Review

Are there depression and anxiety genetic markers and mutations?
A systematic review

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Abstract

Background: Genetic factors may encourage or even cause the occurrence of mood disorders such as anxiety and/or depression. However, despite the significant amount of work and sophisticated technology is not fully elucidated which genes or regions of nuclear or mitochondrial DNA, or which types of genetic changes, alone or in combination, can represent reliable genetic markers of anxiety and/or depression.

Objective: To identify whether there are genetic changes that can cause depression or anxiety and if there are genetic markers that can be used to detect these changes.

Methods: A systematic review of 01.01.2004 to 03.28.2014 was held by VHL (Virtual Health Library). The search was performed with the descriptors “anxiety”, “depression”, “mutation” and “genetic markers”. The selected articles were indexed in MEDLINE. The information pertinent to the study was selected, categorized and analyzed. Of the 374 articles found, 29 met the eligibility criteria.

Results: FMR1 gene polymorphisms, dopaminergic (DAT, DRD, COMT), serotonin (5-HTTLPR, HTR1A, HTR2A), interleukins, MCR1, HCN (potassium channel), neurorregulinas, GABAergic (GABA, GAD, DBI) DBI, GABA (Gabra) receptors and GAD genes (GAD1, GAD2) appear to contribute to generate condition of depression or anxiety like. Mutations in mitochondrial DNA in 124pb allele of D2S2944 in o fl1 and 2 loci of chromosomes 4 and 7, respectively, and the chromosomes 8p, 17p and 15q appear to be associated with the origin of depression or anxiety.

Conclusion: Some studies show only associations with one of the disorders, mainly anxiety. Few have shown association with both simultaneously. Other studies showed specific association of gender, or even specific ethnic groups. It was noticed, controversies over certain markers. Interesting results were observed in combination of changes, especially in cases of SNPs, indicating that perhaps this is the most appropriate way to find reliable markers.

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1. Introduction

The emergence of depression and its possible association with anxiety raises a debate about neurochemical reconfiguration, which attempts to highlight the connections between genetic indicators of this phenomenon and the mutations involved in this process. Thus, several studies have indicated genetic susceptibility in understanding the development of depression and anxiety, by considering polygenic loci and their environmental factors.

Vendruscolo et al. (2006), based in classic studies, claim that the influence of genetic factors on such psychopathologies has been widely demonstrated (Vendruscolo et al., 2006; Cloninger 1987; van de Wetering et al., 1999), but this effect is still poorly understood at the molecular level. Therefore, the identification and characterization of predisposing genes would certainly be a major advance for preventing and treating psychological disorders such as alcoholism and anxiety.

As a result of gaps in diagnosis and etiology of depression/anxiety, there was a need for studies that show genetic influence in the origin of those disorders. Holmans et al. (2007) emphasize that when performing a study of genomewide linkage scan, families with at least a pair of ill relatives (other than parent–child pairs) were recruited, and DNA markers at all chromosomes were assayed to search for locations where ill subjects have inherited the same sequence variants (within families) more often than expected by chance. Those markers are likely to be close to genes that contribute to disease susceptibility, which can be identified by using other methods. The Genetics of Recurrent Early-Onset Depression (GenRED) sample was recruited to carry out a large-scale genome scan.

It is known that a portion of psychopathologies, such as anxiety and depression, can have in their etiology considerable genetic factors (Goodson et al., 2012) and, because of that, this study is based in the following research questions: are there genetic changes able to cause depression or anxiety diagnosis? And, are there genetic markers that can be used to detect such changes? This survey was conducted through a systematic review aiming to identify which genetic markers are known at present, so that new clinical therapeutic approaches are used, improving the diagnosis, treatment and prognosis of people affected.

2. Methods

It was conducted a search in the literature through the online databases of the Virtual Health Library (VHL), that hosts the base of MEDLINE, in March 2014, by limiting itself to articles published between January 1, 2004 to March 28, 2014. The reason to limit the search between 2004 and 2014 was because before this period, a number of published works were little expressive and at the same time not addressed directly to the genetic markers and the mutations related to depression and anxiety. In addition, after completion of the sequencing of the human genome in 2003, genetics has gained much importance in the context of the etiology of various diseases considered idiopathic. Initially, the following descriptors were used, in Portuguese, for searching in the VHL:

#1. “genetic markers” (Descriptors in Health Sciences [DeCS, in Portuguese]);
#2. “mutation” (DeCS term);
#3. “anxiety” (DeCS term); and
#4. “depression” (DeCS term).

A similar search strategy was held in the PubMed database, by using the same terms mentioned above.

The analysis of the article followed eligibility criteria previously determined. The survey was carried out in four phases: 1 AND 3, 1 AND 4, 2 AND 3, 2 AND 4. Initially, a search was conducted for those combinations by using the filter “subject descriptor”, but it did not find results either for combination 1 AND 3 or for combination 1 AND 4, it was found only for combinations 2 AND 3 and 2 AND 4. Therefore, the following search strategy was performed: in the first and second times, it searched articles by using the filter “title, summary, subject”; in the third and fourth times, it searched articles by using the filter “subject descriptor “; it adopted the following inclusion criteria: (1) written publications in English, in Spanish or in Portuguese; (2) studies about the topic mutations that cause anxiety or depression; (3) studies about genetic markers for anxiety or depression; (4) original articles with full text accessible through the Portal of Periodicos CAPES (The Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), a virtual library connected to the Brazilian Ministry of education with content restricted to authorized users; and (5) prospective or retrospective observational studies (descriptive or analytical, except for case studies), experimental or almost experimental. The exclusion criteria were as follows: (1) other study designs, e.g. case reports, case series, literature reviews and comments; (2) non-original studies, including editorials, reviews, forewords, short communications and letters to the editor.
Each article was read in its entirety, and the information was entered in a spreadsheet that included authors, year of publication, the study sample description, key data, and databases. Some studies found about depression or anxiety, treated them only as co-morbidity developed after the patient has received the diagnosis of other diseases as cancer, Parkinson disease, Huntington disease, Schizophrenia, Bipolar disorder and were not included because the etiologies of depression and anxiety were secondary for those base diseases not being necessarily resulted from a mutation or from the expression of a specific gene.

Other studies, although dealing with the theme, were deleted because they had mutations that were not at the level of genes. Many of them were just errors of transcription or translation of DNA and RNA, respectively. Others were post-translational modifications, by generating proteins with altered functions.

Another example is the post-translational modifications in proteins that form the cell membrane receptor of serotonin, serotonergic changes, and consequently diagnosis of depression or anxiety.

