Genetics of Autism Spectrum Disorders

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Autism spectrum disorders (ASDs) are a clinically complex group of childhood disorders that have firm evidence of an underlying genetic etiology. Many techniques have been used to characterize the genetic bases of ASDs. Linkage studies have identified several replicated susceptibility loci, including 2q24-2q31, 7q, and 17q11-17q21. Association studies and mutation analysis of candidate genes have implicated the synaptic genes *NRXN1, NLGN3, NLGN4, SHANK3,* and *CNTNAP2* in ASDs. Traditional cytogenetic approaches highlight the high frequency of large chromosomal abnormalities (3%–7% of patients), including the most frequently observed maternal 15q11-13 duplications (1%–3% of patients). Newly developed techniques include high-resolution DNA microarray technologies, which have discovered formerly undetectable submicroscopic copy number variants, and genomewide association studies, which allow simultaneous detection of multiple genes associated with ASDs. Although great progress has been made in autism genetics, the molecular bases of most ASDs remains enigmatic.

Introduction

Intense investigation of the origins and treatment of autism has been fueled by the high prevalence of this complex childhood disorder of brain development that affects nearly 1 per 500 children worldwide. Autism typically presents before 3 years of age and is characterized clinically by three distinguishing features: impaired social skills, impaired verbal and nonverbal communication, and restrictive interests and repetitive behaviors [1]. Autism is the most severe condition among a group of autism spectrum disorders (ASDs) that also includes Asperger syndrome, pervasive developmental disorder not otherwise specified, and rare syndromic forms such as fragile X and Rett syndromes. The prevalence of ASDs is estimated at 1 per 150 children, with a male–female ratio of 4:1 [1]. Autism has a major genetic component. Risk is high among siblings of affected individuals, and studies of monozygotic twins show that heritability is 60% to 90% [2], making autism one of the most genetic of all developmental neuropsychiatric disorders. Appropriately, autism is sometimes referred to as "the autisms" to convey its clinically variable and etiologically complex nature, which may also include the influence of environmental factors [3].

The search for the genetic bases of autism has been facilitated by both traditional and emerging approaches, including linkage, association, cytogenetic, and copy number variant (CNV) analyses. This article reviews the current status of the genetic underpinnings of ASDs and describes several known genetic syndromes in which autistic features are common. Although much has been learned about the biology of autism, the overall results emphasize the deep level of complexity of ASDs and the vast amount of work still required to pinpoint the evidently multiple disease-causing or risk alleles. Identification of the responsible genes will not only catapult our understanding of the biologic pathways and mechanisms leading to autism but will also inform molecular diagnostics and novel therapeutic interventions that are needed to make progress in this rapidly growing field.

Linkage Studies

Genetic linkage studies are designed to identify regions of the genome that are shared between affected family members. Many designs have been used, including parametric linkage (which makes explicit assumptions about the nature of the genetic model, such as mode of inheritance) and nonparametric analysis (in which the mode of inheritance is unclear). The genetic markers that are used may cover the entire set of chromosomes or correspond to specific chromosomal regions or single genes. Linkage data may be reported as a logarithm of odds (LOD) score; LOD scores greater than 3.6 are typically considered significant at the genomewide level for complex disorders, and LOD scores greater than 2.2 are considered suggestive [4].

Because the mode of inheritance in ASD is complex, few parametric linkage studies have been reported. Laumonnier et al. [5] used parametric fine-mapping to study a single large pedigree with 13 males with autism

[5]. Statistically significant linkage was identified on Xp22.33, which contained the *NLGN4* gene. The gene was sequenced and found to contain a 2–base pair deletion in all affected patients. The parametric approach has successfully led to the identification of additional ASD loci, including the *MECP2* gene, which is responsible for most cases of Rett syndrome [6], and the *CNTNAP2* gene, which underlies epilepsy, mental retardation, and autism [7].

Nonparametric or "model-free" approaches in ASDs, including affected sibling pair analysis (the most widely used approach), provide suggestive to significant evidence of linkage on almost all chromosomes; however, only a few loci have been replicated [8]. At least three loci (2q24-2q31, 7q, and 17q11-17q21) have been shown by at least two studies to have genomewide significance. [8]. In one of the largest linkage screens, the Autism Genome Project Consortium (AGPC) investigated about 1160 multiplex autism families using a genomewide screen with 10,000 markers and found suggestive evidence of linkage at 11p12-p13 [9].

