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Review

Autism spectrum disorder in the genetics clinic: a review

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Autism spectrum disorders (ASDs) are a heterogeneous group of neurodevelopmental disorders affecting social communication, language and behavior. The underlying cause(s) in a given individual is often elusive, with the exception of clinically recognizable genetic syndromes with readily available molecular diagnosis, such as fragile X syndrome. Clinical geneticists approach patients with ASDs by ruling out known genetic and genomic syndromes, leaving more than 80% of families without a definitive diagnosis and an uncertain risk of recurrence. Advances in microarray technology and next-generation sequencing are revealing rare variants in genes with important roles in synapse formation, function and maintenance. This review will focus on the clinical approach to ASDs, given the current state of knowledge about their complex genetic architecture.

Conflict of interest

Nothing to declare.

MT Carter[a] and SW Scherer[b,c]

[a]Division of Clinical and Metabolic Genetics, [b]The Centre for Applied Genomics and Program in Genetics and Genomic Biology,The Hospital for Sick Children,Toronto, ON,Canada, and [c]McLaughlin Centre and Department of Molecular Genetics, University of Toronto,Toronto,ON, Canada

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Corresponding author: Melissa T. Carter, Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, ON, Canada.
Tel.: 416 813 5340;
fax: 416 813 5345;
e-mail: melissa.carter@sickkids.ca

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Autism spectrum disorders (ASDs) describe individuals with persistent deficits in communication and social interaction, and repetitive, restricted behaviors and/or interests. There is wide variability within 'the spectrum'; affected individuals may have average intelligence or mild to severe intellectual disability. It is a descriptive diagnosis, without implying an underlying pathology. When first described, autism was considered a psychiatric disturbance caused by aloof parenting. However, the association of autism with intellectual disability and seizures suggested a developmental brain disorder with an 'organic' cause. Today, ASDs are considered genetically influenced neurodevelopmental disorders, with abundant evidence pointing to dysfunction at the level of the synapse. There is extensive genetic heterogeneity, with perhaps hundreds of genetic variants involved. The evidence so far points to a role for rare (<1% population frequency) variants.

Evidence for the genetic basis of ASDs will not be presented here; the reader is referred to other review articles (1, 2). This article will focus on aspects most relevant to the clinician. There are no genetic variants that have thus far been associated solely with ASDs; candidate genes are also implicated in intellectual disability, epilepsy, and psychiatric conditions, suggesting shared biologic pathways. We will first address the approach to genetic testing of individuals with ASDs in the clinic. We will then briefly discuss some of the rare but promising candidate genes arising from recent research studies.

Genetic testing

It is estimated that a specific genetic etiology can be determined in up to 15% of individuals with ASDs (3). The literature on the subject of 'diagnostic yield' of genetic testing in ASD patients, however, suffers from extreme variability in sample size, inclusion criteria and type of genetic testing. Nonetheless, several themes emerge:

- The most consistently reported single-gene disorders associated with ASDs (~5% of cases) are fragile X syndrome, Rett syndrome, tuberous sclerosis, and *PTEN* mutations

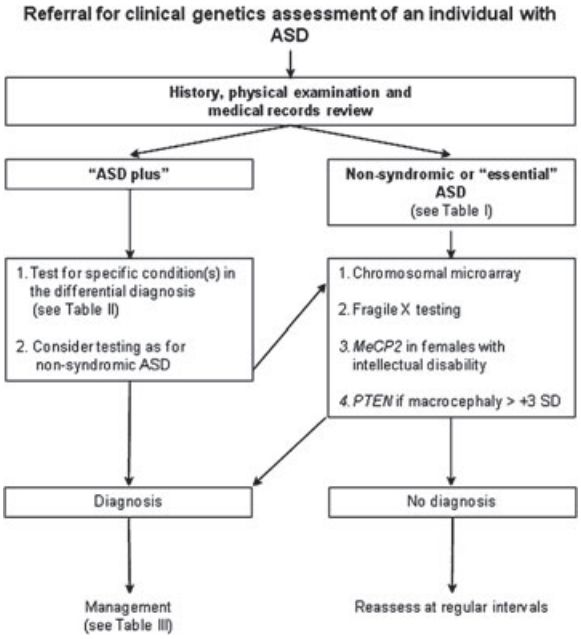

Fig. 1. Flow chart depicting clinical approach to genetic investigation for individuals with autism spectrum disorders (ASDs).

