

Genetic Polymorphisms and Generalized Anxiety Disorder: a systematic review

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OBJECTIVE: Generalized Anxiety Disorder is a disease characterized by feelings of anxiety, fear, excessive worrying and tension in the face of life experiences. This study aims to identify genetic polymorphisms associated with Generalized Anxiety Disorder described in scientific literature.

METHOD: This review was set up by searching PubMed/Medline, Web of Science and Scopus database using the following key words: "gene and generalized anxiety disorder", "SNP and generalized anxiety disorder" and "polymorphism and generalized anxiety disorder".

RESULTS: We found ten polymorphic varieties of nine genes that showed association and seven polymorphic varieties of three genes that showed no association with Generalized Anxiety disorder: genes NPY, BDNF, BLC2, DED2, RGS2, HTR1A, MAOA, ERS2 and 5-HTT showed association, whereas BDNF, ERS1 and TPH showed no association with the Disorder. Conflicting results regarding BDNF come from different studies.

CONCLUSION: This review identified a variety of genetic polymorphisms, that have been studied in relation to Generalized Anxiety Disorder. Taken jointly, their results are inconclusive, showing that more genetic studies focused on this mental disorder are necessary.

KEYWORDS: Polymorphisms, Generalized anxiety disorder, Gene.

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INTRODUCTION

Generalized Anxiety Disorder (GAD) is characterized by anxiety and persistent, chronic and excessive worry about various life situations.¹ It is a common and sometimes disabling condition often associated with stressful life events that involve significant loss or danger.^{2,3} It normally expresses itself by long-term worries, tension, nervousness, fidgeting, and symptoms of autonomic system hyperactivity.⁴ We have previously examined the role of anxiety in suicidal ideation of populations under significant external stress.⁵

It is estimated that the prevalence of anxiety disorders ranges from 10.7% to 16.6%, worldwide.⁶ In Brazil, the prevalence is 10% - 18%,⁷ with a predominance in the female gender.⁸ GAD has been shown to affect 4% - 7% of the population at some time in their lives; 3% to 5% have a current GAD diagnosis.^{9,10}

Several studies have shown that mental disorders are caused by environmental factors, but genetic factors are important contributors. The neurobiology of this disorder is still unclear, although it has been consistently shown that environmental and genetic factors may increase the risk.⁴ Genetic epidemiology has produced convincing evidence that anxiety and related disorders

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are influenced by genetic factors and that the genetic component is highly complex, polygenic, and epistatic.¹¹

A proper study of the role of genetic factors in the genesis of mental disorders has become mandatory. The identification of associated genes will probably explain the proportion of the genetic risk for developing GAD: several risk genes have been identified, but no major gene has been implicated.¹² GAD is inheritable and tends to form familial clusters. A significant number of genomic loci associated with symptoms of this disorder have been reported.¹³

Association studies correlate allelic and genotypic frequencies between mentally affected individuals bearing no familial relations vs. mentally healthy controls. Such association studies aim to identify susceptibility loci. Most association studies concentrate on genes hypothetically related to the appropriate phenotypes (candidate genes). Studies with several candidate genes putatively involved in the development of mental disorders have been investigated in different populations in the world.¹⁴⁻¹⁷ Despite this, studies examining the association of GAD with genetic polymorphisms still seem to be scarce. Thus, this study aims to identify genetic polymorphisms associated with Generalized Anxiety Disorder in the literature.

METHODS

Literature Search

We identified eligible studies for a systematic review by searching PubMed/Medline, Web of Science and Scopus databases using the following key words: “gene and generalized anxiety disorder”, “SNP and generalized anxiety disorder” and “polymorphism and generalized anxiety disorder”. Only articles in English in which human beings were studied were selected for analysis. Case-control studies were selected if data were available regarding the roles of polymorphism in generalized anxiety disorder. The review took place in October, 2016.

Inclusion Criteria

In our study, the inclusion criteria were as follows: (1) articles that described a relationship between polymorphisms and generalized anxiety disorder, (2) a case-control study design, and (3) articles that provided sufficient genotype data for estimating an odds ratio with a 95% confidence interval. We excluded articles that did not examine the association of polymorphisms with Generalized Anxiety Disorder, review articles and meta-analyses.

