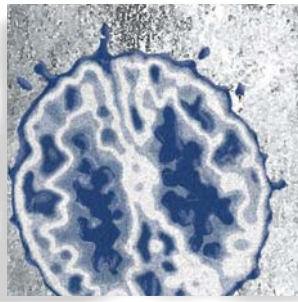


# Translational research

## *Multiple rare variants in the etiology of autism spectrum disorders*

Joseph D. Buxbaum, PhD



*Recent studies in autism spectrum disorders (ASDs) support an important role for multiple rare variants in these conditions. This is a clinically important finding, as, with the demonstration that a significant proportion of ASDs are the result of rare, etiological genetic variants, it becomes possible to make use of genetic testing to supplement behavioral analyses for an earlier diagnosis. As it appears that earlier interventions in ASDs will produce better outcomes, the development of genetic testing to augment behaviorally based evaluations in ASDs holds promise for improved treatment. Furthermore, these rare variants involve synaptic and neuronal genes that implicate specific pathways, cells, and subcellular compartments in ASDs, which in turn will suggest novel therapeutic approaches in ASDs. Of particular recent interest are the synaptic cell adhesion and associated molecules, including neurexin 1, neuroligin 3 and 4, and SHANK3, which implicate glutamatergic synapse abnormalities in ASDs. In the current review we will overview the evidence for a genetic etiology for ASDs, and summarize recent genetic findings in these disorders.*

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### Autism spectrum disorders

**A**utism, also referred to as autistic disorder (designated as OMIM #209850, by Online Mendelian Inheritance in Man, an online database of human genes and genetic phenotypes), is a developmental neuropsychiatric disorder that was first described in 1943 by Dr Leo Kanner.<sup>1</sup> DSM-IV (*Diagnostic and Statistical Manual, 4th Edition*, American Psychiatric Association), or similar criteria are used for diagnosis of autism and other disorders in this spectrum, referred to as the pervasive developmental disorders (PDD). DSM-IV criteria for autism include onset by age 3, impairments in social interaction and in social communication, as well as repetitive and stereotypic patterns of behaviors or restricted interests. Asperger syndrome represents a higher-functioning form of ASD. Pervasive developmental disorder-not otherwise specified (PDD-NOS) also involves deficits in all three domains (social interaction, social communication, characteristic behaviors/interests), but the deficits do not reach threshold criteria for an autism diagnosis. In this review, Asperger syndrome,

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## Selected abbreviations and acronyms

<b>ASD</b>	<i>autism spectrum disorders</i>
<b>CV</b>	<i>common variant</i>
<b>RV</b>	<i>rare variant</i>
<b>OR</b>	<i>odds ratio</i>
<b>CNV</b>	<i>copy number variant</i>

and PDD-NOS will be referred to collectively as autism spectrum disorders (ASDs).

## Epidemiological twin studies of ASDs

ASD twin studies have shown that the concordance rate for monozygotic (MZ) and dizygotic (DZ) twins ascertained for ASD differed substantially, with an MZ:DZ ratio of approximately 10 to 1.<sup>2-5</sup> In these studies, estimates of heritability (ie, the proportion of the variance explained by genetic causes) in ASDs were above 93%, with little or no evidence for shared or nonshared environmental factors. These conclusions agree with multiple, independent family studies, which show a very strong aggregation of ASDs within families, consistent with a genetic etiology for ASDs, with little support for environmental factors (eg, ref 6). Note, however, that risk for ASD is not transmitted in a simple manner. This is exemplified both in the family studies (eg, ref 6) and in the genetic conditions that can result in an ASD diagnosis, which are typically non-Mendelian and include X-linked inheritance, de novo mutations, and chromosomal alterations, as well as transmission of unbalanced translocations (see below).