- The most common microscopically visible chromosome abnormalities (overall yield ~2–5%) are idic(15), sex chromosome aneuploidy, and various large deletions and duplications
- The most consistently reported submicroscopic chromosome abnormalities detected by chromosomal microarray (overall yield ~10–20%) are recurrent copy number variants (CNVs) at 16p11.2, 15q11-13, 22q11.2, as well as a growing number of rare *de novo* CNVs
- Metabolic investigations have low yield (<1%) in idiopathic ASD probands (4, 5), but may be considered in light of possible treatment modalities and high recurrence risk (RR)

The basic clinical approach (Fig. 1) following history, physical examination and medical record review is to determine whether the individual has 'essential' or 'non-syndromic' ASD, versus 'ASD plus' (also referred to as syndromic or complex ASD). An individual with non-syndromic autism is generally non-dysmorphic, healthy (aside from the common co-morbidities associated with ASDs; see Table 1), with normal growth and neurologic exam and no major congenital anomalies. This group accounts for 75% of children with ASDs (6). The remaining 25% have 'ASD plus' (see Table 2). This approach serves to narrow the possible genetic diagnoses based on clinical features. Table 3 shows some examples of management implications for individuals with such diagnoses.

Testing for 'ASD-plus'

The approach to testing for individuals with ASD-plus is the same as for any patient presenting for a clinical genetics assessment due to a neurodevelopmental disorder. Chromosomal microarray is usually warranted, as is single- or multigene panel testing if available for the suspected diagnosis. ASDs may be a recognized part of the clinical spectrum (e.g. in tuberous sclerosis, Timothy syndrome, and CHARGE syndrome), but given the high incidence of ASDs in the general population (~1%), the association might be coincidental. For example, we recently diagnosed a child with Beckwith-Weidemann syndrome based on his advanced growth parameters, even though he was referred for evaluation because of ASD.

Testing strategy for 'non-syndromic' ASDs

Recommendations for genetic testing in children with non-syndromic ASDs have been published (7–9). The tests most consistently recommended are chromosomal microarray and fragile X (both sexes) and *MeCP2* testing (females only). *PTEN* mutation analysis should be considered in individuals with absolute macrocephaly. The rationale for each test is briefly discussed below.

Chromosomal microarray

Chromosomal microarray, with its ability to detect submicroscopic CNVs, is now a recommended first line investigation for clinical genetic testing for ASDs (10–12). Large, rare, and *de novo* CNVs are more common in individuals with autism than in controls (13–16). The CNVs most commonly reported in ASD probands are discussed below; most are also present in controls, albeit at a much lower frequency. Each is rare (found in ≤1% of probands), and are often inherited from a parent who is deemed 'unaffected'; however, detailed information about the parents' phenotypes are rarely published. These recurrent CNVs are not fully penetrant for ASDs, and may be associated with other neurodevelopmental disorders such as intellectual disability, psychiatric conditions, attention-deficit hyperactivity disorder or epilepsy. No specific dysmorphic syndromes are associated with these CNVs (although dysmorphic features may be present), making chromosomal microarray essential for diagnosis.

15q11-13 duplication

The most frequent finding with G-banded karyotype in patients with ASDs is supernumerary isodicentric chromosome 15 (idic 15), which contains one or two extra copies of the *SNRPN* gene. It is usually derived from the maternal homolog when associated with ASDs and intellectual disability (17). Genome-wide array-based studies consistently show interstitial duplications of this region at 15q11-q13 in ~1% of autistic individuals with normal karyotype, adding support to implication of increased dosage of this region in ASD.

Triplications of 15q11-q13 are associated with non-specific or absent dysmorphic features, and congenital

