Chapter 11

Genetic Etiology of Autism

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1. Introduction

Autism Spectrum Disorders (ASD) are severe neurodevelopment disorders characterized by impairment in social interaction and communication, and repetitive and stereotyped behaviors. Motor deficits, aggressive behavior, abnormal sleep patterns, gastrointestinal problems, epilepsy and intellectual disability are also observed. Manifestations are observed before three years of age with early stimulation being recommended (Baird et al., 2006; Faras et al., 2010; Bronsard et al., 2011; Miles, 2011; Angelidou et al., 2012). Due to the great phenotypic variability of carriers and the subjectivity of the differential diagnostic criteria of "Pervasive Developmental Disorders" (American Psychiatric Association, 2000), ASD is today considered the most appropriate denomination. The general term, autism, is often used as a synonym for ASD.

ASD were described more than seven decades ago (Sanders, 2009) and many neurobiological changes have been illustrated in carriers, yet the diagnosis is still based on behavioral aspects using diagnostic scales. However, even though there is a detailed “checklist” made up of several scales, most are not translated and validated in different countries, which hinders standardized and efficacious diagnosis (Marteleto et al., 2008; Rapin & Goldman, 2008; Sato et al., 2009; Biederman et al., 2010).

The prevalence of ASD varies by region, but it is believed to be around 1:150 individuals. However, higher prevalences of up to 1:88 children have been described (Currenti, 2010; Angelidou et al., 2012). The tentatives to explain such high prevalence rates involve changes in diagnostic criteria, greater knowledge of the general population and the exposure of the genetic material of fetus to internal and external toxic agents (King & Bearman, 2009; Lintas & Persico, 2009; Avchen et al., 2011).

Although many environmental factors are related to the pathogenesis of autism, such as the rubella virus whose disruptive effects in the brain may result in autistic behavior, the participation of genetic components is certain. The estimated concordance rate for identical twins ranges from 60 to 90%, while among dizygotic twins and non-twin siblings the rate is from 5 to 31% (Bailey, et al., 1995; Rosenberg et al., 2009; Hallmayer et al., 2011). Based on studies of twins, heritability was estimated to be between 60 and 80% (Geschwind, 2011; Hallmayer et al., 2011).

In up to 10% of ASD cases it is possible to identify etiological, genetic or environmental factors (syndromic autism). Thus, in about 90% of the cases there is no known cause (non-syndromic autism). A multifactorial etiology can be assigned to these idiopathic cases after the exclusion of environmental and genetic causes, and using specific evaluations (Veenstra-Vanderweele et al., 2004). Scientific discoveries until now have shown that there are multiple genetic factors (polygenes) involved in the predisposition to ASD which, associated with an external trigger (environmental factor), would result in the behavioral framework for autism. However, these factors alone also result in changes in the brain that lead to autistic behavior. Thus, the same factors may be present in two children with one having autism and the other not. There is no doubt that science has elucidated many biological mysteries about autism, yet for every issue clarified, another, even more complex, appears.

2. Environmental etiology

Prenatal or perinatal infections by viral agents such as rubella and cytomegalovirus, as well as exposure to toxic agents, such as thalidomide, valproic acid and alcohol, are some of the best-known environmental causes of ASD (Chess et al., 1978; Christianson et al., 1994).

'Allergenic' environmental factors and autoimmune problems during pregnancy may also be involved in the etiology of autism. The presence of circulating maternal antibodies against fetal brain proteins suggests the possibility of their transposition in the blood-brain-barrier. Studies have demonstrated the presence of pro-inflammatory cytokines in the fetal brain, such as TNF (tumor necrosis factor) which is preformed in maternal mast cells (Vojdani, 2008; Angelidou et al., 2012).

Even premature birth has been implicated as a cause of ASD. Babies from gestations of less than 28 weeks have a high risk of neurological problems. A study in Atlanta, USA, showed that children born in the 33rd gestational week have a greater risk for autistic characteristics (Limperopoulos et al., 2008).

There is a link between oxidative stress and immune response (Viora et al., 2001). There are suggestions that environmental factors trigger oxidative stress in individuals genetically susceptible to autism, which would lead to losses in methylation and secondary neurologic deficits (Dardeno et al., 2010). Increased levels of oxidative stress markers have already been described in the cord blood of mothers who had premature births compared to those of mothers who had full term births (Joshi et al., 2008).

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Premature birth is associated with the formation of reactive oxygen species (Davis & Auten, 2010). Stress typically results in the release of corticotropin-releasing hormone (CRH) with elevated levels of this hormone in plasma being associated with premature births (Warren et al., 1992; Chrousos, 1995). CRH may stimulate the release of a cytokine, interleukin-6 (IL-6), by mast cells, which are part of the immune system. IL-6, by injuring the blood-brain barrier due to stress related to CRH and mast cells, increases its permeability (Esposito et al., 2001). With the increased permeability, neurotoxic molecules can reach the brain and cause an inflammatory process that contributes to the pathogenesis of ASD (Theoharides, 2008; Valent et al., 2012). This process has suggested a new possibility for the etiology of ASD.

3. Overlapping genetic etiologies

Many genomic regions, with genes implicated as candidates, have been associated to the etiology of autistic behavior, although the results of some studies have not been replicated. Even so, it is estimated that all proposed regions together would be involved in the etiology of less than 1% of cases. In addition, scientific evidence shows that changes in regions reported in ASD have also been described in other neuropsychiatric diseases, which suggests that there is an etiological connection with phenotypes attributed to other neurodevelopment abnormalities (Griswold et al., 2012). For example, some rare mutations associated with increased risk for ASD and schizophrenia have already been reported in 15q13.3, 16p11.2 and 22q11.21 and in the *NRXN1* gene (Weiss et al., 2008; Levinson et al., 2011; Sanders et al., 2011).

