

## Anxiety disorders: Current progress and new treatment perspective

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**Abstract:** Anxiety disorders (AD), with early onset and probability of relapse, are the psychiatric disorder of the highest prevalence worldwide. Much is discovered about the synaptic mechanisms of AD, what has been utilized in medical treatment. However, there is a shortage of genetic cures, which may be possible along with the progress of genetic technologies. Based on family studies and twin studies, genetic epidemiological research has demonstrated a moderate level of familial aggregation. To date, Single nucleotide polymorphism (SNPs) and genome-wide association studies (GWAS) have found quite a few variants reaching genome-wide significant, such as on NTRK2, PDE48. Given that environmental factors substantially contribute to the onset of AD, Gene  $\times$  Environmental (G $\times$ E) interaction can provide a new perspective into the pathology of AD, though it is now only limited to several candidate genes. Some variants are found related to anxiety sensitivity, which can predict AD and panic disorder (PD). Epigenetic modification of DNA, especially methylation, appears to exert great influences on the gene expression which modulates the effects of environmental factors on AD risk. A large-scale combination of GWAS, G $\times$ E interplay and epigenetics will enable us to fill the blank of genetic treatment and find more effective techniques, such as CRISPR or demethylation drugs, to prevent and cure AD. To convey new ideas of potential genetic treatment, this review provides an overview of the overall research in genetics of AD and discusses how genetics is expected to be utilized in the anxiety treatment.

### 1. Introduction

Anxiety disorders, including generalized anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, specific phobias, separation anxiety disorder and selective mutism, unlike the transient anxiety naturally caused by stress or horrible scenes in daily life, are persistent and difficult to control, and always impair patients' daily activities. Moreover, at both the genetic [1] and phenotypic [2] level, it has been proven that there are some commonalities among different kinds of anxiety disorders.

AD is the most prevalent psychiatric disorder. Nearly 1 in 5 adults in the U.S. has had an anxiety disorder [3]. In a systematic review of prevalence studies across 44 nations, anxiety disorders affected 1 in 14 people around the globe at any time [4]. In most cases, the onset is in adolescence or early adulthood. Therefore, it's of great importance to identify people at risk and interfere them with useful treatment for young ages. In addition, anxiety disorders often co-occur with other mental or somatic illnesses like major depression and gastrointestinal disorders.

Anxiety disordered people are excessively in fear or anxiety and will try very hard to avoid perceiving threats in the environment. It should be mentioned that this kind of response is not in proportion to the real situation that the person faces with, different with daily anxiety or fear caused by pressure in work or study. Anxiety is a condition of anticipation about potential future hazards, whereas fear is a response to a perceived current threat [2].

In the criteria for diagnosing anxiety disorders, the fear or anxiety should be marked rather than slight, persistent rather than transient, and give rise to deficits in crucial social, vocational, or other aspects of functioning [5]. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is the most used reference for diagnosing anxiety disorders.

According to numbers of twin studies and family studies that have already been done in the past few years, anxiety disorders aggregate in families, and twin heritability is estimated to range from 30-60%, which varied due to different age groups and specific trait being assessed [6, 7].

In mice, several genes, such as the Phosphodiesterase 4B (PDE4B) gene, are found associated with anxiety-like behaviors [8]. As to anxiety disorders in human, similar to most complicated genetic traits, studies on numbers of linkage and candidate gene of anxiety disorders have been conducted, but most associations have failed to be proven robust [9, 10].

Genome-wide association studies (GWAS) have been used in many research on neurological diseases and have proven to be successful in identifying common genetic variants that contribute to the susceptibility to disorders. However, due to the small sample sizes of anxiety disorders, the detection of genetic variants and gene linked to AD has made very slow progress [11]. Recently, GWAS of specific kind of ADs have been conducted, but few are able to be replicated [12]. Moreover, it still remains unknown that which genetic variants contribute to most kinds of anxiety disorders.

