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Review Article

Genetic and Environmental Factors Involved in Schizophrenia Development

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Abstract

Due to its complexity, schizophrenia is an intriguing disorder being described as a heterogeneous and multifactorial disease. It is characterized by the presence of a psychotic behavior, unrealistic and disorganized thinking, and a marked social dysfunction. This disorder affects 1% of world population presenting a high impact at family level and huge expenditure on public health. In this paper we intend to perform a bibliographic search concerning the genetic and environmental risk factors involved in schizophrenia development. A bibliographic search was performed using the words: schizophrenia, genetic factors, non-genetic factors, multifactorial heritage. Criteria used in papers selection included the interest of the subject, limiting the search to scientific papers written in English or Portuguese, with publication date in a 10 years period or of previous years when the content and experimental evidences were relevant for the theme. As results of this search, it was seen that the genetic influence in this pathology is well stablished, however, the exact nature of the type of transmission is not clear yet. Several environmental factors involved in schizophrenia development have already been identified. Available data allow to conclude that, in most cases, the genetic component consists of multiple genes acting additively, being the genotype expressed only when the number of genes and non-genetic factors present is above a threshold number.

Keywords: *Schizophrenia; Genetic Factors; Non-Genetic Factors; Multifactorial Inheritance; Schizophrenia Signs and Symptoms*

Introduction

Psychiatric disorders, namely schizophrenia, are pathologies very discussed among the scientific community. There are several hypotheses concerning the aetiology of schizophrenia and some of them are discussed in this work.

Table 1 shows the historic evolution of the concept of schizophrenia.

4600 a.C.	Hippocrates describes schizophrenia as an organic *delirium*.
1851	Morel describes schizophrenia as early dementia: a disturbance that affects young individuals that present successive states of brain decadence with the appearance of a terminal stage of psychiatric dissolution.
1871	Ewald Hecker describes hebephrenia as mental deterioration and aggressive behaviour in young individuals.
1896	Kraepelin distinguishes between schizophrenia and maniac-depressive psychosis.
1899	Kraepelin distinguishes the term of young dementia in three clinical forms: hebephrenic, catatonic and paranoid. The author does not believe in patient's recovery.
1902	Kraepelin sees success in patient's recovery.
1911	The Swiss psychiatrist, Eugene Bluer, coined the term "schizophrenia". He was the first to describe the symptoms as positive or negative.
1921	Jaspers does not consider psychosis as an organic manifestation, however, believes that psychosis helps in the discovery of the psychical side of all human beings.
1953	Minkowski describes schizophrenia as a withdrawal from reality.
1993	World Health Organization (WHO) defines diagnosis criteria for schizophrenia using the national classification of diseases (CID-10).

Table 1: *Historic evolution of the concept of schizophrenia [1].*

Materials and Methods

In this bibliographic search, scientific papers and other publications were collected using websites: PubMed, Science Direct and B-On as well as Academic Google and AltaVista Search.

Keywords used in the search were: Schizophrenia, genetic factors, non-genetic factors and multifactorial heritage. From the first search 117 papers were retrieved. Several criteria were used in the selection of papers, to narrow the number of papers to be used in the work, and included the interest of the theme, scientific papers and studies written in English or Portuguese, with publication date within a 10 years period or from previous years when content and experimental evidences were relevant to the study. These criteria allowed the selection of 66 studies that were used in the preparation of this work.

Discussion

Epidemiology

As mentioned before, schizophrenia is a long term severe mental disturbance, incapacitating at social, professional and interpersonal level [2,3].

Murray and Lopez [4] report a prevalence rate of 0,92% for men and 0,9% for women. Higher prevalence, close to 1%, was reported in studies conducted in Latin America and Brazil [5].

Despite the contribution of several authors and the evolution of the concept of schizophrenia, the conceptual and clinical definition of the disease is far from having consensus.

This is a severe neuropsychiatric disease that presents 20 times higher suicide rates and an average life expectancy 20% lower than general population [6] and involves an enormous direct social cost (associated with hospitalizations, attendances, medication) as well as indirect due to unproductiveness and familial repercussions.

The clinical picture of the disease includes changes in almost all functions of psychiatric area, like perception, thought, language, memory and execution functions. Symptoms can be divided in two groups: positive and negative. According with table 1, positive symptoms are characterized by the presence of psychiatric manifestations that should be absent, while negative traits involve the absence of psychiatric manifestations that should be present [7,8].

