

Genetics of autism

Genética do autismo

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Abstract

Autism is a neuropsychiatric disorder with profound family and social consequences. An extraordinary number of genetical-clinical, cytogenetics and molecular studies were done in recent years. A multiloci epistatic model involved in the causation of autism have emerged from these studies.

Keywords: *Autistic disorder/genetic; Chromosome disorders; Chromosome aberrations; Developmental disabilities; Genes.*

Resumo

O autismo é uma doença neuropsiquiátrica com profundas conseqüências sociofamiliares. Inúmeros trabalhos investigaram pacientes e famílias com metodologia genético-clínica, citogenética e biologia molecular. Os resultados destes trabalhos apontam para um modelo multiloci com interação epistática associado à etiologia do autismo.

Descritores: *Transtorno autístico/genética; Transtornos cromossômicos; Aberrações cromossômicas; Deficiências do desenvolvimento; Genes.*

Introduction

For more than three decades, there has been crucial evidence that most psychiatric disorders, including schizophrenia, bipolar disorder and autism, have a strong genetic component. In the last 15 years, innumerable gene loci have been associated with these and other mental disorders, principally through genetic linkage analysis. However, only a few specific genes have been identified. Most of these genes can only be identified when literally hundreds of affected individuals and their relatives are analyzed. Promising new research techniques and methods have emerged that might further the investigation of the genetic and environmental causes of these disorders.

Advances in human genetics research have paved the way for increasing knowledge of the biological pathways of cognitive and affective disorders, as well as of certain types of psychoses. Due to the great difficulty in comprehending alterations in encephalic functions, understanding the physiopathology of the nervous system has become highly attractive. As previously mentioned, studies of families with one or more affected members, as well as twin and adoption studies, have shown that mental disorders such as autism have a strong genetic component.¹ However, none of these diseases follow a Mendelian inheritance pattern, which suggests interaction among multiple genes.

The autistic phenotype is broadly varied. Individuals with classic autism, lacking verbal communication and presenting severe mental deficiency, as well as autistic individuals presenting verbal abilities and normal intelligence, have been described. Developmental abnormalities are usually detected in the first three years of life and persist into adulthood.² The Diagnostic and Statistical Manual of Mental Disorders⁴ and the International classification of diseases⁵ created the diagnostic category of Global Development Disorders and Pervasive Developmental Disorders (PDDs). In general, these are all designated as autism. The PDDs affect social interaction, communication and behavior and are highly prevalent, up to 5 cases per 1000 children, with a 4:1 male/female ratio.^{3,6-8}

The etiology of autism is still unknown. Hundreds of studies have been conducted in attempts to reveal the genetic factors associated with the disease. The neurobiological causes associated with autism, such as convulsions, mental deficiency, fewer neurons and synapses in the amygdala, hippocampus and cerebellum;⁹ encephalitis,⁹ and a higher concentration of circulating serotonin, suggest a strong genetic component. In fact, studies with twins have actually shown that the concordance with autism ranges from 36% to 92% in monozygotic (MZ) twins, whereas concordance is low or null in dizygotic (DZ) twins.¹⁰ However, when cognitive and social abnormalities are considered, the level of concordance rises to 92% among MZ twins and 10% among DZ twins.¹¹ Another relevant fact is that, although the risk of autism recurrence is low (2%-8%), the relative risk is 50-200 times greater than the prevalence of the disorder in the general population.^{6,12}

It is believed that there are from 3 to more than 10 genes related to the disease.¹³⁻¹⁴ Furthermore, the autism spectrum can be found in practically all chromosome abnormalities.¹⁵ The 15q11-13 region, critical in the Prader-Willi/Angelman syndrome, shows alteration in 1% to 4% of autistic patients.¹⁶ Structural incoherencies in the 17p11.2 region, critical in the Smith-Magenis syndrome, have also been reported in autistic individuals.¹⁷ Likewise, patients with tuberous sclerosis, Rett syndrome, phenylketonuria, neurofibromatosis or autism-related fragile X syndrome form etiological subgroups.^{7,18} Approximately 30% of fragile X individuals present the autism spectrum.^{6,19} However, there is discordance on the degree of prevalence of fragile X in autism patients, ranging from 7%-8%.²⁰⁻²¹

