Genes most linked to depression and its possible treatment

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ABSTRACT
Depression is considered one of the most common and serious psychiatric disorders, according to the World Health Organization (WHO). It stands out as one of the leading causes of disability worldwide, significantly affecting the quality of life of affected individuals. In Brazil, epidemiological studies indicate that the lifetime prevalence of depression affects about 15.5% of the population, an alarming rate that highlights the importance of better understanding this condition.

Keywords: Depression, Genetic factors, Therapies.

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INTRODUCTION

Depression is considered one of the most common and serious psychiatric disorders, according to the World Health Organization (WHO). It stands out as one of the leading causes of disability worldwide, significantly affecting the quality of life of affected individuals. In Brazil, epidemiological studies indicate that the lifetime prevalence of depression affects about 15.5% of the population, an alarming rate that highlights the importance of better understanding this condition.

The etiology of depression is complex and multifactorial, involving an interaction between environmental, psychological, biological, social, and genetic factors. Understanding these multiple influences is essential for the development of more effective and personalized therapeutic approaches. Among the factors identified, genetic predisposition has been shown to be particularly relevant, contributing with about 40% of susceptibility to the development of depression.

Given the high prevalence and significant impact of depression, many studies have focused on unraveling the pathophysiological mechanisms underlying the disease. Scientific research has advanced towards identifying the genes involved and understanding how their variations can influence the predisposition to depression. This knowledge is crucial not only for early diagnosis, but also for the creation of therapeutic strategies that can be adjusted according to the genetic profile of each individual.

The correct understanding of the main genes associated with depression is therefore fundamental for the adequacy of treatment, allowing for more targeted and potentially more effective interventions. As science advances in the decoding of genetic factors and the integration of this knowledge with other areas of study, it is expected that new therapeutic approaches can be developed, contributing to the improvement of results in the treatment of depression.

METHODOLOGY

The present study is a narrative review. The search began with the definition of descriptors and the choice and consultation of search platforms. A search was carried out in the PUBMED, LILACS, and SCIELO online databases from January to July 2024. The following descriptors were used: "Adenomatous polyposis"; "Conduct"; "Management" with the Boolean operator "AND", which were obtained through the Decs/MeSH platform as health descriptors. Data analysis was conducted in a standardized manner, based on the following inclusion criteria: time frame from January 2014 to February 2024; English and Portuguese language and full text available.

The articles were selected from the analysis of two evaluators, in which the studies were mapped independently, discussing the results and continuously updating the data graph form in order to elaborate an iterative process. The titles were sequentially evaluated, and then abstracts of all publications identified by the searches for potentially relevant articles. Divergences regarding the

selection of articles and data extraction by consensus and discussion with a third reviewer, if necessary. In addition, studies were included in manual searches of journals, based on the search for citations, and searches for gray literature.

RESULTS

The search resulted in 494 publications, of which only 18 publications met the objectives proposed in the study from the application of the inclusion and exclusion criteria, as well as from the reading of titles and abstracts.

On the Pubmed platform, using the descriptors present in the title and abstract, 215 articles were found from 1964 to 2024. A time restriction of 10 years (2014 to 2024) was defined, and 85 articles were found. With the inclusion criteria, Portuguese and English were used, 35 studies were excluded, resulting in 50. Only papers available in full text were selected, resulting in 115.

On the Lilacs platform, using the descriptors present in the title and abstract, 115 articles were found from 1964 to 2024. A time restriction of 10 years (2014 to 2024) was defined, and 75 articles were found. With the inclusion criteria used in Portuguese and English, 22 studies were excluded, resulting in 53.

On the Scielo platform, using the descriptors present in the title and abstract, 215 articles were found from 1964 to 2024. A time restriction of 10 years (2014 to 2024) was defined, and 80 articles were found. With the inclusion criteria, Portuguese and English were used, 52 studies were excluded, resulting in 28. Only papers available in full (FULL TEXT) were selected, resulting in 28.

Among the selected articles, the duplication of papers was checked, resulting in 196, with 52 duplications. The next analysis criterion comprised the reading of the titles in the double-blind format with two evaluators, in which the selected materials were only those approved twice, resulting in 36 studies. Subsequently, the abstracts were read by the same evaluators, resulting in 15 studies.