Table 1. Features of essential (non-syndromic) autism

Clinical feature	Comments
Non-dysmorphic	May have mild, non-specific dysmorphic features
Normal growth	Height and weight within normal range for age
Normal head circumference	May have relative or absolute (mild) macrocephaly, especially between ages 2–5 when there is often an acceleration of head growth which subsequently stabilizes
Normal neurologic examination	May have mild to moderate hypotonia and/or hyperextensibility of small joints; mild coordination and balance issues; toe-walking without spasticity
Epilepsy	25% have had at least one seizure; electroencephalographic (EEG) abnormalities without seizures are common
Gastrointestinal disturbance	Some have extremely selective diets; 45% have ongoing issues with constipation, diarrhea, bloating and/or cramping; parents may report improvement with gluten- and/or casein-free diet
Sleep disturbance	Delayed sleep onset, frequent night-waking, early morning waking, apparent lack of need for sleep
Regression	Present in 30%; may lose language (both expressive and receptive) and eye contact but not typically motor skills; peak age 13–18 months
Behaviors	Attention-deficit hyperactivity symptoms; hypersensitivity to noise and other stimuli; hyposensitivity to pain and other stimuli; repetitive stereotypic movements; self-hitting, biting or head-banging; tantrums
Family history	May or may not have a family history of ASD and/or psychiatric conditions (anxiety, depression, psychosis)

ASD, autism spectrum disorder.

malformations are rare (18). These individuals tend to have moderate to severe intellectual disability, epilepsy (sometimes intractable), hypotonia and motor delays. Language is impaired or absent in most. Interstitial duplications, in contrast, present with wider variability and a less severe clinical picture (19).

16p11.2 CNVs

Recurrent CNVs at 16p11.2 are present in 1% of patients with ASDs. They are also found at lower frequencies in studies of schizophrenia (particularly the duplication (20)) and idiopathic developmental delay with or without congenital anomalies (particularly the deletion (21)). As with other recurrent CNVs in ASD, phenotype is variable, and penetrance incomplete. The deletion is more often *de novo* compared to the duplication. Probands with the deletion often have intellectual disability (usually mild), with particular difficulty in expressive language, and as-yet vaguely defined behavioral manifestations (22). Individuals with deletions tend to become overweight in mid-childhood and have relative or absolute macrocephaly (21) whereas duplication carriers tend to be underweight due to restrictive eating behaviors, and have smaller head circumference than expected for body size (23).

22q11.2 CNVs

Deletions at 22q11.2 are known to increase risk of psychiatric and neurodevelopmental disorders, in addition to congenital anomalies. This deletion confers a 20-fold increased risk of schizophrenia and a 60% risk of any psychiatric disorder (24), and 20–50% of carriers have autistic features (25). The reciprocal duplication is nearly as common as the deletion in ASD probands, and co-existence of ASD with 22q11.2 duplication has been reported anecdotally (26) and confirmed by case–control analyses (27). The duplication has been associated with a wide range of clinical manifestations in the case report literature (28). It has not been specifically implicated in psychiatric disease thus far, aside from anecdotal reports.

7q11.23 duplication

Williams-Beuren syndrome (WBS) is caused by deletion of a 1.5 Mb region at 7q11.23. A reciprocal duplication of this region was first reported in 2005 (29), and is found in approximately 0.2% of probands with ASDs (16). Since then, clinical details have been published on 24 individuals, most ascertained because of developmental delay (30, 31). Some consistent phenotype trends are emerging: duplication carriers may have a short philtrum and thin lips (in contrast to the long philtrum and full lips of WBS) (32). In contrast to WBS, which is characterized by relative strength in verbal skills and social gregariousness with poor visuospatial skills, individuals with the reciprocal duplication consistently show the opposite. In 40% of reported duplication cases, behavioral features consistent with ASD are present.

1q21.1 CNVs

A recurrent 1.35-Mb deletion at 1q21.2 is associated with developmental delay, dysmorphic features, cardiac abnormalities, epilepsy, learning disability and schizophrenia (33–36). Deletions and duplications at this locus have a combined frequency in ASD of

Table 2. Clinical features in 'ASD plus' which may be associated with a known genetic disorder for which clinical testing is available

