Diagnosis and Management of Autism Spectrum Disorder in the Era of Genomics
Rare Disorders Can Pave the Way for Targeted Treatments

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KEYWORDS

- Neurodevelopmental disorders • Autism spectrum disorders • Genetics
- Copy number variants • Chromosomal microarray • Whole-exome sequencing

KEY POINTS

- Like all neurodevelopmental disorders, ASD is a heterogeneous group of disorders characterized by a constellation of symptoms and behaviors that occur in early development.
- Genetic testing is the only standard medical workup recommended for all children diagnosed with ASD; more than 25% of children with ASD have an identified genetic cause.
- Clinical features, particularly presence of intellectual disability, epilepsy, motor impairment, or certain dysmorphic features, support a likely underlying genetic etiology.
- The comorbidity of intellectual disability and ASD requires that future studies carefully examine early developmental trajectories and cognitive abilities in these genetic variants and syndromes, so as to confirm the diagnostic specificity of ASD.
- Common phenotypes and natural history studies within genetic syndromes can help to inform prognosis and treatment targets.

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous group of disorders defined by impaired social communication function and the presence of restricted, repetitive patterns of behavior or interests.[1] Although the diagnosis of ASD is based on

behavioral signs and symptoms, the evaluation of a child with ASD has become increasingly focused on the identification of the genetic etiology of the disorder. With the advances made in genetic testing over the past decade, more than 25% of children with ASD have an identifiable, causative genetic variant or syndrome, and this rate continues to increase with improved methods in genetic testing. In fact, the term "idiopathic autism" has become increasingly obsolete in this era of genomics, sometimes replaced by the descriptor of "nonsyndromic autism" for cases without a defined genetic etiology. The identification of genetic variants has been accompanied by a concerted effort to define more homogeneous clinical syndromes that are informed by the underlying genetic etiology of a child's ASD. In the future, such characterization will facilitate targeted treatments based on mechanisms of disease and common clinical features. Here we present the clinical phenomenology of ASD, including evaluation and treatment, in the context of our growing appreciation of the genetic basis of this neurodevelopmental disorder.

DIAGNOSIS OF AUTISM SPECTRUM DISORDER IS NOT ETIOLOGY-BASED

As with all the neurodevelopmental disorders, the diagnosis of ASD is based on a collection of behavioral and developmental features, not on presumed or known etiology. However, specific clinical characteristics may provide useful clues for the identification of the underlying etiology. Therefore, the diagnostic evaluation of a child with known ASD, as will be outlined in later sections, is motivated by a search for causative or associated genetic variants and syndromes.

ASD is defined by a dyad of impairments in social communication skills and the presence of repetitive patterns of behavior or restricted interests in the early developmental period, with deficits leading to functional impairment in a variety of domains. The diagnosis must be made by an experienced clinician, using a combination of parent report, direct examination of the child, and standardized developmental and behavioral testing when needed. The combination of these tools can then be assimilated into a "best clinical estimate" based on diagnostic criteria established in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). In May 2013, the revised DSM-5 was published, and in it significant revisions were made to the diagnostic conceptualization of ASD (Box 1). Two fundamental changes were made. First, the separate categories of social function and communication in DSM-IV were merged into one category of social communication impairment. This change shows that deficits in communication, both verbal and nonverbal, are intimately linked to social deficits, particularly early in development. Second, the diagnostic categories (autistic

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Box 1

Changes from *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR) to DSM-5 for autism spectrum disorder

1. Broad category of autism spectrum disorder (ASD) replaces discrete diagnostic categories (autistic disorder, pervasive developmental disorder, not otherwise specified, Asperger disorder)

2. Separate domains of social and language impairment merged into one domain of social communication function

3. Symptom severity ratings generated for the 2 domains based on functional impairment

4. Sensory sensitivities added into repetitive behaviors/restricted interests domain

5. Although symptoms must begin in early childhood, age 3 is no longer a strict age of onset

disorder, Asperger disorder, and pervasive developmental disorder, not otherwise specified [PDD-NOS]) were removed and, instead, one umbrella diagnosis of ASD was created. This change from categories to a continuum better captures the true spectrum of symptom severity of this disorder and shows that often the separate diagnostic categories were not consistently applied across clinical or research centers.