To better analyze the data, the following stage involved the comparison between the articles and the division of the results obtained from the reading of each one of them in three categories:

- MUTATIONS IN NUCLEAR DNA (Mutation in the allele 124pb D2S2944, Pre-mutation in the FMR1 gene, Chromosomal Loci);
- GENETIC POLYMORPHISM (Dopaminergic genes (DAT, DRD and COMT), Serotonergic gene (5-HTTLPR, HTR1A, HTR2A), Interleukins gene, MC1R gene, HCN gene (potassium channels), Neuregulin genes, GABAergic genes (GABA, GAD and DBI), DBI gene, GABA receptor Genes (GABRA), GAD genes (GAD1 and GAD2) and CHANGES IN THE MITOCHONDRIAL DNA.

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**Fig. 1.** Flow chart showing study selection for the review. Abbreviations: VHL, Virtual Health Library; DeCS, Health Sciences Descriptors.

**Fig. 2.** Genes involved in anxiety (red), depression (blue) and both (green): chromosome 1q31 – RGS2, 2q34 – D2S944, 5p15.3 – DAT, 5q11.2-q13 – 5HT1A, 11p13 – BNDF11q13 – CFL1, 11q23 – DRD2 12q21.1 (cromossom 2); ID 1622 in Homo sapiens. GABRA3 – Location: Xq28 (Cromossom X); ID 2556 in Homo sapiens. GABA6 – Location: 5q34 (Cromossom 5); ID 2559 em Homo sapiens. GAD1 – Location 2q31 (Cromossom 2); ID 2571 in Homo sapiens. MC1R – Location: 16q24.3 (cromossom 16); ID 4157 em Homo sapiens. HCN4 – Location: 15q24.1 (cromossom 15); ID 10021 em Homo sapiens. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Table 1
Are there depression and anxiety genetic markers and mutation? Studies and main findings.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>Sample</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodson et al. (2012)</td>
<td>PLoS Genet.</td>
<td>A population of heterogeneous stock mice descended from known progenitor strains.</td>
<td>The authors confirmed experimentally that fore-brain-specific inactivation of C11 decreased anxiety in knockout mice. Also, the results indicate that similarity of function of mammalian genes can be used to recognize key genetic regulators of anxiety and potentially of other emotional behaviors.</td>
</tr>
<tr>
<td>Adachi et al. (2009)</td>
<td>J. Neurosci.</td>
<td>Mice with knockdown of Mecp2 expression in basolateral amygdala.</td>
<td>The data show that the loss of Mecp2 in the basolateral amygdala (BLA) results in an increase in anxiety-related behavior. Furthermore, the results are consistent with the idea that Mecp2 acting as a transcriptional repressor in the BLA mediates these behavioral process.</td>
</tr>
<tr>
<td>Lifschytz et al. (2012)</td>
<td>Int. J. Neuropsychopharmacol.</td>
<td>The authors studied male mice carrying a mutation that causes lower Rgs2 gene expression, employing mice heterogeneous (Het) or homozygous (Hom) for this mutation, or wild-type (WT).</td>
<td>The findings demonstrate a relationship between Rgs2 gene expression level and a propensity for anxious and depressive-like behaviour and reduced social interaction that may involve changes in serotonergic receptor expression.</td>
</tr>
<tr>
<td>Samaco et al. (2012)</td>
<td>Nat. Genet.</td>
<td>Mecp2 duplication mice (Mecp2-TG1) with reduced Crh and Oprm1 levels was analyzed.</td>
<td>The increased MeCP2 levels impact molecular pathways underlying anxiety and social behavior, and provide novel insight into potential therapies for MeCP2-related disorders.</td>
</tr>
<tr>
<td>Fukui et al. (2007)</td>
<td>J. Neurosci.</td>
<td>One Vmat2 line of 129/C57BL/6 mice.</td>
<td>The findings suggest that Vmat2 heterozygotes display a depressive-like phenotype that is devoid of anxiety-like behavior.</td>
</tr>
<tr>
<td>Kishi et al. (2009)</td>
<td>Neurosci. Res.</td>
<td>Analysis of case-control samples (325 MDD patients, 155 BP patients and 80 controls) in the Japanese population.</td>
<td>In this study, the authors could detect no evidence of genetic association between 4 markers near HTR2A and mood disorders in the Japanese population, but sample sizes, especially BP, were probably too small to allow a meaningful test.</td>
</tr>
<tr>
<td>Kelmendi et al. (2011)</td>
<td>Neurosci. Lett.</td>
<td>285 Caucasian patients with DSM-IV mood disorders and/or obsessive compulsive disorder and 384 Caucasian controls.</td>
<td>The findings suggest HCN4 as a genetic susceptibility factor for mood and anxiety disorders; however, these results will require replication using a larger sample.</td>
</tr>
<tr>
<td>Kulikova et al. (2008)</td>
<td>Bull. Exp. Biol. Med.</td>
<td>Genetic analysis included 156 subjects (74 men, 82 women, mean age 20 ± 5 years).</td>
<td>The carriers of VA1 + 9 + genotype are characterized by the highest basal dopamine concentration in the striatum, which probably determines increased anxiety of these individuals.</td>
</tr>
<tr>
<td>Wu et al. (2011)</td>
<td>Psychiatr. Genet.</td>
<td>181 depressed Mexican–American patients and 185 Mexican–American controls.</td>
<td>The frequency of one of the five haplotypes identified was higher in depressed patients when compared with controls. In-silico functional analysis indicates that SNPs have significant impact on the protein function. The MC1R gene might be associated with major depressive disorder and with treatment response to desipramine.</td>
</tr>
<tr>
<td>Traks et al. (2008)</td>
<td>BMC Med. Genet.</td>
<td>153 patients with MDD and 277 healthy control individuals were recruited.</td>
<td>Our study established increased risk for MDD related to the IL2O and IL24 haplotype and suggests that cytokines may contribute to the pathogenesis of MDD. Since none of the block 2 SNPs were individually associated with MDD, it is possible that other polymorphisms linked to them contribute to the disease susceptibility. Future studies are needed to confirm the results and to find the possible functional explanation.</td>
</tr>
<tr>
<td>Surguladze et al. (2012)</td>
<td>Transl. Psychiatry</td>
<td>A total of 91 healthy Caucasian adults.</td>
<td>We suggest that the epistatic effect of reduced effective connectivity may underlie an inefficient emotion regulation that places these individuals at greater risk for depressive disorders.</td>
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<tr>
<td>Schosser et al. (2010)</td>
<td>Am. J. Med. Genet. B: Neuropsychiatr. Genet.</td>
<td>1398 patients of White European ancestry with a diagnosis of MDD and 1304 ethnically matched controls from three clinical sites in the UK.</td>
<td>We found no single marker or haplotype associations that withheld correction for multiple testing. Our findings do not provide evidence that NRG1 plays a role in MDD or that this gene explains part of the genetic overlap with BPD.</td>
</tr>
<tr>
<td>Licinio et al. (2009)</td>
<td>Arch. Gen. Psychiatry</td>
<td>Two hundred sixty-four controls and 272 Mexican Americans with major depressive disorder (MDD) from Los Angeles who were assessed by the same bilingual clinical research team.</td>
<td>Association analyses of patients with MDD and controls showed that 6 SNPs were associated with MDD (rs12273539, rs11030103, rs6265, rs28722151, rs41282918, and rs11030101) and 2 haplotypes in different blocks (one including Val66, another near exon VIII) were significantly associated with MDD. One recently reported 5’ untranslated region SNP, rs6188880, was associated with antidepressant response after adjusting for age, sex, medication, and baseline score on the 21-item Hamilton Depression Rating Scale.</td>
</tr>
<tr>
<td>Anttila et al. (2007)</td>
<td>J. Neural Transm.</td>
<td>The sample consists of 119 patients with treatment-resistant MDD and 392 controls.</td>
<td>The combination of 5-HT1A GG and BDNF GA genotypes is associated with an increased risk of depression.</td>
</tr>
<tr>
<td>Pham et al. (2009)</td>
<td>Depress. Anxiety</td>
<td>Our study sample consisted of 589 cases and 539 controls selected from a large population-based twin registry based upon a latent genetic risk factor shared by several anxiety disorders, major depression, and neuroticism</td>
<td>Of the 26 SNPs genotyped in stage 1, we identified two markers in CARB4 that met the threshold (p ≤ 0.1) to be tested in stage 2. Phenotypic associations of these two markers failed to replicate in stage 2.</td>
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Table 1  (continued )