Clinical feature	Diagnoses to consider
Overgrowth	Simpson-Golabi-Behmel syndrome (*GPC3*)
	Sotos syndrome (*NSD1*)
	Lujan-Fryns syndrome (*MED12*)
	PTEN
Intractable seizures or infantile spasms	Tuberous sclerosis
	Angelman syndrome (*UBE3A*, *SLC9A6*)
	ARX
	Channelopathies (e.g. *SCN1A*)
	Creatine deficiency disorders
	Pyroxidine-dependent epilepsy
	SSADH deficiency
Muscle weakness or severe hypotonia	Duchenne/Becker muscular dystrophy (*DMD*)
	Myotonic dystrophy type 1 (*DMPK*)
Ataxia	Angelman syndrome (*UBE3A*, *SLC9A6*)
	Ciliopathies (multiple genes)
Motor, cognitive or behavioral regression	Lysosomal storage disorders (e.g. Sanfilippo syndrome)
	Neuronal ceroid lipofuscinosis
	Biotinidase deficiency
Acute/intermittent decompensations	Mitochondrial disorders of energy metabolism
	ADSL deficiency
	Urea cycle disorders
Breathing abnormalities	Ciliopathies (multiple genes)
	Pitt-Hopkins syndrome (*TCF4*)
	Rett syndrome (*MECP2*)
Hand/foot anomalies	Syndactyly
	Timothy syndrome (*CACNA1C*)
	Smith-Lemli-Opitz syndrome (*DHCR7*)
	Polydactyly
	Ciliopathies (multiple genes)
	Smith-Lemli-Opitz syndrome (*DHCR7*)
	Adducted thumbs
	MASA syndrome (*L1CAM*)
Pigmentation abnormalities	Tuberous sclerosis (*TSC1*/*TSC2*)
	Neurofibromatosis type 1 (*NF1*)
	PTEN
Multiple congenital anomalies and/or dysmorphic features	Autosomal dominant
	CHARGE syndrome (*CHD7*)
	CFC/Noonan/Costello syndrome (multiple genes)
	Cornelia de Lange syndrome (*NIPBL*)
	Cohen syndrome (*VPS13B*)
	Kleefstra syndrome (*EHMT1*)
	Rubinstein-Taybi syndrome (*CREBBP*)
	Autosomal recessive
	Smith-Lemli-Opitz syndrome (*DHCR7*)
	X-linked
	ARX
	Cornelia de Lange syndrome (*SMC1A*)
	Opitz syndrome (*MID1*)
	Renpenning syndrome (*PQBP1*)
	Borjeson-Forssman-Lehmann syndrome (PHF6)

ASD, autism spectrum disorder.

0.2% (2). Common features of the deletion include microcephaly (50%); mild intellectual disability (30%); mild dysmorphic facial features, eye abnormalities, and behavioral manifestations including autism. Fewer patients with the duplication have been described; common findings include relative macrocephaly, frontal bossing, hypertelorism, developmental delay, intellectual disability, and autistic features. The deletion or duplication may be inherited from a clinically unaffected parent (33, 34).

Fragile X testing

Fragile X testing is widely recommended because the condition is relatively common, with health and reproductive implications for family members who carry the premutation allele. Autism has long been recognized as part of the clinical spectrum of fragile X syndrome (37). The prevalence of fragile X syndrome among individuals with ASDs is 1.5–3%; rates of ASDs among males with fragile X syndrome range from 18% to 67%, while that in females is 10–23% (38–41). Because pre-pubescent children with fragile X syndrome may not exhibit the typical physical manifestations of the syndrome (such as long face, large ears, and macro-orchidism), it is important to rule out in all children presenting with developmental delay, regardless of sex. Mosaicism for the expanded repeat or promoter methylation may lead to a milder phenotype, so even children with relatively mild impairments and autistic features should be tested (42, 43).

MeCP2

MeCP2 mutation testing is recommended for all girls with ASDs and global developmental delay, especially in the presence of Rett syndrome features.

Since its discovery as the causative gene in over 80% of girls with Rett syndrome (44), *MECP2* has been suspected to play an important role in the underlying pathogenesis of ASD. Rett syndrome was considered a distinct subtype of ASD in the Diagnostic and Statistical Manual (DSM) IV-TR (although the DSM-5 removes Rett syndrome from this category), because the symptoms in the earliest stages of the disorder are similar to those of idiopathic autism. Distinguishing features of classic Rett syndrome include partial or complete loss of acquired purposeful hand skills and spoken language, gait abnormalities and postnatal deceleration of head growth (45). However, 0.8–1.3% of females with ASDs but no features of Rett syndrome, nonetheless have an *MECP2* mutation (8). These girls may, with age, go on to meet clinical diagnostic criteria for classic or atypical Rett syndrome, but many do not (46).

