SAD diagnosis, and 29 SAD probands had a possible PD diagnosis. Because the second diagnosis was not definite, these subjects were retained in their respective PD-only or SAD-only categories. However, neither alternate placement of these subjects in the combined PD and SAD group, nor their exclusion from the analyses, changed the main findings.

Assessments

The diagnostic assessments were administered by trained doctoral- and masters-level mental health professionals. Interviewers first observed interviews being conducted by a clinically trained supervisor, and then completed training practice interviews and prepared interview narratives on which they received discussion and feedback. No interviewer entered the field until the co-rated interviews had been passed by the supervisor. Interview consistency was monitored throughout the study by the supervisor who compared narrative summaries to actual interviewer diagnosis and returned interviews for checking or further interviewing where there was lack of clarity, inconsistency, or missing information.

Diagnoses were ascertained using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version modified for the study of anxiety disorders and updated for DSM IV (SADS-LA IV).(27) A medical history was obtained during the course of the interviewing via a medical problem checklist that included 64 questions grouped in the following categories: cancer, cardiovascular, dermatologic, endocrine/glandular, gastrointestinal, genitourinary, hematological, infections, metabolic, musculo-skeletal, neurological/neuromuscular, respiratory, systemic, and a free-response "other" category. Subjects were asked if they had ever experienced each of the conditions, and if so, the age at onset. Syndrome conditions were not grouped together but were probed in the respective medical categories. In order to obtain more detailed information on IC, we also included an interviewer-administered screen, based on consensus criteria developed by the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK).(28) To screen positive, probands were required to have experienced several weeks of pain, pressure, or discomfort coming from the bladder, *as well as* several weeks of increased urinary urgency ["compelling urge to urinate, which is difficult to postpone"] or frequency [voiding ≥ 8 times per 24 hours, including ≥ 2 at night], during a time that they were not pregnant or having a urinary tract infection. Because of the current debate over criteria required for a diagnosis of IC (29,30), we also tested alternate definitions requiring (1) both urinary urgency *and* frequency; (2) increase in pain, pressure or discomfort as the next urination approached, and/or decrease following voiding, and (3) both (1) and (2). Similar classifications have been used in other recent studies.(31,32)

Finally, medical history on first-degree relatives of 690 (99.6%) probands was obtained during the interview using the Family History Screen (FHS), with the proband as the informant. The FHS has been demonstrated to have good validity, reliability, and agreement with best-estimate diagnoses.(33) Final psychiatric diagnoses were made by a clinically trained person based on all available diagnostic information using the Best Estimate

Procedure.(34) The person determining the diagnosis was uninvolved in the interviewing, and was blind to the subject's syndrome and genetic data.

Statistical Methods

All statistical analyses were performed in Statistical Analysis Software (SAS) Version 9.0 (Cary, NC). Differences in demographic characteristics between cases and controls were examined using Chi-Square tests for categorical variables (or Fisher's Exact test, if one or more cell had an expected cell count of less than 5), and an Analysis of Variance (ANOVA) for age. The rates of medical conditions for each proband group were analyzed using a multivariate logistic regression model, with the medical condition of interest as the dichotomous outcome variable, the proband group as the risk factor of interest, and age and sex included as covariates for adjustment. Contrast matrices were included to compare the PD, SAD, and the PD + SAD groups each to the normal controls, as well as the PD, SAD and the PD + SAD groups to each other. The same methods were employed for outcomes in the first-degree relatives, with the further addition of a dichotomous variable indicating whether or not the proband endorsed having the same symptoms. For analyses of onset ages, a linear regression model was used, with the age of onset as the continuous dependent variable, the proband group as the independent variable, and age and sex as covariates. Even though all analyses had been adjusted for age and sex, we repeated the analyses using only subjects 30-60 years of age (N = 446), such that the groups were equalized on age and gender. These analyses replicated the findings (details not shown but available upon request).

Results

Demographics

Subject demographic characteristics are shown in Table 1. As compared to controls, probands with an anxiety disorder were more likely to be female (77 vs 56%), and (by design, as controls had to be ≥ 30 years of age to ensure passage through the age of risk) younger (mean age, 38[SD 11.8] v 51[14.5] yrs). Controls were more likely to be married and to have a college degree. There were no demographic differences between probands with PD and those with SAD. All data presented are adjusted for proband age and gender, in addition to other variables as specified.