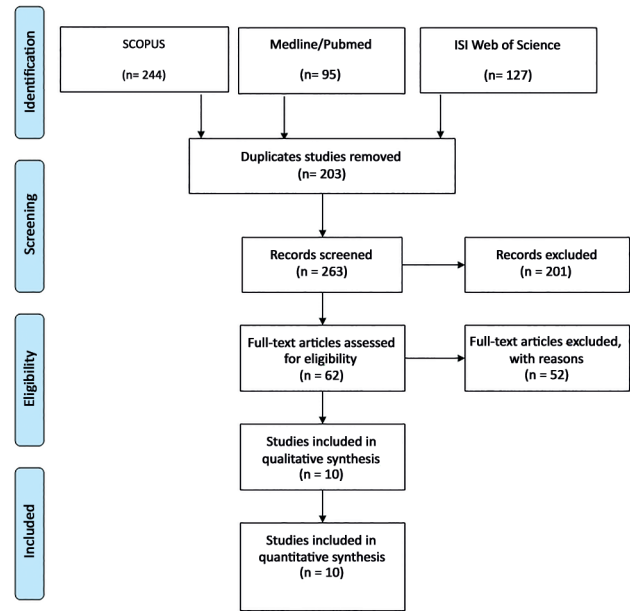


Figure 1 - Flowchart for the search and selection of articles included in this review, following the PRISMA protocol.

RESULTS

The selection of articles followed the PRISMA protocol,¹⁸ as shown in Figure 1. After discarding duplicate hits, 263 articles were initially identified through the search terms; 201 of these were preliminarily excluded, leaving sixty-two which were submitted to analysis. Six reviews and 46 other articles, which did not meet our inclusion criteria, were subsequently excluded. Ten articles related to the proposed theme were included in this study.

Table 1 shows that the ten included studies^{2,4,19-26} were reported in 2003 (one), 2005 (one), 2009 (one), 2010 (two), 2011 (two), 2015 (three). The number of included cases and controls studies varied substantially. Eight out of the ten studies presented substantially more controls than cases.

As shown in Table 1, eleven genes were reported in terms of having or not having genetic polymorphism associations with Generalized Anxiety Disorder: (1) NPY (Neuropeptide Y), (2) BDNF (Brain derived neurotrophic factor), (3) BLC2 (B-cell lymphoma 2), (4) DRD2 (Dopamine receptor D2), (5) RGS2 (Regulator of G-protein signaling 2), (6) HTR1A (5-Hydroxytryptamine Receptor 1A), (7) MAOA (Monoamine oxidase A), (8) ESR1 (Estrogen Receptor 1), (9) ESR2 (Estrogen Receptor 2), (10) 5-HTT (Serotonin transporter) and (11) TPH (Tryptophan hydroxylase);

Table 1 - Studies on genetic polymorphisms with associations to Generalized Anxiety Disorder.

Reference	Candidate gene	Polymorphism	Sample, N	Country	Age	Genotyping method	Results
Amstadter et al, 2010 ¹⁹	NPY	Rs16147	Patients, 41 Controls, 575	USA (Florida)	Adults	TaqMan	Association with increased risk of GAD
Carlino et al, 2015 ²⁰	BDNF	Val66Met (rs6265)	Patients, 91 Controls, 581	North-Eastern Italy	Adults	Illumina array	Association with GAD in females
Sipilä et al, 2010 ²¹	BLC2 DRD2	Rs12454712 Rs4245146	Patients, 103 Controls, 206	Finland	Adults	Sequenom MassArray	Association with GAD. Association with GAD.
Koenen et al, 2009 ²	RGS2	Rs4606	Patients, 41 Controls, 566	USA (Florida)	Adults	TaqMan	Association with GAD.
Molina et al, 2011 ²²	HTR1A	C(-1019)G	Patients, 85 Controls, 974	Spain	Adults and Elderly	Sequenom MassArray	Association with comorbid MD and GAD.
Moreira et al, 2015 ⁴	BDNF	Val66Met	Patients, 121 Controls, 695	Brazil	Adults	TaqMan	Met allele associated with increased BDNF in GAD.
Tadic et al, 2003 ²³	MAOA	T941G	Patients, 34 Controls, 132	Germany	Adults	PCR-RFLP	941T allele is associated with GAD in females.
Ryan et al, 2011 ²⁴	ESR2 ESR1	Rs1256049 Rs2234693 RS9340799 rs498693 rs1271572	Patients, 87 Controls, 850	France	Elderly	PCR SNP KASPar	The A allele is associated with an increased risk of GAD. No association. No association. No association.
Wang et al, 2015 ²⁵	BDNF	Val66Met (rs6265)	Patients, 108 Controls, 99	China	Adults	TaqMan	No association.
You et al, 2005 ²⁶	5-HTT TPH	5-HTTLPR 5-HTT VNTR A218C	Patients, 138 Controls, 90	China	Adults	PCR conventional	SS genotype and S allele were associated with GAD. No association. No association.