Moreover, many genes involved in nonsyndromic intellectual disabilities (ID) and in epilepsy have also been implicated in the etiology of nonsyndromic ASD. These genes probably belong to a continuum of neurodevelopment disorders that manifest in different manners depending on associated genetic and environmental factors. The identification of changes is crucial for patients and for counseling of families, as well as for the identification or exclusion of the presence of specific genetic diseases in patients with ASD (Betancour, 2011).

Many patients with chromosomal or monogenic diseases have autistic behavior as one phenotypic manifestation of the disease. A scientific enigma to be elucidated refers to the possible causes of the varying severity of symptoms or the presence/absence of manifestations in carriers in the same family. They are not free from rare or common mutations associated with behavioral phenotype in isolation. Thus, in autism, studies on gene interactions are fundamental and what is called overlapped etiology can be an additive effect between different genes, some of them more significants.

4. Genetic anticipation

Genetic anticipation studies are fundamental in the elucidation of inheritance mechanisms for any genetically influenced condition, because, in addition to the clinical importance and

guidance in genetic counseling, these investigations can assist in the elucidation of the recurrence risks in future generations (Constantino et al., 2010).

Following a promising approach in the investigation of complex disease etiologies, studies on endophenotypes ("intermediate phenotypes") may be used to direct the search for the etiology of ASD (Weinberger et al., 2001). Manifestations related to autistic behavior are often observed in varying degrees of severity in unaffected individuals of previous generations in the same family, thereby characterizing the phenomenon of genetic anticipation in ASD (Losh et al., 2008).

A Swedish study reported that the existence of individuals with schizophrenia and bipolar disorder in the family is a risk factor for the occurrence of autism. The authors found an association between schizophrenic parents or siblings with increased risk of ASD. Bipolar disorder also proved to be a risk factor, but not as strong as schizophrenia (Sullivan et al., 2012).

Studies of autistic families have also shown a significant increase in the recurrence of ASD in first-degree relatives of carriers. For example, siblings of individuals with ASD have a 22- to 25-fold higher risk of having the disorder (Lauritsen et al., 2005; Abrahams & Geschwind, 2008). There are significantly higher risks of ASD in offspring of parents with ASD and those with familial history of psychiatric problems. Depression and personality disorders have been reported to be more common in mothers of children diagnosed with ASD than in mothers of children with normal development (Daniels et al., 2008; Constantino et al., 2010). Even some non-affected individuals of different generations in the same family may show subtle impairment in cognitive development, language changes or in social interaction; this is termed the *broad autism phenotype*. This phenotypic diversity of autistic behavior and psychiatric manifestations in families of the patients indicate that the genetic factors that influence ASD may be composed of distinct elements that manifest differently between affected and non-affected family members (Pickles et al., 2000; Szatmari et al., 2000; Goldberg et al., 2005).

In the molecular field, studies on genealogies with multiple affected family members and studies on twins suggest that allelic variations are associated with increased susceptibility to ASD and that there are etiological factors common to both ASD and milder autistic phenotypes (Lundstrom et al., 2010; Arking et al., 2008; Wang et al., 2009). Hence, epidemiological studies have been developed with families in an attempt to clarify the relative proportions of cases of autism and *broad autism phenotypes* in the population that might explain these complex mechanisms of genetic transmission.

5. Associated syndromes and comorbidity in autism

Similar to intellectual disabilities or delay in motor developmental, the autistic behavioral phenotype can occur alone or as part of the spectrum of phenotypic manifestations in a particular condition of environmental, genetic or multifactorial etiology. In some situations, the autistic behavioral phenotype is observed in individuals with only one other clinical manifestation, such as epilepsy. This simultaneous occurrence (co-occurrence) has been discussed

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much and is referred to in the literature either as an association or as comorbidity. Probably the truth is, that in most cases, the different manifestations result from the same causal factor, which suggests the term "association" is more appropriate than "comorbidity".

Monozygotic and dizygotic twin studies indicate a variety of neuropsychiatric diagnoses associated with ASD, including attention deficit and hyperactivity disorder (ADHD) and anxiety disorder (Lichtenstein et al., 2010). High frequencies of these diseases have been reported in children with autism, as has bipolar disorder in adolescents and young adults (Munesue et al., 2008; Simonoff et al., 2008). The wide range of clinical behavioral symptoms among carriers may be justified and be a good argument to consider the diagnosis of ASD alone, with all the possible manifestations expected in the spectrum, as no individual is exactly like another. In this way, families would be less anxious and confused on receiving three or four diagnoses for the same child.

There are a number of diseases associated with autism, whose genetic etiology is well established, i.e. autistic behavior is one of the possible manifestations. The most common is Fragile X syndrome (FRAXA). This is the most frequent form of inherited mental retardation and is considered a monogenic cause of ASD. Symptoms include neurodevelopmental delay, anxiety, hyperactivity, and autistic-like behavior, which are accompanied by macroorchidism and distinct facial morphology. It is caused by the expansion of the CGG trinucleotide repeat in the 5' untranslated region of the fragile X mental retardation 1 (*FMR1*) gene resulting in loss of the Fragile X Mental Retardation Protein (FMRP), an RNA-binding protein abundant in the brain and gonads of affected men. FMRP has multiple functions in the RNA metabolism, including mRNA decay, dendritic targeting of mRNAs and protein synthesis. In neurons lacking FMRP, a wide array of mRNAs encoding proteins involved in synaptic structure and function are altered. As a result of this complex dysregulation, in the absence of FMRP, spine morphology and functioning is impaired (De Rubeis et al., 2012). Frequencies of between 2% and 3% of FRAXA have been observed in studies on boys with ASD, while in boys with FRAXA, the frequencies of ASD range from 20% to 40% (Kaufmann et al., 2004; Shibayama et al., 2004). Tuberous Sclerosis, another monogenic disease that results from mutations in the *TSC1* and *TSC2* genes, is observed in about 1% of individuals with ASD and is regarded as the second most common genetic cause of the autistic phenotype (Smalley, 1998).

