

# **THE GENETICS OF PANIC DISORDER**

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## **ABSTRACT**

Panic disorder (PD) is one of the most common anxiety disorders, with a prevalence of 3.4-4.7%. Although PD seems to have no known cause, and its underlying etiology is not well understood, studies have consistently shown that genetic factors explain about half of the variance. It is likely that most cases of PD have a complex genetic basis. Existing data suggest, however, that the genetic architecture underlying PD is heterogeneous and differs between cases. For example, the degree of genetic complexity, and the pattern of genes involved might differ in familial vs. non-familial cases, in early- vs. late-onset cases, or when different comorbid conditions, gender, and potential intermediate or subphenotypes are considered. At the molecular genetic level, linkage and association studies, the latter including traditional candidate gene and recent genome-wide studies have been used to study PD. Although no robust molecular genetic findings have emerged so far, it is conceivable that the first PD susceptibility genes will be identified in the coming years via the application of modern molecular genetic methods and through multi-centre collaborations to bring together combined, large data sets. Such findings could have a major impact on our understanding of the pathophysiology of this disorder, and would provide important opportunities to investigate genotype-phenotype correlations as well as the interaction between genetic and environmental factors involved in the pathogenesis of PD. Here, we summarize the latest genetics findings about PD, and give an overview of anticipated future developments.

## INTRODUCTION

Panic disorder (PD) is one of the anxiety disorders, a group that includes specific and social phobia, agoraphobia (AG), generalized anxiety disorder, separation anxiety disorder, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder. PD is a serious psychiatric disorder (Table 1) with a high lifetime prevalence—between 3.4 to 4.7% in the United States population [1, 2]; it is also associated with severe social and occupational impairments. The American Psychiatric Association (APA) defines PD as an episode of abrupt intense fear accompanied by additional physiological or cognitive symptoms (Table 2).

Although PD has no known cause and its underlying etiology is not well understood, studies have consistently shown that neurobiological factors are key to the disease process. Furthermore, PD shows high comorbidity with several other psychiatric and medical conditions, and there is evidence of shared etiological factors with some of these disorders. For instance, other anxiety disorders, mood disorders, and substance use disorders are frequently observed in patients with PD (Table 1). Currently, a diagnosis of PD is made by collecting patient information, conducting clinical interviews, and observing PD symptoms. Nevertheless, there is growing hope that the underlying etiology of PD and the biological pathways involved will soon be identified. Studies have consistently observed that genetic inheritance is a strong risk factor for PD. Furthermore, the success of modern technology in analyzing a variety of genetic disorders, has increasingly allowed investigators to identify genetic risk factors, even if their effect sizes are moderate.

In this article, we review current genetic research on PD, including a discussion of the phenotypic aspects and neurobiological concepts that are receiving increased consideration in recent studies. We also discuss the extent to which our understanding of PD is likely to be increased via the results of current and future molecular genetic studies.

## **PD – FEATURES OF INHERITANCE**

### ***HERITABILITY***

The familial aggregation of PD has been established by several independent studies and has been shown to be stronger than in other anxiety disorders. Supplementary table 1 shows the results of 19 controlled PD family studies, i. e. in each study also independent non-PD families have been analyzed. The family studies revealed a relative risk (RR) to first-degree relatives of individuals with PD that ranged from 2.8 [3] to 14.7 [4]. Furthermore, twin studies (Supplementary Table 2) have confirmed that genetic factors are largely responsible for the familial clustering of PD [5, 6, 7, 8, 9, 10, 11, 12, 13]. In the largest and most informative twin studies—The Vietnam Era Twin Registry [10, 13], the Virginia Twin Registry [6, 7], and the Australian and Netherlands Twin Registries [8]—more than 1,000 twin pairs were analyzed in each study and it was estimated that additive genetic factors explain approximately 30-46% of the variance in PD. Hettema and colleagues [14] combined data from five family and three twin studies selected via defined inclusion criteria. Their analysis yielded heritability estimates of 48% (95% CI 41-54%), with the remaining variance explained predominantly by non-shared environmental factors. Stress, perinatal factors, substance abuse, and life events—e.g., exposure to violence, social isolation, loss—have been proposed as non-shared environmental factors; in contrast, parental separation, poverty, and parenting dimensions such as criticism/rejection or overcontrol are believed to be shared environmental risk factors for PD [15].