<table>
<thead>
<tr>
<th>Authors</th>
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<th>Sample</th>
<th>Main findings</th>
</tr>
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<tbody>
<tr>
<td>Thoeringer et al. (2007)</td>
<td>J. Psychiatr. Res.</td>
<td>Não consta no resumo.</td>
<td>In conclusion, these results suggest a central role of DBI genetic variants in the susceptibility for the development of anxiety disorders that are characterized by the occurrence of panic attacks.</td>
</tr>
<tr>
<td>Hunter et al. (2012)</td>
<td>Am. J. Med. Genet. B: Neuropsychiatr. Genet.</td>
<td>460 women participants WHO completed self-report questionnaires assessing symptoms of depression [Centers for Epidemiological Studies Depression Scale (CESD)], anxiety [State-Trait Anxiety Inventory (STAI) and Social Phobia and Anxiety Inventory (SPAI)], and mood [Positive and Negative Affect Schedule (PANAS)].</td>
<td>Genetic variants in CRHR1 that associate with differential cortisol activation may also modulate levels of anxiety related to the stress of raising a child with FXS among women who carry an FMR1 premutation.</td>
</tr>
<tr>
<td>Hunter et al. (2008)</td>
<td>Behav. Genet.</td>
<td>119 males and 446 females age 18–50 ascertained from families with a history of fragile X syndrome and from the general population.</td>
<td>The results suggest that premutation carriers may be at risk for emotional morbidity; however, phenotypic differences were subtle and of small effect size.</td>
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<tr>
<td>Roberts et al. (2009)</td>
<td>Am. J. Med. Genet. B: Neuropsychiatr. Genet.</td>
<td>Ninety-three females with the FMR1 premutation and 2159 women from the National Comorbidity Survey Replication (NCS-R) dataset.</td>
<td>Major depression in females with the FMR1 premutation may not be characterized as an episodically chronic recurrent disorder as it is in community samples and may have a genetic basis given the relationship with CGG repeat length and lack of association with all child and most demographic factors.</td>
</tr>
<tr>
<td>Rodriguez-Revenga et al. (2008)</td>
<td>Psychiatr. Genet.</td>
<td>Examined psychiatric and depressive symptoms in 34 FMR1 premutation carrier mothers of children with fragile-X syndrome in comparison with two control groups (39 mothers with a non-fragile-X syndrome mentally retarded child and 39 mothers from the general population).</td>
<td>Both groups of mothers with a mentally retarded child showed greater susceptibility to psychological problems than the control group without a mentally retarded child, but FMR1 premutated mothers evidenced a higher tendency to depression. These results suggest that, despite the stress of caring for a child with mental retardation, the premutation by itself could be responsible for some psychiatric traits.</td>
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<tr>
<td>Beem et al. (2006)</td>
<td>Behav. Genet.</td>
<td>347 males and 448 females, and to DSM-IV major depression in a subsample of 210 males and 295 females.</td>
<td>The association of the 124-bp allele to depression in females was not replicated, but there were significant associations (not significant after correction for multiple testing) with anxiety and anxious depression in males. However, the association occurred in the absence of evidence for linkage in this region on chromosome 2. Combining other risk factors, the 124-bp allele had a strong association with DSM-IV major depression specific to those with histories of alcohol abuse/dependence and/or ASPD. In addition mtDNA sequences can predispose individuals towards the development of some “mental health” disorders.</td>
</tr>
<tr>
<td>Langbehn et al. (2006)</td>
<td>Drug Alcohol Depend.</td>
<td>We have analyzed the Iowa Adoption Study data to test this association. D2S2944 allele typing was available for 247 subjects from the Iowa Adoption Studies.</td>
<td>These results suggest that OF11 contains either linked genes with independent influences on anxiety-related responses and ethanol drinking or a pleiotropic gene with simultaneous effects on both traits.</td>
</tr>
<tr>
<td>Boles et al. (2005)</td>
<td>Am. J. Med. Genet. B: Neuropsychiatr. Genet.</td>
<td>15 mothers of children with MIMD and 17 mothers of children with autosomal recessive metabolic disorders (ARMD).</td>
<td>Results suggest that DNA sequence variations in one or more genes in the 15q25-q26 region can increase susceptibility to major depression and that efforts are warranted to identify these genes.</td>
</tr>
<tr>
<td>Vendruscolo et al. (2006)</td>
<td>Genes Brain Behav.</td>
<td>453 rats deriving from an F2 intercross between the inbred rat strains Lewis (LEW) and the spontaneously hypertensive rats (SHR)strains were selected.</td>
<td>These regions of chromosomes 15q, 17p, and 8p might contain genes that contribute to susceptibility to major depression and related disorders. Evidence for linkage has been reported independently in the same regions of chromosome 15q for major depression and of chromosome 8p for related personality traits. Recent studies suggest that mutations/polymorphisms of mitochondrial DNA (mtDNA) are associated with neuropsychiatric diseases. No significant impairment was detected. The data did not support our hypothesis that these disorders in this family are caused by mtDNA mutation(s).</td>
</tr>
<tr>
<td>Levinson et al. (2007)</td>
<td>Am. J. Psychiatry</td>
<td>In 631 European-ancestry families with multiple cases of recurrent early-onset major depressive disorder, 88 SNPs were genotyped, and multipoint allele-sharing linkage analyses were carried out.</td>
<td>Recent studies suggest that mutations/polymorphisms of mitochondrial DNA (mtDNA) are associated with neuropsychiatric diseases. No significant impairment was detected. The data did not support our hypothesis that these disorders in this family are caused by mtDNA mutation(s).</td>
</tr>
<tr>
<td>Holmans et al. (2007)</td>
<td>Am. J. Psychiatry</td>
<td>Microsatellite DNA markers were studied in 656 families with two or more such cases (onset before age 31 in probands and age 41 in other relatives), including 1494 informative “all possible” affected relative pairs (there were 894 independent affected sibling pairs).</td>
<td>Recent studies suggest that mutations/polymorphisms of mitochondrial DNA (mtDNA) are associated with neuropsychiatric diseases. No significant impairment was detected. The data did not support our hypothesis that these disorders in this family are caused by mtDNA mutation(s).</td>
</tr>
<tr>
<td>Munakata et al. (2007)</td>
<td>Mutat. Res.</td>
<td>Maternally inherited family with bipolar disorder and depression.</td>
<td>Same findings establish a functional link between functional hypoperontergena and altered mPFC-AMY network dynamics. Findings also highlight a novel approach that can be used to investigate the role that various genetic risk factors play in mediating brain circuit-based endophenotypes observed across neuropsychiatric illnesses.</td>
</tr>
<tr>
<td>Dzirasa et al. (2013)</td>
<td>J. Neurosci.</td>
<td>Knockin mice carrying the R439H Tph2 allele, equivalent to the human R441H TPH2 allele identified in subjects with MDD.</td>
<td>Recent studies suggest that mutations/polymorphisms of mitochondrial DNA (mtDNA) are associated with neuropsychiatric diseases. No significant impairment was detected. The data did not support our hypothesis that these disorders in this family are caused by mtDNA mutation(s).</td>
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</tbody>
</table>
3. Results

