Diagnosis and Management of Autism Spectrum Disorder in the Era of Genomics

Rare Disorders Can Pave the Way for Targeted Treatments

Elizabeth Baker, BA, Shafali Spurling Jeste, MD*

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

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Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, UCLA, 760 Westwood Plaza, Los Angeles, CA 90095, USA
* Corresponding author.
E-mail address: sjeste@mednet.ucla.edu

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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

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