DISCUSSION

Depression is one of the main causes of disability today, characterized by a mood disorder that affects the behavior of individuals and the way they see themselves, it is a condition that affects millions of people around the world and has had an increase in incidence after the COVID-19 pandemic, in severe cases, depression can lead to suicide. It had its origin in Greece in the period before Christ. Throughout its evolution, it has undergone changes in the descriptions of symptoms, causes and is currently included in the International Statistical Classification of Diseases (ICD). {3}

The emotional disorder of depression is considered a public health problem and has been studied more frequently, both in clinical studies and in more in-depth studies such as genetic studies for this disease. The most well-known and scientifically relevant genes are: serotonin transporter,

serotonin receptor, serotonin encoders, neurotrophic factor, catechol, oxytocin receptor, differentiation antigen 38, FK506-binding protein 5, respectively expressed by the SLC6A4, 5-HT, HTR1A/2A, COMT, OXTR, CD38, FKBP5 genes. {4}

The SLC6A4 gene is involved in the regulation of serotonin, a neurotransmitter that plays an important role in mood and emotion and its variations have been linked to depression. The COMT gene encodes an enzyme involved in the breakdown of neurotransmitters such as dopamine, in addition it can affect dopamine regulation and, in turn, cognitive function and mood. Brain-derived neurotrophic factor (BDNF) is a protein that plays a role in the survival and growth of nerve cells, its changes have been associated with depression as BDNF is involved in brain plasticity and neuronal regeneration. HTR1A and HTR2A are genes that encode serotonin receptors, mutations in these genes can affect the brain's response to serotonin, which has implications for mood and depression. {3,4}

The OXTR gene plays a significant role in the functioning of the oxytocin system in the human body. It is a hormone that also plays a role as a neurotransmitter involved in the regulation of a variety of behaviors and physiological functions, such as the maternal relationship with the child of protection and affection, it also plays a role in behavior before society in aspects of social interactions, such as the promotion of trust, empathy, cooperation and behavior, in addition to having effects on anxiety because it has anxiolytic effects, that is, it can reduce anxiety. {4,5}

The CD38 and FKBP5 genes play important roles in biological processes and systems that are related to various aspects of health, including the functioning of the immune system, stress response, and regulation of metabolism. CD38 is an enzyme that plays a crucial role in regulating the metabolism of NAD+ (nicotinamide adenine dinucleotide), an essential enzyme involved in many cellular processes, including energy production. CD38 is involved in intracellular signaling and immune system regulation. FKBP5 is a protein that acts as a co-activator of glucocorticoid receptors, which are involved in the stress response. It regulates the sensitivity of cells to stress hormones such as cortisol. FKBP5 is also an important regulator of the immune system's response to inflammation, genetic variants of the FKBP5 gene have been linked to an increased susceptibility to post-traumatic stress disorder (PTSD) and depression, especially in individuals who have experienced traumatic events. {3,5}

It is essential to highlight that depression is a complex disease and the product of multiple factors, which many other elements are part of its development, such as the environment, experience, and genetics, as already mentioned. {6,7,8}

The treatment for depression is still the subject of much study within the scientific community, so that medications have different mechanisms and properties that behave differently in

individuals, in addition behavioral therapy is essential for all individuals regardless of classification, and for any treatment the goal is based on the complete remission of all symptoms of depression. {7}

It is important to note that for pharmacotherapy to take effect, a latency period of at least 2 weeks of treatment is required and for the visualization of symptom improvement of at least four weeks, the main classes of medication are tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin and norepinephrine decapitation inhibitors and others. {7}

The TCAs used in Brazil are amitriptyline, clomipramine, imipramine, maprotiline and nortriptyline. These drugs act to reduce the reuptake of 5-HT and NA, causing these neurotransmitters to stay longer in the synaptic cleft. Adverse effects include anticholinergics that include constipation, xerostomia (dry mouth), blurred vision, sedation and urinary retention, they can also cause weight gain, arrhythmias, orthostatic hypotension, reduced seizure threshold and cognitive changes. {8}

MAOIs act by inhibiting the enzyme monoamine oxidase, responsible for the degradation of 5-HT, NA and DA. This class has more severe adverse effects, such as syncope, anticholinergics, tachycardia, sexual dysfunction and peripheral edema, and selegiline and tranylcypromine are available in Brazil. [6,7,8}

Another class of drug are SSRIs, they inhibit the reuptake of 5-HT in the synaptic cleft which increases the availability of monoamine and leads to serotonergic action, they also have anticholinergic, adrenergic and histaminergic action that justify the adverse effects of drugs in this category, in addition to having few adverse effects compared to other classes. The main representatives of this class are fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram and escitalopram and the main adverse effects are gastrointestinal, headache, lack of coordination, sleep and energy level changes. In some cases, sexual dysfunction and hyponatremia may occur. And finally, SNRIs, represented by venlafaxine and duloxetine, are inhibitors of 5-HT and NA, among the adverse effects we have nausea, vomiting, insomnia, vertigo and headache, in addition to constipation, bleeding and sexual dysfunction. {6,8}

CONCLUSION

In summary, it is possible to identify that in addition to environmental, social and personal factors, there are also some genes that may be involved in the development of depression. That is why family history is important for a coherent evaluation of the cases, and it is necessary to combine therapeutic measures that allow the resolution of symptoms and ensure the patient's quality of life. Thus, the search for a complete state of health must be developed.

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