The list of medical conditions associated with the autistic phenotype, including genetic syndromes, is growing. Examples of genetic conditions associated with autism and the gene regions involved are: Angelman Syndrome (*UBE3A*), Rett syndrome (*MECP2*), neurofibromatosis (*NF1*), Timothy syndrome (*CACNA1C*), Smith-Lemli-Opitz syndrome (*DHCR7*), CHARGE (*CHD7*), Cohen syndrome (*VPS13B*), Noonan syndrome (*PTPN11*), 2q37 deletion syndrome, Cornelia de Lange syndrome (*NIPBL, SMC1A* and *SMC3*), DiGeorge/Velocardiofacial syndrome (22q11), Smith-Magenis (*RAI1*), Williams-Beuren syndrome (7q11.23) and Phelan-McDermid syndrome (22q13.3) (Berg et al.,2007; Phelan, 2008; Delahaye et al., 2009; Van der Aa et al., 2009; Laje et al., 2010; Betancour, 2011).

Many inborn errors of metabolism also seem to contribute to at least 5% of ASD cases as the deficiency of certain enzymes in metabolic diseases can result in the accumulation of substances

that may have toxic effects on brain development. An example is phenylketonuria, an autosomal recessive disorder that, if untreated, leads to excessively high levels of phenylalanine and toxic metabolites, resulting in intellectual disabilities and ASD (Manzi et al., 2008).

Mitochondria are intracellular organelles that have the function of producing energy. In the mitochondria ATP production, free oxygen radicals and reactive oxygen species (ROS) are produced and then normally removed from the cells by anti-oxidant enzymes. When the production of ROS and free radicals exceeds the limit, oxidative stress occurs, that is, ROS combine with lipids, nucleic acids and proteins in the cells leading to cell death by apoptosis or necrosis. Since brain cells have limited antioxidant activity, a high lipid content and high requirement for energy, it is more prone to the effects of oxidative stress. Some patients with ASD and mutations in mitochondrial DNA have already been reported (Fillano et al., 2002; Dhillon et al., 2011). The first study involving bioenergetic metabolism disorders in ASD was directed by Coleman & Blass (1995), who reported lactic acidosis in four children with autism. Later Lombard (1998) proposed that mitochondrial oxidative phosphorylation can cause abnormal brain metabolism in children with autism resulting in acidosis. A study by Pons et al. (2004) described five children with ASD who had abnormal respiratory chain enzyme activity, characterized by the *A3243G* mutation. Graf et al. (2000) described two brothers with autism associated with a mitochondrial DNA *G8363A* RNA(Lys) mutation.

All these diseases, in addition to peculiar and specific clinical signs and symptoms, have autism as a common manifestation. However, with so different genetic etiologies and probably, the involvement of different interaction mechanisms, what do they have in common that explains the autistic behavior? The autistic behavior is attributed to changes in neurodevelopment and all these diseases cause changes in the brain structure and/or functioning, probably damaging cerebral areas that are linked to autistic symptoms.

In the clinical practice, the recognition of these conditions is fundamental, as it allows the targeting of laboratory tests and assists in the initial breakdown of etiological heterogeneity which categorizes specific cases of autism as syndromic or nonsyndromic. This definition is important because of possible implications in the prognosis and recurrence risk (Miles, 2011; Gurrieri, 2012).

6. Chromosomal alterations

Numerical and structural chromosomal alterations, visible by conventional cytogenetic techniques, occur in about 6 to 7% of ASD cases and have already been described in all autosomal and sex chromosomes. These findings justify karyotyping by GTG banding as part of the etiological work-up protocol of carriers (Castermans et al., 2004; Shen et al., 2010).

Some human chromosomal aneuploidies are known to increase the risk for ASD; the most common, as identified in studies of individuals with autism, are trisomy 21 (Down syndrome), monosomy of chromosome X in women (Turner syndrome), uniparental X disomy in men (Klinfelter syndrome), Y disomy and 45,X/46,XY mosaicism. Structural abnormalities include 15q11-13 duplication and deletions of 2q37, 22q11.2 and 22q13.3 (Betancour, 2011).

Due to the high number of cases that have been described and the type of genes located in them, the association of eight chromosomal regions is well established in autism including: 1q21, 7q11.23, 15q13, 15q11-13, 16p11.2, 17p11.2, 22q13.3 and 22q11.21. Rearrangements involving these regions are detected by classic cytogenetic techniques but it is recommended that more sophisticated techniques, such as array comparative genomic hybridization (array-CGH), are used for their evaluation (Gillberg, 1998; Griswold et al., 2012).

As expected, unbalanced changes are more frequently found in dysmorphic individuals and with delays in neuropsychomotor development due to the "extent of damage" because they result in significant gains and losses of gene content. Balanced rearrangements, however, are less frequent and can be related to mutations in DNA breakpoints. Some are so rare that it is difficult and risky to consider them a cause of autism. However, some occur at high enough frequencies to be considered risk factors for the disease. Identifying balanced changes is important for genetic counseling, not only due to the etiologic implications, but also because these changes may predispose descendants to unbalanced rearrangements (Carter, 2011; Sherer & Dawson, 2011; Nowakowska et al., 2012).

However, chromosomic analysis detects only 3-5 megabase abnormalities. New technologies using DNA or chromosomal microarrays can identify submicroscopic abnormalities. Microdeletions and duplications, e.g., may be identified with microarrays in individuals with ASD who previously had normal kariotype. Therefore, if cytogenetic analysis is negative in clinically diagnosed ASD, molecular techniques are necessary.