### ***MODE OF INHERITANCE***

Although inheritance related to a single gene may play a role in some PD family pedigrees (see below), family and twin studies support the view that most PD cases have a complex genetic basis. This notion is corroborated by preclinical studies suggesting that, in animals, anxiety-like behaviors and emotional activity analogous to panic and anxiety are controlled by

multiple genes [16]. However, the number of susceptibility genes, the disease risk conferred by each gene, and the degree of interaction between them, if any, all remain unknown.

Furthermore, it must be assumed that the genetic architecture underlying PD differs among cases. For example, the degree of genetic complexity and the pattern of genes involved might differ in familial vs. non-familial cases, in early- vs. late-onset, or when differences in comorbid conditions or gender are considered. Therefore, a detailed documentation of disease course—including longitudinal, neurobiological, and psychophysiological examinations (see below)—may greatly benefit future genetic studies.

### ***PD AND COMORBID DISORDERS***

It is well known that PD is associated with a wide variety of other medical and psychiatric conditions. In particular, other anxiety disorders, substance use disorders, and mood disorders (e. g, major depressive disorder (MDD) and bipolar disorder (BD)), are commonly observed in individuals with PD (Table 1). Indeed, the National Comorbidity Survey Replication (NCS-R) report [17], which is the largest survey of the prevalence and correlates of mental disorders in the US, found that 80% of PD patients had one or more of these disorders. Family and twin studies suggest that some of these comorbid disorders share some genetic liability with PD; however, there is also evidence for that PD has a distinct genetic basis (see below). The following describes those disorders which have been strongest implicated by the NCS-R report within the context of PD. Most of the family studies cited in the following involved the use of healthy or control family samples in addition to the families of affected cases.

***PD and Agoraphobia (AG):*** PD occurs most often in conjunction with AG; individuals with this disorder fear and avoid settings that are unfamiliar or where they perceive that they have little control. The NCS-R report estimated that approximately 64% of PD patients met

diagnostic criteria for AG [17]. In addition, PD-AG seems to be associated with a more severe disease course; for example, increased number of both panic attacks and other comorbid disorders are more frequent in individuals with PD-AG than in those with PD only [1, 17]. Whether AG also impacts age of onset (AO) for PD still remains uncertain. Kessler and colleagues [1] found similar AO in PD and PD-AG groups, but a family study from Iowa reported that individuals with PD-AG had an earlier AO than those with PD only [18]. Nevertheless, studies have consistently shown that most of genetic risk factors seem to be shared between PD and AG [18, 19, 20, 21].

***PD and Other Anxiety Disorders:*** The NCS-R report suggested that, as with AG, all other anxiety disorders have a high lifetime prevalence in those with PD [1]. Specific and social phobias, in particular, are among the most common comorbidities in PD (34.3%, 31.1%, respectively) followed by posttraumatic stress disorder (21.6%), generalized anxiety disorder (21.3%), and OCD (8.2%). However, most family studies suggest that risk genes contribute more specifically to each anxiety disorder [18, 19, 21, 22, 23]. However, OCD may be an exception; one family study found evidence for a shared genetic PD-OCD liability [19]. This finding would be consistent with an OCD family study noting that the relatives of OCD patients had increased risk for PD and AG [24]. However, a subsequent study suggested that these families may represent a ‘distinct genetic subtype’ of PD (or OCD) [25].

Twin studies have also considered the relationship between PD and other anxiety disorders. Hettema and colleagues [26] analyzed data from the Virginia Adult Twin sample using a multivariate modeling approach. They found two genetic factors common across the disorders; the first loaded strongly in PD, AG, and generalized anxiety disorder, whereas the second loaded primarily in specific phobias. Social phobia appeared to be influenced by both factors. Evidence for genetic factors that are shared between anxiety disorders is also provided by studies that have investigated personality traits that are elevated among all

anxiety disorders. According to some authors these traits may act as intermediate phenotypes for the observed comorbidity [27].

***PD and Major Depressive Disorder (MDD):*** The NCS-R report found that in patients with PD, lifetime risk for MDD was 34.7% [1]. While most family studies suggest that the majority of the underlying genetic risk is not shared between both disorders [18, 20, 28, 29, 30, 31], other family studies [32] and one twin study [12] did find evidence of shared genetic factors between PD and MDD. The hypothesis that some personality traits in PD that are also frequently seen in MDD patients may act as intermediate phenotypes has been raised [33], although several non-genetic factors may also be involved in the comorbidity between PD and MDD. For example, PD- and MDD-specific risk factors might interact on the protein level—e. g., via common and/or connected neurotransmitter pathways—or common environmental factors might be present. In addition, some authors have suggested that PD might cause the development of MDD (or vice versa) [33].

