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GENETIC DISORDERS (F GOES, SECTION EDITOR)

Genetics of Anxiety Disorders

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Abstract

Purpose of Review Anxiety disorders are among the most common mental disorders with a lifetime prevalence of over 20%. Clinically, anxiety is not thought of as a homogenous disorder, but is subclassified in generalized, panic, and phobic anxiety disorder. Anxiety disorders are moderately heritable. This review will explore recent genetic and epigenetic approaches to anxiety disorders explaining differential susceptibility risk.

Recent Findings A substantial portion of the variance in susceptibility risk can be explained by differential inherited and acquired genetic and epigenetic risk. Available data suggest that anxiety disorders are highly complex and polygenic. Despite the substantial progress in genetic research over the last decade, only few risk loci for anxiety disorders have been identified so far.

Summary This review will cover recent findings from large-scale genome-wide association studies as well as newer epigenome-wide studies. Progress in this area will likely require analysis of much larger sample sizes than have been reported to date. We discuss prospects for clinical translation of genetic findings and future directions for research.

Keywords Anxiety · Genetic · Epigenetics · GWAS

Introduction

Anxiety and fear are normal emotional reactions to threatening situations. However, in patients with anxiety disorders those reactions get out of proportion and disturb daily life. Anxiety disorders are among the most common mental disorders with a lifetime prevalence of over 20% [1], including diagnoses of generalized anxiety disorder, panic disorder, and phobias (social phobia, agoraphobia, and specific phobia). Obsessive–compulsive disorder and post-traumatic stress disorder have recently been removed from the diagnostic category of anxiety disorders in the newest version of DSM due to their distinct causative and neurobiological characteristics. These disorders will therefore not be included in this review. Anxiety disorders are highly comorbid and are considered one of the primary causes of disability worldwide. They present with massive chronicity and rank sixth among all mental and somatic disorders in terms of "years lived with disability" (YLDs) and "disability adjusted life years" (DALYs) at a rate of 389.7 DALYs per 100,000 people [2]. Anxiety disorders are etiologically highly complex disorders; the two factors most widely acknowledged to be involved in their pathogenesis are genes and stressors such as life events. These factors are known to increase the liability to anxiety disorders independently and in concert. Herein, we focus on the current state of knowledge regarding inherited and acquired genetic and epigenetic risk to anxiety disorders.

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Genetic Epidemiology

Due to the fact that anxiety disorders tend to aggregate in families, the involvement of genes in the etiology of anxiety disorders was suggested well before the era of modern genomics [3, 4]. The risk in first-degree relatives of patients to develop an anxiety disorder is approximately four to six times higher compared with relatives of healthy control subjects [5].

In twins studies, heritability estimates ranged around 30–50% [5]. Family and twin studies further indicate that genetic contributions cross the diagnostic boundaries of anxiety disorders and are shared between normal and pathological anxiety. First-degree relatives of patients with one specific anxiety disorders are also at risk for a range of other anxiety disorders, and twin studies have documented genetic overlap of almost all anxiety disorders [6–8]. Unlike monogenic diseases, anxiety disorders are not caused by mutations in a single gene. Segregation analyses point to a complex genetic inheritance pattern comprising interactions of multiple susceptibility genes of small individual effect [4]. In accordance with this polygenic model of anxiety disorders, linkage studies have identified several potential chromosomal risk loci that co-segregate with anxiety disorders in families [9].

Candidate Genes

To date, most association studies of anxiety disorder have focused on candidate genes, which have to be chosen based on limited a priori hypotheses, focusing on either their position under a linkage peak, genomic regions contributing to anxiety traits in animal models (QTLs), or their biological function. Candidate genes for anxiety disorders commonly include genes related to monoaminergic neurotransmitter systems and hypothalamic-pituitary-adrenal (HPA) axis function. Among the most frequently studied candidate genes are the *5HTTLPR* polymorphism of *SLC6A4*, the val158met polymorphism (rs4680) of *COMT*, a promoter length polymorphism of *MAOA*, and a *RGS2* variant (rs4606).