As also shown in Table 1, ten polymorphic varieties of nine genes (NPY, BDNF, BLC2, DRD2, RGS2, HTR1A, MAOA, ERS2 and 5-HTT) showed associations with Generalized Anxiety Disorder; seven polymorphic varieties of three genes showed no association with the disorder: BDNF, (polymorphism Val66Met) ERS1 (polymorphisms Rs2234693, RS9340799, rs498693, rs1271572) and TPH (polymorphisms 5-HTT VNTR and A218C).

Table 2 shows reported genotypic and allelic frequencies; four studies reported associations with GAD.^{22,23,25,26} Seven polymorphisms (BCL2, DRD2, HTR1A, BDNF, MAOA, 5HTT, TPH) had their genotypic and allelic frequencies reported. Among these, the following association with Generalized Anxiety Disorder were

described: (a) the Met allele of the BDNF gene was associated with increased BDNF protein levels in GAD;²² (b) the 941T allele of the MAOA gene was associated with GAD in females;²³ (c) the SS genotype and S allele of the 5-HTT gene were associated with GAD;²⁶ (d) the A allele of the ERS2 gene was associated with an increased risk of GAD, but the authors failed to report the frequency of allele occurrence.²⁴

DISCUSSION

Few articles described relationships of Generalized Anxiety Disorder and genetic polymorphisms. This sporadic sequence of publication indicates that the disorder has not been the target of great interest in genetic studies.

Table 2 - Genotype and allele frequencies of polymorphisms. Blue filled cells indicate reported associations with Generalized Anxiety Disorder.

REFERENCE	Candidate gene	Genotypes n (%)			<i>p</i>	Alleles n (%)		<i>p</i>
Molina et al ²²	BDNF	Val/Val	Val/Met	Met/Met	<i>p</i> 0.029	Val	Met	<i>p</i> 0.157
		Cases 75 (62.0)	41 (33.9)	5 (4.1)		0.79	0.21	
		Controls 507 (72.9)	175 (25.2)	13 (1.9)		0.85	0.15	
Tadic et al ²³	MAOA	T	GT	GG	<i>p</i> 0.078	T	G	<i>p</i> 0.018
		Cases female 22 (64.7)	10 (29.4)	2 (5.9)		54 (79.4)	14 (20.6)	
		Controls female 58 (43.9)	54 (40.9)	20 (15.2)		170 (64.4)	94 (35.6)	
Ryan et al ^{24 *}	ESR2 RS1256049	GG	GA	AA	<i>p</i>	G	A	<i>p</i> 0.02
		No values posted	No values posted	No values posted		No values posted	Author stated association, but posted no value	
You et al ²⁶	5-HTT (5-HTTLPR)	SS	LS	LL	<i>p</i> 0.002	S	L	<i>p</i> 0.044
		Cases 94 (68)	31 (22)	13 (9)		219 (79)	57 (21)	
		Controls 44 (49)	40 (44)	6 (7)		128 (71)	52 (29)	
Sipila et al ²¹	BCL2	TT	TC	CC	<i>p</i>	T	C	0.0029
		Cases -	-	-		0.5825	0.4175	
		Controls -	-	-		0.4550	0.5450	
Sipilä et al ²¹	DRD2	CC	CA	AA	<i>p</i>	C	A	<i>p</i> 0.0010
		Cases -	-	-		0.1931	0.8069	
		Controls -	-	-		0.3191	0.6809	
Molina et al ²²	HTR1A	GG	GC	CC	<i>p</i> 0.010	G	C	<i>p</i> 0.054
		Cases 22 (26)	52 (61)	11 (13)		96 (57)	74 (43)	
		Controls 243 (25)	464 (48)	267 (27)		950 (49)	998 (51)	
Wang et al ²⁵	BDNF	GG	GA	AA	<i>p</i> 0.87	G	A	<i>p</i> 0.98
		Cases 28 (25.9)	55 (50.9)	41 (27.7)		111 (51.4)	105 (48.6)	
		Controls 24 (24.2)	54 (54.5)	21 (21.2)		102 (51.5)	96 (48.5)	
You et al ²⁶	5HTT (VNTR)	12/12	12/10	10/10	<i>p</i> 0.778	12	10	<i>p</i> 0.981
		Cases 109 (79)	26 (19)	3 (2)		244 (88)	32 (12)	
		Controls 70 (78)	19 (21)	1 (1)		159 (88)	21 (12)	
You et al ²⁶	TPH (A218C)	AA	AC	CC	<i>p</i> 0.893	A	C	<i>p</i> -
		Cases 31 (22)	73 (53)	34 (25)		135 (49)	141 (51)	
		Controls 18 (20)	50 (56)	22 (24)		86 (48)	94 (52)	