The changes in DSM-5 raised concerns that previously diagnosed children would lose services because of changes in nomenclature and a resulting loss of diagnosis. Since then, several studies have compared DSM-IV and DSM-5 diagnoses with structured diagnostic assessments, such as the Autism Diagnostic Observation Schedule (ADOS) with mixed results. Some studies demonstrate very high consistency, whereas others demonstrate more discrepancy, particularly in those previously given a PDD-NOS diagnosis.[2,3] Of note, from a clinical perspective, a child diagnosed through DSM-IV need not be reevaluated for diagnostic purposes simply because of the changes in DSM-5.

Like most neurodevelopmental disorders, ASD has a strong male predominance.[4] There are 2 primary reasons for this uneven gender distribution. First, there exists a diagnostic bias, as boys tend to exhibit more externalizing and disruptive symptoms that facilitate referrals for diagnosis, and girls manifest symptoms such as anxiety and depression that may delay the diagnosis.[5–7] Second, specific genetic factors may protect girls from developing ASD ("female protective effect").[8,9] Support for this theory comes from studies demonstrating a greater ASD-related genetic load in female individuals with ASD compared with male individuals with ASD, and in clinically unaffected female relatives compared with unaffected male relatives of individuals with ASD. Further substantiation of the greater genetic load in female individuals is found by the higher rate of ASD in siblings of female individuals with ASD compared with male individuals with ASD.

CLINICAL HETEROGENEITY

Variability in clinical presentation is rooted in severity of impairment and comorbidities. Intellectual disability, ranging from mild to severe, occurs in 70% of children.[10] Language impairment can range from deficits in pragmatic use of language to complete lack of spoken language, with 30% of children with ASD remaining minimally verbal despite intensive intervention.[11] Other sources of heterogeneity result from neurologic comorbidities (epilepsy, sleep impairment, motor delays and deficits) and psychiatric disorders (depression, anxiety, irritability, attention deficit hyperactivity disorder). This heterogeneity in clinical presentation requires that treatments, both pharmacologic and behavioral, move away from a "one-size-fits-all" approach and, rather, become tailored to a child's individual clinical profile. As discussed in the following sections, the identification of causative genetic variants can facilitate the characterization of more homogeneous clinical subgroups that, in turn, can guide more targeted therapies.

HERITABILITY OF AUTISM SPECTRUM DISORDER

ASD is one of the most heritable neuropsychiatric disorders, as recognized from the earliest twin studies,[12] with concordance rates in monozygotic twins approaching 70%. Recurrence rates in siblings of children with ASD range from 5% to 20%, with higher rates if the proband is a female. In large prospective cohort studies of infants with older siblings with ASD, the rate of developing ASD has been reported in 18% of infants.[13] The recurrence rate increases to 33% if a family has 2 children with ASD. These heritability estimates can be useful when counseling patients about family planning based on family history of ASD.[14] Considerable research efforts have been

dedicated to prospective studies of infant siblings of children with ASD, with the goal of identifying early risk markers and predictors of ASD in this high-risk cohort. Because of the genetic heterogeneity of the sample, no single developmental trajectory or clinical predictor of ASD has been discovered. In fact, these studies have been most successful in identifying overall differences between high-risk and low-risk infants, thus reflecting an endophenotype of elevated risk rather than specific predictors of ASD. By 12 months of age, high-risk infants demonstrate more atypical behaviors, such as reduced social interest and affect, social smiling, orienting to name, imitation, and atypical eye contact. Earlier in infancy, prebehavioral biomarkers of risk include differences in resting state electroencephalogram (EEG) patterns and face processing.[15] These studies have been instrumental in reinforcing that atypical patterns of both brain development and behavior can be quantified early in the developmental period, before formal clinical diagnoses can be made, which, in turn, has justified continued research in early risk markers for ASD.