7. Candidate genes

According to recent findings, some common mutations, epigenetic mechanisms, chromosome alterations, rare single gene mutations, copy number variations (CNVs) and single nucleotide polymorphisms (SNPs) result in the autistic phenotype. Because of national and international consortia, many linkage and genome-wide association studies have evolved which elucidated candidate genes and susceptibility of genomic regions relevant to ASD. In contrast to polygenic or complex genetic models for autism, suggested in the majority of cases, a few forms of ASD are known to be caused by single gene defects, such as in FRAXA (Chiocchetti & Klauck, 2011; Dhillon et al., 2011).

According to a review by Betancour (2011) more than 100 candidate genes for autistic behavior are also related to syndromic or nonsyndromic intellectual disabilities. Many are also associated with epilepsy, with or without intellectual disabilities; this suggests that these neurodevelopment disorders have risk factors in common with ASD.

Mutations in a single gene may be autosomal dominant, recessive or X-linked. Some, not always related to syndromic cases, are highly penetrating and appear at sufficiently high frequencies to be considered monogenic causes of autism. Of the growing list, the most important candidate genes are: *NLGN3*, *NLGN4*, *SHANK2*, *SHANK3*, *NRXN1*, *NRXN3*, *PTCHD1/PTCHD1AS*, *SHANK1*, *DPYD*, *ASTN2*, *DPP6*, *MBD5*, *CDH8* and *CNTNAP2*. It is

important to note that most of these act on neurotransmission in the central nervous system (Sherer & Dawson, 2011).

There are reports of more than two hundred candidate genes in the literature. According to Swanwick et al. (2011), they can be classified into four categories: 1) rare - genes involved in rare monogenic forms of ASD. This type of allelic variant includes rare polymorphisms and mutations directly related to ASD (*NRXN1* and *SHANK3*); 2) syndromic - genes related to syndromes with phenotypic manifestations in a significant subpopulation of carriers that include autistic symptoms *(FMR1* and *MECP2*); 3) association - genes with common polymorphisms that confer a small, probably additive risk, for ASD, that were identified from association studies derived from cases of unknown etiology (*MET* and *GABRB1*) and 4) functional - genes with functions related to the biology of ASD that are not included in the other categories (*CASDP2* and *ALOX5AP*). Among these, the ones that belong to the first two categories are the most strongly related to the pathogenesis of ASD (El-fishawy & State, 2010). There are indications that *de novo* point mutations occur in approximately 5 to 20% of the cases (O'Roak et al., 2011).

Persico and Bourgeron (2008) proposed that there are three main pathways involved in the pathogenesis of ASD. The first entails genes that affect cell migration, the second disruptions of the glutamate-GABA harmony and the third involves synaptic formation and maintenance and dendritic morphology. All these pathways play a fundamental role in the central nervous system, particularly in the serotonergic process (Berkel et al., 2010; Durand et al., 2007).

Recent studies have given more support to evidence that a large subset of genes, involved in the outgrowth and guidance of axons and dendrites, is implicated in the etiology of autism. However, many studies are still needed in order to understand the role of isolated genes and gene regions in ASD and to identify the associations between them and to identify new candidate genes that act within the molecular pathways (Hussman et al., 2011; Griswold et al., 2012).

But despite the large number of previously identified candidate genes, the number of patients with changes in these genes does not reach 1% of the total cases, which further highlights the extreme heterogeneity seen in the pathogenesis of ASD. The findings have led to a paradigm shift in the concept of the genetic architecture of common neurodevelopmental diseases, stressing the importance of individual patterns, rare mutations and overlapping in genetic etiology. They have also converged on specific neurodevelopmental pathways, providing insights into pathogenic mechanisms (Mitchell, 2011).

8. Single Nucleotide Polymorphisms (SNPs), Quantitative Trait Locus (QTL) and risk for ASD

Of the techniques that supported the rapid advance in molecular genetics, comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) genotyping array have allowed the qualitatively and quantitatively identification of the genes and genomic rearrangements involved in the autistic phenotype (Alárcon et al., 2008; Whalley, 2011; Mefford

et al., 2012). The use of these molecular sequencing tools has also enabled the identification of high frequencies of common variants in some genes, such as SNPs, in individuals with SD. SNPs, causing about 50% of all currently known variations in genetic material, are the most numerous variants in the genome. Moreover, SNPs are considered genetic markers that can be used to identify genes associated with complex diseases (Malhotra & Sebat, 2012).

Unlike CNVs, SNPs seem to be more penetrating in ASD. *De novo* SNPs, although less frequent, seem to have more deleterious effects and confer higher risk for autistic behavior (Chahrour et al., 2012). Associations between some SNPs of mitochondrial and nuclear genes and predisposition to ASD have been reported by several studies (Ramoz et al., 2004; Silverman et al., 2008; Smith et al., 2009). Studies have shown SNPs in the *GABRA2, GABRA3, GABRA4, SLC25A12, FOXP2, CNTNAP2, CNTNAP2* and *BDNF* genes (Li et al., 2005; Segurado et al., 2005; Alárcon et al., 2008; Cheng et al., 2009; Scott-Van Zeeland et al., 2010; Jiao et al.,2011). In the Genome-wide Association Studies (GWAS) involving 4305 individuals with ASD and 6941 controls, strong association signals were revealed in six SNPs of two genes encoding neuronal cell-adhesion molecules, cadherin 10 (*CDH10*) and cadherin 9 (*CDH9*). These findings were replicated in two independent cohorts and implicated neuronal cell-adhesion molecules in the pathogenesis of ASD (Wang et al., 2009).