The largest studies examined *SLC6A4* (1161 cases vs. 1051 controls), with no consistent evidence of association with the *5-HTTLPR* promoter variant [10]. Nonetheless, the interest in treatment prediction based on *5-HTTLPR* genotypes is unbroken and has yielded promising results. The low-expression genotype has been successfully linked to a more favorable response to 1 week of in vivo exposure therapy in adult patients suffering from panic disorder [11] and better treatment outcome in children with different anxiety disorders [12]. However, the association between *5HTTLPR* genotype and cognitive behavioral therapy outcome in children did not replicate in another study cohort. In line with previous results, individuals with the low-expression genotype showed more positive treatment outcomes, but the effects were only small and non-significant [13]. Notably, a pharmacological investigation of *5-HTTLPR* and sertraline treatment in patients with social phobia showed no effect of the genotype on treatment outcome [14]. A recent comprehensive meta-analysis of the 23 most widely studied candidate variants in panic disorder found an experiment-wide significant association for *COMT* rs4680, whereas results for other candidate genes remain inconsistent, negative, or did not clearly replicate [15]. The rs4680 variant has been linked to more favorable treatment response to venlafaxine in generalized anxiety disorder [16]. However, no effect of the *COMT* variant rs4680 has been found for outcomes of cognitive behavioral therapy in social phobia [17]. The long, more active alleles of the *MAOA* gene increasing *MAOA* expression and enzyme activity were found to be linked to panic disorder in women [18]. Moreover, in patients diagnosed with panic disorder, the long *MAOA* allele was associated with a significantly less favorable outcome following cognitive behavioral therapy in a controlled multicenter study [19]. *RGS2* has been implicated in the etiology of anxiety disorders by animal studies [20]. Independent and meta-analytical analyses of panic disorder patients and healthy controls further supported the relevance of *RGS2* in anxiety [21]. Interestingly, *RGS2* variants were reported to indicate how likely patients with social phobia benefit from sertraline treatment [14]. Undoubtedly, candidate gene studies have added to our understanding of the genetic architecture of anxiety disorders. However, the probability of a specific candidate gene to be causally related to the disorder can be assumed to be very low due to our limited knowledge of the pathogenesis of anxiety disorders. An association with a candidate gene in a single study is therefore likely to configure a false positive, as most candidate genes identified in one study have never been independently replicated. Furthermore, anxiety disorders are believed to be highly polygenic and common variants are expected to have only modest or small effect sizes, so that a small set of candidate genes is not a valid model to explain the etiology of anxiety disorders. Therefore, much larger sample sizes covering more of the genomic variation are required to detect reliable results.

Genome-Wide Association Studies

Unlike candidate gene studies, which require a priori knowledge for gene selection, genome-wide association studies (GWAS) offer an unbiased approach to test the associations of common genetic variants across the whole genome. GWAS test hundreds of thousands to several million variants requiring a large number of samples. The level of probability needed to reach "genome-wide significance" in a standard (analysis or GWAS) is therefore the standard alpha = 0.05 divided by the approximate number of tests (~ 1,000,000 SNPs), for a derived multiple testing value of significance at $p < 5 \times 10^{-8}$. Recent GWAS of anxiety disorders are summarized in Table 1.