Schizophrenia shows up during adolescence or beginning of adult life (15 - 35 years old), with an earlier onset in men, who suffer the first hospital admission around 25 years old while in women is around 30 years old [9]. However, in individuals having first degree relatives with psychotic disturbances, the onset of schizophrenia is earlier, and no difference is observed between men and women [10].

First symptoms are related with focusing problems, tension states of unknown origin, insomnia and lack of interest in social activities with consequent isolation [10,11].

After an initial stage, that can last several months, symptoms get worse and the patient presents a strange and unreal conversation [12].

Negative Symptoms	Positive Symptoms
Affective changes Unchanged facial expression Decrease of spontaneous movements Lack of expressive gestures Lack of visual contact Decrease or absence of affective response Inappropriate affection Lack of vocal modulation	**Hallucinations** Auditory Voices that make comments Voices that talk to each other Somatic Tactile Olfactive Visual
Alogia Speech poorness Speech content poorness Thought blockage Longer response time	**Delusions** Jealous Guilt Sin Grandeur Religious Somatic Being controlled Mind reading Thought transmission Thought insertion Thought withdrawal
Abulia-apathy Lack of personal care and hygiene Lack of work or studies persistence Physical anergy	**Bizarre behaviour** Clothes Semblance Social behaviour Sexual behaviour Aggressive/agitated Repetitive/estereotyped
Anhedonia Few interests Few recreative activities Affective relations commitment Few friends	**Formal change of thought** Derailment Incoherence Lack of logic Accelerated speech Reverberation Neologism
Attention Decreased concentration	

Table 2: *Frequent symptoms in schizophrenia [13].*

Positive symptoms are characterized by hallucinations and delusions. Auditive hallucinations like fake sounds (hearing voices) are the most common. However, delusions are thought changes of paranoid or bizarre character. Psychotic symptoms occur normally between 17 and 40 years of age. Yet, most patients present some light schizophrenia symptoms before the first psychotic episode. After this initial event, the occurrence of psychotic symptoms is sporadic and intercalated by remission periods [14].

Negative symptoms start at the initial stage of the disease. These can coexist with the positive symptoms and persist after treatment. The most common symptoms are affective difficulties, anhedonia and alogia. These reflect on low self-esteem, lack of emotions and general loss of interest in life. Negative symptoms tend to be more common in older patients [14].

Other signs include lack of attention, disorganized thought and speech, disorganized or catatonic behaviour. Incoordination of ideas can be extreme, even leading to inconsistent speech. Cognitive damage can occur along development of other symptoms like hallucinations that can appear sporadically [14].

Causes of Schizophrenia

Causes of schizophrenia are still not known, however, it is believed to be a complex multifactorial pathology. The personality disorganization observed in schizophrenia can result from the interaction of cultural, psychological and biological variables and among these are genetic factors [15].

Genetic Component of Schizophrenia

Since century XIX, researchers started to associate schizophrenia to certain families. During decades, studies of families of schizophrenic patients have demonstrated a strong correlation between the degree of kinship and the probability of developing the disease. Individuals with familial predisposition to schizophrenia show several structural changes in brain, including reduced size and increased ventricles, that are characteristics of schizophrenic patients [16]. According with this study, individuals without any schizophrenic family member have 1% of probability of developing the disease; for those having a distant family member with this disorder, this probability increases to 3 - 5%. In individuals with a direct family member with the disease, the risk is 10%, and 40% in cases where the disease affects both parents. Between true twins, the probability increases to 65% [16].

However, heritage does not explain all cases of the disease, around 60% of schizophrenic individuals do not have close relatives with the disease [4,17]. In this way, the genetic component explains a big percentage of cases of this disorder but not all of it, however, it is not possible to deny the presence of this component in schizophrenia etiology.

Moreover, DNA analysis suggests that there is not a unique gene involved in schizophrenia; on the other hand, several genes seem to be related with the disease, and their effect can be independent or cumulative [18].

Although the enormous efforts done to identify susceptibility genes of schizophrenia, so far, few data were obtained from molecular genetic studies. Several reasons can explain the problems in identifying genes involved in schizophrenia aetiology, like the role of environmental factors with strong impact in disease development, that can mask genetic factors.