Proband Medical Conditions

Lifetime rates of medical conditions for probands with PD, SAD, and both PD and SAD, as well as for normal controls, are shown in Table 2. Among the conditions hypothesized *a priori* to constitute the syndrome, rates of interstitial cystitis (IC) symptoms, mitral valve prolapse (MVP), and chronic headaches were significantly elevated in probands with either PD or SAD, as compared to normal controls. Rates for thyroid disorders did not differ between groups. The findings were strongest for interstitial cystitis. After adjusting for age and gender, probands with PD were eight, and those with SAD five, times as likely as controls to screen positive for IC symptoms. These elevated rates were not accounted for by possible confounders of IC symptoms (such as bladder cancer, surgery, calculi, infection, or radiation; tuberculosis; herpes), and remained significant following testing with modified criteria for IC (see methods). The nationwide prevalence is below 0.5%; yet twenty-three (4%) anxiety probands, as compared to only 1 (< 1%) control, reported having been diagnosed with IC by an urologist or physician. These findings were specific to IC symptoms, and not present for other genitourinary problems.

After adjusting for age and gender, probands with PD were also at a two-fold or higher risk, as compared to controls, for mitral valve prolapse (but not any other cardiovascular

problems) and chronic headaches, as well as specific gastrointestinal (ulcers, colitis /irritable bowel syndrome), metabolic (hypercholesterolemia, hypoglycemia), respiratory (bronchitis), and skin disorders. With ulcers excepted, the same conditions were also elevated in probands with SAD. Migraines were more common among PD than SAD probands, but there were no differences in rates of any other medical conditions, nor any differences in their ages at onset, between the PD and SAD probands. Within the PD group, findings did not vary by presence/absence of agoraphobia. When the models for syndrome outcomes (i.e., IC, MVP and chronic headaches) were re-tested adjusting for other elevated medical conditions, the findings remain unchanged.

Overall, probands with PD were more than five times as likely as controls, and those with SAD four times as likely, to report any medical condition. Probands who had both PD and SAD were at the highest risk, reporting conditions at more than six-fold the rate of controls. When the medical conditions were stratified by whether or not they belonged to the *a priori* syndrome hypothesis, there was a significant *proband group x syndrome* interaction ($p = .048$), indicating that elevation of medical problems among anxiety probands was greater for syndrome-specific than for general medical outcomes, and therefore unlikely to be due to generalized over-reporting resulting from anxiety.

Comorbid Psychiatric Diagnoses

Lifetime comorbid psychiatric disorders for the probands with PD and SAD are shown in Table 3 (controls were diagnosis-free). No significant differences between PD and SAD probands were found, although probands who had *both* PD and SAD were more likely to have generalized anxiety disorder (GAD) and recurrent major depressive disorder (MDD) than those with either PD or SAD alone. The presence of GAD, specific phobia, and MDD were also each associated with increased risk for IC symptoms, but not any other medical conditions. For example, 35% of PD/SAD probands with comorbid GAD, as compared to those 17% of those without, had IC symptoms (AOR = 2.4 [1.4, 4.3] $p = .003$); similarly for comorbid MDD (26 v 17%, OR = 1.7 [1.1, 2.7] $p = .03$) and specific phobia (27 v 16%, (OR [95% CI] = 1.8[1.2, 2.9], $p = .007$).

First-Degree Relatives

Finally, we examined the rates of medical conditions (as reported by the proband) among the first-degree relatives (FDRs) of probands with and without an anxiety disorder (Table 4). After adjusting for age and sex, as well as the number of FDRs per family, relatives of probands with PD or SAD, as compared to those of controls, were also at higher risk for IC symptoms, mitral valve prolapse (trend level only), chronic headaches, and thyroid disorders (Table 4). Fourteen (2%) probands with PD or SAD, but no control, reported that one or more of their relatives had been diagnosed with IC by a physician. Overall, probands with either PD or SAD reported a medical condition in an FDR at more than twice the rate of controls. These elevated rates remained significant following either (1) further adjusting for whether or not the proband reported having the same medical condition as that he/she ascribed to the relative, or (2) the exclusion of cases where the proband had the same condition. These observations are consistent with the original hypothesis, and argue against reporting bias by the proband, as well as against transmission of medical conditions independently of the anxiety disorders.

