



(REVIEW ARTICLE)



Genetic factors in relation to anxiety and panic disorders in humans

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Abstract

Mental health is a state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community. It is an integral component of health and well-being that underpins our individual and collective abilities to make decisions, build relationships and shape the world we live in.

Mental health is affected when suffering from any mental disorder, among the most prominent: anxiety disorder and panic disorder, which will be addressed in the present systematic review.

In this review we can determine the different factors that affect the emotional health of a patient, but above all, we analyze the possible genetic factors that can trigger these conditions, such as the various genes and neurotransmitters involved in anxiety disorder and panic disorder, as well as the mechanism of action in the body of individuals suffering from these disorders.

Keywords: Anxiety; Panic; Neurotransmitters; Genetic factors; Mental disorders; Physiology; Genes; Enzyme; Central nervous system

1. Introduction

1.1. Anxiety and panic disorder

Mental health is a state of mental well-being that allows people to cope with life's stressful moments, to develop all their abilities, to be able to learn and work properly, and to contribute to the improvement of their community¹. Mental health is more than the mere absence of mental disorders. It occurs in a complex process, which each person experiences in a different way, with varying degrees of difficulty and distress and social and clinical outcomes that can be very different¹.

Anxiety (OMIM: 607834) is a normal and healthy reaction that is triggered by a threat or danger. Anxiety becomes an anxiety disorder when this reaction is activated in usually non-threatening/dangerous situations or in a persistent manner, to the point that it significantly interferes with daily life². anxiety disorders constitute a group of psychological and neurological disorders that represent various forms of abnormal or pathological fear and anxiety³.

People with panic disorder suffer from sudden and frequent attacks. Such attacks are characterized by a sudden wave of fear or discomfort, or a feeling of losing control, even when there is no real danger or clear trigger⁴.

This is why both disorders are similar to the point that they show exaggerated reactions to non-dangerous situations. There are several factors and circumstances that establish anxiety and panic disorders, among these factors, there are genetic factors of which the most relevant ones that were previously collected for the writing of this review will be addressed.

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From several studies, new proposals involving neuroanatomical and neurofunctional aspects have emerged. The electrical and chemical transmission of information and how this is associated with different behaviors demonstrate the relevance of the regulation of neurotransmitter production and reuptake in the central nervous system (CNS). Although this regulation is directly related to gene expression, while certain candidate genes have been identified that contribute a percentage to this predisposition, they are not totally determinant⁵.

2. Physiology of anxiety and panic disorders and associated neurotransmitters

The main areas and systems involved in the neurophysiological mechanisms of anxiety are the hypothalamic-pituitary-adrenal (HPA) axis, the limbic system and the prefrontal cortex (PFC)⁶. Within these areas and systems, the main neurotransmitters involved in emotional responses are adrenaline, steroid hormones (or glucocorticoids), serotonin and dopamine⁵.

In various studies, changes in serum cortisol level patterns have been observed in relation to abnormal adrenocorticotrophic hormone levels in mood disorders such as major depressive disorder, anxiety disorders, psychological stress and physiological stressors such as hypoglycemia, fever, trauma, fear, pain or temperature extremes⁵. Serotonin is associated with anxiety disorders such as obsessive-compulsive disorder at low levels⁷. Dopamine is one of the most important neurotransmitters involved in behavioral responses to naturally anxiogenic environmental stimuli and thus plays a key role in anxiety and fear⁸.

3. Possible genetic factors involved

It was found that there are also genetic factors that appear to influence the development of anxiety disorders, especially panic disorder and agoraphobia with panic attacks⁹. Anxiety disorders have been shown to belong to the group of so-called multifactorial disorders, in which multiple susceptibility genes of small individual effect interact with each other and with environmental factors to constitute the overall risk for the disorder¹⁰.

One of the candidate genes is the *RGS2* gene that is involved in regulating G-protein signaling that modulates brain serotonin and norepinephrine receptors, which play an essential role in emotional responses¹¹. In one study, we examined whether variation at the *RGS2* locus influences intermediate phenotypes for anxiety disorder at the level of behavior and brain function¹². Another gene identified as a candidate gene is the *SLC6A4* gene that encodes the SERT (Serotonin Transporter) protein and is responsible for extracellular serotonin (5-HT) reuptake¹³ which causes increased reactivity in the amygdala, therefore, it is a possible factor involved in anxiety and panic.