It is possible that screening for SNPs may identify new biological mechanisms that are involved in predisposition to ASD. However, GWAS, although promising, has revealed few common alleles and many results have still to be replicated (Ma et al., 2009; Manolio et al., 2009; Klein et al., 2010). It is clear that SNPs may have variable expressions or reduced penetrance. But, while it is apparent that rare variations can play an important role in the genetic architecture of these diseases, the contribution of common variations to risk for ASD is less clear (Jiao et al., 2011; Sherer & Dawson, 2011). Additionally, a strong Association between SNPs in the 5p14.1 and 5p15.2 regions and ASD has also been reported (Wang et al., 2009).

However, the results of Stage 2 of the Autism Genome Project Genome-Wide Association Study, which incremented 1301 ASD families to the investigation bringing the total to 2705 families analyzed (Stages 1 and 2), showed that no single SNP has a significant association with ASD or selected phenotypes at the genome-wide level and concluded that common variants affect the risk for ASD but their individual effects are modest (Anney et al., 2012).

These controversial results about the role of SNPs in the predisposition for ASD do not rule out participation in the phenotype, but motivate the investigation of biological phenomenon that would explain their participation. Probably a single SNP does not affect the risk, but perhaps the additive effect of several SNPs, in specific combinations, with the participation of environmental determinants cannot be discarded in etiologically complex diseases.

From another standpoint, the Quantitative Trait Locus (QTL) approach is one of the most suitable methods to find susceptibility of loci. This approach follows the assumption that ASD occur as a continuum of severity, a position supported by findings of elevated levels of ASD symptoms in parents and siblings of cases compared to controls, and variations in ASD traits that have been found in the general population. One study to identify the loci that underlie ASD symptoms in children with attention-deficit/hyperactivity disorder (ADHD) in-

vestigated both the total level of ASD symptoms as well as scores of three ASD symptom domains, thus taking into account potential differential genetic origins of different ASD symptom domains. QTL linkage analyses for the different ASD domains were carried out using 5407 SNPs spanning the entire genome. Findings suggest that some QTLs are ASD specific, although the 15q QTL potentially has pleiotropic effects for ADHD and ASD (Nijmeijer et al., 2011). The genetic analysis of quantitative traits that are phenotypically linked, such as in ASD and ADHD, can reduce the heterogeneity of diagnosis and indicate loci related to susceptibility (Lu et al., 2011).

There is a QTL related to language delay located close to the 7q35-36 region. Interestingly this region is mapped in the *CNTNAP2* gene, a strong candidate for predisposition to autistic behavior; it is well known that communication abilities are qualitatively impaired in autistic individuals. The significant delay in language ("age of first word") is observed in about half of affected children (Alárcon et al., 2008). The relationship of SNPs in the *CNTNAP2* gene has already been described, as has the association of the gene and its SNPs to language development delay in autistic and non-autistic individuals (Alárcon et al., 2008; Arking et al., 2008; Tan et al., 2010; Stein et al., 2011; Whalley et al., 2011).

Additionally, the transcription factor encoded by the *FOXP2* gene has already been linked to the development of language. This factor binds to the promoter of the *CNTNAP2* gene regulating its expression during development. There are reports of changes in the *FOXP2* binding site in patients with ASD, which suggests that a reduced expression of the *CNTNAP2* gene may be the underlying etiology of one of the phenotypic characteristics of ASD (Vernes et al., 2008; Poot, et al., 2009). In addition to these, it has been suggested that *WNT2* and *EN2* are related to language development in autism (Lin et al., 2012).

Promising results on the influence of genetic bases in neurobehavioral disorders have also been obtained through studies on CNVs. All these emerging genetic technologies have brought more valuable approaches to improve the understanding of the etiology of ASD. Advances in the use of molecular biology tools have provided a promising manner to study gene-gene and gene-environment relationships in disorders (Gurrieri, 2012; Li et al., 2012). This combination of tools in the search for the etiology will reflect in the possibility of targeting the diagnosis, prognosis, early interventions and genetic counseling. However, more data and the reproducibility of findings are necessary to establish the genetic components of these diseases.

9. Copy Number Variations (CNVs) in ASD

Copy Number Variations (CNVs), submicroscopic variations that are less than 500kb in size in DNA, are widespread in normal human genomes. The most common CNVs tend to be large (> 500Kb) and contain several genes, while rare or *de novo* CNVs are smaller (< 100Kb), sometimes interrupting a single gene. On average, there are more than 1000 CNVs in the genome, accounting for ~4 million base pairs of genomic difference. Although SNPs outnumber CNVs in the genome by three orders of magnitude, their relative contributions to

genomic variation (as measured in nucleotides) are similar. Thus, in addition to 0.1% of genetic difference at the nucleotide sequence level, another 0.1% of genetic difference is apparent at the structural level (Malhotra & Sebat, 2012).

The rate of genome-wide nucleotide substitutions is estimated at 30–100 per generation and ~1 per exome. In contrast, the global rate of structural mutation events is lower: CNVs > 10 Kb in size occur at a rate of ~0.01–0.02 per generation (Marshall et al., 2008; Conrad et al., 2011; Levy et al., 2011; Sanders et al., 2011). Nucleotide substitutions probably account for the majority of disease risk alleles, but based on sheer size and potential to impact genes (or multiple genes), structural mutations are, on average, more pathogenic. Thus, CNVs, *de novo* CNVs in particular, seem to be a class of variants that have large effect on disease risk (Malhotra & Sebat).

