

Genetics of Autism

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Autism or autistic disorder is a severe neurodevelopmental disorder that is typically diagnosed before 3 years of age. The main symptoms of autism consist of impairments in communication and social interaction, restricted interests and repetitive patterns of behavior. Other associated features include mental retardation and epilepsy, observed in ~70% and ~30% of autistic cases, respectively. Autism is the best known of the broad class of pervasive developmental disorders (PDD) recognized in the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association. PDD is an umbrella diagnosis that encompasses autistic disorder, Asperger's disorder, PDD-not otherwise specified (PDD-NOS), Rett syndrome and childhood disintegrative disorder. Due to its great diversity of clinical severity, autism is also known as autistic spectrum disorder (ASD), the term that is commonly used in the literature now. The primary clinical diagnosis criteria are from DSM-IV or ICD-10. However, many recent studies have used newer diagnostic instruments such as the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) to increase diagnostic reliability and comparability.¹

The prevalence of autism

Epidemiological surveys of autism have been conducted in many countries, though with differences in criteria and case finding procedures. The estimated prevalence of autism has increased since the mid-1980s from 3-5/10,000 to a current estimate of 1/150 for ASD in the US. This increase is most likely attributable to changed diagnostic practices and increased detection. The prevalence in males is approximately four times higher than females.^{2,3} In Thailand, a recent study (2005) estimated the prevalence to be 9.9 per 10,000 children at 1-5 years of age.⁴

Causes of autism

Approximately 90-95% of autistic cases are classified as "idiopathic" and the main causes are genetic or environmental or a combination of both. Twin studies have reported 60-92% concordance in monozygotic twins compared to 0-10% concordance in dizygotic twins. The recurrence rate in siblings of affected children is ~4-7%, significantly higher than the general

population prevalence. Linkage and association studies have also revealed substantial evidence for the involvement of genetic variations in the development of autism.²

Teratogenic agents, rubella, valproic acid and thalidomide are recognized causes of autism. Organic mercury, previously used as a preservative for certain injectable vaccines, and the measles-mumps-rubella (MMR) vaccine, which never contained mercury, have both been under scrutiny; however no scientific evidence for a relationship between vaccines and autism has been identified.⁵ It remains unclear whether those who developed autism after such a teratogenic agents exposure have genetic susceptibility.

Types of idiopathic autism

According to Miles and Mccathren,² idiopathic autism can be divided into two types, essential autism and complex autism.

Essential autism is defined by the absence of physical abnormalities, accounting for ~70% of children with idiopathic autism. Children with essential autism have a better outcome overall. They are also more likely to be male and have a higher sibling recurrence risk.

Complex autism is defined by the presence of dysmorphic features, microcephaly and/or structural brain malformation, indicating some alteration of early embryogenesis. About 30% of children with idiopathic autism have complex autism. Complex autism is associated with a poorer prognosis, a lower male-to-female ratio, and a lower sibling recurrence risk.

Chromosomal abnormalities in autism

Chromosomal abnormalities were found in 7.4% (129/1,749) of autistic cases with a range from 0 to 54%.^{6,7} This proportion is higher in ASD patients with dysmorphic features and mental retardation. About 1-2% of individuals with autism have a chromosomal duplication in the Prader-Willi/Angelman region of 15q11-13. Within the 15q11-15q13 locus, ubiquitin protein ligase E3A (*UBE3A*) and gamma-aminobutyric acid A receptor beta 3 (*GABRB3*; an inhibitory neurotransmitter receptor) are currently thought to be candidate genes.^{2,8} Also, duplication of 7q11.23 syndrome, resulting in language delay, mental retardation and autistic-like behaviors may first be referred for evaluation of autism,

even if they do not ultimately meet the diagnostic criteria for ASD.^{9,10} Recently, deletion or duplication of chromosome 16p11.2 have been reported in patients with ASD and may account for ~1% of ASD cases.^{11,12} Likewise, deletions involving 22q13 have been recognized for some cases with autistic features.¹³ The SH3 and multiple ankyrin repeat domains 3 gene (*SHANK3*; a synaptic adaptor protein), a candidate gene, is located at 22q13. Other regions that are implicated in the ASD by chromosomal abnormalities in multiple patients included 5p15, 17p11 and Xp22.⁷