Discussion

This report clinically confirms and extends previous investigations of the possible chromosome 13 syndrome. (8,9,11,18) In the present study, probands with PD or SAD, as well as their first-degree relatives, were more likely to have symptoms of IC, as well as

mitral valve prolapse (MVP), and chronic headaches. Findings for hyperthyroidism, though in the same direction, were not significant, but six additional medical conditions not tested in previous studies were elevated. The associations were strongest for the IC symptoms, consistent with the high lod scores obtained in our previous genetic studies.(9,11) We tested multiple definitions of IC to accommodate the controversy in the literature over the requirements of frequency and urgency of urination as criteria for a diagnosis (29,30), but found no differences. Furthermore, 4% of probands with an anxiety disorder, and 2% of their first-degree relatives had received a formal diagnosis of IC by a physician— a striking number given the very low nationwide prevalence of the disorder. Two aspects of our observations bear particular note. First, the elevated rates of medical symptoms reported by probands *vis a vis* normal controls were specific— for example, to MVP but not other cardiovascular problems, to IC but not other genitourinary problems. Second, the ascribing of medical symptoms to first-degree relatives by the proband was not influenced by whether or not the proband had the same symptoms. It is unlikely therefore that the findings of this study are driven by a generalized over-reporting of symptoms disorders resulting from anxiety disorders.

The findings in the probands and their first-degree relatives are consistent with a pleiotropic model for PD, and suggest that the syndrome includes SAD, and possibly other disorders along the mood-anxiety spectrum as well. Although no study thus far has investigated the syndrome genetically in phobias, the elevated rates of all syndrome conditions in probands with SAD in the present study, coupled with previous evidence that SAD co-segregates with PD(3), are consistent with the hypothesis that the possible chromosome 13 syndrome may convey a broader vulnerability to fear and anxiety as opposed to a PD-specific mechanism. Although the biological mechanisms of this syndrome are still unclear, dysregulation of the autonomic nervous system has been postulated as a source(35,36). Perception of a threatening stimulus activates the amygdala, stimulating release of corticotrophin-releasing factor (CRF) from the hypothalamus and norepinephrine (NE) from brainstem nuclei, notably the locus ceruleus (LC) which comprises more than 70% of all NE projections to the forebrain. When activated, the LC projects to a number of cortical and sub-cortical sites (e.g., prefrontal cortex, amygdala, hippocampus) implicated in the mediation of the fear response.(22) In euthymic individuals, the LC-NE and CRF systems cross-regulate their activities; dysregulation of this system has been implicated in the increased reactivity and stress associated with anxiety phenotypes. The CRF and LC systems, however, also activate the hypothalamus-pituitary-adrenal axis (HPA) response and the sympathetic branches of the autonomic nervous system. The dysregulation leading to the increased fear response can therefore also result in excessive efferent output to muscles in pulmonary, cardiovascular, genitourinary and gastrointestinal organs, thereby accounting for the coexistence of PD and the syndrome's other medical conditions.

Data for a number of syndrome conditions are consistent with this model. Patients with IC, for example, demonstrate abnormal vasomotor tone, increased density of sympathetic neurons in their bladder, and increased excretion of norepinephrine.(14,37,38) Animal models have also found a marked decrease in cortisol response to stress in cats with feline IC.(39) Patients with mitral valve prolapse (MVP) similarly manifest elevated norepinephrine levels and increased vagal tone.(40) Interestingly, MVP in panic patients tends disproportionately to be of the non-calcified type, whose etiology has been linked to autonomic function,(41) and a study of 20 patients with both PD and MVP found that the MVP symptoms can be ameliorated by treating with only PD medication.(42) Similar links to autonomic dysregulation have been noted for gastrointestinal disorders, (43,44) migraines (45), and hypercholesterolemia.(46,47)