CNVs are gaining importance in the scenario of ASD. They represent a significant source of genetic diversity and seem to significantly contribute to changed behavioral phenotypes (Sebat et al., 2007; Rees et al., 2011). To have an idea, *de novo* CNVs have already been reported to be three to five times more common in families of individuals with ASD than in controls, and more often presenting the syndromic form of autism, that is, with the most severe phenotypes (Miller et al., 2010; Pinto et al., 2010; Shen et al., 2010; Sanders et al., 2011). In fact, CNVs, in particular *de novo* CNVs involving many genes, confer risk for ASD. However, although they are important in this respect, they rarely interrupt a single gene or have complete penetrance and many give a wide-ranging risk including risk for other problems such as intellectual deficiency, epilepsy and schizophrenia (Geschwind, 2011; O'Roak et al., 2011).

Up to 40% of CNVs in autism are inherited from apparently normal parents, consistent with the suggestion of incomplete penetrance. Both *de novo* (non- inherited) or inherited CNVs occur at the same locus in unrelated individuals, and some of them coincide with those seen in other gene-related diseases associated with ASD, including developmental delay and intellectual deficiency (Cook & Scherer, 2008; Lee & Scherer, 2010). Thus, some apparently have a pleiotropic effect.

De novo CNVs have been observed in from 7-10% of cases in simplex families, in 2-3% in multiplex families and approximately 1% of normal controls. Rare *de novo* CNVs have already been observed in 5.8-7.9% of carriers and in 1.7-1.9% of unaffected siblings in simplex families (Levy et al., 2011; Sanders et al., 2011), while *de novo* mutations in coding regions participate in < 20% of cases of ASD (Malhotra & Sebat, 2012). In addition, about 10% of ASD cases with *de novo* CNVs have two or more CNVs (Sebat et al., 2007; Christian et al., 2008; Marshall et al., 2008).

Many of the variations occur in gene regions that contain synaptic genes, and it seems that some involve haploinsufficient regions or dominant inheritance. Others seem to express recessive forms as in the cases of the *NHE926*, *PCDH10* and *DLA1* genes identified in studies of individuals with consanguineous parents. Other rare variations were found deleted in homozygous (Bourgeron, 2009; Ramocki & Zoghbi, 2008; Morrow et al., 2010).

There are descriptions of *de novo* and inherited CNVs, sometimes in combination in a given family, implicating many novel ASD genes such as *SHANK2, SYNGAP1, DLGAP2* and the

X-linked *DDX53-PTCHD1* locus, of an enrichment of CNVs disrupting functional gene sets involved in cellular proliferation, projection and motility, and GTPase/Ras signaling, (Pinto et al., 2010). Another pathway with many of these variations is that related to the development of synapses, and maintenance and motility of neurons, the NLGN-NRXN-SHANK pathway (Bourgeron, 2009).

But, CNVs have been regarded as "rare variants" within the panorama of the etiology of ASD and it is important to emphasize the care that should be taken in associating them in the etiology, especially those not previously described. Accuracy is required in the study of these changes during the formation of control groups. On the other hand, when it comes to autism, on finding the same CNVs in carriers and controls is not a reason to dismiss their participation in the phenotype, given the complexity of factors that may be acting jointly and in combination in different cases.

10. Reduced penetrance and pleiotropic effects

Incomplete penetrance and variable expressivity are discussed greatly in the literature in an attempt to explain the complexity of the biological phenomena involved in ASD (Zhao et al., 2007; State & Levtt, 2011; Coleman & Colbert, 2012).

While some genomic regions seem to play very important roles in predisposition for autism and others not so much, there are some for which there is much divergence in published data. For example, the variations that involve 15q11-13, 16p11.2 and 22q11.2 are among the most commonly found CNVs in patients with autism, however the resulting behavioral phenotype varies from normal to strongly affected (Cook & Scherer, 2008; Adzhubei et al., 2011; Devlin & Scherer, 2012). The explanation for the recurrence of rearrangements in these regions is that they are flanked by low repetition segments containing 99% of the identity, which due to their genomic structure predisposes them to non-allelic homologous recombination and a high mutation rate (Cottrell et al., 2011). However, another four regions in which large deletions are observed (2q22.1, 3p26.3, 4q12 and 14q23) are not flanked by unstable elements and also have a strong potential for involvement in the etiology of autism (Nicholas et al., 2007; Cottrell et al., 2011; Griswold et al, 2011).

With the recent clinical and research use of high resolution array-based strategies for characterizing CNVs in children with developmental disabilities, there has been a significant increase in the diagnosis of interstitial 15q duplications, including small, atypical duplications. The association between ASD and 15q duplications has been described in many case reports since the 1980s and sparked interest in 15q11-13 as a candidate region in autism linkage studies. Prevalence estimates of proximal 15q duplications in cohorts of patients with autism range from 0.5% to 3%, depending on ascertainment criteria and methods used to identify the duplications (Simon et al., 2010). This region contains receptors of an inhibitory neurotransmitter, gamma-aminobuytric acid (GABA) that acts on a complex channel receptor mainly permeable to chloride anions to reduce neuronal excitability. GABA signaling is also

established before glutamatergic transmission suggesting that GABA is the principal excitatory transmitter during early development (Takayama & Inoue, 2004; Ben-Ari et al., 2007).

In multiplex families, i.e. those with more than one affected individual, different individuals have similar microdeletions or microduplications and exhibit autistic, broad or normal phenotypes (Fernandez et al., 2010; Kumar et al., 2008). The microduplication of 15q11-13, which seems to have a major impact on the expression of ASD, is a good example of different effects in carriers. For example, Veltman et al. (2005) reported a female proband referred for evaluation of a possible ASD. Genetic analyses indicated that the proband, her father and one of her sisters, carried a paternally derived interstitial duplication involving 15q11-13. The proband showed evidence of ASD (PDD-NOS), borderline mental retardation, mild hypotonia and joint laxity. Her father and her sister were of normal intelligence and neither was thought to have an ASD, although speech/language difficulties and some autistic type behaviors were reported to have been present early in the development of the sister.