The most studied single anxiety disorder is panic disorder. The first GWAS attempt in anxiety disorders has been conducted for this disorder and included 200 patients and 200 controls of a Japanese population, reporting several potential novel susceptibility loci [22]. However, a follow-up study including more patients failed to show any significant

Table 1 Genome associations of anxiety disorder phenotypes

Reference	Sample size (*N*)	Phenotype	Significant SNP	Nearest gene	*P* value
Otowa et al.	400	Panic disorder	rs860554	*PKP1*	4.60×10^{-8}
Erhardt et al.	438	Panic disorder	rs7309727	*TMEM132D*	5.10×10^{-7}
Otowa et al.	2435	Panic disorder	rs10144552	*BDKRB2*	4.43×10^{-6}
Trzaskowski et al.	2810	Anxiety-related behavior	rs16879771	*CAP2*	6.27×10^{-7}
		Anxiety-related behavior	rs1952500	*STXBP6*	4.12×10^{-7}
Walter et al.	11,127	Phobic anxiety	rs4911015	*LINC00351*	7.38×10^{-7}
Dunn et al.	12,282	Generalized anxiety symptoms	rs78602344	*THBS2*	4.18×10^{-8}
Stein et al.	14,592	Social anxiety	rs708012	*MTCH1,FGD2*	1.55×10^{-8}
		Social anxiety	rs78924501		3.58×10^{-8}
Davies et al.	730	Anxiety sensitivity	rs13334105	*RBFOX1*	4.39×10^{-8}
Deckert et al.	1370	Agoraphobia symptoms	rs78726293	*GLRB*	3.30×10^{-8}
Otowa et al.	2294	Composite anxiety disorders	rs4692589	*MFAP3L*	8.63×10^{-7}
Otowa et al.	18,186	Composite anxiety disorders	rs1709393	*LOC152225*	1.65×10^{-8}
		Composite anxiety disorders	rs1067327	*CAMKMT*	2.86×10^{-9}
Meier et al.	31,880	Composite anxiety disorders	rs7528604	*PDE4B*	5.39×10^{-11}
Purves et al.	114,019	Composite anxiety	rs10959577		5.52×10^{-10}
		Composite anxiety	rs7723509		4.47×10^{-8}

association of these genes with panic disorder [23], and also a combined meta-analysis on 1147 panic cases and 2578 controls resulted in no genome-wide significant finding [24]. More robust support has emerged for a role of the transmembrane protein 132D (TMEM132D) gene in the etiology of panic disorder. An initial GWAS of 909 cases with panic disorder and 915 controls reported association of a variant located in *TMEM132D* on 12q24 [25]. Furthermore, risk genotypes were associated with higher *TMEM132D* mRNA expression in human post-mortem frontal cortex [25]. A subsequent meta-analysis of eight independent case-control samples (1670 cases vs. 2266 controls) identified genome-wide significance replication, when the analysis was restricted to European ancestry cases with primary panic disorders [26•]. Currently, the function of this gene is only poorly understood, but it is referred to play a role in threat processing [27].

The first GWAS of anxiety-related behaviors (negative cognition, negative affect, fear, social anxiety, and anxiety composite) in 2810 children followed up by replication in another sample of 4804 children revealed no genome-wide significance. More interestingly, this study aimed to identify the amount of phenotypic variance that can be explained by common genetic variants (appearing in > 5% of the population), this so-called SNP heritability was estimated at 10% [28]. As SNP heritability estimates are limited to common variants, and do not include other aspects of heritability captured by twin studies including rare variants, insertion/deletion events, potential effects of epigenetics, and gene × environment effects on heritability, heritability estimates of twin studies are markedly higher than from most large-scale genome-wide association studies. Walter et al. performed a GWAS of phobic anxiety measured by the eight-item Crown-Crisp index in 11,127 individuals and also failed to identify significant associations [29], but observed a SNP heritability of 17% in this large sample. A GWAS on generalized anxiety disorder symptoms reported a significant association with variant intronic to thrombospondin 2 (*THBS2*) in a sample ($N = 12{,}282$) of Hispanic/Latino adults estimating SNP heritability at 7%. However, meta-analysis with replication samples did not support this association [30]. A GWAS aiming to uncover the genetic underpinnings of social anxiety symptoms reported genome-wide significant associations in African and European ancestry subgroups, but not in trans-ethnic meta-analyses. The SNP heritability of social anxiety symptoms across ancestries was estimated at 12% [31]. A GWAS in small cohort of twins ($N = 730$) observed a variant within *RBFOX1* to be associated with anxiety sensitivity passing the threshold for genome-wide significance [32]. Finally, genome-wide significant associations were observed for agoraphobic symptoms and variants in the *GLRB* gene. In addition, *GLRB* risk genotypes were found to modulate gene expression in brain tissue, as well as cell cultures. Interestingly, partial Glrb knockout mice demonstrated an agoraphobic phenotype [33•].