Our observations are together consistent with a pleiotropic model wherein mutations in one (or more) genes result in a vulnerability common to the syndrome conditions. The region of chromosome 13 implicated in the syndrome(9,11)encompasses, among others, genes encoding the endothelin B receptor (a relevant candidate, related to vasoconstriction), the serotonin 2A (HTP2A) receptor, and multiple transcription factors. Mutations in these genes have not thus far however been associated with either PD or SAD, and further research is required to identify candidate genes, their products, and how they lend susceptibility to the anxiety phenotype. Alternatively, it is also possible that rather than sharing common genetic vulnerability, the anxiety disorders simply serve as an independent risk factor for specific medical conditions. Thereby, in the context of the present study, only PD or SAD would be heritable, and then increase the odds of developing IC, MVP, and headaches in the first-degree relatives. Because the relatives in our study were not randomly distributed with respect to anxiety symptoms (anxiety probands were required to have a family history of anxiety, and controls required to have none), our data do not allow us to distinguish between these alternative models.

There are other limitations as well. First, information on first-degree relatives was acquired from the proband, using the family history screen. Even though the reporting of family medical symptoms was found to be uncorrelated with the proband's self-reports, other reporting biases cannot be ruled out, as family data were not independently verified. Because the family history screen is skewed toward under-reporting, however, we believe that such biases would shift effect sizes toward the null hypothesis. A related limitation is that only information on selected symptoms hypothesized *a priori* were ascertained for relatives, and additional relationships of medical and psychiatric co-morbidity could not be determined. Finally, because of the stringent inclusion criteria (see methods), results may not be generalizable to all forms (e.g., milder, non-familial) of PD and SAD.

Despite these limitations, there are also a number of novel inclusions, such as the use of NIDDK criteria to test for IC, and a case-control design incorporating a family history requirement and onset prior to age 31 to capture the most robust forms of the disorders. Finally, DNA samples have been collected on these subjects, and a sub-set has also been imaged using functional MRI paradigms that target processing of affect and emotion. Integration of data from these modalities will allow us to best address the genetic and neurobiological pathways that predispose to the anxiety phenotype.

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Table 1

Demographics of probands with panic disorder only (PD), social anxiety disorder (SAD), panic disorder and social anxiety disorder (PD +SAD), and normal controls.

	PD Only N = 219	SAD Only N = 199	PD+SAD N = 173	Controls N = 102	P Value ^a
Age (Yrs, SD)	38.6 (12.0)	38.8 (12.3)	38.4 (11.5)	50.6 (14.2)	F = 27.5, d.f. = 3, p < .0001
Female (N, %)	177 (81)	141 (71)	139 (80)	58 (57)	$\chi^2 = 25.6$, d.f. = 3, p < .0001
<i>Marital Status (N, %)</i>					
Never Married	115 (53)	61 (28)	89 (51)	26 (25)	$\chi^2 = 33.7$, d.f. = 6, p < .0001
Presently Married	61 (28)	60 (30)	59 (34)	50 (47)	
Divorced, Separated, or Widowed	41 (19)	26 (13)	25 (14)	28 (27)	
<i>Race/Ethnicity (N, %)</i>					
Non-Hispanic White	172 (80)	157 (80)	136 (80)	84 (80)	$\chi^2 = 4.9$, d.f. = 9, p = .84
Non-Hispanic Black	14 (7)	12 (6)	13 (8)	9 (9)	
Hispanic	20 (9)	12 (6)	12 (7)	6 (6)	
Other	9 (4)	15 (8)	9 (5)	6 (6)	
<i>Education (N, %)</i>					
<High School	8 (4)	16 (8)	9 (5)	0	$\chi^2 = 12.8$, d.f. = 6, p = .04
High School, < College	81 (37)	68 (34)	75 (43)	30 (29)	
≥ College Degree	130 (59)	115 (58)	86 (50)	69 (68)	
<i>Employment (N, %)</i>					
Full-Time	111 (52)	81 (42)	73 (43)	56 (54)	$\chi^2 = 8.6$, d.f. = 6, p = .19
Part-Time	29 (14)	33 (17)	30 (17)	16 (16)	
Unemployed	69 (33)	78 (41)	65 (39)	32 (31)	

Ns vary due to missing data.