Association between syndromes and autism

Strong associations have been reported between autism and 3 syndromes, Fragile X syndrome, Rett syndrome and Tuberous sclerosis complex.^{2,8}

Fragile X syndrome is the most common X-linked mental retardation. The incidence of clinically diagnosed as ASD in cases with Fragile X syndrome is around 15% to 20%. Conversely, the most common mutation, expanded CGG repeats >200 in the *FMR1* gene has been reported in 3% to 10% of unselected patients with autism. This implies overlapping clinical features between the two disorders. Now, *FMR1* mutation screening

is recommended in all autistic cases.

Rett syndrome is an X-linked dominant PDD, almost exclusively found in females. Typical Rett syndrome cases usually feature mutations in the *MECP2* gene. Rett syndrome may be difficult to diagnose by clinical findings alone in early childhood, and usually features a period of normal development followed by gradual loss of language, seizures and stereotypic hand movements. In early childhood, females with ASD are usually recommended for *MECP2* mutation screening after a normal *FMR1* screening test.

Tuberous sclerosis complex (TSC) is an autosomal dominant neurological disorder, usually divided into type 1 (TSC1) and 2 (TSC2) cases. Some studies report that almost 50% of mentally retarded individuals with TSC have autism. It is not too difficult to diagnose TSC in late childhood because these cases have typical clinical features involving abnormalities of the skin (hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques and ungual fibromas), brain (cortical tubers, subependymal nodules, seizures, mental retardation/developmental delay), kidney (angiolipomas, cysts), and heart (rhabdomyomas, arrhythmias). However, in early childhood cases with ASD

TABLE 1. Genetic susceptibility loci of autism (summary from OMIM)¹⁷

Locus	OMIM No.	Chromosome	Candidate gene	Method identification
AUTS1	209850	7q22	N/A	Linkage
AUTS2	607270	7q11.2	<i>KIAA0442</i>	Chromosomal abnormality t(7;20)(q11.2;p11.2)
AUTS3	608049	13q14.2-q14.1	N/A	Linkage Chromosomal abnormality - Deletion of 13q12-q14 - Deletion of 13q14-q22
AUTS4	608636	15q11	<i>UBE3A</i> <i>GABRB3</i> <i>GABRA4</i> <i>GABRG3</i>	Chromosomal abnormality Inverted duplication of 15q11-q13
AUTS5	606053	2q	<i>cAMP-GEFII</i> <i>SLC25A12</i>	Genome wide linkage
AUTS6	609378	17q11	<i>SLC6A4</i>	Genome wide linkage
AUTS7	610676	17q21	<i>ITGB3</i>	Fine mapping linkage Association study
AUTS8	607373	3q25-q27	<i>OXTR</i>	Linkage
AUTS9	611015	7q31	<i>MET</i> <i>RAY1</i> <i>WNT2</i> <i>DVL1</i>	Linkage Association Chromosomal abnormality: t(7;13)(q31.3;q21) Association study and knockout mice
AUTS10	611016	7q36	<i>EN2</i>	Quantitative trait linkage Association study
AUTS11	610836	1q24.2	N/A	Linkage
AUTS12	610838	21q	N/A	Linkage
AUTS13	610908	12q14	<i>AVPR1A</i>	Linkage
AUTS14	611913	16p	More than 25 genes	Genome wide scan Deletion/duplication 16p11.1
AUTS15	612100	7q35-q36	<i>CNTNAP2</i>	Quantitative trait linkage Chromosomal abnormality (inversion 7q) Genome wide linkage Family-based association mapping
AUTSX1	300425	Xq13	<i>NLGN3</i>	Genome wide linkage A mutation in siblings with ASD
AUTSX2	300495	Xp22.3	<i>NLGN4</i>	A mutation in siblings with ASD
AUTSX3	300496	Xq28	<i>MECP2</i>	Mutations of the <i>MECP2</i> gene in sporadic cases of autism