The linkage data indicate that many loci may underlie risk of autism, which is consistent with the well-accepted hypothesis that many genes may be associated with autism. To address the limitation of reduced linkage signals due to marked genetic heterogeneity, some studies have made an effort to increase sample homogeneity by focusing on selected characteristics (or endophenotypes) of autism, such as language measures (eg, age at first word), developmental milestones (eg, bladder and bowel control), developmental regression, and restricted repetitive and stereotyped patterns of behavior, interests, and activities (eg, obsessive-compulsive behavior). Such endophenotypes, which can also be found in nonautistic family members and in the general population, facilitate the mapping of quantitative trait loci (QTL) that individually contribute to the overall autism phenotype. In the first mapping study of an autism QTL, Alarcon et al. [10] investigated 152 multiplex families and found strong QTL evidence for age at first word, a measure of language delay, on chromosome 7q34-7q36. Such findings suggest that "subtyping" autism patients will help narrow the search for specific autism susceptibility genes.

Association Studies

Genetic association studies examine differences in allele or genotype frequencies between two groups. The case-control association design compares unrelated subjects with disease with healthy control subjects selected from the general population. The family-based association design, including the widely used transmission disequilibrium test, uses unaffected parents as controls for their affected offspring. One advantage of the family-based design over the case-control design is that the former avoids the potential confounding effects of population stratification (ie, when cases and controls are not properly matched for ethnicity or geographic origin), which may lead to spurious and false positive associations. Typically, the genetic markers selected for an association analysis correspond to small chromosomal regions or single genes. The selection of a candidate region/gene for autism might be based on its location within a significant autism linkage region, its involvement in a metabolic pathway hypothesized to be involved in ASDs (eg, serotonin, glutamate, and γ-aminobutyric acid), or its known function in brain development [11]. The number of candidate genes that have been tested for association is extensive; Table 1 presents a partial listing. Below, we highlight two of several candidate genes with some evidence for association with autism.

CNTNAP2 (7q35)

A role for *CNTNAP2* in autism was first indicated by linkage analysis [7]. This finding has been substantiated by a series of recent studies in autism showing further association of common genetic variation in *CNTNAP2*, including a two-stage association design by Alarcon et al. [12•] and a genomewide association study (GWAS) by Arking et al. [13]. Further evidence involving rare *CNTNAP2* coding variants provides further support for this gene in autism disease risk.

RELN (7q22)

The positional candidate gene reelin *(RELN)* functions as a signaling protein that guides brain development during neuronal migration, formation of cortical layers, and synaptic plasticity. Examination of postmortem brain tissue in autistic and control samples indicated that *RELN* mRNA was significantly reduced in the frontal cortex and cerebellum in autism [14]. Although at least three studies have shown statistically significant associations, five studies did not find any significant associations with genetic variation in *RELN* (reviewed by Freitag [15]).

Recently, GWAS in autism have become feasible using high-density whole genome single nucleotide polymorphism (SNP) microarrays. Weiss et al. [16] performed GWAS using about 500,000 SNPs genotyped in about 800 families from the Autism Genetics Resource Exchange (AGRE) using the Affymetrix (Santa Clara, CA) 5.0 platform [16] and a National Institute of Mental Health autism sample set genotyped on the Affymetrix 5.0 platforms. The overall results of the combined dataset indicate that common variants of major effect do not underlie most of the genetic bases of autism in these samples. Nonetheless, genomewide significant associations were detected with SNPs on chromosomes 5p15 and 7.