In studies of idiopathic cases, the most common change is the 16p11.2 microduplication/microdeletion, comprising a region of around 600 Kb. Microduplication of 16p11.2 is present in autistic and schizophrenic individuals but is also seen in normal individuals. This variation is also observed in cases of ASD with and without dysmorphic signs (Fernandez et al., 2010; Shinawi et al., 2010). Microdeletions of 16p11.2 seem to be more penetrating (around 100%) and are associated with the presence of major dysmorphic signs, while microduplications have reduced penetrance (~50%) and are associated with minor dysmorphic signs (Ramocki & Zoghbi, 2008; Bourgeron, 2009; Fernandez et al., 2010).

One possible explanation for these cases, as already mentioned in previous sections, is that probably there are other genetic components that are contributing to the disease in these families that, depending on how they are associated in individuals, result in different phenotypes (Griswold et al., 2012). But it is also very likely that different CNVs display different penetrance depending on the sensitivity of the affected gene to dosage (number of copies), the function of the gene and the affected region.

Endophenotypes (or intermediate phenotypes) are defined as heritable traits that form a causal link between genes and observable symptoms. Brain based endophenotypes offer several important advantages over clinical phenotypes in the search for pleiotropic genes in ASD. They provide insight in the causal chains of action leading from gene to symptom expression, they aid in forming etiologically more homogeneous subgroups of patients (Gould & Gottesman, 2006).

In addition to the variability of simple and more complex genetic mechanisms proposed in the expression of the ASD phenotype, environmental factors via epigenetic mechanisms seem to be very important.

11. Epigenetic in autism

Particularly in light of recent findings on mutations in the genes that encode synaptic molecules associated with the communication between neurons, genetic factors are considered to be the most important contributors to the pathogenesis of autism. Epigenetic mechanisms, such as DNA methylation and modifications to histone proteins, regulate DNA structure and gene expression, but without changing DNA sequence. Epigenetic abnormalities are associated with several neurodevelopmental diseases. Many features of autism are consistent with an epigenetic dysregulation, such as discordance of monozygotic twins, parental origin and the gender-dependent effects of some alterations. Since epigenetic modifications are known to be affected by environmental factors such as nutrition, drugs and mental stress, ASD are not only caused by congenital genetic defects, but may also be caused by environmental factors via an epigenetic mechanism.

An example of this phenomenon in ASD is the mechanism of action of the *SHANK3* gene. *SHANK3* is strongly suspected of being involved in the etiology of ASD since several mutations have been identified in a particular phenotypic group of patients with ASD. SHANK3 (also known as *ProSAP2*) regulates the structural organization of dendritic spines and is a binding partner of neuroligins; genes encoding neuroligins are mutated in autism and Asperger's syndrome (Durand et al., 2007). It codes a synaptic scaffolding protein enriched in the postsynaptic density of excitatory synapses and plays important roles in the formation, maturation and maintenance of synapses. Haploinsufficiency of the *SHANK3* gene causes a developmental disorder, 22q13.3 deletion syndrome (known as Phelan-McDermid syndrome), which is characterized by severe language and speech delay, hypotonia, global developmental delay and autistic behavior. Five CpG-islands have been identified in the gene, and tissue-specific expression is epigenetically regulated by DNA methylation. Cumulative evidence in animal models has shown that several *SHANK3* variants are expressed in the developing rodent brain with their expression being regulated by the DNA methylation of intragenic promoters (Uchino et al., 2006).

Additionally, oxidative stress in brain cells occurs due to environmental and genetic causes and leads to decreased activity of the methionine synthase enzyme, which participates in DNA methylation processes. So, when the activity of this enzyme is impaired, affected individuals can exhibit attention deficits and other signs, including autistic symptoms, due to defects in the expression of genes that are controlled by this epigenetic mechanism (Naviaux, 2008; Dhillon et al., 2011).Therefore, environmental factors may activate intracellular pathways during embryonic development thereby causing epigenetic changes in neural function that would explain the relationship between environmental signals and genome in the regulation of individual differences in behavior (Zhang & Meaney, 2010).

Studies carried out in Sweden involving 208 autistic children with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) and Asperger's syndrome (AS) obtained interesting results. The authors observed that advancing paternal age is associated with an increasing risk for ASD in offspring, that autistic-like traits in the normal population are affected by both young and advancing paternal age and that autistic similarity within pairs

of twins seems to increase with advancing paternal age. It was suggested that this result may be related to factors such as *de novo* mutations in germ lines, exposure to toxic agents during life and epigenetic alterations (Lundstrom et al., 2010; Hultman et al., 2011). Advancing maternal age was also reported as a risk factor for autism (Parner et al., 2012). However, the explanations for these phenomena are still only speculative.

12. Exome sequencing

The development of the next generation sequencing has radically modified the scientific landscape, making it possible to sequence all exomes of any person. The power of this approach has been demonstrated by a number of studies which have identified pathogenic mutations in diseases that have been difficult to make by traditional genetic mapping.

Exons are coding regions of the genome responsible for the development of functional elements of the body, such as proteins. It has become clear that exome sequencing has great potential with respect to sporadic diseases and the identification of *de novo* mutations. Whole-exome sequencing (WES) of patient-parent trios has proven to be a successful screening tool for the identification of candidate genes causing complex phenotypes such as in ASD, learning disability, and schizophrenia (Choi et al., 2009; Bilguvar et al., 2010; Vissers et al., 2010; Gilman et al., 2011; Pagnamenta et al., 2012; Sanders et al., 2012).