Evidence does not support a role for *MECP2* mutation testing in males with idiopathic ASDs (47, 48). Inactivating *MECP2* mutations associated with Rett syndrome in females are occasionally found in males with early-onset encephalopathy, characterized by minimal developmental progress and early death, typically

Table 3. Management implications for selected autism-associated genetic diagnoses

Management implication	15q11-q13 DUP (mat)	16p11.2 DEL	22q11.2 DEL	7q11.23 DUP	1q21.1 DEL	FXS	Rett	PTEN	TS
Family planning									
Recurrence risk counseling	+	+	+	+	+	+	+	+	+
Prenatal diagnosis	±	±[a]	+	±[b]	±[c]	+	+	+	+
Identification of other family members at risk for medical complications	+	+	+	+	+	+	−	+	+
Screen/monitor for medical complications	+	+	−	+	+	+	+	−	+
Seizures	−	−	+	−	−	−	−	+	−
Endocrinopathy	−	+	−	−	−	−	−	−	−
Obesity	−	−	−	−	−	−	+	−	−
Scoliosis	+	−	+	+	+	−	−	−	+
Congenital anomalies	−	−	−	−	−	−	−	+	+
Tumor screening									

ASD, autism spectrum disorder; DEL, deletion; DUP, duplication; FXS, fragile X syndrome; TS, tuberous sclerosis; ±, consider offering prenatal genetic testing, but only after evaluating the CNV-positive parent for the presence or absence of a neurocognitive phenotype, and following careful genetic counseling addressing the issues of phenotypic variability, incomplete penetrance and the possibility of that a CNV-negative fetus may go on to develop an ASD due to unidentified genetic/genomic variants segregating within the family.

[a]16p11.2 deletions appear to be highly penetrant conferring risk for a range of neurocognitive disorders including ASD. For autistic probands carrying this deletion, deletion negative ASD siblings and apparently normal transmitting parents have been reported.

[b]Almost all individuals with 7q11.23 duplications develop neurocognitive abnormalities (prominent speech delay, developmental delay, ASD, attention deficit-hyperactivity disorder (ADHD) and anxiety disorders), but individuals with neither speech nor cognitive impairment have been reported.

[c]Deletions of the distal 1q21.1 region appear to be highly penetrant for neurocognitive abnormalities [intellectual disability (ID), ASD and schizophrenia] and/or congenital abnormalities (congenital heart disease and renal abnormalities), but apparently normal carriers have been reported.

from aspiration pneumonia (49). Sequence variants in conserved nucleotides within the 3′UTR of *MECP2* have been documented in males with idiopathic ASDs, but the pathogenicity of these variants is not clear (50, 51). For autistic males with severe intellectual disability (ID), truncal hypotonia and progressive spasticity, one should consider *MECP2* duplication in the differential diagnosis (52).

PTEN

All individuals with ASD who have a head circumference >3 standard deviations above the mean for age should be considered for *PTEN* mutation analysis. Although uncommon, there are possible implications for cancer prevention in the proband and possibly other family members. Mutations in the tumor suppressor gene *PTEN* cause a spectrum of overlapping phenotypes. Cowden syndrome is an adult-onset condition characterized by tumors of the thyroid, breast, and endometrium, and characteristic skin findings. Bannayan-Riley-Ruvalcaba syndrome (BRRS) presents with developmental delay with or without autistic features, macrosomia, intestinal hamartomatous polyposis, and skin findings (pigmented genital macules and lipomas). Both disorders have absolute macrocephaly. Both phenotypes can be present in the same family, and even in the same individual (53). *PTEN* mutations are found in at least 1% of individuals with ASD and macrocephaly (5, 54, 55). Generally, the macrocephaly is extreme (>3 standard deviations above mean), and other features of BRRS and/or Cowden syndrome may or may not be present at diagnosis. Long-term prospective studies are needed to determine the proportion of autistic individuals with *PTEN* mutations who will eventually develop tumors. This condition is autosomal dominant, therefore, parents and siblings need to be tested and regularly screened for associated cancers if found to carry the mutation.

Metabolic screening for inborn errors of metabolism

ASDs are not, on their own, an indication to screen for inborn errors of metabolism; however, any features on history or physical exam that create suspicion for particular metabolic conditions – particularly if treatable – should be selectively tested for. Some notable examples to keep in mind include undiagnosed phenylketonuria, Sanfilippo syndrome, Smith-Lemli-Opitz syndrome, and adenylosuccinate lyase deficiency.