***PD and Bipolar Disorder (BD):*** BD has also been associated with PD; lifetime risk of BD appears to be 14.4% in PD patients (NCS-R report) [1]. However, most family studies are not consistent with the notion that shared genetic factors underlie this comorbidity [20, 30].

***PD and Schizophrenia:*** The NIMH Epidemiologic Catchment Area Study (ECA) study estimated that schizophrenia occurs more frequently in PD patients [34]. One family study (Bonn/Mainz) similarly found increased risk of PD in the relatives of schizophrenic patients without PD. However, the schizophrenia risk in PD relatives was not increased compared to controls. The authors concluded that there might be shared genetic factors between both disorders present in only a small subgroup of PD or schizophrenia cases [35].

***PD and Substance Use Disorders:*** Most substance use disorders co-occur frequently in individuals with PD. Alcohol abuse/dependence disorder (AD), present in 25% of PD cases [1], is the most-studied comorbid condition associated with PD. All controlled family studies report increased rates of AD in the relatives of those with PD, even if AD was not present in PD patients [28, 36, 37]. However, the reason for this association is difficult to interpret. Some authors have hypothesized that AD develops as an attempt to self-medicate PD and associated anxiety symptoms [38], whereas other authors have suggested that a specific electroencephalography (EEG) trait, namely low voltage alpha (LV), is an intermediate phenotype for both disorders. This is based on observations that LV occurs more frequently in patients with AD comorbid for an anxiety disorder (including PD) than either AD-only or non-AD subjects [39]. However, this finding remains unreplicated.

According to the NCS report, cigarette smoking is seen in 35.9% [40], and cannabis use/dependence is seen in 20.6%, of individuals with PD [1]. The most common explanation for these comorbidities is that these may trigger anxiety and, ultimately, PD in susceptible individuals [41, 42].

***PD and Other Medical Disorders:*** Several studies have noted an association between PD and other medical disorders. Specifically, respiratory, metabolic, cardiovascular, gastrointestinal, genitourinary, and connective tissue disorders have been reported to be more frequent in PD patients, as have labile hypertension and chronic headaches [43]. However, one of the most intriguing findings concerns the so-called ‘panic syndrome’ initially found in some multiplex PD families [44], which showed strong linkage to chromosome 13q32 [45]. The syndrome describes the familial co-occurrence and transmission of PD and interstitial cystitis (IC) symptoms, mitral valve prolapses (MVP), chronic headaches, and thyroid disorders. A follow-up study conducted with an independent sample provided further evidence that this syndrome may represent a distinct PD phenotype [46]. That study found that in some families, the first-



degree relatives of patients with PD—and also those with social phobia— showed elevated rates of IC, MVP, headaches, and thyroid disorders. Irrespective of first-degree relatives, the frequency of the co-morbid conditions was between 8% (thyroid disorder) and 34% (chronic headaches) in PD patients [46] indicating that this syndrome may represent a substantial fraction of PD.

### ***PD AND PERSONALITY TRAITS***

Several studies have focused on personality traits associated with PD. Anxiety sensitivity (AS) and behavioral inhibition (BI) are among the personality traits most often associated with PD, although neuroticism (N) and harm avoidance (HA) have also been implicated in PD as well as in other anxiety disorders and MDD. Some investigators believe that these traits may represent intermediate phenotypes that are more directly influenced by the underlying risk genes than PD itself, and/or that they predate the onset of PD. Furthermore, because these traits are also associated with other anxiety disorders (as well as MDD), they may moderate the comorbidity between these disorders. If shared genetic factors contribute to the observed association between some personality traits and PD, the disease status would represent rather a (quantitative) extreme of dimensions that underlie ‘normal’ personality.

***PD and Anxiety Sensitivity:*** AS, described as the tendency to interpret sensations of physiological arousal as having harmful physical, psychological, or social consequences [47]. The misinterpretation engendered by AS is believed to contribute to a ‘fear of fear’ cycle, in which anxiety about the sensations further increase arousal. Studies have shown that AS predicts the number, frequency, emergence, and onset of panic attacks as well as the likelihood of developing PD or another anxiety disorder [48, 49, 50]. However, other studies

failed to observe elevated AS in offspring at risk for an anxiety disorder [51], confusing the issue of whether AS is associated with PD or represents an intermediate PD trait.