Initially, the aforementioned search strategies resulted in 374 references. After browsing the title and abstract of the retrieved citations for eligibility based on study inclusion criteria, 345 articles were excluded and 29 articles were further retrieved and included in the final sample (Fig. 1). Articles from MEDLINE database matched the inclusion criteria of the present study.

The 29 studies were distributed into the previously determined sixteen categories as follows: MUTATIONS IN NUCLEAR DNA (Martin Goodson et al., 2012; Adachi et al., 2009; Samaco et al., 2012; Fukui et al., 2007) (four studies), [Mutation in the allele 124pb D2S2944 (Langbehn et al., 2006) (one study), Pre-mutation in the FMRI gene (Hunter et al., 2012, 2008; Rodriguez-Revenga et al., 2008; Roberts et al., 2009) (four studies), Chromosomal Loci (Vendrauscolo et al., 2006; Holmans et al., 2007) (three studies)]; GENETIC POLYMORPHISM (Kulikova et al., 2008; Reif and Lesch. 2003) (two studies) [Dopaminergic genes (DAT, DRD and COMT) (Kulikova et al., 2008) (one study), Serotonergic gene (5-HTTLPR, HTR1A, HTR2A) (Kishi et al., 2009; Surguladze et al., 2012; Dzirasa et al., 2013; Anttila et al., 2007; Licinio et al., 2009; Lifschytz et al., 2012) (four studies), Interleukins gene (Traks et al., 2008) (one study), MC1R gene (Wu et al., 2011) (one study), HCN gene (potassium channels) (Kelmendi et al., 2011) (one study), Neur- egulin genes (Schosser et al., 2010) (one study), GABAergic genes (GABA, GAD and DBI) (Pham et al., 2009) (one study), DBI gene (Thoeinger et al., 2007) (one study), Genes De Receptores GABA (GABRA) (Pham et al., 2009) (one study), GABA receptor Genes (GABRA) (Hettema et al., 2006) (one study)] and CHANGES IN THE MITOCHONDRIAL DNA (Boles et al., 2005; Munakata et al., 2007) (two studies). Among the 29 studies, some studies were referenced in more than one category. The categorization of studies aims to a better organizational quality systematic review and it is not compulsory that each article must be referenced only in their respective category. The Fig. 2 provides an overview of the main genes cited on this paper and their location on chromosomes. Table 1 provides an overview of all studies included in the final sample and of all data elements used during the data analysis process.

4. Discussion

Studies have shown that the development of a parcel of mood changes, such as anxiety and depression, can be facilitated or triggered by genetic factors of the patient. Currently, there are in the international scientific literature a significant quantity of tests showing evidence of the relationship of genetic changes with anxiety and/or depression, both in animals and in human beings (Martin Goodson et al., 2012). The most of changes investigated diverse and range from nuclear or mitochondrial DNA, loss-of-function mutations or duplication of chromosomal regions, microsatellite changes, and single-nucleotide polymorphisms (SNPs). Not only genes which the relationship with the mood behavior are well defined, such as serotoninergic, dopaminergic, GABAergic, but also several genes or regions of DNA has been identified and related to anxiety or depression. Generally, these works aims to identify reliable genetic markers for those behavioral disorders, in order to facilitate the diagnosis and the treatment.

5. Mutations in nuclear DNA

Interesting findings have been obtained in studies that investigate the relationship between anxiety and the gene that encode methyl-CpG binding protein 2 (MECP2 – Gene ID 4204), a DNA-binding protein that acts as a transcriptional repressor, which loss of function due to its gene mutation causes a neurological disorder called Rett Syndrome (Adachi et al., 2009; Samaco et al., 2012), Adachi et al. (2009), by using specific deletion of Mecp2 (Gene ID 17257), the vector-mediated in the basolateral amygdala of the mice, showed that the full operation of this gene is required for a normal anxiety behavior. Furthermore, the results indicate that the increase in anxiety-related behavior in mice tested is related to loss of transcriptional repression due to the deletion of the gene Mecp2, which would act jointly with histone deacetylases (HDACs). In another study, hybrid mice expressing Mecp2, in a level two times higher than normal, exhibited increased anxiety. The authors also demonstrated the direct relationship of overexpression of MECP2 and corticotrophin-releasing hormone (Crh) gene (an eponymous neuropeptide encoder which, among other effects, is also involved in increasing anxiety), possibly due to the activation promoted by the product of the first gene, as was also demonstrated the MECP2 binding to the promoter of Crh. Nevertheless, the reduction in the expression of Crh in those animals was accompanied by suppression of anxiety behavior Samaco et al., 2012.

Goodson et al. (2012) through Merge analysis for tracking of candidate genes from quantitative trait loci (QTLs), in heterogeneous stock (HS) mice, identified the coflin-1 gene (Cfl-1 Gene ID 12631) (Actin depolymerizing factor), as a gene involved in the regulation of anxiety in these animals. In harmony with previous findings in silico, the authors also demonstrated experimentally that the forebrain-specific inactivation of this gene is related to the reduction of anxiety.

The vesicular monoamine transporter 2 gene (VMAT2 Gene ID 7561), expressed mainly in the central nervous system, encodes a transmembrane protein which function involves the transport of monoamines from the cytoplasm into secretory vesicles. The investigation of heterozygous mice for Vma2 gene (Gene ID 214084) compared to wild mice, generally showed that the mutated animals presented many features of depressive disorders, such as anhedonia, locomotor retardation, and sensitivity to stress, however, without displaying anxiety behaviors Fukui et al., 2007.