The transmission pattern of schizophrenia is not completely stablished and usually does not follow the mendelian transmission model, being in most cases sporadic [19].

Forty-nine genes were identified whose expressions are different between healthy individuals and schizophrenic patients [20]. Analysis of gene functions showed that they are involved in biochemical pathways that affect specific functions in brain like synaptic neurotransmission, signal transduction, cytoskeleton dynamic and neuronal development [20]. Change in dendritic spines density is observed, and this is consistent with decreased synaptic density observed microscopically in post-mortem brain exams of schizophrenic individuals. These changes are fundamental for the adaptation of the individual to changes that occur during learning and for the development of changes known as synaptic plasticity.

Change in gene expression observed in schizophrenic patients suggests that this disease blocks the synaptic plasticity in the prefrontal cortex, that leads to problems in learning and social interaction, that are usually associated with this pathology.

According with epigenetic studies, dopamine and serotonin receptors show high affinity to antipsychotic agents, allowing to predict its relationship with the development of schizophrenia [18].

Genes that might be involved in the development of schizophrenia are in several regions of the human genome, and in this way, loci with higher susceptibility for schizophrenia development have been mapped in several chromosomes, like: 1q21-22, 6p25, 8p21, 10p14, 13q32, 18p11 and 22q11-13 [21-24]. Despite the studies in this field and the increase in candidate genes, so far, no gene has been associated directly to schizophrenia.

Individuals with a microdeletion in chromosome 22 (q11) are carriers of the Velocardiofacial syndrome. These individuals have a higher risk of development of psychiatric disorders, including schizophrenia [25]. Murphy and co-workers observed in a group of patients with this syndrome, that around 20 - 30% have developed schizophrenia [26]. The gene coding for catechol-O-methyltransferase (COMT) is one of the missing genes in that region of chromosome 22 in individuals with that syndrome, and it can be responsible for the incidence of schizophrenia in these patients. This is one of the enzymes that metabolize catecholamines like dopamine [25,27]. Two polymorphisms present in codons 108 and 158 of the *COMT* gene that lead to a substitution of valine (higher enzyme activity) for methionine (lower enzyme activity), have been studied. However, no significant correlation was observed [28].

Biological function of COMT and its relationship with the microdeletion 22q11, make this gene a good candidate for molecular marker of schizophrenia [25,27].

Another chromosomic region pointed out by researchers as a good schizophrenia marker is at chromosome 13 (q34), namely, gene *G72* and the gene coding for D-aminoacid oxidase (DAO), being observed a synergic effect between them, related with susceptibility to schizophrenia. DAO stimulates N-methyl-D-aspartate production, that is a stimulant of glutamate receptors in brain. Decrease in glutamate is related to bad performance of the frontal lobe and hippocampus function, since its decrease can affect dopamine function linking it to schizophrenia [29].

Gene coding for neuregulin 1 (NRG1) is another candidate marker for this disorder [2]. This gene is expressed in synapsis of CNS and acts in expression and activation of neurotransmitter receptors, including glutamatergic receptors. Altered levels of this protein are related with schizophrenia. Mutations in this gene lead to increased levels of plasma neuregulin-1 protein, provoking dysfunction of neurotransmitters [2].

In the same way, the gene coding for dysbindin, located in the short arm of chromosome 6 (p22.3) whose product links to dystrobrevin, is associated with schizophrenia. This association is probably due to the role of dysbindin in glutamatergic synapses [30].

The gene coding for the dopaminergic receptor D3 was investigated with the goal of finding a possible correlation between a polymorphism of this gene and schizophrenia. This gene is located in chromosome 3 (q13.3) being composed of six exons and five introns, with a length of more than 40.000 bp [31]. This gene has a polymorphism of a single nucleotide (change of adenine to guanine in exon 1) [31], that leads to an aminoacid substitution of serine to glycine in the N-terminal extracellular domain of D3 receptor (Ser9Gly). Concerning phenotypic changes associated with this polymorphism, a functional study showed differences in affinity for dopamine between alleles. Homozygous cells for glycine have more affinity for dopamine than heterozygous cells or homozygous for serine. It is likely that the substitution of a polar residue of serine by a hydrophobic residue of glycine alters the tertiary structure of D3 receptor, and consequently the affinity of dopamine to its receptor [32]. This change might influence the insertion of the receptor in the neuronal membrane, however, it was not possible to observe association between this polymorphism and schizophrenia [33].

