Mini Review

Genetic basis of autism spectrum disorder

Abstract

Autism Spectrum Disorder (ASD) comprises a wide range of neuro-developmental disorders characterized by difficulties with social communication and interaction, as well as restricted and repetitive patterns of behavior, interests and activities. It has a number of symptoms including cognitive, behavioral, and sensory symptoms. In addition, sleeping and eating difficulties, synesthesia as well as dysregulation and difficulty with initiation, planning and organization of tasks, are present. The identification of chromosomal abnormalities and Mendelian syndromes among individuals with Autism, along with linkage data from genome screens and candidate-gene studies, has helped delineate the complicated genetics that underlies Autism Spectrum Disorder.

Keywords: genetic, autism spectrum disorder, genetic mutations, chromosomal microarrays

Literature survey

The greatest progress in the discovery of genetic causes of Autism is from identification of genetic mutations and disorders that can predispose to Autism. Using standard evaluation techniques such as the use of chromosomal microarrays (CMAs), a genetic cause can be identified in 20-25% of children in the Autism spectrum. A small number of cases have been discovered by tracing exposure to specific teratogens. For the remaining 75-80% of the cases, the causes remain unknown. Medical Genetics clinics have found the highest percentage of disorders, whereas specialized Autism clinics have found the lowest. The Genetic Association Database provides online access to genetic data for Autism and other disorders. Many reviews of the current status of candidate genes and loci are available. SFARIGENE is a new web-based search engine for genetic, autism spectrum disorder, genetic mutations, chromosomal microarrays acting synergistically with other genes.

Table 1 lists some of the known Autism-related genes organized by pathogenesis of the disease. Particularly interesting are the synaptic cell adhesion molecules such as Neurexin 1, Neuroligin 3 and 4, and SHANK3, which implicate Glutamnergic synapse abnormalities with ASD. Mutations in the X-linked Neuroligin-3 (NLGN3) and Neuroligin-4 (NLGN4X and NLGN4Y) genes have been linked to Autism. Laumonnier et al. have identified a two base-pair deletion in NLGN4 in members of a French family exhibiting X-linked mental retardation. Jamain et al. identified a C-to-T transition in the NLGN3 gene in two siblings, one with autism and the other with Asperger Syndrome. People suffering from ASD and carrying mutations in NLGN4 and NLGN3 are typically non-dysmorphic. Genetic testing of NLGN4 and NLGN3 is important in families suspected of having X-linked Autism. The SHANK3 gene is crucial for the development of language and social cognition. SHANK3 mutations and small cytogenetic rearrangements have been implicated with ASD. In addition, SHANK3 mutations have been found in Attention Deficit Hyperactivity Disorder (ADHD) and language disorders; suggesting that they may cause disease by acting synergistically with other genes.

Table 1 Some of the known Autism-related genes

<table>
<thead>
<tr>
<th>Protein name (Function)</th>
<th>Gene/Locus</th>
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<tbody>
<tr>
<td>Neuronal cell adhesion and/or synapse function</td>
<td></td>
</tr>
<tr>
<td>Neurolgin 3 (synapse formation and function)</td>
<td>NLGN3X Xq28</td>
</tr>
<tr>
<td>Neuroligin 4 (synapse formation and function)</td>
<td>NLGN4X Xp2323</td>
</tr>
<tr>
<td>Neurexin 1 (transsynaptic binding partner for Neuroligin)</td>
<td>NRNXN1 2p163</td>
</tr>
<tr>
<td>SH3 and multiple ankyrin repeat domains (organizes postsynaptic density and binds Neuroligin)</td>
<td>SHANK3 22q13</td>
</tr>
<tr>
<td>Contactin-associated protein-like 2 (synaptic binding partner for contactin molecules involved in neuronal migration)</td>
<td>CNTNAP2 7q36</td>
</tr>
<tr>
<td>Contactin 4 and Contactin 3 (neuronal expressed adhesion molecules)</td>
<td>CNTN4 and CNTN3 6p26-p25</td>
</tr>
<tr>
<td>Protocadherin 10 (cadherin-related neuronal receptor)</td>
<td>PCDH10 4q28</td>
</tr>
<tr>
<td>Neuronal cell adhesion molecule</td>
<td>NRCAM 7q31</td>
</tr>
<tr>
<td>Neuronal activity regulation</td>
<td></td>
</tr>
<tr>
<td>Methyl CpG-binding protein 1 (CAN methylation-dependent transcriptional repressor)</td>
<td>MECP2 Xq28</td>
</tr>
<tr>
<td>Ubiquitin protein ligase E3A</td>
<td>UBE3A 15q11-q13</td>
</tr>
</tbody>
</table>
Chromosomal abnormalities at the 15q11-q13 locus are commonly found in people with Autism. A “chromosome 15 phenotype” has also been described in individuals with chromosome 15 duplications. Among other candidate genes are the FOXP2, RAY1/ST7, IMMP2L, and RELN genes at 7q22-q33 and the GABA A receptor subunit and UBE3A genes on chromosome 15q11-q13 (Table 1). Mutations in the serotonin transporter gene (5-HTT) on 17q11-q12 are more frequent in individuals with Autism than in non-Autistic populations. In addition, animal models and linkage data from genome screens have implicated the oxytocin receptor at 3p25-p26.

### Future direction

Awareness of the symptoms and causes of Autism is relevant for a pediatrician. In light of the increasingly high prevalence of ASD, pediatricians are likely to come across cases of this disorder in their practices. However, the genetics of Autism is still far from understood since we are only beginning to understand what controls human behavior. Promising strategies need to be applied to identify common genetic risk variants. Systems biology approaches, including array-based expression profiling, can provide an insight into Autism Spectrum Disorder, in which both genetic and phenotypic heterogeneity is a dominant theme.

### Acknowledgements

None.

### Conflict of interest

The author declares no conflict of interest.

### References


### Table Continued....

<table>
<thead>
<tr>
<th>Protein name (Function)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Deleted in Autism</td>
<td>DIA1 (c3orf58) 3q</td>
</tr>
<tr>
<td>Ataxin 2-binding protein 1</td>
<td>A2BP1 16p13</td>
</tr>
</tbody>
</table>

### Neurodevelopmental genes

- Engrailed 2 (homeobox gene involved in midbrain and cerebellum development)
- Homebox A1 (involved in hindbrain development)
- Homeobox B1 (involved in hindbrain development)
- Reelin (signaling protein involved in neuron migration)
- WNT2 (signaling protein involved in embryonic patterning, cell proliferation and cell determination)
- FOXP2 (transcription factor involved in embryogenesis and neural functioning)
- ARX homebox gene
- Patched domain containing 1 gene

### Sodium channel

- Sodium channel, voltage-gated, type VII
- Na+/H+ exchanger isoform 9

### Calcium channel

- Calcium channel, voltage-dependent, type I, alpha 1C subunit
- Calcium channel, voltage-dependent, alpha 1H subunit
- Calcium channel, voltage-dependent, type I, alpha 1F subunit

### Neurotransmitter genes

- GABA receptor Subunits
- Serotonin Receptor

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