5.1. The mutation of the 124pb allele of D2S2944

The association of the 124pb allele of D2S2944 with major depression was reported by Zubenko et al. (2002b) and Langbehn et al. (2006) and for Zubenko et al. (2002c) and Langbehn et al. (2006), being corroborated by other authors (Philibert et al., 2003; Langbehn et al., 2006). This marker occurs in the genome 2q34 (214.78 Mb) and its various alleles are defined by tetranucleotide repetitions that vary in length from 104 to 128 base pairs.

Furthermore, Zubenko et al. (Zubenko et al., 2002c; Langbehn et al., 2006) showed that the association with depression was specific to 124 bp allele. They compared subjects with major depression recurring, non-psychotic and early-onset (before the age of 26 years old). The controls were individuals with no history of any psychiatric disorder. Individuals with single depressive episode have not been studied. In their study, the association with D2S2944 seemed to be gender specific. They observed the odds ratio of 4.5 for the Association of the 124pb allele with recurrent major depressive disorder in females (p=0.001) and only 1.6 in men (p=0.27).

According to the study of Beem et al. (2006), where the 124pb allele of D2S2944 association was tested with quantitative measures of anxiety, depression, and neuroticism, assessed by questionnaires applied in subjects of European descent, it was found evidence of a weak association level of D2S2944 allele 124pb with anxiety, depression or neurosis. The biggest evidence of association found, occurred in men for anxiety and depression. Due to the
variation in the population, in the criteria for the selection of themes, and in the choice of phenotypes in this study, it was found results different of Zubenko et al. (2002c) (Zubenko et al., 2002b; Beem et al., 2006), that conduced Beem et al. (2006) to consider the possibility that this region is not involved in the development of major depressive disorder.

In the study of Langbehn et al. (2006), the analyses were made with adult subjects of adoption, taken from their birth parents during the first weeks after birth and raised in foster homes. These analyses have shown that, after controlling for other risk factors, the D2S2944 allele 124pb has a strong association with major depression (DSM-IV), which is specific to those with stories of abuse or alcohol dependence (adjusted odds ratio = 10.53; p = 0.01).

5.2. Pre-mutation FMR1 gene

In the context of genetic studies related to anxiety and depression, a special event has been observed in the spectrum of disease, the fragile X syndrome, also known as Martin & Bell syndrome, considered the second most common inherited cause of mental retardation and the most common known cause of autism. It is a genetic disorder caused by mutation of the FMR1 gene (fragile X mental retardation gene/Gene ID 2332) located chromosome Xq27.3, responsible for the formation of dendrites in neurons (Franco, 2003).

The gene mutation observed is represented by CGG repeat polymorphism in tandem in 5’ untranslated region of exon 1. The disease is manifested when noted above 200 repetitions, therefore it is full mutation. When the number of repetitions is less than 200, the disease does not manifest itself; it is called incomplete mutation or pre-mutation (between 55–199 repetitions) (Hunter et al., 2012). It has been shown that the pre-mutation is also involved in well-defined clinical entities such as premature ovarian failure, tremor/ataxia syndrome fragile X-associated, and distinct neurocognitive changes with behavioral phenotype that include psychiatric disorders (Hunter et al., 2012; Rodriguez-Reverenga et al., 2008).

The evidence mount up showing that, once unstable, this repetition is capable of expansion through the generations and the women with a pre-mutation allele (55–199 repetitions) are in risk of passing full mutation allele (> 200 repetitions) to their offspring (Hunter et al., 2012). Pre-mutated alleles are able to expand to a full mutation in the following generation, with maternal transmission (Hunter et al., 2012; Snow et al., 1993; Nolin et al., 1996). In other words, women who carry a pre-mutation allele are at risk of having a child with fragile X syndrome.

The increasing evidence suggesting that the carriers of pre-mutation can be vulnerable to anxiety and depression symptoms is important (Hunter et al., 2012, 2008; Rodriguez-Reverenga et al., 2008; Roberts et al., 2009). The tests has indicated that the mood and anxiety disorders would be modulated by genetic factors that influence the responses of endogenous cortisol, which could modulate anxiety and symptoms of depression (Hunter et al., 2012).

Investigation of mood and anxiety measures in 119 men and 446 women aged 18–50 years selected from families with a history of fragile X syndrome and of the general population were evaluated by Hunter et al. (2008). The results were analyzed by means of a linear model with length of repetition as the main predictor for adjustments in possible confounding factors. The authors observed that the length of the repetition was not associated with anxiety, but it was marginally associated with depression. They concluded that the carriers of pre-mutation may be at risk for emotional morbidity with subtle phenotypic differences with a little expressive manifestation.

Roberts et al. (2009) conducted a study of predictor frequency of mood and anxiety disorders in 93 mothers with a pre-mutation of FMR1 gene, compared to 2159 women of the database of National Comorbidity Survey Replication (NCS-R). At the end of the study, they considered the fragile X syndrome as a model to study the relative contributions of genetic and environmental factors for psychiatric disorders in mothers of children with disabilities. The authors report that women without prior marriage and with less length of CGG repeat are associated with an increased likelihood of major depressive disorder.

5.3. Chromosomal loci

Previous studies have mapped two chromosome loci in mice, associated with the anxiety behavior, called Ofn-1 (chromosome 4) and Ofn-2 (chromosome 7). Ofn-1 showed beyond an association with anxiety, a tendency to alcoholism. Seeking to better understand the role of Ofn-1 in anxiety, Vendruscolo et al. (2006) studied mice genetically marked and found a relationship of Ofn-1 (chromosome 4) and anxiety and alcoholism linked to female gender. Now, it should be necessary to assess the genes involved in these two concurrent disorders association.

Subsequently, an analysis of connection of 656 families showed suggestive wide genomics linkage in the chromosome 15q and also in the chromosomes 17p and 8p when the sex of the affected relative pair was taken into account (Holmans et al., 2007). Levinson et al. Holmans et al. (2007), in the study of Holmans et al. (2007), studied the map of DNA markers of SNPs at chromosome 15q25-q26 to analyze genetic linkage in this chromosomal region where it was previously reported evidence of association with early onset major depression. 88 SNPs were genotyped by studying 631 European families with multiple cases of recurrent MDD. After analyzing multipoint alleles sharing linkage the statistic studies of Kong and Cox, a variation in the sequence of one or more genes in the region 15q25-q26 presented association to the MDD. It is necessary now to establish what exactly are those genes in that region involved with depressive disorder.