Other studies were performed with the gene coding for dopamine transporter (SLC6A3) located in chromosome 5 (p15.3). This transporter plays an important function in the regulation of dopamine levels, acting in the re-uptake of synaptic dopamine to neurons. These studies suggest that a polymorphism of this gene (A1343G) can be associated with the development of schizophrenia since the presence of this polymorphism alters the availability of the transporter and consequently the amount of synaptic dopamine [33].

Moreover, the gene coding the dopaminergic receptor D2 (DRD2) was investigated. This receptor acts as self-receptor in dopaminergic cell bodies and as post-synaptic receptor. This gene is in chromosome 11. Schizophrenic individuals usually have higher frequency of the 141Cins allele, that might lead to increased expression of this gene [33]. This finding supports the dopaminergic hypothesis, pointing that the presence of this allele can be associated with dopamine hyperactivity. Besides DRD2 allele previously mentioned, other two polymorphisms of this gene are also frequently associated with neuropsychiatric diseases: DRD2 TaqIA and DRD2/Del [34,35].

In vivo studies using Positron Emission Tomography in healthy individuals showed that there is a big variability in the density of D2 receptors in brain. This variability can be explained by individual genetic variation or influence of environmental factors. However, other factors like age, neuroleptic drugs consumption, alcohol, nicotine, cocaine and apiaceous can affect the density of D2 receptors. But, the bigger variation observed (till 3 times higher) suggests a strong genetic contribution [36].

Gene *OKSC12b* has been reported in studies with monozygotic twins, as a gene that could code for proteins that protect the healthy twin from schizophrenia. This theory was based on the fact that this gene is only expressed in lymphocytes of the healthy twin. Based on this report, a case control study was performed, and it was expected that the absence of expression of this gene could be a peripheric marker of the disease, but results did not confirm differences in gene expression [37].

Some studies suggest that the serotonergic system might be related with schizophrenia development. Serotonin is associated with sensory, motor and cortical function. The hypothesis that the serotonergic system might be related with schizophrenia development is based on the fact that increase in serotonin can promote schizophrenia. In this way, studies were performed on the genes coding serotonin receptors that control its release in neurons. Polymorphism G681C of the 5HT1DB receptor gene was investigated as a risk factor, but no evidences were found to associate it with schizophrenia [37]. One polymorphism present in 5HT2A receptor gene was also investigated. This receptor is one of the main targets of atypical antipsychotics and was mapped in chromosome 13. This polymorphism (C516T) did not show association with schizophrenia [38].

Adenosine activity was associated with schizophrenia development since it modulates most neurotransmitters. Activation of A1R receptor of adenosine decreases neuronal excitability, inhibits synaptic activity and inhibits the release of neurotransmitters like glutamate, dopamine and serotonin. In this way, it was suggested that adenosine reduction can be involved in schizophrenia development. Adenosine deaminase enzyme (ADA) acts in maintenance of adenosine levels, catalysing its deamination into inosine. So, the most frequent polymorphism of the gene coding ADA is the transition of G to A in nucleotide 22, resulting in substitution of asparagine for aspartic acid that results in a decrease in enzyme activity, consequently interfering in adenosine levels [39].

Apolipoprotein E (ApoE) coding gene, located in the chromosomic region 19q13.2, was under study for several neurodegenerative disorders. ApoE is the main lipoprotein expressed in brain and myelinic membranes. Studies reveal that allele 4 of this gene is involved in schizophrenia development and increases the risk of early onset of the disease [40].

NOS1AP gene codes for the adaptor protein of neuronal nitric oxide synthase 1 or CAPON. This protein is involved in several physiopathological processes that can be related with schizophrenia. This gene is associated with several forms of neuronal plasticity, neurotoxicity, release of neurotransmitters and glutamate neurotransmission. Post-mortem samples of prefrontal cortex of schizophrenic patients showed an increase in the expression of this gene, and it was observed a relationship between the markers in the gene *NOS1AP* (rs4657181, rs945713, rs4592244, rs108000405, rs4145621) and the clinical dimension of schizophrenia. It was concluded that this gene can influence the susceptibility and modify the clinical characteristics of schizophrenia [41].