O´Roak et al. (2012) studied all coding regions of the genome for parent-child trios exhibiting sporadic ASD, under the hypothesis that *de novo* mutations underlie a substantial fraction of the risk for developing ASD in families with no previous history of ASD or related phenotypes (simplex families). They observed that these mutations are overwhelmingly paternal in origin and positively correlated with paternal age, consistent with the modest increased risk for children of older fathers. It was also possible to estimate 384-821 loci which could be considered pathogenic.

The analysis the homozygosity is used to define loci that may be involved in recessive homozygous mutations that cause diseases characterized by genetic heterogeneity (Lencz et al., 2007; Nalls et al., 2009). Starting from this concept, Chahrour et al. (2012) used homozygosity analysis to identify probands from non-consanguineous families that showed evidence of distant shared ancestry, suggesting potentially recessive mutations. The WES of 16 probands revealed validated homozygous, potentially pathogenic, recessive mutations that segregated perfectly the disease in 4 of 16 families. The candidate genes that were found, *UBE3B, CLTCL1, NCKAP5L,* and *ZNF18,* encode proteins involved in neuronal activities.

Neale et al. (2012) studied 175 trios to assess *de novo* mutations. They found strong evidence that *CHD8* and *KATNAL2* are genuine autism risk factors. However, the small increase in the rate of *de novo* events, when taken together with the protein interaction results, were consistent with an important but limited role for these mutations in ASD, similar to that documented for *de novo* CNVs. According the authors, the data indicated that most of the observed *de novo* events are unconnected to ASD; those that do confer risk are distributed

across many genes and are incompletely penetrant. The results support polygenic models in which spontaneous coding mutations in any of a large number of genes increases risk by 5- to 20-fold.

Iossifov et al. (2012) did not find significantly greater numbers of *de novo* missense mutations in ASD children versus unaffected, but gene-disrupting mutations (nonsense, splice site and frameshifts) were twice as frequent in the first group. Based on this differential and the number of recurrent and total targets of gene disruption they estimated between 350 and 400 autism susceptibility genes. Many of the genes are associated to the FMRP protein, reinforcing links between autism and synaptic plasticity. They suggested that genes associated to *FMRP* are especially targets of cognitive disorders that are dosage-sensitive.

Another aspect of exomes should also be considered. Mitochondria are cellular organelles that function to control energy production necessary for brain development and activity. Although each individual is typically characterized by a single mitochondrial DNA type, the fact is that each individual is a population of mitocondrial DNA genomes, and the presence of multiple types within an individual is termed heteroplasmy. Although each individual is typically characterized by a single mitocondrial DNA type, in fact to date, more than 400 mitochondrial mutations have been associated with human disease and most were observed in heteroplasmic states, with pathogenic mutations coexisting with normal mitochondrial genomes. This suggests that the heteroplasmic level is of particular interest, as the disease phenotype becomes evident only when the percentage of mutant molecules exceeds a critical threshold value. Although this value differs for different mutations and in different tissues, it is usually in the range of 70%~90%. However, all the various techniques that have been employed to detect heteroplasmy have disadvantages. WES allows rapid detection of not only nuclear mutations but also mitochondrial mutations that also seem to be involved in the etiology of ASD. In this context, Li et al. (2012) sequenced the mitochondrial genome of 131 healthy individuals of European ancestry. In 32 individuals they identified 37 heteroplasmies at frequencies of 10% or higher at 34 different sites in the mitochondrial DNA indicating that variations commonly occur in mitochondrial DNA. These variations may impact on energy levels and influence brain development and function. Next generation sequencing should provide novel insights into genome-wide aspects of variation or heteroplasmy useful in the study of human disorders including autism.

All these results show that there are a lot of regions/genes being identified by very advanced methods, but no common etiology can be proposed. It is clear that whatever the proposed model to explain ASD, all aspects such as environmental, oligogenic, *de novo* mutations, polygenic, multifactorial, pleiotropic effects, combination of locus heterogeneity, heteroplasmy, among others, do not apply to all cases. Perhaps ASD emerge due to highly specific and individual biological patterns. The possibility of distinguishing primary and secondary effects will require a better understanding of the underlying biology and identification of the association between genetic and environmental factors within the phenotypic context of each family. The bottom line is that you must have a systemic view of the problem.

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13. Conclusion

Knowledge about the biological mechanisms involved in the etiology of ASD has increased significantly over the past three years. A genetic etiology of these disorders is certain, as certain as is their complexity. An understanding of the genetic factors involved is crucial to establish future intervention strategies. Although the current emphasis on deciphering ASD has demonstrated the necessity of multidisciplinary approaches, clinical geneticists have an important role in diagnosis and research of autism. The interpretation of this new genetic data requires a set of skills. It is important to know how to get and to interpret genetic tests, family pedigrees, to analyze dysmorphic, neurologic, and medical phenotypes, to interpret heterogeneity, develop rational genetic models, and to design researchs.

Despite the numerous known or, at least, allegedly involved causes of predisposition for ASD, the etiology is identified in a few cases (~ 10%) thereby highlighting the importance of genetic testing in affected individuals. The discovery of an etiological agent in a given case will, very probably, not interfere in treatment. However, this will reduce the distress of parents by explaining the cause of the problem and clarify about the possibility of familial recurrence. On identifying the etiologic agent, genetic counseling can be better targeted. Thus, a clinical-genetic evaluation of the patient is important as are the karyotypic analysis, molecular test for FRAXA, the investigation of inborn errors of metabolism, performing imaging tests and multiplex ligation-dependent probe amplification (MLPA) for at least three hot spots in ASD (15q11-13, 16p11.2 and 22q11.2). These are strategies available to better assess the etiology ASD. Certainly, in the not too distant future, other more sophisticated genetic research tools will be commercially available. The question that remains is whether the interpretation of results will accompany the speed of technical advances.

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