Studies on gene-environment interaction have found that SLC6A4 and the brain-derived neurotrophic factor (BDNF) Val homozygotes are highly related to anxiety [13, 14]. And epigenetic research, which focus on reversible modifications attached to DNA, have proven that DNA methylation plays an important part in the pathogenesis of AD [15]. However, these studies are mainly limited to several principally functional candidate genes, thus calling for a comprehensive analysis across the genome.

Currently, psychotherapy and drug treatment are the two main methods for curing anxiety disorders. No genetic ways have been utilized in the treatment [16]. A number of people are unwilling to receive medication due to its slow effect, adverse side effects and withdrawal symptoms. Although psychotherapy has been proven efficient, it is reported that the effects may be greatly exaggerated [17].

With the aim to improve the treatment for anxiety disorder, this review sum up how anxiety disorders are diagnosed and the genetic pathogenesis that have been studied to date in GWAS, G×E interaction and epigenetics. Based on the current genetic research, this article describes what role the gene play on anxiety phenotypes. Moreover, potential gene-related technology to cure anxiety disorders is proposed in this paper, and put forward what kind of studies are necessary to promote development in genetic treatment for AD.

## **2. Diagnose**

Except for anxiety disorders per se, there are also other mental diseases that may lead to pathologically increased anxiety. Besides, anxiety also functions as a sign of a somatic condition, such as hypoglycemia in diabetic patients or myo-cardial infarction. Therefore, thorough examination and evaluation on both mental and physical health are needed to find out what is the real cause of a patient's rise of anxiety.

The symptoms showed in the psychological evaluation will be compared to the criteria of diagnosing an anxiety disorder. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association, is used most commonly. And the gist of each disorder in the tenth edition of the International Classification of Diseases (ICD -10) is highly similar to the one in DSM-5 [5]. Moreover, the detailed criteria will be modified as versions are updated.

Though different anxiety disorders may share semblable features or symptoms, they can be distinguished by some defining diagnostic characteristics. However, there will be overlapping that interferes with the diagnose, such as between social anxiety disorder and selective mutism. Therefore, more inquiry into patients' motivations for their fears and related behaviors is required to fuel the solution to the current diagnostic conundrums.

## **3. Genetic Epidemiology**

Genetic epidemiology usually refers to twin studies and family studies. Family studies aim to find out the difference between the rates of illness in members of an AD patient's family tree with rates of

relatives of a healthy control. Higher rates of the first set, as measured by odds ratio (OR) or a relative risk (RR) greater than 1.0, indicate familial aggregation [18]. Twin studies, working for exploring relative influence of both genetic and ambient factors on AD, usually involve the comparison of the phenotypic similarity between monozygotic (MZ) and dizygotic (DZ) twin pairs.

Data from twin studies and family studies including panic disorder, phobia, obsessive-compulsive disorder (OCD) and generalized anxiety disorder (GAD) were analyzed in a 2001 meta-analysis [19] and significant familial aggregation was demonstrated. Combining with large-scale twin studies of PD and GAD, the authors of the meta-analysis figured out heritabilities of 0.43 and 0.32 for each disorder.

Anxiety disorder twin heritability estimates are consistently low to moderate (20–60%) across subtypes [16, 20]. Shared environment is more likely to influence in childhood, decline during adolescence and even absent in adult anxiety [21]. In a study towards GAD in older adults, polychoric correlations for GAD across sex were 0.23 for MZ and 0.13 DZ twin pairs.

## 4. The Pathogenesis of AD

### 4.1 Causal gene

Single nucleotide polymorphism (SNPs) is the best-understood source of genetic variation that raised the risk of being hit by mental disorders. Genome-wide association studies (GWAS) analyze the relevance between certain genetic variants and a specific disorder or trait.

A 2019 study [22] disclosed three SNPs that has reached genome-wide significant through a GWAS combining anxiety disorders and other stress-related disorders ( $n = 21880$ ); of those, one was located on the Phosphodiesterase 4B (PDE4B) gene, which is proven related to anxiety-like behavior in mice [8].