^aBased on an Analysis of Variance (ANOVA) for age, and a chi-square test for all other variables.

Table 2

Lifetime rates of medical conditions for probands with panic disorder only (PD), social anxiety disorder (SAD), panic disorder and social anxiety disorder (PD +SAD), and normal controls.

Medical Symptoms ^b	PD Only (N = 219)		SAD Only (N = 199)		PD + SAD (N = 173)		Controls (N = 102)	
	N (%)	AOR (95% CI) ^a	N (%)	AOR (95% CI) ^a	N (%)	AOR (95% CI) ^a	N (%)	
<i>Genitourinary</i>								
IC Symptoms ^{c,d}	33 (15)	9.4 (2.4, 29.4) ****	19 (9)	4.9 (1.4, 17.7) **	19 (11)	6.0 (1.6, 21.5) ***	3 (3)	
Other Kidney Problems	20 (10)	1.9 (.7, 5.2)	13 (7)	1.3 (.5, 3.8)	12 (7)	1.4 (.5, 4.1)	6 (6)	
Other Bladder Problems	24 (11)	1.8 (.8, 4.6)	17 (8)	1.5 (.6, 3.8)	9 (5)	.8 (.3, 2.3)	9 (9)	
<i>Cardiovascular</i>								
Mitral Valve Prolapse ^c	36 (16)	2.5 (1.1, 5.8) *	31 (16)	2.5 (1.2, 5.7) *	32 (19)	3.0 (1.9, 7.0) *	8 (8)	
Hypertension	27 (12)	.9 (.5, 1.8)	21 (10)	.7 (.4, 1.4)	30 (17)	1.4 (.8, 3.8)	27 (26)	
<i>Neurological</i>								
Chronic Headaches ^c	75 (34)	3.8 (1.8, 8.0) ****	49 (25)	2.6 (1.2, 5.4) *	73 (42)	5.5 (2.6, 11.4) ****†	10 (10)	
-Migraine	64 (24)	4.0 (1.9, 8.8) ****	31 (16)	2.0 (.9, 4.6)¶	58 (34)	5.1 (2.3, 11.1) ****	11 (11)	
-Non-migraine	44 (20)	3.3 (1.3, 8.1) *	38 (19)	3.3 (1.3, 8.2) *	51 (30)	5.6 (2.2, 13.8) ****§	7 (7)	
<i>Endocrine</i>								
Thyroid Problems ^c	17 (8)	1.6 (.6, 5.1)	18 (9)	2.0 (.6, 5.8)	9 (5)	1.0 (.3, 3.2)	6 (6)	
-Hyperthyroid	6 (3)	4.4 (.4, 41)	3 (2)	2.5 (.2, 28.3)	3 (2)	2.7 (.2, 30.1)	1 (1)	
-Hypothyroid	14 (6)	1.8 (.6, 5.5)	15 (8)	2.2 (.7, 6.8)	6 (4)	1.1 (.3, 3.8)	5 (5)	
<i>Metabolic</i>								
Diabetes	10 (4)	1.6 (.5, 4.8)	9 (5)	1.5 (.5, 4.7)	5 (3)	1.0 (.2, 4.7)	8 (8)	
Hypercholesterolemia	35 (16)	2.3 (1.2, 4.7) *	27 (14)	1.9 (.9, 3.8)	30 (17)	2.7 (1.3, 5.8) **	18 (18)	
Hypoglycemia	22 (10)	4.6 (1.3, 16.6) *	15 (8)	3.6 (1.0, 13.4) *	15 (9)	3.0 (1.0, 14.6) *	3 (3)	
<i>Gastrointestinal</i>								
Colitis / IBS	37 (17)	6.2 (2.2, 17.2) ****	23 (12)	3.9 (1.1, 11.0) *	25 (14)	5.1 (1.8, 14.7) ****	5 (5)	
Ulcers	24 (11)	4.6 (1.5, 14.8) **	12 (6)	2.3 (.7, 7.9)	19 (11)	4.7 (1.5, 15.3) *	4 (4)	
Gall Bladder Problems	13 (9)	1.1 (.4, 3.3)	9 (5)	.9 (.3, 2.7)	14 (8)	1.6 (.5, 5.1)	7 (7)	
Hepatitis / Jaundice	10 (5)	1.9 (.5, 6.9)	6 (3)	1.2 (.3, 5.0)	12 (7)	3.0 (.8, 11.8)	4 (4)	
<i>Respiratory</i>								

