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The Etiology of Autism

Mayada Elsabbagh, PhD, Miriam McBreen, MA

McGill University, Canada

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Introduction

In recent years, there has been a major shift away from understanding autism as a narrowly defined, categorical disorder to understanding it as a spectrum of conditions that affect individuals differently.[1] As such, the impact of autism varies; some individuals can lead independent and fulfilling lives, but many develop substantial medical, educational and social difficulties that have a serious negative effect on their quality of life.[2] The heterogeneity of the condition has led some scientists to suggest that instead of one unique phenomenon, there are probably many "autisms" with different underlying biological processes and developmental pathways.

The current Diagnostic and Statistical Manual of Mental Disorders includes "autistic disorder," "Asperger's disorder" and "pervasive developmental disorder not otherwise specified" (PDD-NOS) as types of autism. Research has thus far failed to map these clinical subgroups onto a specific etiology or developmental pathway leading to each disorder. Today, there is increasing appreciation of the heterogeneity in the expression of the condition along numerous phenotypic dimensions, which overlap with those found in other conditions and in the general population.[4,5] As a result, the next edition of the Diagnostic and Statistical Manual of Mental Disorders will replace current categorical "subtypes" with a single category labelled "autism spectrum disorder."

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Recent Research Results

Twin and family studies have demonstrated that both genetic and non-genetic factors contribute to an increased susceptibility to autism.[6] The involvement of some genetic factors is stronger than others and so far a heterogeneous mix of pathways, rather than a single causal pathway, has been indicated. There is, however, growing evidence for the involvement of genetic risk factors that interfere with synaptic development and plasticity. Risk factors include common and rare genetic risk variants, as well as non-genetic risk factors. Common genetic variants tend not to be associated with very high risk for autism relative to the general population, but replication and confirmation of the role of these variants is still awaited. Among the clearer associations with autism are rare (defined as occurring in <1% of the general population)[6,7] *copy number variants*. Moreover, there is much overlap between some rare genetic syndromes and autism.

Currently, large-scale studies are ongoing to ascertain the extent to which each genetic risk factor is implicated in the etiology of the disorder. Hence, none of the genetic variants that have been identified so far can be considered clinically useful for the identification of autism in the general population.[8] Nevertheless, the testing for genetic variants of individuals diagnosed with a developmental disorder, including autism, aims to improve medical care by identifying variants that may give rise to co-morbid medical problems (e.g., the medical complications associated with tuberous sclerosis and micro-deletion and -duplication syndromes, such as epilepsy, and renal and gastrointestinal problems) and by establishing the risks of potential recurrence in future offspring of parents who already have a child with the condition. Non-genetic factors that increase the risk of autism are still poorly understood, and could include *epigenetic* and environmental factors.[9] Interactions between genetic and non-genetic factors can further contribute to autism risk in complex ways.[10]

The behaviours that are characteristic of autism first emerge and then evolve over the first few years of postnatal development. Nevertheless, recent evidence from studying infants at-risk for the condition suggests that alterations in brain development begin much earlier than the appearance of behavioural symptoms.[11] However, different infants exhibit variable early expression of autism both at the level of brain and behaviour that diverge into different developmental pathways over time.[10] As such, by adulthood, autism is associated with changes in a wide range of neurobiological systems. Many have suggested that autism is the consequence of an atypical process of specialization in various brain networks, and specifically in the social brain.[10]

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Research Gaps

There is widespread hope that translation of the current body of evidence into valid biological markers for autism, a condition currently defined on the basis of behavioural criteria, will advance research and practice. The discovery of biomarkers could not only reveal causes of the conditions, but also be clinically useful in complementing or improving the behavioural diagnosis of autism and enabling earlier detection of the condition. Recently, molecular genetic techniques (e.g., chromosomal microarray, CMA) have been developed for detecting submicroscopic deletions and duplications. Several scientific-industry consensus reports have advocated the use of these more powerful techniques as a test for genomic abnormalities for individuals with a range of developmental conditions, including autism. Studies using CMA to test very large samples of individuals who are already diagnosed with a developmental disorder have shown some form of genetic anomaly in 5–10% of individuals.[7] In addition to indicating co-morbid medical problems and recurrence risk, it is suggested that CMA testing may help families to understand the genetic contribution to the condition and thus provide insight into possible causes or factors leading to autism.

There are currently no scientific or industry guidelines for how CMA results should be reported to participants, but first steps towards such guidelines are underway.[7] Attempts to translate new genomic findings into clinical applications have resulted in mixed reactions from the scientific community and the public.[7,12] Difficulties often arise in cases where genetic variants are identified but their clinical significance remains unclear. The limited information regarding these variants means that accurate prediction of recurrence risk and developmental outcomes is not yet possible in most cases. In the future, a key scientific challenge will be to develop sufficiently large databases of genetic variants to ascertain their clinical utility in isolation or in combination with other genetic and non-genetic risk factors.

Other attempts to translate research on the neurobiological basis of autism into useful applications for identification and intervention have also met a number of key scientific challenges. First, experience in other areas of biomedical research highlights how challenging it can be to translate biomarker discovery into clinical applications, and very few clinically-useful biomarkers have as of yet been identified for neuropsychiatric conditions. Second, the identification of autism biomarkers has so far proved elusive, partly because definitions of the condition itself have changed considerably over time and are still developing. Researchers have primarily focused on mapping biomarkers onto clinically-defined categories, but such categories

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do not capture the current understanding of the increasingly multidimensional and complex clinical, cognitive and behavioural phenotype that is associated with autism and its overlap with other disorders. Third, developmentally invariant biomarkers for autism are particularly challenging because the phenotypic manifestations unfold as development progresses, especially during infancy and early childhood, reflecting dynamic developmental interactions among multiple risk factors.[10] Fourth, several proposed biomarkers were found not to be universal, and none has indexed the presence of autism in a majority of cases (poor sensitivity). Candidate biomarkers tend also to be associated with a range of other neurodevelopmental conditions and not only with autism (poor specificity). Finally, measuring some putative biomarkers is currently expensive, laborious and reliant on a high degree of technical expertise, restricting the possibility of their application in most clinical settings.

Conclusions and Implications for Parents, Services and Policies

Despite major advances in the understanding of the genetic, neurobiological and developmental underpinnings of autism, many aspects of the condition are still poorly understood. Recent attempts to translate the current understanding of the neurobiology of autism into clinically-useful applications have been met with scientific and societal challenges. These challenges underscore the biological heterogeneity of the condition, which contributes to a complex picture of autism. Information received by the general public, however, rarely reflects this level of complexity.

The scientific community needs to continue building the understanding of autism as a complex condition that is probably determined by multiple, yet to be understood pathways that lead to heterogeneous outcomes. Ideally, biomarker discovery should lead to an increased understanding of the complex nature of the autistic spectrum, rather than to deterministic or reductive thinking about the condition.

Major challenges to be overcome include the current absence of systematic input from the community affected by autism and research about what determines the perspectives of various stakeholders. Failure to contextualize emerging evidence on neurobiology within the unique needs of diverse communities would only serve to undermine their potential value. Through adequately-supported processes of knowledge translation, more involvement of families and clinicians in the research process will improve the integration of evidence into practice. By contextualizing existing and new research knowledge within the real-life experiences of affected

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families, science communication regarding autism biomarkers can serve its primary purpose of informing the public and contributing to ethically-informed knowledge translation. In the future, parents' decisions and preparations can be better supported if they know which of the many forms of autism could develop in their child. In the meantime, families have the right to receive scientifically-grounded information about the causes and biological manifestations of autism alongside evidence-based services.

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