Environmental Component of Schizophrenia

One of the simpler forms of understanding how environmental factors contribute to any condition consists in examining the way the condition is shared by identical twins. In schizophrenia, studies with twins indicate that the agreement rates between identical twins at world level are around 41-65%, suggesting that genetic and non-genetic factors play a significant role. However, to define genetic and environmental factors is not simple.

During the last two decades, scientific studies led to one hypothesis based on processes associated with brain development being related with schizophrenia development. Several studies suggest that disturbances during intrauterine life or just after birth might be fundamental in the aetiology of some cases of schizophrenia.

Fetus bad nutrition, involving reduction of oxygen, iodine, glucose and iron supply can interfere with normal development of brain structures, making the individual susceptible to the development of this pathology [42].

Besides fetus bad nutrition, also diabetes, chronic pulmonary disease, anaemia, maternal food deficiency during the first trimester of gestation seem to be involved [43]. Moreover, premature birth (before 33 gestation weeks) can increase the risk of schizophrenia development [43]. Perinatal events and complications during birth causing hypoxia or ischemia can lead to damage in hippocampus and cerebral cortex [43]. However, although meaningful, the referred effects are of small magnitude and can only explain a small percentage of schizophrenia cases [43].

Individuals born in winter and beginning of spring have increased risk of developing schizophrenia in a percentage between 5 and 15%, depending on winter severity. On the other hand, schizophrenia with predominance of negative symptoms, is associated with summer births, mainly in June and July [44-47].

Studies have demonstrated that schizophrenic individuals born in winter have a lower cephalic perimeter at birth. This fact is pointed out as resulting from changes in vitamin D, due to its seasonal fluctuations. Therefore, urban environments increase the risk of development of the disease not only due to stress but also due to higher prevalence of hypovitaminosis D, resulting from decreased outdoor activities and exposition to UVB rays [48].

On the other hand, high latitudes, weak air quality and dark skin, mainly in cold weather, reduces skin capacity to synthetize vitamin D3, the most bioavailable form [42,49,50].

It is common that healthy pregnant women show deficiency in 25-hydroxi-vitamin D. In this way, prenatal hypovitaminosis D, till the second year of age, can be pointed out as one of the causes of schizophrenia [50].

Also, prenatal exposition to lead, a neurotoxic agent, seems to be associated to double risk of schizophrenia development [51,52]. Preliminary data in mice seems to indicate synergism between lead exposure and mutations in *DISC1* gene, leading to a behaviour similar to schizophrenia [51,52].

Infection by viruses, namely infection by *Influenza* during the second or third trimester of pregnancy, increases the percentage of birth complications. On the other hand, the formation of the amygdalo-hippocampus complex, associated with schizophrenia etiology, occurs in the second trimester of gestation, being its development affected by fever [53,54].

Moreover, acute infection by *T. gondii*, a teratogenic intracellular parasite of the CNS, responsible for toxoplasmosis, is frequently associated with psychiatric symptoms. It is believed that one third of world population is infected by this parasite and, although during many years it was considered an asymptomatic infection, nowadays this pathology is related with serious consequences in physical and psychic health, specially schizophrenia [55,56]. Like *T. gondii*, the parasite responsible for rubella, virus *Rubella*, is also a teratogen of the CNS. Upon exposure to rubella before birth, there is a 10 - 20 times increased risk of developing schizophrenia in adult life. It has also been described the relationship between viral infection of CNS by cytomegalovirus or paramixovirus during childhood and the development of schizophrenia in adult [56-58].

Other studies demonstrated that individuals with medium/acute otitis show a 6,4 times higher risk of developing auditory hallucinations and this risk increases 10 times if otitis is on the dominant side of the brain [59,60].

Moreover, prevalence of schizophrenia in urban areas is twice of the one in rural areas. This difference is several times associated to environmental characteristics, like social fragmentation, disorganization, instability and lack of communication between inhabitants [44,61].

Among environmental factors associated with schizophrenia, the abusive use of certain psychotropic drugs, including marijuana, is several times pointed out as triggering factor of this disorder, at least in predisposed individuals [62]. Cannabinoid receptors are present in regions implicated in schizophrenia, like: prefrontal cortex, basal lymph nodes, hippocampus and anterior cingulate cortex. In this way, changes in endocannabinoid system in these regions seem to be related with negative symptoms of schizophrenia. On the other hand, there are functional interactions between dopamine and cannabinoids: these drugs block the dopaminergic receptor D2, decreasing the positive symptoms of schizophrenia [62].