ADVANCES IN GENETIC TESTING

In part because of the well-established heritability of the disorder, genetic testing for children with ASD has been routinely performed for decades. Initially, the standard test in children was composed of karyotyping alone, which could identify abnormalities only larger than approximately 3 to 5 million base pairs, visible under a light microscope. However, recent advances in genetic methods have led to the identification of contributory mutations in up to 30% of children with ASD.[16,17] The first breakthrough technology was the chromosomal microarray analysis (CMA).[18] Any structural chromosomal duplication or deletion that is larger than 1 kB and causes a deviation from the control copy number is considered a copy number variant (CNV). CNVs can be inherited or sporadic (de novo), with the latter type of mutation considered more likely to be pathogenic. The 2 types of CMA technologies that are most widely used include the array-based comparative genomic hybridization (aCGH) and the single nucleotide polymorphism (SNP) array, both of which permit high-resolution molecular analysis of chromosome copy number. The SNP array has the advantage of being able to detect specific inheritance patterns, such as uniparental disomy, which cannot be detected by aCGH.[19] Both aCGH and SNP arrays provided the first opportunity to perform relatively unbiased genome-wide surveys of chromosomal deletions and duplications with much greater resolution.
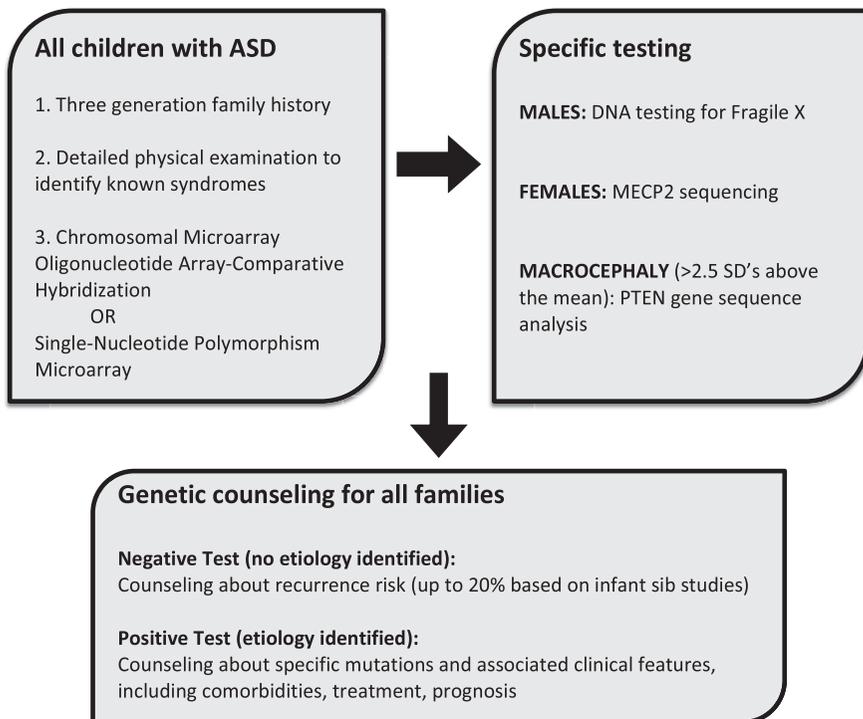
However, there are limits to the resolution of CMA testing, and point mutations and microdeletions cannot be identified using these methods. More recently, whole-exome and whole-genome sequencing technology has facilitated investigations at the level of the single base pair, allowing for analysis of single gene defects and for the identification of partial loss of gene function.[16,17,20,21] Most large-scale exome-sequencing studies have been based on data from simplex families, or families with only one affected child (such as the Simons Simplex Collection, a registry of simplex families funded by the Simons Foundation), leading to a growing appreciation of the role of de novo mutations in the pathogenesis of ASD. From these large cohorts of thousands of children, more than 500 candidate genes have been identified, each with 50% chance of being contributory or causative. Network analyses of the functions of the potentially causative genes finds genes implicated in synaptic formation and integrity and in chromatin modulation.[22,23]