6. Genetic polymorphism

The genetic polymorphism not only enables the variability among individuals but also change in response to treatment or predisposition to certain diseases. In major depression disorder (MDD), some genetic polymorphisms have been studied in association with the increased risk of depression and anxiety. Among the target genes studied, there are the transporters (DAT), receptors (DRD) degrading enzymes (COMT) of dopamine (DA); the receptor (5HTR) and the serotonin transporter promoter (5HTTLPR); brain-derived neurotropic factor (BDNF); and other proteins such as interleukins, melanocortin receptor (MC1R), Hyperpolarization activated cyclic nucleotide-gated (HCN) and Neuroglin 1 (NRG1) (Kulikova et al., 2008). It was shown through studies of Positron Emission Tomography (PET) that there is a specific interaction between markers of dopaminergic activity and anxiety (Kulikova et al., 2008; Rei Rief and Lesch, 2003).

6.1. Dopaminergic genes (DAT, DRD and COMT)

In the striatum, the DAT protein (dopamine active transporter) is located in the synaptic endings and the axons of dopaminergic neurons. DAT determines the distance of diffusion of dopamine in the extracellular space (Kulikova et al., 2008; Cragg and Rice, 2004). The non-translated 3’ region of the exon 15 of DAT gene (Gene ID 6531) contains a fragment with a variable number of DNA repetitions (3–13 repetitions of 40 bp) (Kulikova et al., 2008; Vandenbergh et al., 1992). Alleles with 9 and 10 repetitions appear in 98% of the population. The density of DAT in individuals with
Dopamine receptors belong to the family of D2 receptor (DRD2, DRD3, and DRD4) just like DAT, are located on presynaptic membrane and modulate the activity of ion channels. The TaqIA punctual polymorphism is located in the 3’ non-translated region of the gene (Gene ID 1813)). This secondary allele, called A1+, is associated with reduced DRD2 density. About the Catechol-O-methyltransferase enzyme (COMT/Gene ID 1312) it plays a central role in the catabolism of dopamine in the prefrontal cortex. A punctual mutation V158M in exon 4 of COMT induces a decrease of 40% in the enzymatic activity in carriers of alleles M (Kulikova et al., 2008; Chen et al., 2004).

In an interesting study Kulikova et al. (2008) correlated the aforementioned polymorphisms in DAT (9+), DRD2 (A1+) and COMT (M) with anxiety. However, the MM genotypes were excluded from the study because they were associated with an increase in dopaminergic neuron activity, which leads to an inhibition of the tonic activity in the striatum and, consequently, a decrease of DAT and DRD2 in basal dopamine levels. Therefore, only the V genotypes were considered.

The number of dopamine-related receptors in A1+ individuals is significantly lower than A1− individuals, so the release of dopamine in this region will occur sooner in A1+ individuals. The lifetime of dopamine in the extracellular space and the area of diffusion are higher in A1+9− individuals. Thus, carriers of V genotype A1+9+ are characterized by highest level of basal concentration of dopamine in the striatum, which probably determines an increase of anxiety in those individuals Kulikova et al. (2008).

6.2. Serotonergic genes (5-HTTLPR, HTR1A, HTR2A)

A change in neural transmission of serotonin was singled out as a susceptibility factor for mood disorders such as MDD (Kishi et al., 2009). The protein carrier of serotonin presents a polymorphism found in the promoter region of the gene (5-HTTLPR Gene ID 6532), called the short allele (S), which is also related to the predisposition to the development of MDD. The S genotype along with the COMT-M genotype, which was previously cited was studied in relation to connectivity of neural circuits to emotional facial expressions. It has been shown that under the processing condition of fear, an interaction between 5-HTTLPR (S) and COMT (M), low-activity alleles were associated with the reduction of mutual connectivity in fusiform bilateral circuit/occipital inferior region, right superior temporal gyrus/superior temporal sulcus, bilateral lower cortex/prefrontal medium and right amygdala (Surguladze et al., 2012).

The selective serotonin reuptake inhibitors (SSRIs), which are the biggest therapeutic agents for MDD, block the transport of serotonin in one presynaptic neuron, by increasing the extracellular serotonin levels and stimulating the 2A receptors (5-HTR2A/ Gene ID 3356) in postsynaptic neuron (Kishi et al., 2009). However, analyzing the genetic association of two functional SNPs Gene ID 3356) in postsynaptic neuron (Kishi et al., 2009). How- ever, analyzing the genetic association of two functional SNPs (rs7997012 and rs1928040) in HTR2A, which are associated with the therapeutic response to the SSRIs, with mood disorders in case-control samples in a Japanese population, no association was found (Kishi et al., 2009).

The Tph-2 enzyme (human tryptophan hydroxilase-2) participates in the synthesis of serotonin 5-HT (Zhang et al., 2005; Dzirasa et al., 2013). An animal model was developed to mimic a mutation found in humans, the TPH2 (Gene ID 121278) observed in a group of subjects carriers of MDD. This mutation produced by “knocking” (Tph2KI) showed lower basal levels of 5-HT (Jacobsen et al., 2012; Dzirasa et al., 2013). The work also showed that the functional changes in 5-HT homeostasis increased the risk of MDD, causing deficits in microcircuits between the prefrontal cortex (mPFC) and the basal amygdala (Dzirasa et al., 2013).

Many studies have associated the C1019G polymorphisms of the serotonin receptor 5-HT1A (Gene ID 3350) and the BDNF (brain-derived neurotrophic factor Gene ID 627) G196A (Val66Met) to MDD and to the action of antidepressants (Anttila et al., 2007). The BDNF modulates signaling pathways that rapidly affect synaptic function, but which also have long term effects on gene expression (Licinio et al., 2009). Thus, it was tested whether the carriers of the GG of 5-HT1A C1019G and the carriers of A allele of BDNF G196A have a major risk depression and treatment resistance. The association of 5-HT1A C1019G with the risk of depression was not found. However the combination of the 5-HT1A GG and BDNF GA+AA genotypes is associated with a significant increase in the risk of depression (Anttila et al., 2007).

A study has identified 83 new SNPs: 30 in untranslated regions, 4 in coding sequences, 37 in introns, and 12 in upstream region; 3 of 4 rare SNPs coding were nonsynonymous (with change in the amino acid generated). The analyses of patients with MDD and controls showed that 6 SNPs were associated with MDD (rs12273539, rs11030103, rs6265, rs28772251, rs41282918, and rs11030101) and 2 haplotypes in different blocks (one including Val66, another near exon VIIIb). These results provide a detailed description of the sequence of changes of BDNF in Mexican Americans. Among the 130 SNPs detected in this study, 83 are new and only 47 had already been reported in the National Center for Biotechnology Information dbSNP database (http://www.ncbi. nlm.nih.gov/projects/SNP). But, from these new polymorphisms, 89% are rare variants with a minor allele below 1%. This is not a surprise because this study was conducted with a large sample of 537 subjects in a specific ethnic group that had not been investigated extensively. The results suggest that the genetic variation in the BDNF gene in different populations can be great and this heterogeneity may contribute to explain controversial results in BDNF associations with depressed patients of different populations (Licinio et al., 2009).