As it is obvious, there are environmental factors that affect expression of genes normally expressed in schizophrenia. For instance, smokers have a higher expression of genes coding for enzymes involved in tobacco smoke metabolism than non-smokers [20].

Diagnosis

A specific diagnosis test for schizophrenia does not exist. Diagnosis is done by analysis of patient's symptoms and his clinical history. Brain mapping techniques have been developed with the aim of allowing detection or determining the existence of signs of tissue loss in parts of the brain or correlate abnormal structures with specific symptoms [63].

Structural or functional Nuclear Magnetic Resonance is a tool particularly useful for evaluating brains with high degree of detail. Another mapping technique is Positron Emission Computer Tomography, that provides information of blood flow and brain metabolism [63].

According with the Diagnostic and Statistical Manual (DSM-V) of the American Psychiatric Association, schizophrenia is diagnosed when two of the five types of symptoms are present: hallucinations, delusions, disorganized speech, disorganized or catatonic behaviour and negative symptoms like diminished emotional expression [14]. Once these requirements are identified, the schizophrenic individual must show deterioration at work, in social relations and in self-care. To confirm diagnosis, symptoms should provoke social/occupational disfunction and persist for a minimum period of six months. The use/effect of psychotropic substances should be excluded for diagnosis [14]. Disease evolution is variable, and prognosis is better for women [14].

Early detection of Schizophrenia

Identifying individuals with risk of developing psychosis, before any manifestation of the disease, is still a challenge for science. As already referred, there are several risk factors associated with schizophrenia, however, since it is a low incidence disorder, it is so far unviable to use them as risk markers for schizophrenia.

In general, schizophrenia starts with non-specific symptoms or negative symptoms. The period from the appearance of the first symptoms until diagnosis, is called "duration of non-treated disease". Sometime after, the first positive symptoms show up that corresponds to "duration of non-treated psychosis", period from the start of psychotic symptoms until diagnosis and treatment. Studies show that these periods are long and can last a few months or even years [64].

Evaluation of "high risk mental states" through symptoms or indicative behaviours allows to predict the possibility of future disease [64].

For the identification of an individual with risk for development of schizophrenia, operational criteria were stablished that include: intermittent, brief and limited psychotic symptoms; attenuated positive psychotic symptoms and genetic risk associated with recent deterioration.

Evaluation of risk mental states is done through standardized interviews and evaluation scales, following the patient for a period of months to a year. The percentage of followed individuals that developed the disease is 40% [64].

The period of subclinical signs and symptoms that precedes the development of psychosis is called the prodromal phase [65,66]. This period can last weeks or even several years, and it is common the development of comorbid disorders during this stage. In the prodromal phase behaviour changes or deterioration occur, preceding the onset of clinical psychotic symptoms. Since 1960, symptoms of the prodromal period are used in assessment scales designed to identify persons at risk for developing a psychotic disorder [65,66].

Basic symptoms are considered a core feature of the illness and include subjective experiences of thought, language, perception and motor disturbances; impaired bodily sensations; impaired tolerance to stress; disorders of emotion, thought, energy, concentration and memory; and, disturbances in social functioning [65,66].

The importance of the genetic component in early detection of schizophrenia

Schizophrenia is associated with genetic mutations, so, a genetic test should be essential in its diagnosis.

As a disease with a hereditary genetic component, other patient family members can be carriers of the same mutation.

Medical history gives important orientations concerning possible age of onset of symptoms in the same family. However, in certain families a slight anticipation on age of onset from one generation to the next, is observed. It is essential to teach patients relatives for a better understanding of the disease and the importance of early diagnosis.

Early detection of the pathology is essential since it will allow early start of the treatment, increasing the chance of patient recovery.

Diagnosis of mental disorders like schizophrenia, is difficult and discussible. Since the pathology can only be confirmed by the post-mortem brain exam, mental health professionals depend on psychological and symptomatic evaluation for patient's diagnosis.

MicroRNAs (miRNAs) have been widely used in studies of neuro-degenerative and psychiatric diseases, including schizophrenia. However, biomarkers for schizophrenia had only be found in nervous cells of the brain, that can only be collected after patient death. Yet, the olfactory epithelium is one of the few accessible neuronal tissues that contain neurons and stem cells. Previous studies showed that tissues derived from the olfactory epithelium and stem cells can be easily collected *in vivo* providing a very effective method in diagnosis of schizophrenia.