GUIDELINES FOR GENETIC TESTING IN AUTISM SPECTRUM DISORDER

The guidelines for genetic testing for ASD have been revised to reflect the advances in methods, which, in turn, have led to larger populations of individuals with known

genetic syndromes and variants associated with ASD. In 2000, the American Academy of Neurology and Child Neurology Society published guidelines on the screening and diagnosis of autism, stating that "high-resolution chromosome studies (karyotype) and DNA analysis for fragile X should be performed in the presence of mental retardation…or if dysmorphic features are present."[24] Revised guidelines for testing were published by the American College of Medical Genetics (ACMG) in 2013 (Fig. 1).[25] After a comprehensive 3-generation family history, ACMG recommends a CMA for all children. Additionally, fragile X testing should be performed in boys and MECP2 testing (for Rett syndrome) in girls. Children with macrocephaly (head circumference >2 SDs above mean for age) should be tested for phosphatase and tensin homolog (PTEN) gene mutations. A positive test result should be followed by testing of parents for the determination of heritability of the variant. After testing is complete, genetic counseling should be provided regardless of results, as there are risks to future siblings regardless of genetic etiology, as described previously.

Of note, no other neuroimaging or medical testing is routinely recommended for children with ASD. However, certain clinical features may prompt further testing (Box 2). Although debate does exist about the implications of the baseline EEG abnormalities found in up to 60% of children with ASD, routine EEG testing is not recommended for all children with an ASD diagnosis. Instead, overnight EEG investigation should be performed in children with a high clinical suspicion for epilepsy or with clear

All children with ASD

1. Three generation family history

2. Detailed physical examination to identify known syndromes

3. Chromosomal Microarray Oligonucleotide Array-Comparative Hybridization
        OR
Single-Nucleotide Polymorphism Microarray

Specific testing

MALES: DNA testing for Fragile X

FEMALES: MECP2 sequencing

MACROCEPHALY (>2.5 SD's above the mean): PTEN gene sequence analysis

Genetic counseling for all families

Negative Test (no etiology identified):
Counseling about recurrence risk (up to 20% based on infant sib studies)

Positive Test (etiology identified):
Counseling about specific mutations and associated clinical features, including comorbidities, treatment, prognosis

Fig. 1. Recommendations for clinical genetic testing in children with ASD. (*Data from* Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2013;15:404.)

Box 2
Medical workup for ASD

Genetic testing: indicated for all individuals with ASD, see Fig. 1.

Metabolic testing: not indicated routinely, consider if multisystem involvement (cardiac, hepatic, renal), lactic acidosis, severe anemia

MRI: perform if focal neurologic examination, macrocephaly, genetic syndromes associated with structural brain abnormalities

Electroencephalogram: perform for episodes concerning for seizure, language regression, specific genetic syndromes associated with epilepsy

Polysomnograph: May be useful for diagnosing treatable sleep disorders (insomnia) and for diagnosing nocturnal seizures.

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evidence of language regression that would suggest electrical status epilepticus of sleep.[26,27] Several genetic syndromes, such as tuberous sclerosis complex (TSC), Rett syndrome, fragile X, and Dup15q syndrome are characterized by a high rate of early-onset epilepsy and ASD. In nonsyndromic ASD, the risk of epilepsy seems to increase with age. The largest cross-sectional study of almost 6000 children with ASD and epilepsy found that epilepsy in ASD was associated with lower cognitive, adaptive, and language ability, as well as greater autism severity, with peak prevalence of epilepsy occurring at age 10.[28]

MORE THAN 25% OF INDIVIDUALS WITH AUTISM SPECTRUM DISORDER HAVE AN IDENTIFIABLE GENETIC CAUSE

With genetic testing now routinely recommended and performed, a growing number of individuals are diagnosed with genetic etiologies for their ASD. Two primary categories of genetic etiologies of ASD exist: single gene disorders and CNVs. Single gene disorders are detected in 3% to 5% of children with ASD, and include syndromes such as fragile X, TSC, Rett syndrome, and neurofibromatosis. At least 20% of individuals with ASD have identifiable, causative de novo copy number variations and single gene mutations that are identifiable by using current genetic testing. No single variation, however, accounts for more than 1% of ASD cases, consistent with the phenotypic heterogeneity of the disorder.[29]