Ryan et al²⁴ described no association of the A allele, but posted no quantitative values.

Moreover, the size of the samples of cases and controls in the published studies varies greatly, which reduces the reliability of the results. Larger samples give greater safety in genetic findings. In most studies, the controls far outnumber the cases, which also limits the validity of the results.

Molecular genetic studies in GAD have been conducted, including linkage and association studies. This review has identified genetic polymorphisms association studies with GAD. The following is a brief description of the reported findings.

NPY is an endogenous peptide with anxiolytic properties that is released during times of stress.²⁷ A study conducted in humans suggests that NPY expression modulates stress reactions and emotional responses.²⁸ The presence of the NPY rs16147 polymorphism and exposure to hurricanes interact to generate a risk for GAD. A significant interaction between the level of hurricane exposure and the genotype resulting from this polymorphism was found;¹⁹ this is a

significant case of gene-environment interaction in the emergence of the disorder. This interaction refers to genetic sensitivity and a susceptibility to an environmental experience, which constitutes a stressful life event.²⁹

BDNF is a candidate gene in anxiety modulation.³⁰ The subject may be described as highly controversial. A wide genomic analysis of the population excluded significant correlations between serum BDNF levels and the Val66Met polymorphism.²⁰ But Chen et al³¹ have reported a significant decrease in serum levels of BDNF in GAD affected females. Additionally they reported that higher levels of trait anxiety were found in subjects bearing the Val/Val BDNF allele compared to Val/Met and Met/Met genotypes.³¹ In contrast, a significant association between the Met allele and risk for GAD ($p = 0.014$) has been reported: the Met allele was significantly associated with an increase in serum BDNF levels compared with the Val/Val genotype in GAD participants ($p = 0.048$).⁴ In another study, the Val66Met polymorphism was not associated with GAD and showed no

influence on BDNF plasma levels.²⁵ Few studies have been conducted about serum BDNF as a biomarker in patients with anxiety disorders.²⁰ Finally, it should be noted that the Met allele of the BDNF Val66Met polymorphism has been implicated in anxiety in animal models.³⁰

The circadian-clock-related genes BCL2 and DRD2 were investigated in an association analysis to test whether they predispose to human anxiety disorders.²¹ BCL2 rs12454712 ($p = 0.0029$) and DRD2 rs4245146 ($p = 0.0010$) showed evidence for association to GAD, whereas rs4245146 ($p = 0.0029$) in DRD2 showed evidence for association to the pooled group of all anxiety disorders.²¹

The rs4606 polymorphism of the RGS2 gene has been significantly associated with GAD: its C allele was associated with increased risk ($p = 0.026$).² The inconsistency about the risk allele between studies raises questions as to whether rs4606 is related to anxiety or whether it is in linkage disequilibrium with some different functional variant.²

Serotonin 1-A receptors are key regulators of serotonin activity and their deregulation might be implicated in GAD. Studies have yielded inconclusive results as to whether the 5-HT1A receptor gene HTR1A has a role in the etiology of GAD.²⁸ A crude association between the C (-1019)G polymorphism of HTR1A and GAD has been reported ($p = 0.003$).²⁸ Molina et al²² reported a main effect of the G(-1019) allele of the HTR1A gene on comorbid MD-GAD ($p = 0.005$).