It is appropriate to mention another study in which the main gene explored is the Rgs2, which product is a member of the Family of Regulators of G proteins signaling (RGS) that modulates negatively the transmission of G protein-coupled receptor. Motivated by previous studies which show that certain SNPs, which promoted reduction of the Rgs2 expression (Gene ID 19735), were associated with anxiety and depression. Lifschytz et al. (2012) conducted an experimental study using mice males homozygous (Hom) and heterozygous (Het) to a Rgs2 mutation, which causes reduction of expression of this gene, as well as of wild animals, demonstrating that the mice Hom displayed more depressive-like characteristics than that of the Het and the savages. Nevertheless, in comparison with wild animals, the Hom and Het mice showed more anxiety in behavioral tests, and also a significant reduction in the levels of expression of the genes of serotonin receptors 5-HT1A and 5-HT1B in raphe nucleus, assessed through real time-PCR. The reported mood changes, possibly, are related to the reduction of serotonin receptors expression; however, it did not provide mechanistic evidence about that probable relationship.

6.3. Interleukins genes

Other proteins that do not participate directly in the synaptic transmission can also present anxiety-related polymorphisms and MDD, as in the case, for example, of interleukins. These molecules are involved in the regulation of the immune system and they may have a role in the pathogenesis of MDD. The Family of Interleukin (IL)-10 (IL-10, IL-19, IL-20, and IL-24) is involved in the inflammatory process and the polymorphism is associated with numerous immunopathologic conditions. When investigated if the SNPs in
these genes are associated with the MDD, no SNPs were individually associated with. The analysis of linkage disequilibrium (LD) indicated the existence of two recombination sites in IL10 gene cluster, thus confirming that the LD pattern previously established this genomic region. It also created two haplotype blocks, both with three SNPs. In addition, the analysis of haplotypes detects a significantly higher frequency of block 2 [IL20 (Gene ID 50604), and IL24 genes (Gene ID 11009), haplotype TGC] in the group of patients compared with healthy individuals. This study found increased risk of MDD related to the haplotypes IL20 and IL24, and suggests that the cytokines may contribute to the pathogenesis of the MDD. Since none of the SNPs of block 2 were associated individually with MDD, it is possible that other polymorphisms associated with them contribute to susceptibility to the disease Traks et al., (2008).

6.4. Gene MC1R

The MC1R receptor (Melanocortin-1 receptor) is involved in several functions, such as pigmentation, antipyretic and anti-inflammatory actions, development of melanoma, modification of oculocutaneous albinism, freckles development, female mechanisms of analgesia, and susceptibility from sun damage induced by ultraviolet radiation. The natural agonist of MC1R (a-melanocortin-stimulating hormone receptor) includes the ACTH1-39 (corticotrophin), which is an important component of the hypothalamic pituitary-adrenal-axis and increases in response to stress. As a result of the multiple-function MC1R, it was explored whether polymorphisms of MC1R gene are associated with MDD in Mexican Americans. A total of 23 SNPs (15 known and 8 new) were found in the sequenced region. Among the common SNPs, the nonsynonymous SNP, rs885479 (R163Q) was associated with the SNP rs12905212 Kelmendi et al., (2011).

6.5. HCN gene (potassium channels)

HCN potassium channels (hyperpolarization activated cyclic nucleotide-gated potassium channels) are involved in the control of neuronal excitability and are widely expressed in the brain. Also, HCN4 channels can regulate mood and anxiety affecting the function of the thalamus, of the amygdala, and of the dopamine systems in the midbrain. In addition to being able to indirectly influence the prefrontal cortical function, the HCN4 gene is a good candidate for mood and anxiety disorders. The HCN4 genotype in patients with various mood disorders (including MDD) and anxiety was analyzed. The major depressive disorder was associated significantly with two SNPs (rs3859014 with \( p=0.02 \) and rs12905212 with \( p=0.04 \), while the anxiety disorders (88 cases of obsessive compulsive disorder) were associated significantly with the SNP rs12905212 Kelmendi et al., 2011.

6.6. Neuregulin gene

The neuregulins are a family of four structurally related proteins that mediate through the connection of extracellular domain of its receptor tyrosine kinase ErbB-1 to the ErbB-4, a variety of cell–cell interactions (Buonanno and Fischbach, 2001; Falls, 2003). The neuregulin 1 (NRG1) is known because it mediates cell–cell interactions of the nervous system, heart, breast, muscle and other organs, and has been implicated in the etiology of breast cancer, heart disease, multiple sclerosis and schizophrenia (Falls, 2003; Schosser et al., 2010). The NRG1 was initially implicated in schizophrenia SZ and has been associated recently to bipolar disorder. The investigation of the association between polymorphisms of NRG1 and MDD was made through a case-control study on the genotyping of a selection of 14 SNPs covering the NRG1 gene. However, from a sample of 1398 patients with MDD and 1304 controls, any significant genotypic allelic association with any of the SNPs genotypes was not found, both in the General Group of MDD or when the sexes were separated (Schosser et al., 2010).

6.7. GABAergic genes (GABA, GAD and DBI)

Gamma-aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the vertebrate central nervous system and regulates various physiological and psychological processes. The GABA abnormalities were observed in individuals with mood and anxiety disorders (Kalueff and Nutt, 2007; Pham et al., 2009). The GABA\(_A\) receptor is the active site of anxiolytic drugs classes as benzodiazepines and barbiturates. Thus, GABA is heavily involved in several processes related to anxiety, where studies suggest a genetic correlation between the Diazepam binding inhibitor (DBI Gene ID: 1622), the genes involved in transcription of the GABA receptor and GAD enzyme with anxiety disorder (Pham et al., 2009).

6.8. DBI gene

In case-control study conducted in Germany including anxiety disorder patients who has been suffering panic attacks, the SNPs DBI gene was investigated because of alleged associations with diseases. The results revealed that the G allele of the exonic SNP rs192506 is over-represented in control group versus patients, with a frequency nearly three times greater in healthy individuals than in anxious patients. Interestingly, this genetic polymorphism led to a change in the amino acid (Valine to Methionine) in the 88 position and functional differences in the activity of DBI. In this way, the polymorphism studied at the DBI seems to decrease the susceptibility to the development of anxiety disorders characterized by panic attacks (Thoeringer et al., 2007).

6.9. GABA receptor genes (GABRA)

The functional GABA\(_A\) receptors are typically composed of five subunits extracted from eight different classes (Pham et al., 2009; Sieghart and Sperk, 2002). Each subunit is encoded by a separate gene and differentially expressed in the brain, suggesting that the mutation in any gene can, in principle, contribute to the symptoms of anxiety-related disorders. The \( \alpha 2 \) subunit GABA\(_A\)\(_\alpha\) expresses primarily in the limbic system, and probably mediates the anxiolytic effects of benzodiazepines (Pham et al., 2009; Low et al., 2000).