CLINICAL RELEVANCE OF GENETIC TESTING: MOVING TOWARD TARGETED PHENOTYPING AND TREATMENT

Parents often voice skepticism about the utility of genetic testing of their child with ASD, highlighting the concern that the knowledge about a causative variant will not actually benefit or inform their child's management and treatment. In the past, knowledge about an associated genetic syndrome or variant did hold more scientific promise than clinical significance. However, recent research efforts have bolstered the clinical impact of the diagnosis of a genetic syndrome or variant associated with ASD, and these advances in the clinical phenomenology of autism genetics are described in the next sections. First, widespread genetic testing has led to the diagnosis of larger cohorts of children with similar variants, which facilitates the identification of common clinical features that can inform more behavioral intervention targets. Second, advances in the identification of causative genes and pathogenic

mechanisms associated with these genes have led to molecular treatment targets that, ultimately, may prevent the development of ASD in certain disorders.

COMMON CLINICAL FEATURES: SYMPTOM CLUSTERS

The level of precision in genetic testing still exceeds the precision in clinical phenotyping of the identified genetic syndromes (Table 1). However, definite symptom clusters, or clinical features, have been identified that are highly associated with genetic etiologies of ASD, leading to the commonly used term "syndromic autism."[30] These clinical features include intellectual disability (ID), epilepsy, and motor impairment (particularly hypotonia or delay in achieving motor milestones). The presence of macrocephaly or microcephaly (defined by head circumference >2.5 SDs from the mean) can greatly narrow the differential diagnosis. Of each of these comorbidities, ID certainly is the most prevalent, and its presence can reinforce the need for genetic testing. A recent report from the Simons Simplex Collection found that the mean IQ of affected female individuals with de novo mutations was 78, whereas the mean IQ of affected male individuals with de novo mutations was 90.[22] Symptom clusters hold clinical utility in that they may strengthen the argument for genetic testing in children with comorbid ID or epilepsy, and they can guide the need for screening and management of comorbidities, particularly seizures.

INTELLECTUAL DISABILITY AND AUTISM SPECTRUM DISORDER IN GENETIC SYNDROMES

The comorbidity of ID and ASD requires that future studies carefully examine early developmental trajectories and cognitive abilities in these genetic variants and syndromes to confirm the diagnostic specificity of ASD. In DSM-5 it is clearly articulated

Table 1
Common clinical features in genetic variants and syndromes associated with ASD

ID and ASD		
Epilepsy	**Motor Impairment**	**Macro/Microcephaly**
TSC (TSC1 and TSC2)	Hypotonia	Microcephaly
Rett syndrome (MECP2)	Rett Syndrome	Rett syndrome or MECP2 mutations
CNTNAP2	NRXN1 deletion	Angelman syndrome
SYN1	2q23.1 deletion	Cornelia de Lange syndrome
Fragile X syndrome	15q11.2-q13 duplication	16p11.2 duplication syndrome
UBE3a (Angelman syndrome)	22q13.3 deletion (SHANK3) (Phelan-McDermid syndrome)	17q21.31 duplication syndrome
1q21.1 deletion	Severe stereotypes	Macrocephaly
7q11.23 duplication	Rett syndrome	PTEN mutations
15q11.1q13.3 deletion and duplication	Motor delays	Fragile X
16p11.2 deletion	AUTS2	1q21.1 duplication syndrome
17q12 deletion	Fox1 (A2BP1)	
18q12.1 duplication	2q23.1 deletion and duplication	
22q11.2 deletion		

Abbreviations: ASD, autism spectrum disorder; ID, intellectual disability; PTEN, phosphatase and tensin homolog; TSC, tuberous sclerosis complex.