Given that the boundaries among the current diagnoses of anxiety disorders are unclear, their high comorbidity and their shared genetic risk factors, it has been hypothesized that focusing on clusters of anxiety disorders might be more efficient than examining a single disorder. Taking this concept into account, the first GWAS using a composite measure of anxiety disorders in 2540 European American and 849 African American subjects found no genome-wide significant

association at a single locus, but gene- and pathway-based analyses suggested several potential susceptibility loci for anxiety disorders [34]. A GWAS meta-analysis including data from seven independent samples ($N = 18,186$) used a categorical and dimensional indicator to capture a range of anxiety diagnoses. For both indicators, significant associations were observed. In the binary analyses, a locus in an uncharacterized non-coding RNA locus on chromosomal band 3q12.3 was identified, and in the dimensional analyses a variant located in the *CAMKMT* gene. SNP heritability estimates were 11% for the dimensional indicator and 14% for the binary indicator [35••]. The largest GWAS of anxiety disorders used binary and dimensional composite measures of anxiety derived from over 100,000 individuals and identified two genome-wide significant loci and reported SNP heritability estimates in the range of 14–35%. Both variants are located within intergenic regions and underscore the potential significance of the non-coding genome in the etiology of anxiety disorders; especially, as the intergenic region on chromosome 9 has previously been associated with neuroticism [36]. An additional novel locus in *NTRK2*, which plays an import role in brain function as a *BDNF* receptor, was found to be significantly associated within the UK Biobank sample, but did not reach significance in the meta-analysis [37••]. Our own group recently conducted a GWAS of 12,655 cases with various register-based anxiety and stress-related diagnoses and 19,225 controls and observed consistent association with *PDE4B* at the level of genome-wide significance. A strong signal of the *PDE4B* gene could be observed in cases with anxiety disorders alone and in combination with genetically related diagnoses of stress-related disorders [38]. Strikingly, mice deficient in Pde4b exhibit behavioral changes in range of tests sensitive to anxiolytic drugs [39]. For most variants identified by GWAS, replication in larger studies is warranted in order to determine whether these or other novel genes truly play a critical role in susceptibility to anxiety disorders. None of these variants have so far been tested for association with therapeutic outcomes. In the first GWAS of psychological treatment response in children with anxiety disorders, no variants passed a genome-wide significance threshold but several variants met criteria for suggestive significance [40].

The Psychiatric Genomics Consortium (PGC) for Anxiety Disorders Workgroup has been formed to conduct well-powered GWAS meta-analyses using the PGC analysis pipeline supplemented by secondary analyses tailored to anxiety research. This PGC effort in cooperation with UK Biobank (https://www.ukbiobank.ac.uk) and the iPSYCH cohort (http://ipsych.au.dk/about-ipsych) aims to include more than 20 samples consisting of approximately 40,000 cases and 80,000 controls. Ongoing large studies from the PGC Workgroup, UK Biobank, iPSYCH, and likely others offer great opportunities to unravel the genetic architecture of anxiety disorders. They will also enable future efforts utilizing other genomic approaches such as CNVs, genome-wide sequencing, and genome-wide transcription analyses.