## Common variant and multiple rare variant hypotheses

In common genetic diseases, such as ASDs, there have been two models for genetic etiology, which are not necessarily mutually exclusive. These are the common disease/common variant (CD/CV) and the common disease/rare variant (CD/RV) models (the latter is also called the multiple rare variant/MRV model).<sup>7-10</sup> CVs are genetic variants that are found to be more widely distributed in the population and are associated with a modest increase in risk, and typically associated with odds ratios (ORs) less than 2 and often with ORs in the 1.1-1.3 range. The interaction of a CV with other CVs and with other factors can act together to increase risk. In contrast, in the MRV model a large number of rare, and

even very rare, variants underlie the disorder. These RVs are typically associated with ORs that can be quite substantial, and may contribute the major part of the susceptibility for a given individual. At the extreme, RVs have high ORs and are equivalent to rare deleterious mutations. Population attributable risk (PAR, ie, the proportion of disease in a population that can be attributed to a given etiological agent) can be quite high for CVs, irrespective of their lower ORs, as the variants are more widespread, while RVs, even with high ORs, will have a low PAR when considered individually. With MRVs, PAR becomes significant when considering the RVs together. CVs and RVs will be treated very differently in the clinical setting, and also require alternative approaches for their discovery.<sup>9</sup> For these reasons, understanding which mechanism(s) underlie a given disease entity can have important ramifications. The CD/CV hypothesis had been challenged from a population genetic perspective<sup>7,8,10</sup> and, as we will note below, there was and is increasing evidence that ASDs can result from RVs, leading to a MRV model to explain much of the ASD risk.

## Methods for identifying genetic loci for ASDs

Genomic variations leading to large-scale deletion and duplications associated with ASDs were first identified by karyotyping (eg, ref 11). More recently, the use of genome-wide arrays to query for copy number variants (CNVs) has identified additional genomic variations associated with ASDs (see below). As these methods evolve and their resolution increases, additional genomic imbalances associated with ASD will certainly be identified. Similarly, the search for both single-base RVs and CVs in disease has also been profoundly affected by the evolution of technology. In the past, such studies focused on CVs or RVs in candidate genes, identified based on biological grounds and/or positional information following linkage analyses (eg, ref 12). With the evolution of genome-wide single-nucleotide polymorphism (SNP) genotyping, the focus on CV SNPs that increase risk for disease has shifted to genome-wide association analyses (GWAS). Similarly, with the development of high-throughput sequencing, hundreds of genes can be sequenced for RVs in ASDs. In the following sections, we will review RVs associated with ASDs, including genetic conditions, CNVs, and mutations (*Table I*).

## Genetic conditions associated with ASDs

A variety of genetic conditions, of which most can be syndromic (ie, associated with recognizable clinical signs, including dysmorphic, metabolic, or neurological features) can present with ASDs. These include 15q11-13 duplications, 22q11 deletion/DiGeorge syndrome, 22q11 duplication syndrome, 22q13 deletion syndrome, adenylosuccinate lyase deficiency, Angelman syndrome (AS), Cohen syndrome, Down syndrome, Fragile X syndrome, *MECP2*-related disorders, neurofibromatosis, untreated phenylketonuria, Potocki-Lupski syndrome, Prader-Willi syndrome (PWS), *PTEN*-associated syndromes, San Filippo syndrome, Smith-Magenis syndrome, Smith-Lemli-Opitz syndrome, Sotos syndrome, tuberous sclerosis, and Williams syndrome.<sup>13-17</sup> For individuals with these syndromes, a proportion of cases can have an ASD diagnosis<sup>18,19</sup> and for some of these conditions, there have been examples of individuals identified with a primary diagnosis of ASD, and only later was the syndrome identified (that is to say that a proportion of individuals with assessed with idiopathic ASDs may have some of these

conditions, perhaps without a typical syndromal presentation).