N/A = not available

TABLE 2. Candidate genes for autism (Modified from Miles and Mccathren RB; Abrahamsa and Geschwind)^{2,8}

Chromosome	Gene	Full name of gene	Gene/protein functions	Supportive evidence
1q42	<i>DISC1</i>	Disrupted in schizophrenia 1	high expression in hippocampus	4
2p16.3	<i>NRXN1</i>	Neurexin 1	cell adhesion molecules and receptors	1
2q24	<i>SLC25A12</i>	Solute carrier family 25 (mitochondrial carrier, Aralar), member 12	calcium-dependent mitochondrial aspartate and glutamate carrier	2
3p25	<i>OXTR</i>	Oxytocin receptor	oxytocin's role in various behaviors, including social recognition and bonding, anxiety, trust, and maternal behaviors	2, 4
6q21	<i>GRIK2</i>	Glutamate receptor ionotropic kainate 2 precursor	glutamate receptors mediate the majority of excitatory neurotransmission in the brain	2
6q23.3	<i>AHI1</i>	Abelson helper integration site 1	highly expressed in brain, particularly in neurons that give rise to the crossing axons of the corticospinal tract and superior cerebellar peduncles	1
7q22.1	<i>RELN</i>	Reelin	key role in neuronal migration during brain development	1, 2, 3, 4
7q31	<i>MET</i>	Met proto-oncogene	development of the cerebral cortex and cerebellum	2, 3
7q31.3	<i>CADPS2</i>	Calcium-dependent activator protein for secretion 2	-highly express in cerebellum	1, 3, 4
7q35	<i>CNTNAP2</i>	Contactin associated protein like 2	-expect to mediate calcium and phospholipid binding a member of the neurexin family which functions in the vertebrate nervous system as cell adhesion molecules and receptors	
7q36.2	<i>EN2</i>	Engrailed homeobox 2	homeobox gene involved in midbrain and cerebellum development	2, 4
9q34	<i>TSC1</i>	Tuberous sclerosis 1	- tumor suppressor gene (major role) - GTPase-activating protein	1, 3, 4
10q23.31	<i>PTEN</i>	Phosphate and tensin homologue	- tumor suppressor gene (major role) - uncommon mutations found in autistic cases	1, 4
12p13.3	<i>CACNA1C</i>	Calcium channel, voltage-dependent, L type, alpha-1C subunit	calcium entry into a neuron plays a key role in determining which signaling pathways are activated and thus specifies a cellular response to calcium	1
12q14- q15	<i>AVPR1A</i>	Arginine vasopressin receptor 1A	subfamily of G-protein coupled receptors	4
15q11-q13	<i>UBE3A</i>	Ubiquitin protein ligase E3A	- Angelman syndrome causative gene - degrade other proteins within cells	1, 3, 4
15q11.2-q12	<i>GABRB3</i>	Gamma-aminobutyric acid (GABA) A receptor beta 3	a subunit of a ligand-gated ionic chloride channel, which is a receptor for GABA, the major inhibitory transmitter of the nervous system	1, 2, 4
16p13.3	<i>TSC2</i>	Tuberous sclerosis 2	- tumor suppressor gene (major role) - GTPase activating protein	1, 3
17q11.1-q12	<i>SLC6A4</i>	Solute carrier family 6 member 4 (serotonin transporter)	regulation of the serotonin from synaptic spaces into presynaptic terminals	2, 3
17q21	<i>ITGB3</i>	Integrin beta 3	- Integrins are known to participate in cell adhesion and cell-surface mediated signalling - interact with SLC6A4 in serotonin system	2
22q13.3	<i>SHANK3</i>	SH3 and multiple anklyrin repeat domains 3	a synaptic adaptor protein	1
Xq13	<i>NLGN3</i>	Neurexin 3	neural synapse formation	1, 3, 4
Xp22.3	<i>NLGN4X</i>	Neurexin 4	neural synapse formation	1, 3, 4
Xq27.3	<i>FMR1</i>	Fragile X mental retardation 1	neural spine maturation and synaptogenesis	1, 3, 4
Xq28	<i>MECP2</i>	Methyl CpG binding protein 2	transcriptional activator or repressor regulation of other genes	1, 3, 4