Study of Mor., *et al*. [67] demonstrated that expression of miR-382 (miR-382-5p) that regulates directly the expression of two genes, *FGFR1* and *SPRY4*, is higher in olfactive cells cultured from schizophrenic patients than from non-schizophrenic individuals. *FGFR1* and *SPRY4* gene products are involved in the signal transduction pathway of fibroblast growth factor. Changes in the regulation of these genes might trigger abnormal development and functioning of the brain associated with schizophrenia. Although promising it is still too soon to consider this strategy a diagnosis method for schizophrenia, since changes in miR-382 expression can occur when the disease already developed. However, if this result is confirmed, it might evolve for a simple and precise diagnosis test that will help in identification and symptoms prevention of the disease and to prepare the patient for the disease challenges [67].

Conclusion

Schizophrenia is a pathology with an important hereditary component, described as a vulnerability of the human organism for the development of the pathology. This susceptibility can evolve or not to disease and if it shows up, its evolution is affected by environmental factors. This leads to stigma risk of a person that still does not have the disease or even might never have it.

Sequencing of the human genome represents a big progress in comprehension of human biology and rational planning of biomedical research. However, it is important to notice that sequencing of a certain genome is only a part of a complex "map" associated to schizophrenia. Genetic information should be used as a guide, from where starts comprehension of diseases and the importance of genetic variation through analysis of complexity and behaviour of regulatory regions, genes, proteins, gene functions and cell systems.

Although the big efforts in identifying candidate genes, so far molecular genetic studies on schizophrenia are still modest. The appropriate use of genomics can help in elucidation of schizophrenia aetiology, allowing to evaluate the role of new genes, genetic variations, variations in gene expression and metabolic pathways of interest. Biochemical, imaging, neuro-anatomical, pharmacological, clinical and genetic data will allow a better understanding of the biological bases of schizophrenia. The availability of these data will have an enormous impact in schizophrenia research.

Pharmaceutical treatments, although effective, have side effects. On the other hand, the initial period of the disease is a "window of opportunity" for the treatment and increases the chance of patient recovery.

Nowadays, studies show that therapeutic measures during the initial stage of the disease can reduce the risk of development of schizophrenia or improve its prognosis, since it decreases the risk of clinical and biological deterioration. In this way, the search for biomarkers of Schizophrenia has increased over the last decade. Schizophrenia biomarkers studied so far have been classified according with their possible use in diagnosis or treatment response [68].

Lai., *et al*. [68] sorted out six categories of biomarker studies (brain-derived neurotrophic factor; inflammation and immune function; neurochemistry; oxidative stress response and metabolism; epigenetics and microRNA; and transcriptome and proteome studies) and discussed the molecules that might be used as potential blood-based biomarkers in schizophrenia [69-71]. Molecules showing differential patterns between individuals with schizophrenia might be used for diagnostic purposes, however, very few studies report the sensitivity and specificity of the discriminability of the tested markers. In this way, it is not clear the potential of these molecules as biomarkers [68].

Moreover, some studies showed that some biomarkers can be more useful as state indicators. Changes in some biomarkers seem to be associated with clinical outcome, treatment responses, and changes of clinical symptoms [72-74]. This suggests that they can be used for specific clinical events.

To be used in schizophrenia diagnosis, it is also crucial that the biomarker does not show similar patterns in other psychiatric diseases. Several psychiatric diseases, like bipolar disorders, share some of the same molecules with schizophrenia, so the identified markers are not specific of schizophrenia [75-78].

New studies for the identification of specific biomarkers for schizophrenia can increase the efficiency of disease diagnosis as well as improve treatment strategies. In the future, it is expected that the discovery of more specific biological markers, as well as a better definition of mental risk states, help in the detection and early intervention in schizophrenia and, who knows, in prevention of the disease.

As discussed previously, several genes are associated with, but not involved in schizophrenia development. Linkage studies on these genes might also contribute to a better and earlier identification of individuals with susceptibility of developing schizophrenia.

This work makes only a brief review on the studies concerning the identification of genetic as well as environmental factors involved in the development of schizophrenia. Much more could be said on the advances in schizophrenia research.

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