Candidate Gene Resequencing

A prevailing hypothesis for the cause of common disorders including autism is the influence of common genetic

Table 1. Genetic characteristics of autism spectrum disorders

Chromosome location	Candidate gene	Known syndrome	Linkage	Association	Mutations	Abnormal karyotype	CNVs
1p36						del	1
1p34.3	*MTF1*			x			
1p13.2			x				
1q21-q44			x*				1
1q42	*DISC1*		x	x			1
2p16	*NRXN1*				x		1
2q24	*SLC25A12*		x*	x*			1
2q32.2	*INPP1*			x			1
2q37	*CENTG2*					del	1
3p25	*OTXR*			x*			1
3p14	*CNTN4*					del/dup	4
3q22			x				
3q25-q27			x*				1
3q27-q28						del	1
4q22-q25			x			del	1
4q35						del	1
5p13-p14			x*				1
5p15			x				2
5q12			x				1
6p21.32	*HLA-DRB1*			x			
6q14.3			x				
6q16.3	*GRIK2*		x	x*			
6q22.1			x				1
6q23	*AHI1*	Joubert			x		
7p21						del	3
7q11		William				del	
7q21.2-q36.2			x				1
7q22	*RELN*		x	x*	x		
7q22	*PIK3CG*			x			
7q22.3	*NRCAM*			x			
7q31	*MET*		x	x*			2
7q31	*GRM8*			x			2
7q31	*FOXP2*			x			2
7q31	*CADPS2*				x		2
7q31.1	*LAMB1*			x			2
7q31.2	*WNT2*			x			2
7q32	*UBE2H*			x			
7q36	*EN2*		x	x*			1

*Replicated.
CNV—copy number variants; del—deletion; dup—duplication; HNPP—hereditary neuropathy with liability to pressure palsy; mat—maternal; NF1—neurofibromatosis type 1; trans—translocation; VCFS—velocardialfacial syndrome.
(*Linkage and association data from* Abrahams and Geschwind [8], Vorstman et al. [25], and Yang and Gill [50]. *CNV data from* Szatmari et al. [9], Christian et al. [35], Sebat et al. [36•], and Marshall et al. [38].)

Table 1. Genetic characteristics of autism spectrum disorders ***(Continued)***

Chromosome location	Candidate gene	Known syndrome	Linkage	Association	Mutations	Abnormal karyotype	CNVs
7q36.1	*CNTNAP2*	Cortical dysplasia-focal epilepsy	x	x*	x		1
8p23						dup	2
9p24			x				1
9q12						del	
9q33-q34			x*				1
9q34.13	*TSC1*	Tuberous sclerosis 1	x		x		1
10p14-p15						del	1
10q11-q21						dup	3
10q23	*PTEN*				x		1
10q23.3-q26.3			x				
11p12-p13			x*	x			1
11q13.4	*DHCR7*	Smith-Lemli-Opitz	x		x		
11q13-q14			x				1
12p13.33	*CACNA1C*	Timothy			x		
12q14.2	*AVPR1A*			x			1
13q12.3			x				1
13q14						dup	3
14q23			x				1
15q11-q13						mat dup	4
15q12	*UBE3A*				x		4
15q12	*ATP10A*			x			4
15q12	*GABRB3*			x*	x		4
15q12	*GABRG3*			x			4
15q12	*GABRA5*			x			4
15q22-q26			x				2
16p13.3	*A2BP1*					trans	1
16p13.3	*TSC2*	Tuberous sclerosis 2			x		
16p13.2	*GRIN2A*			x			
16p13.2	*ABAT*			x			
16p13.13			x				
16p12.1	*PRKCB1*			x			
16p11.2						del/dup	3
16q21						del	1
17p11.2		Potocki-Lupski				dup	
17p12		HNPP region				del	2

*Replicated.
CNV—copy number variants; del—deletion; dup—duplication; HNPP—hereditary neuropathy with liability to pressure palsy; mat—maternal; NF1—neurofibromatosis type 1; trans—translocation; VCFS—velocardialfacial syndrome.
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Table 1. Genetic characteristics of autism spectrum disorders *(Continued)*

Chromosome location	Candidate gene	Known syndrome	Linkage	Association	Mutations	Abnormal karyotype	CNVs
17q11	*SLC6A4*		x	x*			
17q11		NF1 microdeletion				del	
17q21	*ITGB3*		x	x*			1
17q21	*HOXB1*		x	x*			1
19p13			x				1
19q12			x				1
19q13.32	*APOE*			x			
20p13						del	2
20q13.12	*ADA*			x			
21q11			x				
22q11.2		DiGeorge/ VCFS				del/dup	2
22q13.3	*SHANK3*				x	del	3
Xp22.3	*NLGN4X*				x	del	1
Xq12			x				
Xq13	*NLGN3*				x		
Xq21-q25			x				
Xq27.2	*MECP2*	Rett			x		
Xq28	*FMR1*	Fragile X			x		