In some cases, the genetics of the ASD-associated syndrome is well understood. Fragile X syndrome (FXS), caused by a trinucleotide repeat expansion in the fragile X mental retardation 1 (FMR1) gene at Xq27.3, is among the most common syndromes associated with ASDs. Among individuals with FXS, ASD symptoms occur in one quarter to one third of subjects,<sup>20,21</sup> while the prevalence of FXS is estimated to be 2% among individuals identified with an ASD. AS and PWS, as well as 15q11-13 duplications, collectively are also common ASD-associated syndromes, of which each has different molecular etiology.<sup>15,22,23</sup> Rett syndrome, listed among the PDDs in DSM-IV, is caused by mutation in the gene encoding methyl-CpG-binding protein-2 (*MECP2*) and a proportion of girls identified with an ASD are found to have Rett syndrome.<sup>24</sup>

## Novel CNVs associated with ASDs identified by genome-wide scanning

### Novel CNVs in ASDs

Whole genome scans for CNVs use genome-wide array-based methods to search for deletions and duplications. This approach complements karyotyping and targeted methods such as fluorescence in situ hybridization (FISH).<sup>25</sup> There have been several such studies in idiopathic ASDs in the past year,<sup>26-31</sup> along with additional such studies in syndromal ASDs.<sup>32</sup> Several general findings are worth noting (see ref 33 for a more detailed summary). First, there are increased rates of de novo CNVs in ASDs, particularly in simplex families, reaffirming what was clear from medical conditions associated with ASDs, ie, that de novo changes are significant factors in ASD. Second, there appear to be increases in the numbers of de novo CNVs in the syndromal cases. Third, amongst inherited CNVs, there were individuals (parents or sibs) with the CNV without an apparent diagnosis, consistent with variable expressivity of many known genetic disorders. There were even families where a likely causal CNV was found in one affected child but not in another, suggesting independent etiologies. Finally, there were some CNVs that were recurrent (see below) but there were some CNVs that appeared likely to be etiologically significant but that were identified only once. Algorithms are being developed by molecular cyto-

Genetic etiology	Estimated prevalence in ASD
Karyotype abnormalities	5-10%
Fragile X syndrome	2%
15q abnormalities	2%
Tuberous sclerosis	1%
16p11 deletions	1%
22q13 deletions/ <i>SHANK3</i> abnormalities	0.75%
22q11 abnormalities	0.50%
Rett syndrome	0.10%
<i>c30rf58</i> deletions, homozygous	Rare
<i>CNTN4</i> deletions	Rare
<i>DPP10</i> deletions	Rare
<i>DPP6</i> deletions	Rare
<i>NHE9</i> deletions, homozygous	Rare
<i>NLGN</i> deletions/mutations	Rare
<i>NRXN1</i> deletions	Rare
<i>PCDH10</i> deletions, homozygous	Rare
<i>PCDH9</i> deletions	Rare
<i>PTEN</i> mutations	Rare

**Table 1.** Multiple rare variants in autism spectrum disorders (ASDs). While epidemiologically rigorous studies have yet to be carried out, there are reasonable estimates for the prevalence of some of the genetic contributors to ASDs. Some of the more common ones are shown here, together with some of the rare variants identified in recent studies.

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neticists to weight such nonrecurrent CNVs to estimate the likelihood that they are etiologically relevant, considering such factors as size of the CNV, whether it is a deletion or duplication, de novo or inherited origin, gene content, and overlap with known genetic disorders.

## ***CNTN4***

Disruption of *CNTN4*, coding for the CAM contactin 4 which is involved in the formation, maintenance, and plasticity of neuronal networks, has been shown to be a likely cause for cognitive aspects of 3p deletion syndrome, which presents with developmental delay.<sup>34-36</sup> Recently, deletions in cases with idiopathic ASDs indentified CNVs at the *CNTN4* locus in two unrelated individuals.<sup>37</sup>

## ***NRXN1***

The first large, genome-wide SNP microarray study (using earlier generation arrays and hence just 10 000 SNPs) was conducted in over 1000 ASDs families by the Autism Genome Project (AGP) Consortium.<sup>27</sup> With stringent filtering, a total of 254 CNVs were identified as being most relevant to ASD. The AGP identified two female sibs with ASD harboring identical de novo deletions at 2p16, over a portion of the neurexin 1 (*NRXN1*) gene. Additional groups have since confirmed a role for *NRXN1* deletions in ASD.<sup>31,38-41</sup> Neurexins function in the vertebrate nervous system as CAMs with critical roles in synaptogenesis and bind to neuroligins, which represent another family of ASD genes (see below).