Assigned code for supportive evidence: 1 = mutation found in cases with autistic features, 2 = replicated association studies, 3 = analysis of variant in the gene, 4 = mouse model

that have not yet exhibited typical features, a physical examination using a Woods lamp (ultraviolet light) in a darkened room paying special attention to dermatologic findings is recommended.

Location of the autism susceptibility genes

The common strategies used for mapping disease genes in complex disorders are linkage analysis and/or association studies. Linkage studies aim to elicit gene loci by mapping the chromosome location of genes in families. A recent extensive review summarized linkage studies of autism from several reports and found linkage signals on almost all chromosomes, with the exceptions of chromosomes 18 and Y.⁸ To date, only loci on 17q11–17q21 and 7q have been replicated at levels that could be considered significant at the genome-wide level.^{14–16} The otherwise lack of genome-wide significant associations is probably a consequence of genetic heterogeneity in ASD and the current clinical diagnostic criteria for recruiting ASD patients. So far, an officially designated system has not been agreed upon for defining autism susceptible loci, however, OMIM have tentatively identified 15 autism susceptibility loci on several autosomes (1q24, 2q, 3q25–q27, 7q11, 7q22, 7q31, 7q35–q36, 12q14, 13q14, 15q11, 16p, 17q11, 17q21, 21q) and 3 X-linked autism susceptibility loci (summarized in Table 1).¹⁷

Candidate genes of autism

Evidence of a genetic association with autism has been reported for a number of candidate genes, as summarized in Table 2.^{2,8} However, there have been only a few genes implicated as potentially causative for autism. Mutations of the *SHANK3* gene have been reported to be associated with autism in a small number of individuals (~1% cases tested).¹⁸ In addition, rare mutations in the neuroligin 3 (*NLGN3*) and neuroligin 4 (*NLGN4*) genes, located at Xq13 and Xp22.3, respectively, were identified in siblings with ASD.¹⁹ Neuroligins are postsynaptic membrane cell-adhesion molecules which bind to β -neurexins, a family of proteins that act as neuronal cell surface presynaptic receptors. The Autism Genome Project Consortium reported that the Neurexin 1 (*NRXN1*) gene is an autism risk locus, as a de novo heterozygous deletion was found in a pair of affected siblings.²⁰ This finding is consistent with two reports of rare variants in β -neurexin in patients with ASD and disruption of the *NRXN1* in two ASD families.^{21,22} Interestingly, disruption of the contactin associated protein-like 2 (*CNTNAP2*) gene at 7q35, a member of the neurexin superfamily, has been reported.^{23–25} It seems that neurexin and neuroligin genes are prominent candidate genes.

Recent advanced autism research

Recent advances in microarray technologies have shown losses or gains of DNA, called “copy number variations” (CNVs), in autism. The *de novo* deletions or duplications of CNVs are more common in sporadic compared with familial forms of ASD.^{26,27} All human beings carry CNVs, which can be transmitted as a new deletion or duplication of CNVs from a parent. The molecular basis of CNVs in autism has not yet been elucidated. It is possible that deleted or duplicated CNVs may have an effect on the expression of nearby genes resulting in unbalanced regulation of several genes. Interestingly, Morrow *et al.*²⁸ used the powerful