*Replicated.
CNV—copy number variants; del—deletion; dup—duplication; HNPP—hereditary neuropathy with liability to pressure palsy; mat—maternal; NF1—neurofibromatosis type 1; trans—translocation; VCFS—velocardialfacial syndrome.
(*Linkage and association data from* Abrahams and Geschwind [8], Vorstman et al. [25], and Yang and Gill [50]. *CNV data from* Szatmari et al. [9], Christian et al. [35], Sebat et al. [36•], and Marshall et al. [38].)

variation. However, the lack of clear and reproducible evidence for a role of high-frequency alleles in autism lends support to alternative theories, including the role of low-frequency or rare variants. Toward this end, candidate gene resequencing studies hold promise in identifying rare genetic variants and mutations that may also underlie common and complex diseases. An emerging theme in autism genetics has been the identification of mutations in genes that play important roles in the formation and function of the synapse. Of particular interest are genes of the neurexin–neuroligin pathway in ASD pathogenesis [11].

The role of neuroligins in autism was noticed with the discovery of three autistic females with deletions of Xp22.1 that contained the *NLGN4* gene [17]. The first evidence for a causative role of neuroligins was demonstrated by Jamain et al. [18], who examined three neuroligin genes in 36 pairs of affected siblings and 122 trios with ASDs and identified point mutations in the X-linked genes *NLGL4* and *NLGN3*.

The role of neurexins in autism susceptibility was first reported by Feng et al. [19], who screened about 200 autism patients for mutations in the neurexin 1β gene and identified two putative missense mutations in four patients with autism but not in 535 healthy controls. This finding was substantiated in a report by AGPC, which performed linkage and CNV analysis using Affymetrix 10K SNP arrays in about 1160 multiplex autism families and implicated the neurexin family in ASDs [9]. Further evidence for a role of neurexins in autism was recently provided by Kim et al. [20], who identified mutations in *NRXN1* in two unrelated subjects with ASDs.

The SHANK3 protein binds directly to neuroligins and functions within the postsynaptic density of excitatory synapses. *SHANK3* was identified as a candidate gene based on its location within the common 22q13.3 deletion region. Several studies have reported *SHANK3* mutations in unrelated autism families [21,22]. *CNTNAP2*, a member of the neurexin family of neuronal cell adhesion molecules, also has recently been reported to harbor rare ASD-related variants. Bakkaloglu et al. [23] sequenced 635 patients and identified 27 coding changes, of which eight were predicted to be deleterious. These findings, together with other genetic studies of *CNTNAP2* in autism [7,12•,13], provide support for this gene in ASD pathogenesis and related disorders.

Chromosomal Studies

An alternative approach to identifying the underlying genetic causes of neurodevelopmental disorders is traditional cytogenetic analysis using G-banding techniques and fluorescent in situ hybridization. Veenstra-Vanderweele et al. [24] reviewed 11 studies comprising 1826 ASD patients who were karyotyped by routine cytogenetics and noted 54 chromosomal abnormalities, for a high overall rate of about 3%. Other systematic reviews found chromosomal abnormalities in about 6% or 7% of subjects with autism [25,26]. Below, we describe the most frequently reported microscopically visible chromosomal abnormalities currently known in autism. The Autism Chromosome Rearrangement Database, a curated database cataloging known chromosomal abnormalities in autism, can be accessed at http://projects.tcag.ca/autism/.