Genetic counseling for ASD recurrence risk

Parents of children with ASDs are generally aware that their subsequent children are at increased risk to be ‘on the spectrum’, but the magnitude of this risk is often

over- or underestimated (56–58). Genetics services are under-utilized by these families: recent studies show that only 20% of families surveyed have seen a genetics professional, while over 90% of those asked would be willing to accept such an appointment if offered (58, 59). Even parents with completed families may benefit from a genetics assessment, if simply for additional information and reassurance.

In order to provide the family with an accurate recurrence risk (RR) for ASDs, one must have attempted to make a precise genetic diagnosis in the proband, using the testing strategies mentioned above. Below we briefly discuss some of the complexities of genetic counseling for ASDs.

When all testing in the proband is negative or inconclusive

If no apparent genetic cause is identified in the proband – as is the case presently for the majority with ASDs – the RR is extrapolated from empirical studies. Retrospective family studies published prior to the late 1990s estimated the RR for a couple with one autistic child to be 3–10% (60, 61). However, older studies are limited by small sample sizes and biases related to ascertainment, reporting, and stoppage factors (the tendency to choose not to have more children when an affected child is identified in the family). Because the diagnostic criteria for ASDs have broadened over time, they may have missed counting siblings with milder forms. A recent large ($n = 664$), longitudinal, prospective study of high-risk infants (younger siblings of probands with ASD) has shown that the RR is higher than previously estimated, as 18.7% of 'baby sibs' were ultimately diagnosed with an ASD (62). The RR did not change with the severity of ASD symptoms or with the sex of the proband. The sex of the next child, however, does impact on RR, as males are consistently at higher risk for ASDs. When two siblings in one family are affected with ASD, the RR for younger sibs increased to 32.2%, which is consistent with older estimates of 25–35% (61, 63). The incidence of ASDs among the offspring of individuals themselves on the spectrum is unknown, but our anecdotal experience suggests that the risk is probably higher than for siblings. Likewise, no data exists on the RR to half-siblings or third-degree relatives, although it is generally accepted that the RR falls off dramatically with more distant family relationships.

When a de novo pathogenic mutation or CNV is found in the proband

In such cases, the RR is typically quoted as 1%, taking into account the rare cases of gonadal mosaicism in one of the parents, or the possibility that one parent carries a chromosomal rearrangement that predisposes to the CNV, with much higher RR. For example, we reported two siblings with ASDs who were found to have identical '*de novo*' 1p21.1 deletions; the mother was subsequently found to carry the deletion at 1p21.1, with the deleted material inserted into another chromosome (64).

When an ASD 'risk variant' with incomplete penetrance is found in the proband

One of the most difficult scenarios for genetic counseling currently is attempting to give accurate RR figures when chromosomal microarray (CMA) done on the proband reveals a CNV known to demonstrate incomplete penetrance and/or variable expressivity. A common scenario is a child with ASD found to have a duplication of 16p11.2, inherited from an unaffected parent. Arguably, the CNV may not be the sole cause of this child's autism, but having the CNV increases the chances of ASD by an indeterminate amount. The actual risk is likely to depend on the precise combination of other genetic variants, some *de novo* and some inherited, and possibly environmental exposures. Knowing just one of these factors (in this case, the CNV) is not enough to accurately predict the risk to this couple's future children of developing ASD. The issue of prenatal diagnosis in the next pregnancy is, therefore, a difficult one. If, on the other hand, the CNV is *de novo*, the RR of the CNV itself is less than 1%, but the RR for ASDs is not currently predictable. Until more expansive genotype–phenotype studies are conducted, empirically derived RR figures (i.e. ~15–20% for simplex families) should be considered the minimum RR regardless of risk variants found on microarray.

Occasionally, the outcome of testing reveals a genetic condition in the proband (e.g. 47,XXY); however, it is important to not 'explain away' the autism as part of the genetic condition. These conditions may confer an elevated risk of ASDs compared to the general population, but the possibility of co-existing susceptibility factors (such as mutations in other risk genes) should be considered. In these families, the RR estimate for ASDs may be closer to the empiric RR than to the condition-specific one.

Parents frequently ask whether a particular exposure during pregnancy or infancy caused or contributed to the child's autism. Evidence does not demonstrate that any single environmental exposure contributes a significant role (>1%) in causing autism. It is likely that any cause of abnormal brain development or early brain damage has the potential to contribute to ASDs and other neurodevelopmental phenotypes, with the ultimate outcome dependent heavily on genetic background.