Five variants were identified genome-wide significant for lifetime anxiety disorder through the largest GWAS ( $n = 83566$ ) of anxiety phenotypes till now, which was based on self-reported symptoms and diagnoses of participants of the UK Biobank [12]. Among the five variants, one is relevant to the coding regions of NTRK2, which works as a receptor of BDNF and is crucial to the brain's normal function [23]. NTRK encodes a membrane-bound receptor that can phosphorylates itself and certain members of the mitogen-activated protein kinase (MAPK) pathway while binding with neurotrophin.

Table 2 includes the genes related to the variants identified genome-wide significant for anxiety disorders in recent studies. The P-values and sample sizes of the studies are also provided. Besides the most promising findings mentioned above, actually a great number of gene variants have reached genome-wide significant. Among them, GLRB encodes the  $\beta$  subunit of the glycine receptor, which functions as a neurotransmitter-gated ion channel; TMEM16B encodes a member of a family of calcium-activated chloride channels; TRPV6 encodes a membrane protein that works as a calcium channel; ESR1 encodes an estrogen receptor as well as a ligand-activated transcription factor. Therefore, a great many genes do have influence on the onset of anxiety disorders through various pathways.

For children and adolescent anxiety, there haven't been any studies that have successfully found genome-wide significant SNPs yet [16]. But a meta-analysis carried out by the CAPICE consortium, analyzed childhood and adolescent internalizing symptoms (age 3-18 years,  $n = 64641$ ) and pinned down three significant associated genes: WNT Family Member 3(WNT3), C-C Motif Chemokine Ligand 26(CCL26) and Centromere Protein O(CENPO) [24].

Table 1. Summary of genome-wide significant loci [16, 18]

Reference	Phenotype	Sample size	Most significant finding	P-value
Otowa, 2009; 2010	Panic Disorder	1524	TMEM16B	$3.73 \times 10^{-9}$
Erhardt, 2011	Panic Disorder	1824	TMEM132D	$1.2 \times 10^{-7}$
Otowa, 2012	Panic Disorder	3625	BDRKB2	$4.43 \times 10^{-6}$
Trzaskowski, 2013	Anxiety-related behaviors	7614 children	STXBP6, NOVA1 for Negative Cognition; CAP2 for Anxiety Composite	$4.12 \times 10^{-7}$ for Negative Cognition; $6.26 \times 10^{-7}$ for Anxiety Composite
Walter, 2013	Phobia	11127	Chromosome 12	$7.38 \times 10^{-7}$
Otowa, 2014	GAD, PD, agoraphobia, social phobia, specific phobia	3379	MFAP3L	$8.63 \times 10^{-7}$
Davies, 2015	Anxiety Sensitivity	739 twins	RBFOX1	$4.4 \times 10^{-8}$
Otowa, 2016	Composite Anxiety Disorders	18186	CAMKMT	$2.9 \times 10^{-9}$
Decker, 2017	Agoraphobia	1370	GLRB	$3.3 \times 10^{-8}$
Meier, 2019	Composite Anxiety Disorders	31880	PDE48	$5.4 \times 10^{-11}$
Purves, 2019	Composite Anxiety Disorders	83566	NTRK2	$5.2 \times 10^{-8}$
			TMEM106B	$4.8 \times 10^{-8}$
			MYH15	$3.7 \times 10^{-8}$
Levey, 2020	Generalized Anxiety Symptoms	175163	SATB1	$6.2 \times 10^{-11}$
			ESR1	$1.3 \times 10^{-9}$
			LRBIQ3	$8.9 \times 10^{-9}$
			MADILI	$2.0 \times 10^{-8}$
			TCEA2	$3.3 \times 10^{-8}$
Levey, 2020	Generalized Anxiety Symptoms	24448	TRPV6	$2.8 \times 10^{-8}$
Levey, 2020	Composite Anxiety Disorders	192256	AURK8	$1.9 \times 10^{-8}$
			MADILI	$4.9 \times 10^{-8}$

#### 4.2 Gene × environmental interaction

In candidate gene research of gene × environmental interplay for anxiety disorders, serotonin transporter (SLC6A4, its functional promoter length polymorphism 5-HTTLPR) is the gene that has been studied the most in respect to the environment. The short variant, according to Gunthert et al. and Stein et al., altered the influence of daily life stress or earlier childhood abuse on anxiety sensitivity, which predisposes to the onset of AD [13, 25]. Previously, it has been demonstrated that anxiety sensitivity predict panic symptoms [26]. And on the other hand, long allele homozygotes with childhood maltreatment or family adversity had been found that they could increase anxiety sensitivity and AD rates [27, 28].