that "to make comorbid diagnoses of ASD and ID, social communication should be below that expected for general developmental level." In other words, clinicians must consider a child's mental age, not chronologic age, when evaluating his or her social, language, and behavioral abilities, as the use of chronologic age may lead to an overdiagnosis of ASD. For instance, in a recently published study of developmental trajectories in infants with TSC, cognitive impairment by age 12 months (based on a standardized scale of development: the Mullen Scales of Early Learning) was strongly associated with social communication impairments at age 3, as quantified by ADOS. The confirmation of ASD in these children with elevated ADOS scores required additional evaluation by an experienced clinician to determine if the scores were secondary to overall delay or specific to ASD.[31] Disentangling ID from ASD holds implications for intervention. For instance, social communication impairment secondary to global developmental delay may improve with interventions targeting cognitive and, perhaps, motor skills, whereas social communication deficits rooted in limited social motivation or attention may respond better to targeted social skills, play-based, therapies. As another example, language impairment in ASD can result from deficits in low-level auditory processing, processing of speech sounds, attention to speech cues necessary for language learning, social motivation, or motor impairment that can undermine the production of words. Identification of the specific pathway will facilitate the choice of intervention most effective for the language impairment in subgroups of children.

Overall, future efforts in clinical characterization of children with genetic syndromes may be better served by placing greater emphasis on core deficits, such as social communication skills or language, rather than on categorical clinical diagnoses, to then design and direct interventions toward the specific areas of impairment.

TREATMENT OF AUTISM SPECTRUM DISORDER IS NOT YET ETIOLOGY-BASED

Behavioral intervention is the mainstay of treatment for core deficits in ASD, with structured, high-intensity, and autism-directed interventions associated with better outcomes.[32] Under the umbrella term of "ABA" or applied behavioral analysis, falls several effective and distinct methods.[33] The traditional ABA program, based on the work of Lovaas and colleagues,[34] is intensive and individualized, with the use of discrete trials to teach simple skills that then can build to more complex skills. Discrete trial therapy is particularly effective for modifying problem behaviors and for teaching specific cognitive and academic skills. More naturalistic and play-based treatments include pivotal response treatment and Floortime. The only medications approved by the Food and Drug Administration (FDA) for ASD are the atypical antipsychotics risperidone and aripiprazole. Both are approved for the treatment of irritability, defined by physical aggression and tantrum behavior. Their primary, sometimes dose-limiting, side effects include weight gain and sedation. Recent guidelines published by Volkmar and colleagues[35] emphasize that pharmacologic treatment can, particularly by reducing comorbidities and aberrant behaviors, "increase the ability of persons with ASD to profit from interventions and to remain in less restrictive environments." In other words, by improving intrusive or maladaptive behaviors, pharmacotherapy can facilitate a child's ability to engage in and learn from educational and behavioral interventions for their core ASD symptoms.

With the advances in our knowledge about genetic etiologies of ASD and the identification of molecular pathways that may be aberrant in these disorders, there is hope for pharmacologic and behavioral targets that may prevent the development of, or attenuate the impact of, the disease. Two such examples of such treatment targets are provided in the following sections.

TARGETED TREATMENT EXAMPLE 1: TUBEROUS SCLEROSIS COMPLEX

The genes responsible for TSC (*TSC 1* and *2*) encode for proteins that regulate the mTORC1 protein complex. Mammalian target of rapamycin (mTOR) is critical for protein synthesis, cell growth, and axon formation. Inactivation of the TSC genes causes an upregulation of this mTORC1 pathway, resulting in an increase in protein synthesis, aberrant axon formation, and tumor growth. In the past 5 years, based on the known mechanisms of *TSC1/2* regulation of the mTOR pathway, mTOR inhibitors have been studied extensively in mouse models of TSC. These studies have revealed that mTOR inhibitors can reverse the cognitive and social impairments found in adult mouse models after surprisingly short courses of treatment.[36,37] In turn, these promising findings have inspired the investigation of mTOR inhibitors, such as rapamycin, in patients with TSC. Everolimus, an mTOR inhibitor, is now FDA approved for reduction of subependymal giant cell astrocytomas (SEGAs) in children with TSC.[38] Now, with safety profiles established, several international studies are investigating the use of mTOR inhibitors for improving the cognitive delays and behavioral deficits found in children with TSC.[39]