15q11-q13 maternal duplication

The most frequent chromosomal abnormality observed in patients with autism is 15q11-q13, a maternal duplication that affects 1% to 3% of autistic subjects [27]. The recurrent nature of this abnormality is due to the presence of large stretches of highly homologous (> 95%) low copy repeats or segmental duplications that mediate unequal crossing over during meiosis. The maternal duplications frequently observed in autism subjects involve the 15q11-q13 region, where a paternal deletion causes Prader-Willi syndrome and a maternal deletion causes Angelman syndrome. Inheritance of a paternal duplication has either no effect or a very mild effect [27]. The differences in these disorders are caused by the presence of imprinted genes within 15q11-q13 that are expressed from a single parental chromosome. Therefore, deletion of the single active copy of a gene results in total loss of expression that produces the disease phenotype. Two genes thought to be associated with autism in this region are *GABRB3* and the maternally expressed gene *UBE3A*. Physical and behavioral features in these patients include hypotonia, hypogonadism, fine motor delays, speech and language delays, moderate to severe mental retardation, epilepsy, and other behavioral problems [27].

22q11 deletion

The 22q11 deletion syndrome is one of the most common chromosomal abnormalities, with a prevalence of about 1 in 4000 live births [28]. The 22q11 deletion is about 1.5 to 3.0 Mb in size and contains about 40 genes. Like the 15q11-q13 duplication, this region is flanked by segmental duplications that predispose to recurrent chromosomal rearrangements. These deletions also have been associated with the DiGeorge, velocardiofacial (VCFS), and CATCH 22 syndromes. Common features include a characteristic facial appearance, conotruncal cardiac defects, and cleft palate. Multiple psychiatric disorders have been reported, including ASDs, attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, schizophrenia, and bipolar disorder [29]. To determine the frequency of 22q11 deletions in ASDs and ADHD, 100 subjects with a confirmed deletion of 22q11 were examined, and 44 were diagnosed with an ASD and/or ADHD. ASD alone was present in 14 subjects, and nine had ASD and ADHD [28]; 84 of the 100 subjects were younger than 17 years old. Such subjects may present with other psychiatric disorders as adults.

2q37 deletion

One of the primary features of del(2q37) is the presence of developmental delay or mental retardation, short stature, obesity, and brachydactyly—a constellation of features referred to as "pseudopseudohypoparathyroidism." Depending on the size of the deletion, other anomalies can affect the brain, heart, and skin as well as the skeletal, gastrointestinal, renal, and other systems [30]. A diagnosis of autism is also present in 24% to 35% of subjects with del(2q37). In one study, the *CENTG2* gene was identified as a susceptibility gene based on breakpoint (BP) mapping and functional involvement in neuronal processes in the developing brain [31].

17p11.2 duplication

Most cases of dup(17p11.2), known as Potocki-Lupski syndrome, arise through nonallelic homologous recombination (NAHR), a characteristic shared by all of the centromeric disorders discussed herein. The reciprocal deletion of this region causes Smith-Magenis syndrome, a distinct disorder. The typical rearrangements are about 3.7 Mb. Clinical features of this syndrome include dysmorphic features, developmental delay, mental retardation, language impairment, cognitive impairment, and autistic features. Other characteristics include hypotonia, failure to thrive, oralpharyngeal dysphasia, sleep apnea, cardiac abnormalities, electroencephalogram abnormalities, and hypermetropia [32].

Other large chromosomal abnormalities with autism as part of the phenotype include 7q11 deletion (Williams syndrome), 17q11 deletion (neurofibromatosis type 1), trisomy 21 (Down syndrome), and monosomy X (Turner's syndrome) [33].

Copy Number Variants

Rapid advances in genomic DNA microarray technologies have substantially improved our ability to detect submicroscopic chromosomal abnormalities, otherwise known as CNVs. The release of whole genome tiling path bacterial artificial chromosome (BAC) clones by the Human Genome Project in conjunction with improvements in array comparative genomic hybridization (aCGH) methods have allowed screening for chromosomal abnormalities down to about the 150 kilobase (kb) level of resolution, a marked improvement over traditional cytogenetics that

have resolutions of 4 to 5 Mb. Several autism studies have been performed using aCGH-based BAC microarrays. Jacquemont et al. [34] examined 29 patients with syndromic autism using BAC clones spaced about 1 Mb apart and identified eight de novo rearrangements, including six deletions and two duplications. Christian et al. [35] used a 19K whole genome tiling path BAC array on 397 unrelated autism subjects from AGRE and a control group of 372 individuals. A total of 51 autism-specific CNVs were identified in 46 of the ASD patients (11.6%). Seven of the CNVs were de novo, and 44 were inherited. A total of 272 genes were represented in the 51 autism-associated CNVs, and they ranged in size from 189 kb to 5.5 Mb [35].