In addition, the BDNF Val homozygotes were found contributing particularly to greater anxiety through diminished gray matter in the hippocampus [14].

Until now, G×E interaction studies have only involved several primarily functional candidate markers in just a few genes. In result, comprehensive research for G×E interplay across the genome is necessary for finding more genes related to AD onset.

### 4.3 Epigenetics

Epigenetics focus on the reversible modifications that are attached to DNA and alter how genes express with no change in DNA sequences. One of the most common epigenetic alterations is DNA methylation, which usually inhibit gene expression. Such pathways have been proposed as potential mediators of reactions to environmental variables and hence may have a role to play in the pathogenesis of AD and other neurological disorders.

The serotonin transporter (SLC6A4) was studied in children with AD before and after cognitive behavior therapy. Responders of CBT increased in methylation, whereas nonresponders showed a decline [29]. Increased methylation of SLC6A4 has been reported to be a possible result of early life adversity [18]. In bonnet macaques that experienced early life stress, there was a lift in the methylation status of their SLC6A4 [30].

Another neurotransmitter transporter, solute carrier family 6 member 2 (SLC6A2), which is viewed as another important candidate genetic factors of AD [31], was reported silenced because of DNA hypermethylation in its promoter region [32, 33].

Early-life adversity also has epigenetic influence on the BDNF gene. Increased methylation of BDNF were all been recorded in rats that had experienced cat exposure, dietary interventions or stressed caretakers during infancy [34-36].

The other candidate gene, *glutamate-decarboxylase* (GAD1), encodes the rate-limiting enzyme that regulates the course of glutamate synthesizing GABA in the brain [37]. In comparison to control subjects, CpG sites in the promoter and intron 2 region of GAD1 were found under-methylated in PD patients [38].

Moreover, it has been reported that AD participants in the study had considerably higher levels of global DNA methylation when compared to the controls [15].

## 5. Treatment

### 5.1 Current treatment

Nowadays, two major treatments for AD are psychotherapy and medications. It is of great possibility that patients can be helped to the largest extent by a combination form of the two.

Cognitive behavioral therapy (CBT) is the most telling form of psychotherapy for psychotherapy for anxiety disorders. Psychological treatments are equally effective in treating anxiety disorders[39], while about 75% of patients tend to take psychotherapy instead of drug treatment [40]. A meta-analysis(N=337) reported a relapse rate of 14% in CBT for anxiety disorders[41].

However, the effects of CBT and other psychotherapies may be greatly exaggerated [17]. In terms of depression, it has been found that about one fourth of trials on psychotherapy for adult funded by the US National Institutes of Health didn't have the chance to be published. After including those unpublished trials, the mean effect size for psychotherapy declined by over 25% [42].

In drug therapies, certain antidepressants, such as SSRIs and SNRIs, are used most commonly. SSRIs work by binding to the serotonin reuptake pump (SERT) in the presynaptic membrane and inhibiting SERT's reuptake of serotonin in the synaptic gap, hence boosting serotonin levels in the synaptic gap. The neuron synapse can transmit messages more easily if there is more serotonin available. Additionally, SNRIs can bind to the norepinephrine reuptake pump.

Other type of medication, like benzodiazepines and pregabalins may be prescribed in limited circumstances. The use of benzodiazepines, which some experts think may lead to dementia risk with prolonged use [43], continues to be a source of controversy.

The side effects and withdrawal symptoms of drugs are hard to avoid. Moreover, there will be a likelihood of relapse in case of both psychotherapy and drug therapies.