Pham et al. (2009) investigated 26 SNPs of four GABA receptor genes (GABRA2 – Gene ID: 2555, GABRA3 – Gene ID: 2556, GABRA6 – Gene ID: 2559 and GABBR2 – Gene ID: 2566) about the risk for anxiety disorders and depression. However, the results suggest that such polymorphisms do not play an important role in the development of anxiety spectrum disorders. On the other hand, Fiorelli et al. (Pham et al., 2009; Fiorelli et al., 2008]) provided evidence that mice with global deletion of the GABRA3 gene had more depression-related behaviors. The human GABRA3 gene is located in the Xq28 region, an area that has been linked to the genetic transmission of bipolar affective disorder, reviewed by Hayden et al. (Pham et al., 2009; Hayden and Nurnberger, 2006).

The GABRA6 is involved in several factors that contribute to anxiety disorder. Sen et al. (Pham et al., 2009; Sen et al., 2004)
reported an association between a polymorphism of GABRA6 receptor and neuroticism, a personality trait related to anxiety and depression. GABRA6 variation has also been associated with increased production of cortisol and an increase in blood pressure in response to psychological stress (Pham et al., 2009; Uhart et al., 2004).

6.10. GAD genes (GAD1 and GAD2)

The enzyme glutamic acid decarboxylase (GAD) is responsible for the synthesis of GABA from glutamate. The two isoforms, GAD67 and GAD65, are the products of two independently regulated genes, GAD1 (ID: 2571) and GAD2 (ID: 2572), respectively, both of which are expressed in the brain. The GAD1 presents a size about 45 kb and is located at 2q31.1, while GAD2 is about 88 kb and is located at 10 p12.1. They seem to differ in their intraneuronal expression, com GAD65 with GAD65 located at terminals of axons and GAD67 more evenly distributed throughout the neuron (Kaufman et al., 1991; Martin and Rimvall, 1993; Hettema et al., 2006).

Hettema et al. (2006) examined the GAD1 and GAD2 genes for their association with the genetic risk for major depression, generalized anxiety disorder, panic disorder, agoraphobia, agoraphobia, social phobia, and neuroticism (N). The resulting sample of 589 cases 539 controls was inserted in an Association study of two phases in which the candidate loci was surveyed in phase 1. The positive results were tested for replication in phase 2. Six of the several SNPs tested in the GAD1 region showed a significant association in both phases. In addition, a combined analysis of all 1128 individuals indicated that they formed a common high-risk haplotype (p = 0.003). On the other hand, significant results were not found among the 14 markers of GAD2 gene tested.

7. Changes in mitochondrial DNA

Studies have shown that sequences of mitochondrial DNA (mtDNA) can affect the functioning of the brain (Boles et al., 2005). Its role as an etiological factor for the development of anxiety and depression in humans was the object of research and discussion in two relevant works selected here as criteria of this review. That analysis allows us to realize that both have adopted different courses in the process of investigation of the mtDNA function in the above-mentioned diseases.

Boles et al. (2005) showed that mothers of children with maternally inherited mitochondrial disorders (MIMD) suffer more from depression and anxiety, they have greater difficulty in dealing with stress, and receive care in mental health services at a rate much higher than the mothers of children with autosomal recessive metabolic disorders (ARMID), in spite of both disorders generate equal physical and emotional for the patient and for their mothers and matrilineal relatives. In this way, the study brings the hypothesis that the same changes in mtDNA that predispose to disease in the somatic plan also would be related to etiology of psychopathology, especially depression and anxiety.

To assess the level of involvement of mtDNA in the genesis of anxiety and/or depression, Boles et al. (2005) used as subjects of research: a group composed of 15 mothers of children with MIMD and another with 17 mothers of children diagnosed with ARMID. Analyzing the results, it was found that depression and anxiety were more frequent in the groups of mothers of children with MIMDs (Group 1) in comparison with the Group of mothers of children with ARMDS (Group 2). In addition, while most of the mothers of children with “not severe” ARMDS reported very low levels of depression and/or anxiety (second result of the questionnaires applied), mothers of Group 1 exhibit high levels of depression and anxiety.

The most surprising result of the study is the high incidence of mental illness, predominant depression, among the matrilineal relatives of children with MIMD against relatives of matrilineais children with ARMID. This finding cannot be exclusively explained by the fact of taking care of a child with chronic illness, but there is a role of mtDNA in the etiology of metabolic disorders in children affected, also occupying the post of predisposing factor for anxiety and depression in the matrilineal relatives of these children (Boles et al., 2005). However, the small number of individuals belonging to the sample of the study referred to above, as well as the non-inclusion of subjects addressed in other health units, makes the study limited from a much larger universe of possibilities of analysis between metabolic diseases of mitochondrial inheritance and its association with depression and/or anxiety.

With another prospect, Munakata et al. (2007), on the assumption that various mutations or polymorphisms of mtDNA are associated with neuropsychiatric disease, they investigated the types of mutations in the mitochondrial genetic material that could be associated with the development of certain psychopathologies, particularly bipolar disorder and depression. To this end, a patient with major depression and epilepsy was identified in this study. Some family members in the pedigree of the patient had history of bipolar disorder, depression, suicide or psychotic disorder without another specification and the entire mtDNA was sequenced in proband. The purpose was to find genetic changes that were associated with the genesis of certain psychopathologies, such as depression. Nevertheless, two suspicious substitutions in mtDNA were identified: T3394C in MT- ND1 gene and A9115G in MT-atp6 gene. However, after deeper and detailed research, the data did not support the hypothesis of the study that these psychiatric disorders in this family were caused by mutations in the mtDNA (Munakata et al., 2007). This fact does not exclude the importance of mtDNA in the development of anxiety and depression, since only two genes were assessed.

8. Conclusions

There seems to be a consensus that genetic factors, in a portion of the cases, can encourage or even trigger the occurrence of mood disorders such as anxiety and/or depression. However, despite the significant amount of work and the sophisticated technology, it is not fully elucidated which genes or regions of nuclear or mitochondrial DNA, or else, which types of genetic changes, alone or in combination, can represent reliable genetic markers of anxiety and/or depression.

The findings listed in this review illustrate the major advances already occurred, being possible to notice some promising targets that, very soon, may be recognized as genetic markers of mentioned disorders. It is worth noticing that possibly due to the incipient state of the exploration of this theme, few authors have used the term genetic marker in their manuscripts, what in fact, reflected in the volume of articles included in this systematic review, since this term was employed in the search for references in databases.

As presented, some works show only associations with one of the disorders, mostly with anxiety; only a few have shown association with both simultaneously. Others exhibited gender specific association, or even specific ethnic groups. There were also eventually controversies regarding certain markers, which somehow reduced their value as potential markers. Interesting results were observed in combination of changes, especially in cases of SNPs, indicating that, perhaps, this is the most appropriate way to find reliable markers. In order to obtain more consistent results or overcome current controversies, there is a need for a greater range of studies, with representative samples, including subjects of races