To increase the level of resolution for the identification of chromosomal deletions and duplications, higher-density microarrays consisting of oligonucleotides or SNPs have recently been examined in autism research. A seminal study by Sebat et al. [36•] used an oligonucleotide-based aCGH platform called representational oligonucleotide microarray analysis to assess copy number variation in autism subjects from 188 simplex families and 77 multiplex families and 196 control subjects. The study demonstrated that de novo CNVs are found more often in simplex families (10% of cases) than in controls (1%). Using the 10K SNP array, the AGPC identified 624 CNVs, including 222 deletions and 402 duplications [9]. Two additional studies have used the higher-density Affymetrix 500K SNP platform: Weiss et al. [37] analyzed 751 multiplex families, and Marshall et al. [38] examined 427 autism patients. Below, we summarize major findings emerging from the aCGH and SNP genotyping platforms and highlight additional new recurrent chromosomal abnormalities that might have implications in our understanding of the etiology of ASD.

16p11.2 deletion/duplication

The identification and characterization of recurrent 16p11.2 genomic imbalances by three independent groups [37,38,39•] established this chromosomal disorder as the second most frequent in ASDs, with 16p11.2 microdeletions observed in about 0.5% of autism patients. The first report of this microdeletion was made by Sebat et al. [36•] in a single patient with Asperger syndrome. The reciprocal microduplication has also been observed in about 0.5% of autism patients, but the association is less convincing given a higher frequency in control cohorts [16]. The duplication also has been observed in patients with schizophrenia [40] and bipolar disorder [37]. The 16p11.2 microdeletion/duplication spans about 500 to 700 kb, contains about 24 genes, and is flanked by 147-kb low copy repeats that mediate NAHR. Phenotypic characterization of autism patients with 16p11.2 imbalances has not identified any associated dysmorphic features or malformations, although one study indicated a trend toward aggression and overactivity [39•]. Extensive phenotypic characterization is required and under way to better understand the phenotypic consequences of 16p11.2 imbalances in subjects with ASDs.

15q13.3 microdeletion/duplication

A second newly described microdeletion/microduplication syndrome located distal to the Prader-Willi/Angelman region (BP1–BP3) in patients with mental retardation and seizures was first reported by Sharp et al. [41]. Six of 2082 patients (0.3%) with mental retardation had microdeletions involving BP4–BP5 that were not present in 2962 controls. The neurologic phenotype of one of these patients was reported to include mild autism. Miller et al. [42] screened 2886 samples from 1441 individuals with autism and identified five patients with BP4–BP5 15q13.3 deletions, three with BP4–BP5 duplications, and two with overlapping but smaller duplications involving this region. Patients with deletions exhibited a range of phenotypes, including minor dysmorphic features, language deficits, ASDs, ADHD, anxiety disorder, mood disorder, and cognitive impairment. Pagnamenta et al. [43] reported an approximately 2 Mb maternally inherited 15q13.3 microdeletion at BP4–BP5 in three siblings diagnosed with autism/ASD using the ICD-10, Autism Diagnostic Interview–Revised, and Autism Diagnostic Observation Schedule [43].

1q21.1 microdeletion/duplication

A third microdeletion/microduplication syndrome has been identified in 1q21.1 [44,45]. Mefford et al. [45] screened 5218 patients with unexplained mental retardation, autism, or congenital abnormalities and identified 25 patients (0.5%) with overlapping 1q21.1 microdeletions and nine patients (0.2%) with 1q21.1 microduplications. The 25 patients with microdeletions presented with highly variable phenotypes that included mild to moderate mental retardation, microcephaly, cardiac abnormalities, and cataracts; two of them had autism or autistic features. Four of the nine patients (44%) with microduplications had autism or autistic behaviors, and some also presented with mild to moderate mental retardation, macrocephaly, and mild dysmorphic features. Brunetti-Pierri et al. [44] screened 16,557 samples with a wide range of phenotypes, including autism, mental retardation, and/or congenital abnormalities, and identified 27 patients with microdeletions and 17 with microduplications. The variable phenotypes associated with these reciprocal events included facial dysmorphism, a wide range of congenital abnormalities, and behavioral phenotypes such as ADHD, autism, anxiety/depression, antisocial behavior, and aggression. The 1q21.1 microdeletion has been observed in 0.26% of schizophrenia cases [46,47]. The differences in phenotype between subjects with identical chromosomal abnormalities could be caused by variable expressivity or incomplete penetrance.