## **16p11 CNVs**

Another interesting CNV in ASD is in the 16p11 region, which occurs in up to 1% of subjects with ASDs. First reported in the studies by Sebat et al<sup>26</sup> and Christian et al,<sup>28,29</sup> this CNV was also identified in a screen by Weiss et al,<sup>30</sup> in which they investigated 751 multiplex ASD families using 500 000 SNP markers and found a recurrent 16p11 deletion (note that some of these studies relied in part on the Autism Genetic Resource Exchange (AGRE) collection and were hence not fully independent) The CNV has recurrent break points defined by low copy repeats and includes ~30 genes, and multiple studies are being carried out in multiple labs to understand whether this represents a contiguous gene syndrome or whether one or two genes in the interval are responsible for the phenotype.

## **The synaptic genes *DPP6*, *DPP10*, and *PCDH9***

An additional SNP microarray study using 500 000 SNP markers investigated 427 ASD families.<sup>31</sup> This study described many potentially interesting CNVs (277 CNVs in 44% of ASD families) (including the 16p11 deletion). Genes within those CNVs included the synaptic genes *SHANK3*, *NLGN4*, and *NRXN1* (see above and below) and additional synaptic genes, including *DPP6*, *DPP10*, and *PCDH9*. The dipeptidyl peptidases (DPP) *DPP6* and *DPP10*, which actually lack DPP activity and have therefore been proposed to be renamed DPP-like, complex with Kv4 potassium channels and potassium-channel interacting proteins (KChIPs) to regulate channel activity.<sup>42</sup> *DPP6* and *DPP10* are hence important regulators of neuronal excitability, particularly as related to the regulation of firing frequency, integration of signal across dendrites, and neuronal plasticity. *PCDH9* codes for protocadherin 9, a member of the cadherin family of homotypic CAMs, which shows localized expression in particular cortical and thalamic regions in development.<sup>43</sup>

## **Homozygous deletions in *PCDH10*, *DIA1*, and *NHE9***

Recently, homozygosity mapping was used to identify a novel large homozygous deletion at 3q24 implicating the *c3orf58* locus (or deleted in autism 1, *DIA1*), which encodes a protein localized to the Golgi apparatus, and a homozygous deletion at 4q28 implicating the protocadherin 10 (*PCDH10*) locus,<sup>44</sup> which encodes a cadherin superfamily protein essential for normal forebrain axon outgrowth.<sup>45</sup> Gene expression studies in rat neurons showed that expression of these genes is regulated by neuronal activity and hence may be involved in synaptic changes related to learning. A gene adjacent to *DIA1*, the Na<sup>+</sup>/H<sup>+</sup> exchanger 9 (*NHE9*) encoding a membrane protein that exchanges intracellular H<sup>+</sup> for extracellular Na<sup>+</sup>, was identified with a loss-of-function mutation in autism patients with unrelated parents.

## **Novel mutations associated with ASDs**

### ***SHANK3***

The 22q13 deletion syndrome is characterized by global developmental delay, hypotonia, delayed or absence of speech, normal to accelerated growth and head circum-