***PD and Behavioral Inhibition:*** BI is defined as the tendency in childhood to exhibit restraint, withdrawal, and reticence when faced with novel or unfamiliar situations and people [52]. Elevated levels of BI have been found in the offspring of parents with PD [53, 54, 55], although one study failed to support this observation [56]. Like AS, BI seems not to be a developmental risk factor for PD only. Instead, other anxiety disorders seem to be predicted by higher BI, especially social phobia [57, 58]. Interestingly, in offspring at risk for PD and MDD, BI was associated with social phobia [59]. Similar findings have been obtained at the neurobiological level, which point to common pathways underlying BI and PD. For instance, increased amygdala responsiveness (see below) seems to be associated with both conditions. However, this neurobiological abnormality is not specific for BI and PD, and is also seen in other anxiety disorders [15, 60].

***PD and Neuroticism:*** N, a personality trait that reflects an enduring tendency to experience negative emotional states, is one of the three key dimensions of personality according to Eysenck [61] and has been included in most theories of personality since its introduction. The association between N and PD has been described in several prospective and family studies [15]. Furthermore, in large studies of twin pairs it has been shown that genetic determinants of N overlap with those of PD. However, these results were restricted to male patients [62, 63]. Most recently, one of the largest studies investigating personality traits in PD has been published and N was the main personality characteristic of patients with PD compared to controls [64]. Moreover, the authors of the later study performed a subscale analysis and found that the trait Somatic Trait Anxiety, which describes the tendency to experience autonomic arousal, restless, and tense, was more frequent in PD patients than in controls [64].

## ***GENDER EFFECTS***

Females are more susceptible to developing PD and show a greater than twofold elevation in lifetime rates compared to males. According to NCS data, the lifetime prevalence of PD is 1.9% in men and 5.1% in women [65]. AO does not differ between genders. However, whether the higher PD rates in females reflect the presence of gender-specific genetic factors remains under debate. For example, an Australian twin pair study provided evidence that the genetic architecture underlying PD might differ between females and males. They observed disease correlations in their sister and brother PD twin pairs that were absent in opposite-sex sibling pairs [8]. Furthermore, another study of these same twin pairs found evidence that genetic determinants of neuroticism (N ) overlapped with those of panic/anxiety among male, but not female, subjects [63]. In contrast, the Virginia Twin Registry study failed to observe any evidence of gender-specific PD genetic profiles [26]. However, only one study investigated whether parent of origin effects might be present in the familial transmission of PD [66]; while that study found some preliminary evidence for parent of origin effects, this finding remains unreplicated.

## ***AGE OF ONSET (AO)***

The average AO for PD is 23.6 years [1] and differs compared to other anxiety disorders; although there is variation across studies, the AO of specific phobias typically occurs in middle childhood, social phobia in middle adolescence, and OCD in early adulthood. It is assumed that the link between PD and AO is due to age-specific neuroendocrinology or brain developmental processes. Furthermore, age-specific environmental factors may explain the high prevalence in onset that occurs at 23 years. However, genetic factors also seem to influence AO in PD. For example, genetic loading seems to be more pronounced in early-onset (EAO) cases of PD (typically defined by an AO

of < 20 years). The risk of PD for relatives of EAO patients is higher than that for family members of non-EAO patients [67]. This finding could be consistent with the observation that probands from families with at least one additional PD case tend to have an earlier AO than patients with no other affected relatives [68].

### ***RISK MARKERS IN PD***

Several studies report psychophysiological abnormalities in PD, some of which seem to be associated with increased amygdala responsiveness and amygdalar projections to the striatum, hypothalamus, sympathetic chain, and cardiovascular system. For example, higher electrodermal activity, peripheral vasoconstriction, accelerated heart rate, and neuroendocrine abnormalities have been observed in PD patients [69]. In addition, offspring at risk for PD display symptoms of higher physiologic arousal, including accelerated heart rates under stress and neuroendocrine abnormalities [53, 56]. One of the most studied and replicated psychophysiological abnormalities associated with PD is CO<sub>2</sub>-hypersensitivity, which seems to be specific to PD and which might be useful as an intermediate trait marker (see below).