Known Genetic Metabolic Disorders

A number of autosomal recessive metabolic disorders that show an autistic phenotype have been reported. Among these are phenylketonuria, purine metabolism disorders, creatine deficiency syndromes, and urea cycle disorders. A detailed review was recently published on this topic [48].

Known Genetic Syndromes

Fragile X syndrome

Fragile X syndrome (FRAX) is the most common form of mental retardation in males, accounting for about 50% of X-linked mental retardation cases. FRAX is observed in 1 in 4000 males, and 25% to 33% meet criteria for autism [33]. Conversely, the prevalence of FRAX in autism is about 2.1%. The phenotypes range from learning problems to severe mental retardation and autism. The more severe forms of FRAX are usually characterized by distinct facial features, including a long narrow face, prominent ears, mental retardation, and macroorchidism. Cognitive deficits include problems with memory, executive function, and mathematic and visuospatial abilities. Patients are also at higher risk for emotional problems [49].

FRAX is primarily caused by expansions in the length of a CGG repeat that silences transcription of the *FMR1* gene [50]. The full phenotype is observed with more than 200 repeats; fewer repeats are considered premutations that are often found in the mothers. FMRP is an RNA binding protein that negatively regulates protein synthesis, producing immature neurons with abnormally long dendritic spines affecting synaptic transmission and plasticity [49].

Tuberous sclerosis

Tuberous sclerosis (TS) is an autosomal dominant disorder with a prevalence of 1 to 1.7 per 10,000 persons that is characterized by the presence of hamartomata in organs including the brain, skin, kidneys, heart, lungs, and liver. Frequent manifestations include epilepsy, mental retardation, skin lesions, cognitive impairment, and behavioral problems. The frequency of autism in TS is 16% to 65%, whereas TS represents up to 4% of autism cases [33]. The distribution of the lesions varies between organs, causing variability in the phenotype.

Two genes, *TSC1* and *TSC2,* have been identified for TS. The products of these genes, hamartin and tuberin, normally inhibit the phosphatidylinositol-3 kinase/insulin-activated signaling pathway involved in cellular differentiation, migration, and proliferation. Disruption of these genes causes hyperactivation of the mammalian target of rapamycin pathway and other downstream targets, leading to the formation of hamartomatous growths. Cerebral involvement is observed in more than 90% of TS cases, leading to epilepsy, mental retardation, and psychiatric and behavioral problems. A strong association with autism is observed when temporal lobe tubers are present [33].

Rett syndrome

Rett syndrome is an X-linked dominant neurodevelopmental disorder that primarily affects females and is mostly lethal in hemizygous males. Features include arrested development, regression of acquired skills, loss of speech, stereotypical movements, microcephaly, seizures, mental retardation, and autism. The prevalence of Rett syndrome is 1 per 10,000 to 15,000 females. Rett syndrome is caused by mutations in the methyl-CpG binding protein 2 *(MECP2)* gene that functions as a methylation-dependent transcriptional repressor. In mice, decreased *Mecp2* expression causes reduced expression of *Ube3a* and *Gabrb3,* which are two genes in the 15q11-q13 region that are known to be associated with autism [6].

Conclusions

ASDs are a complex set of neurodevelopmental disorders with many genetic etiologies. Linkage and association studies have identified multiple loci and candidate genes for ASDs that support the heterogeneity of these disorders. Several genetic syndromes and metabolic disorders have autism as part of the phenotype. Many advances have been made over the past 2 years in understanding the underlying genetic mechanisms for ASDs. Additional new susceptibility genes and new chromosomal microdeletion/duplication syndromes are being identified at a rapid pace. Future advances, including the identification of new larger sample sets for GWAS and the analysis of subphenotypes to reduce heterogeneity, should continue the rapid advances in the progress of autism research.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently,
have been highlighted as:

- • Of importance
- •• Of major importance

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