ference, mild dysmorphic face, and ASD-like behaviors,<sup>46</sup> and there is good evidence, based on the presence of a recurrent breakpoint, that *SHANK3* is the critical gene in this syndrome.<sup>47</sup> A recent study asked whether mutations in *SHANK3* or chromosomal changes at the *SHANK3* locus were directly associated with idiopathic ASDs, making use of FISH analysis and/or direct sequencing in about 300 cases.<sup>48</sup> The study identified three families with ASD that showed alterations: a family with a proband carrying a de novo deletion in intron 8, removing 142 kb of 22q13; a family with two affected brothers with a nucleotide insertion, creating a frameshift that modified the C-terminal sequence of the protein (derived from germline mosaicism in the mother); and, a family with both monosomy (resulting in autism) or trisomy of 22q13 (resulting in Asperger syndrome) in affected siblings, both arising from a paternal translocation. A subsequent study found one de novo *SHANK3* mutation and two 22q13 deletions in 400 ASD subjects (and an additional deletion in a different cohort).<sup>49</sup> As in the first study, one deletion arose from a paternal translocation, resulting in a child with monosomy at the *SHANK3* locus and a child with trisomy at this locus. The monosomy was associated with autism, while the monosomy was associated with attention-deficit hyperactivity disorder (ADHD). A recent study found one de novo deletion and one missense change (the latter transmitted from a father with epilepsy) in 427 ASD cases.<sup>50</sup> CNVs at the *SHANK3* locus have also been identified in the genome-wide studies noted above.<sup>31</sup> Altogether, these results indicate that haploinsufficiency of *SHANK3* can cause a monogenic form of ASD with frequency of about 0.5% to 1% of ASD cases. Furthermore, trisomy at this locus appears to result in less severe phenotypes, including Asperger syndrome and ADHD.

*SHANK3* is a synaptic scaffolding protein that is abundant in the postsynaptic density (PSD). It has multiple protein interaction domains, interfacing between glutamate (and likely other) receptor complexes and actin regulatory proteins, and therefore appears to be well suited to playing a role in spine morphogenesis and synaptic plasticity.<sup>51,52</sup> When overexpressed in cultured hippocampal neurons, *SHANK3* promoted the enlargement of dendritic spines,<sup>53</sup> while disruption of the related *Shank1* in mice led to smaller dendritic spines and reduced synaptic transmission, along with altered cognitive processes.<sup>54</sup> Dramatically, expression of *SHANK3* in aspinny cerebellar neurons promoted spine formation and

the recruitment of glutamate receptors to the synapse, directing implicating *SHANK3* in the formation and function of glutamatergic synapses.<sup>55</sup>

### *NLGN3/4*

Neuroligins (NLGNs), which are *SHANK3*- and *NRXN1*-interacting proteins, are postsynaptic CAMs that support synapse—including glutamatergic synapse—formation. There are five homologs in the human genome, with *NLGN3* and *NLGN4X* found on the X-chromosome (at Xq13 and Xp22.3, respectively), and *NLGN4Y* on the Y chromosome. Screening for mutations in these genes in over 150 cases led to the identification of two de novo mutations, including a frameshift mutation in *NLGN4* and a C-T transition in *NLGN3* that led to a R451C change.<sup>56</sup> In another study, a mutation in *NLGN4* that leads to a premature stop codon was found in a large pedigree.<sup>57</sup> While the mutation had very high penetrance, expressivity was variable with the 10 males having mental retardation (MR) and/or ASD. *NLGN4* deletions in ASDs were observed in one recent study,<sup>31</sup> but other studies have suggested that *NLGN4* deletions can be associated with little or differing psychiatric phenotypes in some males, including tics, Tourette syndrome, and ADHD.<sup>58-60</sup> A recent study suggests that mutations in *NLGN4Y* might also result in an ASD.<sup>34</sup> Disruption of *Nlgn4x* in mice leads to deficits in reciprocal social interactions and communication.<sup>61</sup> It has been reported that introducing the R451C mutation in murine *Nlgn3* was reported to result in impaired social interactions with an increase in inhibitory synaptic transmission<sup>62</sup>; however, these behavioral deficits were not seen in an independent study.<sup>63</sup>

### *CNTNAP2*

Cortical dysplasia-focal epilepsy syndrome was first described in 2006 in Amish children displaying cortical dysplasia, focal epilepsy, relative macrocephaly, diminished deep-tendon reflexes, language regression, MR, and ASD.<sup>64</sup> The disorder is recessive and caused by mutations in the *CNTNAP2* gene, which codes for contactin-associated protein-like 2 (CASPR2) that is involved in localization of voltage-gated potassium channels (K(v)1.1) at the juxtaparanodes of the nodes of Ranvier. Three recent studies assessed this gene in ASDs. First, following up on a linkage result of a language-related autism QTL, it was