genetic technique of homozygosity mapping to identify autism-susceptible genes. This study used DNA microarrays to study several consanguineous families from the Middle East; children from such families have a high chance of having two identical chromosomal segments. The findings mapped several loci consisting of homozygous deletions, of which likely mutations included the *PCDH10* (Protocadherin 10) and *DIA1* (Deleted in autism 1; also known as c3orf58) genes. The *PCDH10* encodes a cadherin superfamily protein essential for normal axon outgrowth while the *DIA1* encodes an uncharacterized protein. In addition, the deletion of the *DIA1* is near the 5' region of *NHE9* gene. The *NHE9* (Na^+/H^+ exchanger 9, also known as *SLC9A9*) gene encodes a member protein that exchanges intracellular H^+ for extracellular Na^+ , could be interfered expression. Therefore, they sequenced the coding regions of *NHE9* and found a loss of function mutation in an autistic patient from a non-consanguineous US family. Also, they found a much greater number of coding variants in the *NHE9* gene in autistic cases compared with controls. These findings support the possibility that *PCDH10*, *DIA1* and *NHE9* genes could be new candidate genes for autism.

Genetic evaluation of autism

The common problems in pediatric cases with autism are delayed speech, lack of social interests, hyperactivity and rigid/repetitive behaviors. Several components of critical information including prenatal, perinatal and postnatal periods as well as family history of suspected children with autism need to be obtained before beginning any investigation. The patient's parents and siblings may also need to be evaluated if there is any suspicion of ASD, learning disabilities, delayed speech and mental retardation from family history. An accurate diagnosis of the autism is essential, and should be made by appropriately trained professionals using at least one accepted and objective methodology (i.e. DSM-IV, ICD-10, ADOS or ADI-R). An evaluation of the patient's hearing should not be forgotten, because children with significant hearing loss tend to have difficulties with communication and socialization that may be misdiagnosed as autism.²⁹

Clinical evaluation is to identify a known syndrome by a complete dysmorphology assessment and Wood's lamp examination (for Tuberous sclerosis complex). Metabolic testing may be appropriate if symptoms associated with an inborn error of metabolism are present (i.e. clinical decompensation with illness or regression of motor or cognitive skills), but such testing is not routinely recommended. Neuroimaging may also be helpful when there are abnormal findings on neurological exam or a history suspicious for seizures. Genetic testing may be available if a specific diagnosis is suspected because of physical or behavioral characteristics (i.e. Angelman syndrome, Rett syndrome, Tuberous sclerosis complex). Even in children without obvious dysmorphic features, high resolution chromosome analysis is now a standard recommendation. Fragile X DNA analysis should be done in all autistic cases, whether or not the patient shows cognitive impairment and/or the clinical features of Fragile X syndrome. The *MECP2* gene, which causes most cases of Rett syndrome, likely has a genetic etiology in a small number of female cases of autism. Several additional X-linked genes (i.e. *ARX*,

CDKL5, neuroligin-3 and -4) as well as autosomal genes (i.e. *PTEN* for cases with macrocephaly) may be indicated in these patients.^{29,30} (Note: *DNA tests for FMR1, ARX, MECP2 genes are available in Thailand.*) Recent research publications have established the utility of identifying cryptic chromosomal deletions/duplications by whole genome microarray analysis. Clinical testing for these genes is anticipated in the future, adding to the expanding list of specific genetic tests available for autism.

Recurrence risk for autism

In cases of a known genetic cause, the recurrent risk varies from ~1% in a *de novo* chromosomal abnormality or a new mutation, up to 50% in autosomal dominant (Tuberous sclerosis complex) and X-linked dominant inherited patterns (Fragile X syndrome and Rett syndrome). For idiopathic autistic cases, the recurrent risk calculation is based on population based studies known as empirical recurrence risk. The empiric recurrence risk for a full sibling is 4% if the affected child is a girl and 7% if the affected child is a boy. If a family has two children with autism, the recurrence risk is from 25% to 50% (~35% on average).^{2,29}

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