Additionally, because TSC is often diagnosed in utero due to cardiac rhabdomyomas or SEGAs, these infants can be studied prospectively for the evaluation of early developmental trajectories and risk markers for ASD, providing an opportunity to identify common behavioral and developmental characteristics within TSC that could serve as targets for behavioral intervention. In the first large-scale prospective study of development in TSC, infants demonstrated delays in visually mediated behaviors (visual attention, disengagement of attention) in the first year of life. Furthermore, declines in nonverbal cognition in the second year of life predicted symptoms of ASD at 24 and 36 months. This developmental slowing in nonverbal cognition is a trajectory that has not been previously reported in other high-risk groups and, in turn, may represent a TSC-specific developmental trajectory.[31] Based on this finding, the group is now investigating whether a behavioral intervention that targets nonverbal communication (such as visual attention to social information) in the second year of life can prevent the development of ASD in TSC. Ultimately, for infants with TSC, a combination of targeted molecular and behavioral treatments may attenuate or even prevent the neurodevelopmental disabilities that occur early in development.

TARGETED TREATMENT EXAMPLE 2: DUP15Q SYNDROME

Duplication of 15q11.2-q13, or Dup15q syndrome, provides another timely example of the clinical utility of genetic testing for targeted management and, eventually, treatment. Duplications of the 15q11.2-q13 region of maternal origin were first associated with ASD more than 15 years ago, and now these duplications are among the most common CNVs associated with ASD and related neurodevelopmental disorders. Duplication of this region leads to the overexpression of several genes, most notably UBE3A (E3 ubiquitin ligase gene) and a cluster of receptor subunits for the neurotransmitter $GABA_A$. There are 2 major structural versions of this CNV: isodicentric chromosome 15 (idic[15]) and interstitial duplication of chromosome 15 (int.dup[15]). Over the past several years, a national alliance of families affected by this CNV, known as the Dup15q Alliance, has been collecting a registry of patients with the goal of advancing both clinical care and scientific investigation of the disorder. There are now more than 400 patients with clinical data entered into the registry with varying duplication types. Through collaborative efforts, studies have identified neurobiological, developmental, and behavioral features of Dup15q syndrome.

In addition to ASD, this CNV is characterized by early onset of epilepsy, profound hypotonia in early infancy, moderate to severe ID, and, in a subgroup of children, excessive beta-range activity (15–30 Hz) on clinical EEG, with overall clinical severity greater in the idic(15) cases.[40–42] The excessive beta oscillations likely represent an electrophysiological signature of the upregulation of $GABA_A$ receptor genes contained in the duplicated chromosomal region.

As a result of data gathered from the national Dup15q syndrome registry, a recent large cohort study of 95 children with Dup15q syndrome sought to identify common characteristics and potential treatments for epilepsy in this population.[43] Investigators found that epilepsy was much more prevalent in the idic(15) cases than in the int.dup15 cases, multiple seizure types (both generalized and focal) were identified, and that infantile spasms were common, reported in 42% of cases. Both broad-spectrum and focal antiepileptic medications (such as carbamazepine) demonstrated efficacy for seizure reduction, suggesting a multifocal etiology to the epilepsy. Importantly, GABAergic medications, such as benzodiazepines, were relatively ineffective, likely because of abnormalities in gamma-aminobutyric acid (GABA) transmission in the setting of overexpression of GABA-A receptor genes in the 15q region. This key discovery led to the recommendation that benzodiazepine medications, which are commonly used in the epilepsy population as a whole, be avoided in this genetic subgroup.

In parallel to the efforts in epilepsy, investigators have begun to better characterize the social communication phenotype in Dup15q syndrome. Given the significant hypotonia present in these children, there is particular interest in the effects of motor delays on social communication development, particularly eye contact, nonverbal communication, expressive language, and play. Elucidation of the nature of the core deficits of ASD in Dup15q syndrome will facilitate the design and implementation of targeted behavioral interventions that will specifically benefit this subgroup within the autism spectrum.

SUMMARY

Genetic testing for children with ASD is no longer confined to the realm of academia. As cohorts of children with genetic variants and syndromes associated with ASD are identified, common themes across disorders and unique features within disorders can be identified that will ultimately guide targeted interventions rooted in both biological mechanisms and behavior.

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