***PD and Neurobiological Findings:*** Several neuroimaging studies have shown that the amygdala plays a crucial role in processing of fearful material. Incoming stimuli from the thalamus and sensory cortex specifically activate the amygdala, which in turn stimulates various brain areas such as the striatum, hypothalamus, and periaqueductal grey, which are responsible for key panic symptoms. This process is modulated by top-down governance involving information from the frontal, cingulate, and insular cortices as well as the hippocampus. In PD, this anxiety response system is characterized by increased amygdala reactivity or responsiveness [60]. However, amygdala hyperreactivity is also associated with other anxiety disorders as well as in children with BI [15, 60]. Additional family and longitudinal studies are needed to clarify whether this functional abnormality might be useful

as an intermediate phenotype. Abnormalities related to other brain regions—for instance, altered insular function—have also been reported in PD and other anxiety disorders [60].

***PD and CO<sub>2</sub>-Hypersensitivity:*** As noted above, several studies have shown that PD is associated with increased CO<sub>2</sub>-sensitivity. Studies have found that panic attacks can be provoked in a high proportion of PD patients by exposure to CO<sub>2</sub> [70]. PD is thus one of the few psychiatric disorders whose symptoms can be provoked. In addition, the healthy relatives of PD patients showed an increased likelihood of PD symptoms after exposure to CO<sub>2</sub> [71, 72, 73]. Notably, twin studies point to genetic factors underlying this respiratory abnormality [5]. The findings suggest that CO<sub>2</sub>-hypersensitivity may be an alternative manifestation of PD in susceptible individuals, thus representing an intermediate phenotype.

Other studies have shown that PD patients exhibit respiratory abnormalities in the absence of CO<sub>2</sub> exposure. For example, PD patients showed differences in respiratory rate, tidal volume, and inspiratory flow rate compared to healthy controls; electrodermal and cardiovascular measures did not differ between the two groups [74]. However, a concept that might integrate these observed respiratory abnormalities is the suffocation false alarm theory [69], which posits functional and/or structural abnormalities of the respiratory control system located in the brainstem.

***PD and Other Vulnerability Marker:*** Other agents have been reported to provoke panic attacks more frequently in PD patients compared to healthy controls, including yohimbine, cholecystokinin, and caffeine [75]. However, compared to CO<sub>2</sub>, it is less clear whether they represent promising markers for defining intermediate phenotypes.

## **PD – MOLECULAR GENETIC FINDINGS**

In contrast to other neuropsychiatric disorders (e. g, schizophrenia, BD) where genome-wide association studies (GWAS) on large samples have already led to the identification of risk genes, molecular genetic research in PD has, to date, been less successful. Two GWAS have been performed in PD, but the sample sizes may have been underpowered. Most of the genetic studies published to date use linkage or candidate gene methods. The following section summarizes the most promising current molecular findings in PD, which were obtained by genome-wide linkage or association studies. However, since molecular genetic research into PD has not yet led to the identification of any definite risk-gene, we provide a brief overview of the most promising findings and refer to the review by Maron et al. [76] which summarizes all available molecular genetic findings for PD.

### ***LINKAGE STUDIES***

Because of the successful identification of risk genes in several complex disorders via GWAS, the concept of linkage has become less of a focus than in past years. It has become clear that most linkage studies did not provide enough power for the mapping of risk genes with effect sizes usually seen in GWAS. However, linkage results can remain key to the discovery of risk genes that are rare in the general population but exhibit stronger genetic effect sizes. There is hope that such rare, higher-penetrance risk variants exist, given that most of the recently identified GWAS genes explain only a fraction of the heritability seen in complex disorders. Furthermore, the possibility remains that some of the rare higher-penetrance risk genes transmitted in families have already been mapped to chromosomal regions by linkage studies. Those regions may represent ideal candidates for deep or next generation sequencing studies, which are becoming increasingly available and represent a promising tool for the systematic examination of implicated linkage intervals.