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suggested that common variants of *CNTNAP2* may increase risk for ASDs in male-only families, and it was shown that *CNTNAP2* is expressed in language- and cognition-related circuits.<sup>65</sup> This finding was also observed in a related study using overlapping AGRE families.<sup>66</sup> Finally, rare variants of the *CNTNAP2*, and particularly the I869T variant, also show some association with ASD.<sup>67</sup>

## *PTEN*

Our own studies on *PTEN* mutations in ASD can serve to highlight the clinical value of identifying mutations in ASD.<sup>68</sup> Mutations in the *PTEN* gene are associated with a broad spectrum of disorders, including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Lhermitte-Duclos disease, as well as ASDs (reviewed in ref 68). We surveyed head circumference information from hundreds of subjects with ASD and sequenced the *PTEN* gene in 88 individuals showing macrocephaly (defined as a head circumference  $\geq 2$  standard deviations above the mean). We identified a de novo missense mutation (D326N) in a highly conserved amino acid in a 5-year-old boy with autism, MR, language delay, and extreme macrocephaly (+9.6 SD). The identification of this mutation can give important information to the family with regard to recurrence risk, and also improve the care of the affected boy because an appropriate surveillance strategy for *PTEN*-mutation-related conditions can be initiated.

## Etiological yield in ASDs

The importance of evaluating ASD-associated syndromes in the clinical context needs to be emphasized. A recent study used a three-tiered neurogenetic evaluation scheme to evaluate 32 patients with a behavioral diagnosis of an ASD. An overall medical and/or genetic diagnostic yield of 40% was found,<sup>69</sup> although more typical studies have a lower yield (see above) and no published study has done this with modern molecular methods with an epidemiological valid cohort. As our knowledge increases and methods further evolve, it will become straightforward to carry out a comprehensive scan for genetic disorders in ASD, facilitating diagnosis, identifying medical concerns associated with syndromes, and defining subgroups that might be more responsive to specific therapeutic approaches (see below).

## Conclusions

There is overwhelming evidence that ASDs are genetic disorders, but the genetic mechanisms are varied, involving both inherited and de novo changes, as well as mutations, trinucleotide repeats, CNVs, and larger chromosomal abnormalities. An increasing proportion of ASD is being recognized as being the result of RVs associated with high ORs.

*Table 1* summarizes estimates the prevalence of some genetic variants in subjects ascertained for ASDs. Note that an additional 5% to 10% of cases have been identified with CNVs that are not recurrent but are likely pathogenic (based on size, de novo origin, etc). This suggests that, even with our current knowledge, 20% to 30% of ASDs can be given an etiological diagnosis using standard clinical genetic methods, including high-resolution karyotyping, array comparative genomic hybridization (array CGH), and *MECP2* sequencing in girls,<sup>70,71</sup> as well as *PTEN* sequencing in individuals with extreme macrocephaly<sup>68</sup> and the examination of methylation and gene dosage abnormalities in 15q.<sup>72</sup>

It is of interest that synaptic and neuronal cell adhesion molecules (CAMs) are appearing in RVs in ASDs. It is also of interest that cytoplasmic proteins that bind to synaptic CAMs are also being identified. These findings will lead to evidence-based hypotheses as to the molecular and cellular deficits underlying ASDs with differing etiologies. Of particular interest is the replicated finding of *SHANK3* deficits, which directly implicates glutamatergic synapse dysfunction in both autism and Asperger syndrome. This finding is supported by the replicated findings with *NRXN1* and *NLGN3/4*, which can also play a role in excitatory synapse formation, maintenance, and plasticity.