## 5.2 Implications for potential treatments

CRISPR or other genome editing techniques can be used to accurately alter a certain gene. A study has succeeded in knockout of GSK2 beta in D2-expressing neurons in the adult's mPFC (medial prefrontal cortex) by using a CRISPR-Cas9-mediated intersectional approach and has proved that GSK3 beta expressed in the mPFC D2 neurons do contribute to emotional regulation [44]. But the Current GWAS for anxiety disorders reflects that a great number of genes' joint influence rather than a handful of genes have large influence on AD. Therefore, more research, such as more large-scale GWAS or the combination of GWAS and synaptic pathogenesis research, is needed to successfully use genetic editing technique to cure anxiety.

Till now, scientists doesn't have the chance to utilize anxiety genetic research in AD's treatment [16]. Besides SNPs and GWAS, G×E interaction and epigenetics also offer new perspectives.

Since genetic variants and epigenetic modifications are associated with the response to environment, a combination of traditional GWAS, epigenetics and G×E interaction can be useful in selecting the treatment options tailored to specific group of patients.

DNA methylation of the gene of some neurotransmitters, which probably result from early age adversity, is highly related to anxiety disorders. Therefore, demethylation drugs that induce under-methylation may help patients become less sensitive to daily stress and lower the possibility of the onset or relapse of AD.

Genetic treatments may be more suitable for every individual. And it may be possible that genetic treatments will also free patients from withdrawal symptoms and the likelihood of relapse, which are the shortcomings of the traditional treatment for AD.

## 6. Conclusion

Anxiety disorders, a series of disorders mainly diagnosed by DSM-5, is proved to have significant familial aggregation by family studies and twin studies. Genetic reason accounts for this family risk, with a heritability ranging from 20-60%.

To date, few candidate and linkage gene studies of anxiety disorders have yielded conclusive results. In SNPs and GWAS, quite a few variants have been found reaching genome-wide significant for AD. Among these variants, there is one located on PDE48, which has been proven relevant to anxiety-like behaviors, and one related to NTRK2, which is crucial for BDNF. As to children and adolescent anxiety, there is a shortage for identified genome-wide significant SNPs, but three genes WNT3, CCL26 and CENPO have been proven associated with AD by a meta-analysis. Overall, a large amount of GWAS have reached genome-wide significant, which implies that heritability of these phenotypes is explained by a great many genes with minor effects rather than a few genes with huge effects. Therefore, large-scale GWAS with well-characterized samples and more inclusive meta-analysis are necessary for further findings.

Additionally, some progress has been made in gene × environmental interaction and epigenetics of AD. Several variants are found associated with anxiety sensitivity, such as variants on SLC6A4 and BDNF Val homozygotes. Epigenetic alterations, especially DNA methylation, have been found in Neurotransmitter transporters and other candidate genes of AD in people with anxiety disorders or early life adversity. It implies that such pathways may be mediators of the environmental influence on human. Moreover, it has been found that people with AD have higher levels of global DNA methylation. These two kinds of studies are still limited to several candidate genes to date. Given that G×E interplay has appeared to identify a susceptibility locus for AD that is of possibility to be missed in the traditional GWAS [18], a combination of GWAS, G×E interaction and epigenetics will be more inclusive and express the genetic risk of AD better.

Besides, G×E interaction and epigenetic studies support that a large number of genes play a part in the onset of AD, thus meaning that the genetic liability of AD is distributed quantitatively rather than

qualitatively [45]. Studying wider range of gene and quantitatively comparing the whole distribution between cases and controls may be helpful to potential genetic diagnosis and treatment of AD.

Genetic technology hasn't been applied in current treatment for anxiety disorders. Given that AD is more like a quantitative trait, genetic editing technique that aims at one or few genes has little possibility of curing AD, unless certain variants are found significant to the onset. Since anxiety sensitivity is crucial to AD, G×E interplay and epigenetics can probably be utilized in prevention and treatment for AD in the near future. With larger-scale sample and combination of different methods, such as GWAS, G×E and epigenetics, methods, such as GWAS, G×E and epigenetics provide fresh perspectives and powerful technique to improve the diagnosis, prevention and treatment for anxiety disorders.

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