

# Advances in Understanding Autism Spectrum Disorder

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## Abstract

### Keywords

- ▶ autism spectrum disorder
- ▶ genetics
- ▶ environmental factors
- ▶ treatment

Autism spectrum disorder (ASD) appears to have a dramatic increase over the last twenty years and according to the latest estimates, 1 out of 68 children has been diagnosed with this disorder. In this context, it is crucial to provide clinicians with the most updated information on the genetic, epigenetic, and environmental understanding of ASD, as well as to provide the best scientific evidence in order to build successful therapeutic strategies for the patients.

The management of autism spectrum disorder (ASD) is typically complex and multidisciplinary. The core symptoms, consisting of deficits in social communication and language, and a pattern of restricted interests and repetitive behaviors, are best addressed with early and intensive psychoeducational programs that have been shown, on an average, to ameliorate cognitive and social functioning of people with ASD.<sup>1,2</sup>

ASD is a multifaceted brain condition covering a wide range of symptoms. More than 25% of children with ASD do not speak. On the other hand, there are people of average or high intelligence who can live relatively normal lives. Other people with ASD score above average on intelligence tests, but struggle to communicate verbally or make compulsively repetitive movements. In some cases, the disorder might be hardly noticeable, revealing itself only subtly. Whatever the case may be, ASD is a challenge for those who have it as well as for parents and caregivers.<sup>3,4</sup>

ASD appears to have become more common over the past half-century, with a dramatic increase over the last twenty years. According to the latest estimates, ~1 out of 68 children

were diagnosed with this disorder in 2010 in the United States.<sup>5</sup> This growth might be explained to some extent by an increased level of awareness of the disorder in the society and among professionals, as well as by the enhanced diagnostic methods. However, this cannot explain the whole increase in prevalence, suggesting that other factors play a role as well.

The majority of researchers believe that ASD is diagnosed almost five times as often in boys than in girls, begins early in life, perhaps already in the womb. However, sometimes evident symptoms do not appear until later in life. The causes of ASD are, until now, not well understood. Researches on homozygous twins suggest that genes play an important, probably dominant role; but some environmental factors appear to matter too. Recent advanced genome analysis techniques identified several genes associated with ASD. These are often genes that code for proteins associated with synaptic functions.<sup>6,7</sup> Nevertheless, so far, no major causative gene has been identified; hundreds of risk genes have been suggested, with either rare variants that are highly

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penetrant or common variants with little effect.<sup>8</sup> Advances in genetic technologies, large cohort studies, and widespread databases are needed to disentangle the genetic aspects of ASD so as to identify possible causative genes of ASD.<sup>9</sup> Interestingly, until now, many of the genes associated to ASD are linked together in gene networks that seem to converge into a relatively limited number of biological pathways.<sup>10,11</sup> For example, different genes that independently associate with autism, such as the TSC1, the TSC2,<sup>12</sup> the PTEN,<sup>13</sup> or the NF1<sup>14</sup> are biologically closely related to the mTOR pathway.<sup>15</sup> This pathway modulates many processes essential for growth by regulating protein translation rates and hence cell proliferation.<sup>16</sup>

However, because there is no reason to suspect that mutation rates have increased suddenly in a short period of time, the increase in ASD incidence cannot be explained only by genetic factors. Therefore, a wide range of possible causative environmental factors have been considered as well. Possible environmental risk factors include, among others, advanced parents' age, birth order, characteristics of the microbiome, organic toxicants, air pollution, or nutrients. Researchers are now increasingly focusing their attention at the interactions between environmental exposures and an individual's genetic susceptibilities. Moreover, the high epilepsy rates observed in ASD—EEG abnormalities and seizures affect 20–25% of people with ASD—suggest a role for neurobiological factors in the pathogenesis of the disorder.<sup>17</sup>

To date, there is no objective test for autism. Due to a lack of biological markers, ASD is diagnosed by observing behavior, and by asking questions to the caregivers. By doing so, ASD can be spotted with some reliability already by the age of two. But, time lags between a parent first expressing worry and final diagnosis are common. The consequence is that autism has too much time to advance before being treated. Actually, despite considerable progress in understanding the neurobiology of ASD, established treatments for core symptoms are still needed. To date, interventions commonly used for children with ASD include behavioral therapy and medications treating the associated symptoms, while effective pharmacological treatments for core symptoms of ASD are still lacking.

Psychiatric medications are commonly used in patients with ASD, with some studies showing its use in up to one-third of children and two-thirds of adolescents.<sup>18</sup> For years, this use has been based on anecdotal reports and expert opinion rather than on controlled investigations, thus raising concerns about both the efficacy and safety of these practices. More recently, research on the treatment of psychiatric symptoms in ASD has increased, and several controlled clinical trials have been conducted to test the benefits and tolerability of several pharmacological and psychosocial interventions.<sup>19</sup> This body of research provides an evidence-base for assessing the balance between the potential benefits and risks, which is necessary for the rational use of any intervention. Also, treatment of associated medical problems, such as seizure disorders, gastrointestinal symptoms, and Tourette syndrome, is often needed. For future, to develop treatments for autistic patients, it is crucial to understand their clinical development with longitudinal

studies. Longitudinal studies allow to closely follow the developmental trajectories of ASD and detect subtle changes in the behavior at different stages of development, both in terms of progressive appearance of clinical symptoms and impact of life experiences.

On the whole, pharmacologic treatments may increase the ability of people with ASD to better profit from psychoeducational and other interventions. Frequent targets of the drugs include ASD associated conditions, such as anxiety, depression, aggression, self-injures, hyperactivity, inattention, compulsive, repetitive or stereotypic behaviors, as well as, sleep disturbances.<sup>20</sup>

Behavioral and educational interventions can improve or alleviate ASD symptomatology, particularly if it is diagnosed early. Actually, behavioral programs that are implemented as early as possible and in an intensive manner can be sometimes useful in improving cognitive, adaptive, and social-communicative outcomes in young children with ASD.<sup>2,21</sup> These are based on a variety of developmental and behavioral strategies, including the promotion of joint attention, imitation, communication, and joint social participation. Behavioral techniques are particularly useful when maladaptive behaviors interfere with the social life of the person. However, looking at individual responses, some children show dramatic improvements, while others show minimal or no gains.<sup>22</sup> This limited knowledge on what works and for whom leaves open several methodological and theoretical questions. A meta-analysis suggested that early and intensive behavioral interventions seem to be effective in young children, but the same study stressed the need for more rigorous research to extend the findings to a larger population.<sup>23</sup>

The purpose of this special issue is to provide clinicians with the most updated information on the genetic, epigenetic, and environmental understanding of ASD, as well as, to shed light on the diagnosis and early treatment of core symptoms, so as to provide the best scientific evidence on which clinicians can build successful therapeutic strategies for their patients.

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