As the technology for detecting smaller and smaller deletions and duplications improves and as people take advantage of the newest technologies of ultradeep sequencing, the search for RVs in ASDs will enter a new phase. In this context, a useful model for the genetic and genomic architecture of ASD might be that of MR. In MR several hundred genes have been found and the evidence is strong that there are more genes to be found. Not only are some of the MR genes associated with ASDs, but as we discover more and more rare variants in autism, it is becoming increasingly clear that the architecture of MR could represent a good model as to what we will find in ASDs.

There is empirical evidence that ASD can, in some cases, respond to intensive behavioral interventions.<sup>73</sup> Thus, identifying individuals with greater risks of ASD at an earlier age will have important clinical and practical implications. It will require the simultaneous analysis of multiple genetic and genomic mechanisms before effective tools for the molecular assessment of ASD etiology, used in conjunction with behavioral assessment, can be applied in a widespread manner.

As ASD loci continue to be identified, animal models that recapitulate the genetic change(s) can be developed. These models can clarify the function of the gene products *in vivo*, and will ultimately be useful to evaluate novel pharmaceutical interventions. An exciting development which will serve as a useful model going forward

is the elaboration of the mGluR theory of FXS.<sup>74</sup> This in turn has led to the initiation of a recent large-scale clinical trial in FXS in which a reverse agonist of mGlu5 is being assessed in FXS. As additional RVs associated with ASDs are identified, novel therapeutic approaches will arise, some which may be specific to a given RV (“personalized medicine”) and some that might prove effective across ASDs with differing etiologies. □

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## Múltiples variantes raras en la etiología de los trastornos del espectro autista

Los estudios recientes en los trastornos del espectro autista (TEA) refuerzan el importante papel que tienen múltiples variantes raras en estos cuadros. Este es un hallazgo clínicamente importante, ya que con la demostración de que un porcentaje significativo de TEA son el resultado de una etiología de variantes genéticas raras, puede llegar a ser posible el empleo de pruebas genéticas como complemento al análisis de la conducta para un diagnóstico más precoz. Ya que se ha observado que las intervenciones más precoces en los TEA generan mejores evoluciones, el desarrollo de pruebas genéticas complementarias a las evaluaciones basadas en la conducta en los TEA promete un mejor tratamiento.

Además estas variantes raras comprenden genes sinápticos y neuronales que incluyen vías específicas, células y compartimentos subcelulares en los TEA, lo que a la vez sugiere nuevas aproximaciones terapéuticas en los TEA. Recientemente ha tenido un especial interés la adhesión celular sináptica y las moléculas asociadas, que incluyen la neurexina 1, las neuroliginas 3 y 4, y SHANK3 lo que se traduce en alteraciones de la sinapsis glutamatérgica en los TEA. En este artículo se revisa la evidencia de la etiología genética para los TEA y se resumen los hallazgos genéticos recientes en estos trastornos.

## Étiologie des troubles autistiques : beaucoup de variants rares

Les études récentes plaident en faveur de l'existence de nombreux variants rares dans les troubles du spectre autistique (TSA). Ce résultat est cliniquement important car si une proportion significative de TSA provient de variants génétiques étiologiques rares, il devient possible d'utiliser des tests génétiques pour éviter les analyses comportementales pour effectuer un diagnostic plus précoce. Comme il semble qu'intervenir tôt dans les TSA donne des évolutions plus favorables, le développement de tests génétiques pour enrichir les évaluations basées sur le comportement permet d'espérer un traitement meilleur. De plus, ces variants rares portent sur des gènes synaptiques et neuronaux qui concernent des voies, des cellules, et des compartiments sous-cellulaires spécifiques des TSA, suggérant en retour de nouvelles approches thérapeutiques référencées dans ce domaine. Les molécules d'adhésion cellulaire synaptique et associées, (comme la neurexine 1, les neuroliginas 3 et 4 et SHANK3) qui impliquent les anomalies glutamatergiques de la synapse dans les TSA, sont particulièrement intéressantes selon des données récentes. Dans cet article, nous allons donner une vue d'ensemble des arguments en faveur d'une étiologie génétique des TSA et nous résumerons les résultats génétiques récents les concernant.

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