To date, six genome-wide linkage studies have been performed in PD. They are listed together with chromosomal regions that showed suggestive linkage evidence in supplementary table 3. However, the most impressive linkage signals—as defined by the level of significance and sample size—have been observed for four chromosomal regions. The Yale Study of 19 extended US pedigrees with PD by Kaabi and colleagues [77] found the strongest linkage signal on chromosome 4q32-q34 (multipoint p-value of  $5.4 \times 10^{-6}$  at D4S413 (158 Mb)). Notably, Camp and colleagues [78] obtained results in the same linkage region in a sample of 87 extended Utah pedigrees with recurrent early-onset MDD and anxiety disorders (including PD); the male-specific analysis produced a LOD score of 2.60 at D4S2631 (156 Mb). In the Columbia Study of 120 multiplex US pedigrees with PD, Fyer and colleagues [79] observed their best linkage signal on chromosome 15q21 (NPL score of 3.44 at D15S822 (24 Mb)). Strong PD linkage signals were also reported on chromosome 9q31 in a study of 25 extended pedigrees from Iceland (LOD score 4.18 at D9S271 (102 Mb)) [80], and on chromosome 13q32 in 60 multiplex pedigrees from the US with panic syndrome that included IC, MVP, migraine, and thyroid problems (LOD score 3.57 at D13S793 (96 Mb)) [45].

In contrast to other psychiatric disorders—like schizophrenia and BD—no meta-analysis combining different PD linkage samples have been performed so far. However, this approach provides a more powerful tool for the identification of linkage signals associated with genetic effect sizes that are usually too small for their detection by individual studies.

## ***ASSOCIATION STUDIES***

***Candidate Gene Studies:*** Almost all association studies have focused on genes whose function can be plausibly related to PD, either by pharmacological or neurobiological studies. For example, genes that are involved in different neurotransmitter systems (e.g. serotonin, norepinephrine, adenosine, gamma aminobutyric acid (GABA), glutamate), the hypothalamic-pituitary-adrenal (HPA) axis, or that encode for different neuropeptides have been repeatedly

analyzed (for details see Maron et al. [76]). However, as with most other complex disorders, candidate gene studies have not produced robust and replicated association findings in PD. This is complicated by the fact that most studies have used PD samples that were underpowered for the detection of risk variants associated with moderate effect sizes (e. g. >500 cases, >500 controls). In addition, the marker coverage used in most candidate gene studies was not sufficient for capturing the locus-specific pattern of linkage disequilibrium (LD).

***Genome-wide Association Studies (GWAS):*** Two GWAS have been conducted in PD. One study analyzed 200 PD cases and 200 controls of Japanese descent using the Affymetrix 500K array [81]. The best result was observed for the SNP marker rs860544 at the plakophilin-1 (PKP1) gene on chromosome 1q32 ( $p=4.60 \times 10^{-8}$ ). However, the association could not be replicated in an independent PD sample from the same population (558 PD cases and 566 controls) [82].

The second study analyzed 260 PD cases and 260 controls of German descent using the Illumina 300K array [83]. The most significant result was observed at SNP rs7309727 at the transmembrane-protein-132D (TMEM132D) gene on chromosome 12q24, which reached genome-wide significance on the haplotypic level by incorporating three independent PD samples (>900 cases, >900 controls). In addition, the risk genotypes were associated with a higher mRNA expression of TMEM132D in the frontal cortex. A mouse model of extremes in trait anxiety similarly showed that anxiety-related behavior was positively correlated with *Tmem132d* mRNA expression in the anterior cingulate cortex. Functional studies have hypothesized that TMEM132D may act as a cell-surface marker for oligodendrocyte differentiation [84].



## CONCLUSIONS & FUTURE DIRECTIONS

In the past few years, GWAS have provided extraordinary insights into the genetics of several complex diseases. They have shown that common risk variants can be successfully identified by applying this technology. Nevertheless, they have also demonstrated that the effect sizes of the identified risk genes are usually small, and that only large samples provide enough statistical power for successful mapping approaches. In addition, it has been shown that most of the identified risk genes explain only a fraction of disease heritability, suggesting a role for rarer risk variants or other sources of genetic variation. Indeed, for several disorders—including neuropsychiatric phenotypes—such rare mutations have already been identified (see O’Donovan et al. [85] for a review of schizophrenia).

Based on our current knowledge about complex disorders, applying GWAS to large samples must be considered as the next primary goal for PD research. This approach provides a promising tool for identifying the first risk genes in PD. To our knowledge, no single research has yet collected a sufficiently-sized GWAS sample for PD research; thus only multi-centre collaborations on combined PD samples can provide the statistical power needed for robust association findings.