The first extensive triage of the complete genome for chromosomal regions involved in classic autism found approximately 354 associated genetic markers, located in 8 regions of the following chromosomes: 2, 4, 7, 10, 13, 16, 19 and 22.²² However, later studies have shown that the 7q, 16p, 2q, 17q regions are the most significant.²³ More recent studies have provided evidence of linkage with the X chromosome.²⁴⁻²⁵

Genes identified in patients with autism, such as developmental genes associated with the central nervous system,²⁶⁻²⁷ genes in the serotonin system and in other systems regulating neuron function, as well as genes located at chromosomal breakpoints,²⁸ have arisen as candidate genes. In the 15q11-13 region, for example, the cluster of the gamma-aminobutyric acid receptor gene seems to be associated with autism pathogenesis.^{7,28} In addition, expression of the UBE3A gene is predominant in the human brain.³⁰⁻³¹ However, since individuals with chromosomal alterations in this region are not always autistic, it is believed that the changes in these genes are not sufficient to induce development of the disease. This hypothesis reinforces that of autism originating from synergism or epistasis among multiple genes.

Most studies have focused on the 7q22-q33 region. In the 7q22 region, the RELN (previously reelin) gene, which encodes a glycoprotein extensively secreted in neuronal migration, may present alterations that affect cortical and cerebellar development. In fact, abnormalities in cerebellar neurons are among the most significant causes in the pathology of autism.¹¹ Within this region, there are at least another 9 candidate genes.^{6,27,32-34}

In the X chromosome, the Xq22-q23 region, to which the AGTR2 gene has been mapped, is held as important.³⁵ Studies of this gene have demonstrated that the deletion in this region is associated with the high frequency of mental deficiency in autistic individuals. However, the most significant region is Xq13-q21, which contains one of the genes of the neuroligin family. The neuroligins act as mediators of cell interaction (adhesion molecules) between neurons possessing receptors for neuroligin in their plasmatic membranes. The neuroligins are found on the post-synaptic side of the synapses³⁶ and appear to be essential for the efficient function of the same.³⁷⁻³⁸ Mutations in the NLGN3 and NLGN4 genes have been found in two families including members affected by autism or Asperger's syndrome, suggesting that synaptic performance is affected.

Genes that encode proteins participating in the serotonin system are also strong candidates for the study of autistic individuals. Impaired function of this system may result in depression, epilepsy, obsessive-compulsive behavior and affective disorders. In fact, some of these genes, such as the serotonin transporter (5-HTT) and serotonin receptor (5-HTR) genes, have been studied in affected individuals. However, the relationship between the 5-HTT gene and autism is still controversial.³⁹⁻⁴³ As for the 5-HTR genes, it has been shown that autism is not associated with the 5-HTR2B and 5-HTR_{1A} receptors,⁴⁴ although a significant association was found between autism and polymorphism in the 5-HTR2A receptor gene in autistic individuals compared to controls.

Despite all the discordance regarding candidate genes for autism, there are still good reasons to believe that, once the genes involved are known, new therapeutic agents may act on specific molecular targets. In the search for these genes, identifying multiple quantitative phenotypes is fundamental to the selection of some regions. For example, the results of a study involving 75 families, divided into subgroups based on the speech characteristics of the subjects and their blood relatives, suggest that chromosomes 7 and 13 are strongly associated with autism.⁴⁵ The 2q region has also been associated with autism in other populations with speech difficulties.⁴⁶⁻⁴⁷ Such studies suggest that social and cognitive deficits are included in the broad phenotypic spectrum of autism.⁴⁸ Social deficits include loss of emotional response, loss of empathy, hypersensitivity and singular preoccupation with a special interest. Communication deficits, on the other hand, consist mainly of pragmatic communication difficulties or other types of language problems. The amplification of the phenotypic spectrum in autism may facilitate the identification of genes involved in the disorder. Therefore,

multidisciplinary or consortium studies are the best hope for gaining a better understanding of PDDs. Specific diagnostic tests are still unavailable in clinical practice. A diagnosis of autism should result from the creation of a detailed evolutive background of the patient, as well as from family interviews regarding the cognitive and behavioral abilities of the patient. Future clinical investigations will confirm whether autism is associated with the syndromes mentioned.

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