Medical Symptoms ^b	PD Only (N = 219)		SAD Only (N = 199)		PD + SAD (N = 173)		Controls (N = 102)	
	N (%)	AOR (95% CI) ^a	N (%)	AOR (95% CI) ^a	N (%)	AOR (95% CI) ^a	N (%)	
Asthma	31 (14)	1.9 (.8, 4.7)	30 (15)	2.2 (.9, 5.1)	36 (21)	3.2 (1.2, 7.0) [*]	7 (7)	
Bronchitis	36 (17)	4.5 (1.7, 12.2) ^{***}	26 (13)	3.5 (1.3, 9.8) [*]	29 (17)	4.6 (1.5, 12.8) ^{***}	5 (5)	
<i>Other</i>								
Anemia	42 (19)	1.9 (.9, 4.1)	45 (23)	2.7 (1.2, 5.8) ^{**}	39 (23)	2.4 (1.1, 5.1) [*]	11 (11)	
Arthritis	15 (8)	1.1 (.4, 2.7)	15 (8)	1.2 (.5, 3.2)	20 (12)	2.1 (.9, 5.1)	14 (14)	
Cancer (any)	9 (14)	1.6 (.5, 5.5)	6 (3)	1.1 (.4, 2.9)	8 (5)	1.8 (.5, 6.5)	5 (5)	
Skin Disorders ^e	62 (29)	2.1 (1.1, 4.1) [*]	66 (34)	2.8 (1.8, 5.4) ^{***}	55 (32)	2.3 (1.3, 5.0) ^{**}	15 (15)	
STDs ^f	26 (12)	1.9 (.7, 6.1)	24 (12)	2.0 (.7, 6.5)	15 (9)	1.3 (.4, 4.6)	6 (6)	
Any Medical Condition	184 (86)	5.4 (2.8, 10.2) ^{****}	154 (80)	3.9 (2.1, 7.3) ^{****}	148 (88)	6.3 (3.1, 12.5) ^{****}	62 (64)	
Syndrome Related	126 (63)	5.0 (2.8, 8.8) ^{****}	94 (53)	3.5 (2.0, 6.2) ^{****}	107 (66)	5.9 (3.2, 10.7) ^{****†}	26 (27)	
Syndrome Unrelated	159 (72)	3.8 (2.2, 6.5) ^{****}	132 (66)	2.9 (1.7, 4.9) ^{****}	133 (77)	4.9 (2.7, 8.4) ^{****†}	55 (54)	

Ns vary due to missing data.

**** $P \leq .001$;

*** $P \leq .005$;

** $P \leq .01$;

* $P \leq .05$;

^a Odds ratios reflect comparisons between each corresponding anxiety group and normal controls. All odds ratios are adjusted for proband age and sex. Further differences between anxiety groups are indicated as follows:

[§] Proband with PD and SAD have significantly higher rates than those with either SAD only or PD only ($p < .01$)

[†] Proband with PD and SAD have significantly higher rates than those with SAD only ($p < .01$)

[¶] Proband with PD only, or PD and SAD, have significantly higher rates than those with SAD only ($p < .001$)

^b Based on the medical checklist. Other reported medical symptoms, not included in Table 2 due to small Ns, included Acquired Immunodeficiency Syndrome (AIDS) (N = 1), angina/myocardial infarction (N = 5), autoimmune disease (N = 3), cataplexy (N = 3), convulsions, seizures or epilepsy (N = 9), encephalitis (N = 4), enteritis (N = 4), emphysema (N = 3), fibromyalgia (N = 23), meningitis (N = 5), multiple sclerosis (N = 1), myasthenia gravis (N = 4), polio (N = 1), rheumatic fever (N = 4), stroke (N = 6) and tuberculosis (N = 4).

