Mini Review
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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

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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.[1] 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.[2,3] The Genetic Association Database[4] provides online access to genetic data for Autism and other disorders. Many reviews of the current status of candidate genes and loci are available.[5–14] SFARIGENE is a new web-based search engine for candidate genes associated with ASD.[14] 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 Glutaminergic synapse abnormalities with ASD. Mutations in the X-linked Neuroligin-3 (*NLGN3*) and Neuroligin-4 (*NLGN4X* and *NLGN4Y*) genes[6,15] have been linked to Autism.[16,17] Laumonnier et al.[17] have identified a two base-pair deletion in *NLGN4* in members of a French family exhibiting X-linked mental retardation. Jamain et al.[16] 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.[17] The *SHANK3* gene is crucial for the development of language and social cognition. *SHANK3* mutations and small cytogenetic rearrangements have been implicated with ASD.[18,19] 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

Protein name (Function)	Gene/Locus
Neuronal cell adhesion and/or synapse function	
Neuroligin 3 (synapse formation and function)	NLGN3X Xq28
Neuroligin 4 (synapse formation and function)	NLGN4X Xp2323
Neurexin 1 (transsynaptic binding partner for Neuroligin)	NRNXN1 2p163
SH3 and multiple ankyrin repeat domains (organizes post synaptic density and binds Neuroligin)	SHANK3 22q13
Contactin-associated protein-like 2 (synaptic binding partner for contactin molecules involved in neuronal migration)	CNTNAP2 7q36
Contactin 4 and Contactin 3 (neuronal expressed adhesion molecules)	CNTN4 and CNTN3 6p26-p25
Protocadherin 10 (cadherin-related neuronal receptor)	PCDH10 4q28
Neuronal cell adhesion molecule	NRCAM 7q31
Neuronal activity regulation	
Methyl CpG-binding protein 1 (CAN methylation-dependent transcriptional repressor)	MECP2 Xq28
Ubiquitin protein ligase E3A	UBE3A 15q11-q13

Table Continued.....

Protein name (Function)	**Gene/Locus**
Deleted in Autism	DIA1 (c3orf58) 3q
Ataxin 2-binding protein 1	A2BP1 16p13
Neurodevelopmental genes	
Engrailed 2 (homeobox gene involved in midbrain and cerebellum development)	EN2 7q36
Homeobox A1 (involved in hindbrain development)	HOXA1 17p15.3
Homeobox B1 (involved in hindbrain development)	HOXB1 17q21-22
Reelin (signaling protein involved in neuron migration)	RELN 7q22
WENT2 (signaling protein involved in embryonic patterning, cell proliferation and cell determination)	WNT2 7q31
FOXP2 (transcription factor involved in embryogenesis and neural functioning)	FOXP2 7q31
ARX homeobox gene	ARX Xp22.13
Patched domain containing 1 gene	PTCHD1 Xp22.11
Sodium channel	
Sodium channel, voltage-gated, type VII	SCN7A 2q
Na^+/H^+ exchanger isoform 9	SLC9A9 (NHE9) 3q24
Calcium channel	
Calcium channel, voltage-dependent, type I, alpha 1C subunit	CACNA1C 12p13.3
Calcium channel, voltage-dependent, alpha 1H subunit	CACNA1H 16p13.3
Calcium channel, voltage-dependent, type I, alpha 1F subunit	CACNA1F Xp11.23
Neurotransmitter genes	
GABA receptor Subunits	GABRB3, GABRA5, GABRG3 15q11.2-q12
Serotonin Receptor	SLC6A4 17q11.1-q12

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.[20] 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.[21]

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.

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Conflict of interest

The author declares no conflict of interest.

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