It is unclear whether incorporating sub- or intermediate phenotypes such as CO<sub>2</sub>-hypersensitivity will be promising in the initial GWAS. Although those phenotypes are potentially less genetically heterogeneous, it is unclear whether this may outweigh the loss of power due to small sample sizes. In any case, the inclusion of PD sub- and intermediate phenotypes is a promising tool for follow-up analyses after the first PD genes have been identified through GWAS. This strategy will allow detailed disease modeling and will provide important information on the genetic architecture of distinct PD phenotypes. For instance, it would be interesting to analyze how the identified PD genes contribute to AO, disease severity (e.g. number of panic attacks), and specific neuroimaging or psychophysiological abnormalities. In addition, detailed genotype-phenotype studies on stratified samples will help

assess whether gender- or family-specific disease architecture exists in PD. Furthermore, identified risk genes can be tested in independent samples with comorbid disorders such as other anxiety or mood disorders, as well as in samples with personality traits (e.g. BI, AS, N, HA) in order to assess the overlap and boundaries between PD and other disorders and conditions on the molecular level.

Finally, the next phase of genetic studies in complex disorders will involve deep sequencing approaches provided by next generation sequencing technology that will enable the detection of rare higher-penetrance risk variants. However, the price per re-sequenced genome, and the complexity of data mining and subsequent analyses pose significant challenges. Therefore, it seems that for the next few years such approaches will be restricted to the genome-wide analysis of a few samples, or of larger samples only in pre-selected chromosomal regions. In PD, this could include the most severely affected patients for genome-wide re-sequencing studies (e.g. extreme EAO cases or patients with an unusually high frequency of panic attacks), as well as cases from families where strong linkage to distinct chromosomal regions has already been reported. For example, families with a ‘panic syndrome’ have shown linkage to chromosome 13q32 [45], and may represent optimal candidates for upcoming next generation sequencing studies.

Identifying PD genes will finally help establish a better understanding of gene-environment interactions in order to identify relevant exogenous risk factors. It has long been recognized that environmental factors are of great relevance to the development of PD, but only some of these factors have been implicated. If such factors can be modulated, future PD prevention and individual genetic risk profiling could become possible. Furthermore, genes that accompany the development of PD are naturally of great interest from an evolutionary perspective, since anxiety and fear are ‘normal’ human emotions with a purportedly strong survival value. Therefore, studying the locus-specific genetic architecture of identified PD

genes will be of great interest; such work includes analyzing their LD structure, as well as elucidating their conservation within and across species.

In conclusion, we predict that molecular studies of sufficiently large samples will lead to the identification of PD risk genes in the coming years, and that these discoveries will contribute to our understanding of the underlying neurobiology of anxiety-related disorders and behaviors. In addition, these findings will most likely impact the nosology of anxiety disorders, and lead to the development of improved prevention strategies.

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The authors report no biomedical financial interests or potential conflicts of interests.

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## TABLES

**Table 1** Panic Disorder (PD): Basic characteristics potentially relevant for genetic studies

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- Lifetime prevalence: 3.4-4.7% (females 5.1%, males 1.9%)
  - Estimated heritability: 48%
  - Complex genetic inheritance in most cases
  - Average age of onset: 23.6 years
  - Comorbidity with other psychiatric disorders: 80%
    - Other anxiety disorders: 8.2-64.0%
    - Major depressive disorder (MDD): 34.7%
    - Bipolar disorder (BD): 14.4%
    - Schizophrenia: 17.3%
    - Alcohol abuse/dependence disorder: 25.0%
    - Cannabis abuse/dependence disorder: 20.6%
    - Smoking: 35.9%
  - Associated personality traits: Anxiety sensitivity (AS), behavioral inhibition (BI), neuroticism (N), harm avoidance (HA)
  - Neuroimaging findings: Amygdala hyperactivity
  - Psychophysiological findings: Respiratory abnormalities (incl. CO<sub>2</sub>-hypersensitivity)
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**Table 2** Panic Disorder (PD): Clinical characteristics adopted from the Diagnostic and Statistical Manual of Mental Disorders 4<sup>th</sup> ed. (DSM-IV)

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Recurrent panic attacks – defined as a discrete period of intense fear or discomfort – in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes

- Palpitations, pounding heart, accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, lightheaded, faint
- Derealization or depersonalization
- Fear of losing control or going crazy
- Fear of dying

At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following

- Persisting concern about having additional attacks
- Worries about the implications of the attack or its consequences
- A significant change in behavior related to the attacks

The panic attacks are not due to the direct physiological effect of a substance or a general medical condition  
The panic attacks are not better accounted for by another mental disorder, such as other anxiety disorders

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