^c Medical conditions hypothesized *a priori* as part of the syndrome are highlighted. Comorbidity among syndrome conditions was as follows: 12% of probands who reported IC or MVP symptoms reported both; similarly, 16% of those reporting IC or chronic headaches, 5% of those with IC or hyperthyroidism, 15% of those with MVP or hyperthyroidism, and 7% of those with headaches or hyperthyroidism, reported both.

^dIC symptoms were assessed based on NIDDK screening criteria (see methods). Furthermore, 23 (4%) of anxiety probands (6 PD, 9 SAD, 8 PD + SAD) but only 1 normal control reported having been diagnosed with IC by a physician or urologist.

^eSkin Disorders includes acne and psoriasis.

^fSTD = Sexually Transmitted Diseases; includes syphilis, gonorrhea, and herpes

Lifetime Psychiatric Comorbid Conditions among probands with panic disorder only (PD), social anxiety disorder only (SAD), and panic disorder and social anxiety disorder (PD + SAD).

Table 3

	PD Only N = 219	SAD Only N = 199	PD+SAD N = 173	Controls N = 102
Diagnosis ^a	N (%)	N (%)	N (%)	N (%)
Specific Phobia	79 (37%)	57 (29%)	65 (38%)	N/A
Generalized Anxiety Disorder	26 (12%)	15 (8%)	40 (23%) ^b	N/A
Obsessive Compulsive Disorder	15 (7%)	14 (7%)	16 (9%)	N/A
Post Traumatic Stress Disorder	49 (26%)	31 (16%)	44 (25%)	N/A
Recurrent Major Depressive Disorder	72 (34%)	54 (27%)	76 (46%) ^c	N/A
Drug Dependence	36 (17%)	34 (17%)	34 (20%)	N/A
Alcohol Dependence	43 (20%)	38 (20%)	46 (27%)	N/A

^aBased on DSM-IV criteria (SADS-LA IV interview).

^bProbands with both PD and SAD were more likely to have GAD than those with either PD or SAD alone (AOR = 2.5, [1.5, 2.9], $p = .001$)

^cProbands with both PD and SAD were more likely to have recurrent MDD than those with either PD or SAD alone (AOR = 1.5 [1.2, 1.9], $p = .001$).

Table 4

Rates of medical conditions among first-degree relatives (FDRs) of probands with PD, SAD and PD + SAD, and of controls.

Medical Symptoms in FDRs	PD Only (N = 219)		SAD Only (N = 199)		PD + SAD (N = 173)		Controls (N = 102)	
	N (%)	AOR (95%CI) ^a	N (%)	AOR (95%CI) ^a	N (%)	AOR (95%CI) ^a	N (%)	N (%)
IC Symptoms ^b	28 (13)	2.9 (1.2, 7.2)*	21 (11)	2.3 (1.0, 5.8)*	19 (11)	2.5 (1.0, 6.8)*	7 (7)	
Mitral Valve Prolapse	55 (25)	1.8 (.9, 3.4) ⁺	46 (24)	1.7 (.9, 3.1) ⁺	45 (26)	1.9 (1.1, 3.7)*	18 (17)	
Chronic Headaches	109 (49)	2.8 (1.6, 4.8)*****	82 (42)	2.2 (1.2, 3.7)**	79 (45)	2.4 (1.4, 4.1)****	25 (24)	
Thyroid Problems	49 (22)	2.4 (1.2, 4.7)*	49 (25)	2.8 (1.4, 5.6)*	45 (26)	2.9 (1.4, 5.8)**	14 (15)	
Any Syndrome Condition	149 (68)	2.5 (1.5, 4.1)*****	135 (68)	2.6 (1.5, 4.3)*****	118 (68)	2.5 (1.5, 4.2)*****	48 (48)	

Ns vary due to missing data.

**** P ≤ .001;

*** P ≤ .005;

** P ≤ .01;

* P ≤ .05;

⁺ p < .10

^a Odds ratios compare respective anxiety groups to the normal control group. Odds ratios are adjusted for age, sex, and household size (number of first-degree relatives only).

^b Fourteen first-degree relatives (8 PD, 8 SAD, 3 PD+SAD; 0 controls) had been diagnosed with having interstitial cystitis by a physician