Epigenetics

Epigenetics is one biological field that has been recently highly emphasized. Epigenetic modifications can be long-lasting, but also temporally highly dynamic and responsive to environmental factors and alter gene regulation and expression. Such modifications include DNA methylation (mDNA) at cytosine sites, which can alter DNA binding to regulatory proteins, and histone acetylation and methylation at specific amino acids that alter chromatin availability for transcriptional activity [41]. Previous studies on methylation alterations in anxiety disorders have majorly focused on candidate genes putatively involved in stress response, neurotransmission, and neuroplasticity [42]. Unfortunately, most of these studies were underpowered to detect a signal that survives multiple testing correction [42]. Recent advancements in technology now enable the examination of DNA methylation patterns on a genome-wide level. An epigenome-wide association study (EWAS) assessing more than 480,000 cytosine residues found panic disorder to be associated with significant differential DNA methylation at 40 CpG sites, with mostly relative lower methylation levels in patients compared with controls [43]. Global DNA methylation alterations have also been reported in individuals with anxiety symptoms at sub-clinical level [44]. In a large cohort ($N = 1522$), significantly increased DNA methylation at a single CpG site in the promoter of the *ASB1* gene correlated with high levels of generalized anxiety symptoms [45]. An EWAS in medication-free 89 patients with panic disorders and 76 healthy controls stratified by gender observed a genome-wide association at CpG site regulating *HECA* expression in females. The same locus, located in an enhancer region of the *HECA* gene, was also hypermethylated in a female replication sample [46]. The sample size examined so far in EWAS is noticeably smaller than in GWAS. To enlarge sample size, the PGC Anxiety Disorders Workgroup plans to form a special EWAS working group dedicated to uncover the epigenetic underpinnings of anxiety disorders. As the sample sizes increase and new consortia are built with combined datasets, the field is hopeful that the GWAS and EWAS combined data will be particularly powerful for elucidating genomic markers of risk and resilience in anxiety disorders.

Alternative Phenotypes and Comorbidity

Anxiety disorders rarely occur in isolation, the vast majority of patients with anxiety disorders have other comorbid mental or somatic disorders [47]. In addition, anxiety and related disorders frequently configure precursors of various adult

mental disorders (for example depression [48•], bipolar disorder [49], and schizophrenia [50]). This covariance can at least in part be explained through common genetic effects, which renders traditional diagnosis-based GWAS somewhat difficult [51]. Alternative approaches that consider mental disorders in terms of constellations of symptoms or endophenotypes and analyze these individuals jointly might therefore be more appropriate and could drastically increase statistical power [52]. Genetic underpinnings of anxiety symptoms could be explored simply on the basis of their presence or absence across diagnostic boundaries. In addition, methods leveraging the genetic covariance of disorders have shown substantial improvements in number of loci identified, predictive power of polygenic scores, and informativeness of a bioinformatics analysis [53, 54]. Given the strong genetic correlation pattern of anxiety disorders, anxiety disorders can be jointly analyzed with a wide range of disorders (for example neuroticism, depression, or cardiovascular diseases), which will boost statistical power and facilitate substantial predictions of anxiety risk using genetic data. Moreover, genetic tools might help to dissect causal relationships in the complex network of comorbidities in anxiety disorders. Mendelian randomization is as an approach that uses genetic variants, which are expected to be independent of confounding factors, as instrumental variables to test for causality. Testing variants and genes using this approach may substantiate epidemiological observations about comorbid phenotypes of anxiety disorders, and clarify whether these comorbidities are due to shared genetic etiology, some shared effect of exposures, treatment, or some other factor. Recent advances in methodology even allow to conduct multi-variant Mendelian randomization analysis using summary-level data efficiently separating signals of causality from horizontal pleiotropy (genetic variation affecting multiple phenotypes via independent biological pathways) [55].