Monoamine oxidase (MAOA) is one of the enzymes responsible for the degradation of neurotransmitters. Patients with GAD have been shown to have a significantly higher frequency of the 941T allele compared to healthy control subjects ($p = 0.009$). A higher frequency of the 941T allele was present in females ($p = 0.018$).²³ A significant relationship between the MAOA alleles and the presence of anxious symptoms has been reported.³²

It is still unknown whether genetic variants in the estrogen receptors (ERs) can influence the risk of anxiety. The A allele of ESR2 rs1256049 polymorphism was associated with an increased risk of GAD. There is an association between ESR1 and anxiety in older women.²⁴ The anxiolytic effect of estrogen suggests that women are genetically more susceptible to developing anxiety in later-life. This suggests the potential for developing specific ER-targeted hormone treatments for women most at risk of anxiety.²⁴

The serotonin transporter (5-HTT) and tryptophan hydroxylase (TPH) genes are important candidate genes for psychiatric disorders.²⁶ The genotypic and allelic distribution of 5-HTT VNTR and TPH A218C polymorphisms did not show statistically significant differences between patients and controls.²⁶ In the case of 5-HTTLPR polymorphisms, the SS (short/short) genotype showed significantly higher frequencies in GAD patients than in control subjects ($p = 0.002$);²⁹ similarly,

the frequencies of the S (short) allele were higher in GAD patients vs healthy subjects ($p = 0.044$).¹⁹ Appropriately, the involvement of the 5-HTT in the neurobiology of GAD has been reported.³³

■ CONCLUSION

This review analyzed studies about psychiatric genetics and identified some genetic basis in Generalized Anxiety Disorder. A few candidate genes have been accepted as risk genes for this disorder. At the time of writing, no genes with a major effect on the GAD have been reported. Some genes with small effects appear as risk factors, but the number of studies is not sufficient to allow us to grasp the total significance of the genetic influence on GAD.

Ten polymorphisms that showed association and seven polymorphisms that showed no association with GAD have been discussed. The genes NPY, BDNF, BCL2, DED2, RGS2, HTR1A, MAOA, ERS2 and 5-HTT showed polymorphisms associated with GAD. BDNF, ERS1 and TPH showed no such polymorphisms. This review identified a small variety of genetic polymorphisms that have been studied in relation to GAD, showing that more genetic studies focused on this mental disorder are required. A limitation of this study relates to the absence of description of allelic and genotypic frequencies in some of the articles selected for this systematic review.

■ AUTHOR CONTRIBUTIONS

Alves VM designed the study, wrote the protocol, and managed the literature searches. Alves VM, Moura EL and Correia LTA analyzed the data and wrote of the manuscript. Nardi AE contributed to the critical review of the paper.

■ CONFLICTS OF INTERESTS

Authors declare no conflict of interest with respect to this project.

POLIMORFISMOS GENÉTICOS E TRANSTORNOS GENERALIZADOS DE ANSIEDADE

OBJETIVO: O Transtorno de Ansiedade Generalizada (TAG) é uma doença caracterizada por sentimentos de ansiedade, medo, preocupação excessiva e tensão, frente as experiências de vida. Este estudo visa identificar polimorfismos genéticos associados com TAG, descritos na literatura científica.

MÉTODO: Esta revisão utilizou o banco de dados PubMed/Medline, Web of Science e Scopus, usando as seguintes palavras-chave: “gene and generalized anxiety disorder”, “SNP and generalized anxiety disorder” e “polymorphism and generalized anxiety disorder”.

RESULTADOS: Encontramos 10 polimorfismos que mostraram associação e 7 polimorfismos que não mostraram associação com TAG. Os genes NPY, BDNF, BLC2, DED2, RGS2, HTR1A, MAOA, ERS2 e 5-HTT mostraram polimorfismos associados ao transtorno. BDNF, ERS1 e TPH não mostraram tais associações.

CONCLUSÃO: Esta revisão identificou uma variedade de polimorfismos genéticos, com resultados inconclusivos relativamente ao TAG, mostrando a necessidade de estudos genéticos voltados a este transtorno mental.

PALAVRAS-CHAVE: Polimorfismos, Transtorno de ansiedade generalizada, Gene.

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