The future of genetic testing for ASDs

There is still much to be learned about genetic causes of ASDs and other neurodevelopmental disorders. Currently, genetic testing for ASDs is limited to ruling out known genetic conditions and screening the genome for rare CNVs that confer risks of unknown magnitude. Studies using next-generation sequencing to identify new candidate genes for ASDs are beginning to emerge. The predominant approach has been to identify *de*

novo mutations in protein-coding genes (the exome) that are predicted to be damaging in ASD probands, and absent in control subjects. From 776 individual exomes sequenced to date (65–68), ASD probands have more *de novo* mutations in protein-coding genes, and more that are potentially deleterious, than unaffected siblings. Few recurrent single-gene candidates have yet emerged, supporting a polygenic model for ASDs. Several authors have estimated the total number of ASD-implicated genes to number in the hundreds, each with variable effect (67). Below we highlight only a handful of these genes, which may be the most penetrant for ASDs.

PTCHD1 locus

Deletions in the X-linked *PTCHD1* gene and in the upstream *PTCHD1AS1* non-coding RNA may be associated with intellectual disability with or without ASD (14, 69). A 167-kb deletion spanning exon 1 was reported in two brothers with ASD (13), and subsequently a whole-gene deletion was found in an X-linked pedigree of three males with intellectual disability and an unrelated male with ID and dysmorphic features (69). Deletions of this locus have not been reported in male controls, but are observed in females. Missense mutations in *PTCHD1* were also reported in 6/900 probands with ASD and 2/224 males with ID, with 6/8 of these mutations segregating with the phenotype in the family (69).

Neurexins

Neurexins are cell-adhesion molecules that connect presynaptic and post-synaptic neurons and mediate signaling across the synapse (70), making them attractive candidate genes for ASD. Exonic deletions involving *NRXN1* (at 2p16.3) have been found in 0.4% of probands with ASD, and rarely in controls, in large-scale genomic screening studies (2). Case reports describing autism probands with disruptions of the *NRXN1* locus reveal a variety of phenotypes, including classic autism, Asperger syndrome, 'social difficulties', anxiety, ADHD, language impairment, and non-specific dysmorphic features (71–74). *NRXN1* deletions and duplications are also reported in association with schizophrenia, with a significant excess of deletions (75–79). As with autism, schizophrenia is not universally manifest, as *NRXN1* CNVs are occasionally found in unaffected relatives. Disruptions of other neurexin genes have rarely been associated with ASDs or related disorders as well (80, 81).

SHANK genes

SHANK proteins are a component of the post-synaptic density of excitatory synapses. They serve as 'scaffolding' proteins, which interact with many other proteins to assemble signaling networks at the synaptic membrane and facilitate synapse maturation. The genes are highly conserved in mammals and widely expressed in the central nervous system. *SHANK3* at 22q13 is one of the genes deleted in Phelan-McDermid syndrome, the clinical characteristics of which include ID with severely impaired speech, and autistic features in at least 40% of affected individuals (82–85). *SHANK3* was first implicated in idiopathic ASD when a *de novo* deletion with a breakpoint within a *SHANK3* intron was discovered (86). Gene sequencing in ASD probands suggests that *de novo* disruptions of the coding sequence might contribute to non-syndromic ASD (86–89). *SHANK2* was next implicated, with the discovery of *de novo* deletions in two unrelated male probands with ASD (14). The third member of this gene family, *SHANK1*, was found deleted in a multigenerational family of four males with high-functioning autism, with sparing of two female carriers. A male with high-functioning autism unrelated to this family also has a *SHANK1* deletion (90). More studies are needed, but these cases suggest a milder ASD phenotype and male-limited expression associated with *SHANK1* haploinsufficiency.

Conclusions

The genetic testing and counseling approach to individuals with ASDs will continue to evolve as we learn more about the genetic factors involved and their relative contributions. There have been reports of applying panels of common single nucleotide polymorphisms (SNPs) to assess ASD risk (2, 91), but these approaches likely require more testing. With rapid emergence of whole-genome sequencing studies, which promises to capture the complete complement of genetic variation in a single experiment, there will be an explosion of new data leading to more comprehensive genotype and phenotype studies.

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