Gene × Environment Interplay

While there is a considerable genetic contribution to the pathogenesis of anxiety disorders, the involvement of environmental influences should not be left unnoticed. A large body of literature has thus focused on the identification of environmental and psychosocial influences driving risk or resilience toward anxiety [42]. Genes and environment jointly affect the etiology of anxiety disorders in two ways: (1) gene-environment correlation and (2) gene-environment interaction (G×E). For example, the genetic vulnerability of children to mental disorders was found to covariate with parental behavior and characteristics associated with poor health outcomes [56]. Conversely, G×E occurs when genetic risks respond to environmental exposures in different ways. So far, G×E studies have focused on a small number of predominantly functional candidate markers in a limited number of genes. No genome-wide search for G×E in anxiety disorders has been conducted, probable due to limitations in sample size and environmental risk assessment. It has been estimated that a sample of 10,000 is required to detect a moderately strong G×E at a genome-wide level of significance [57]. The second limitation is the quality of assessment of environmental variables. In most cases, the definition of environmental exposure is vague and the actual timing of the exposure is frequently lacking [58]. In addition, environmental exposures are often not independent of genetic factors leading to spurious results [59]. Therefore, a more precise conceptualization and operationalization of environmental exposures is warranted for future G×E studies. Although currently limited in their scope, G×E studies will undoubtedly lead to new scientific discoveries.

Clinical Implications

Although an era in which individual-level genetic information can be applied in clinical care of anxiety disorders has not yet arrived, that is the ultimate goal. Novel genetic discoveries may provide important opportunities for health-care facilitating advances in therapeutics, risk prediction, and diagnostic classification. First, GWAS can help to identify novel targets for therapeutic development. For several complex disorders, such as schizophrenia, GWAS associations include known targets of effective drugs proofing that genetic discoveries are actually of therapeutic relevance [60, 61••, 62]. However, even with validated genetic findings therapeutic translation will be slow and costly, involving steps from cellular studies to animal models before first potential trials in humans can be conceptualized. Second, an additional therapeutic benefit could be that genetic findings can advance precision medicine by matching patients based on their genetic profiles to the most effective and least toxic treatments options for that individual patient group. Third, genetic findings have a strong potential in risk prediction thereby assisting the development of prevention strategies. Multilocus predictors, such as polygenic risk score including thousands of common variants, have consistently been shown to capture greater proportions of risk as well as markers of genetic vulnerability at the population level. But their clinical utility for individual decision-making, in particular weighting it against ethical concerns of stigmatization, is so far limited due to the polygenicity and modest penetrance of most genetic risk variants for anxiety disorders [63]. A fourth hope is that genetic findings might move anxiety disorder beyond the boundaries of current psychiatric nosology based on symptom-based categorically defined syndromes. As we have outlined, anxiety disorders show substantial genetic correlations with a range of phenotypic traits,

which should be reflected in a bottom-up, etiologically based nosology. In this context, studies on intermediate phenotypes of defined psychological processes such as fear conditioning and generalization might become useful. However, this will be a long iterative process and might in its complexity not be useful in a clinical setting potentially complicating risk communication and decision-making. Finally, genetic reframing of anxiety disorders etiology might in fact reduce stigmatization and increase awareness.

Conclusions

In this brief review, we have examined the current evidence for heritability of anxiety disorders with a particular focus on large-scale, unbiased GWAS results. We also reviewed first EWAS attempts aiming to identify differential DNA methylation patterns associated with anxiety risk. Although both GWAS and EWAS studies report genome-wide significant findings, most of these loci are not consistently replicated. Further, most studies still lack sufficient power to unravel the complex genetic architecture of anxiety disorders. These conclusions immediately suggest directions for future research to satisfy the need for an enhanced prediction of disease risk, course, and responsiveness to clinical interventions. There is need for very large, well-characterized samples and even larger meta-analyses to be conducted by large consortia before unambiguous findings will be available. Second, leveraging of genetic covariance with other disorders is necessary in such a highly comorbid disorder as anxiety. And finally, as anxiety disorder, like most mental disorders, and certainly PTSD, is a result of both environmental risk and biological risk, more emphasis should be given to efforts integrating both risk types. As the field evolves, genetic research might enable us to utilize more effective strategies for the prevention and treatment of anxiety disorders in the future.

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Compliance with Ethical Standards

Conflict of Interest Sandra M. Meier declares no conflict of interest.

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