The *CRHR1* gene encodes the structure of the brain receptors for corticotropin-releasing factor (*CRH*), which is secreted in a situation of danger or during prolonged stress¹⁴. Several studies indicate that genetic variation within the *CRH1* receptor gene (*CRHR1*) affects stress reactivity and that altered *CRHR1* function is associated with stress-related psychopathology, particularly anxiety and depressive disorders¹⁵.

The *COMT* gene is located on chromosome 22 and has allelic variants that correlate with enzyme levels. The most studied variant is known as Val158Met and exhibits a functional polymorphism at codon 158 where a substitution of adenine (A) for guanine (G) in the gene sequence produces a substitution of methionine (Met) for valine (Val) in the *COMT* protein¹⁶. The Met158 variant encodes lower levels of the enzyme breaking down less dopamine, which is why higher levels of dopamine persist at the synapse. Elevated levels of dopamine in the prefrontal cortex are associated with states of anxiety and agitation, producing greater behavioral inhibition and greater intensity in physiological startle reactions¹⁷.

Until 2010, molecular genetic research has focused on candidate genes, especially genes relevant to monoaminergic neurotransmission or stress axis function. However, a meta-analysis of candidate genes only showed an association of panic disorder with variants of the *TMEM132D* gene and, in subsamples, with the *HTR 2nd*, *NPSR 1*, and *MAOA* genes¹⁸.

Another genome-wide association study used dimensional scoring of agoraphobic symptoms and related the main outcome, in the gene encoding the potentially pharmacological *GLRB*, to panic disorder and intermediate phenotypes¹⁹.

Also, it was determined that anxiety disorders do not follow a Mendelian mode of inheritance; rather, segregation analyses point to a complex genetic inheritance pattern of anxiety traits, comprising an interaction of multiple susceptibility genes of small individual effect in addition to environmental influences²⁰. Consistent with a polygenic

etiology model of anxiety disorders, linkage studies have identified several potential chromosomal risk loci that co-segregate with anxiety disorders in families²¹.

Serotonin transporter (*5-HTTLPR*) and Catechol-O-methyltransferase (*COMT*) gene-linked polymorphism. The Met polymorphism has been studied extensively in the field of psychiatric research and is known to be closely related to anxiety disorders, including PD, and it was first reported that individuals with one or two copies of short (S) alleles of the *5-HTTLPR* have less efficient transcription of the *5-HTT* gene compared to those with homozygous long (L) alleles (L/L) and show higher levels of anxiety-related traits²². *COMT* is an important enzyme that metabolizes catecholamines, including dopamine and norepinephrine, and enzyme activity shows allelic variation depending on the genetic locus. Research has shown that *COMT val/Met 158* is associated with panic disorder²³.

4. Conclusion

The main point of interest of this review was the genetic factors involved in mental disorders, mainly anxiety disorder and panic disorder. Throughout this review we have been able to observe that there are several factors related to the aforementioned disorders, which include different neurophysiological systems that affect each disorder, according to the neurotransmitters involved, such as adrenaline, steroid hormones (or glucocorticoids), serotonin and dopamine.⁵ We have also been able to gather information on the various genetic factors that have been studied such as the following: *RGS2* gene, *SLC6A4* gene encoding *SERT* (Serotonin Transporter) protein, *CRHR1* gene encodes the structure of the brain receptors for corticotropin releasing factor (*CRH*), *COMT* gene is located on chromosome 22 and has allelic variants that correlate with enzyme levels, with variants of the *TMEM132D* gene and, in subsamples, with the *HTR 2a*, *NPSR 1* and *MAOA* genes¹⁸, the gene encoding the potentially pharmacological *GLRB* related to panic disorder and finally, the polymorphism linked to the serotonin transporter gene (*5-HTTLPR*) and Catechol-O-methyltransferase (*COMT*). All of them having some influence within anxiety and panic disorders.

There are several factors, including genetic and environmental factors that affect the mental health of an individual, thus causing mental disorders. Among the most prominent mental disorders, anxiety disorder and panic disorder were those selected for our review, where the focus was mainly on the possible genetic causes. Finally, it is concluded that there are genetic factors that alter the emotional state of the individual, including different neurophysiological systems, as well as associated neurotransmitters.

The advance of science and technology has allowed the discovery of genes associated with anxiety and panic disorders, considered of great importance for the analysis and identification of genetic factors for possible diagnoses and to facilitate the distinction of the inheritance of such disorders, as well as the possible origin of them. They are also of great importance to identify the appropriate treatment for each individual.

Thus, recognizing the importance of mental health and its study from different perspectives, in this case, from medical genetics.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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