Genetic findings in autism spectrum disorder

Food & Diet

Clinical practice, assessments, treatment, and parent education/counseling has opened my eyes to a question unanswered. For parents of children who receive an Autism Spectrum Disorder diagnosis (ASD), there are many unknowns. As a treating clinician, these parents turn to you for guidance and answers to their looming questions. These parents often feel their questions have not truly been answered and that they have been provided with little guidance and resources to help lead them in their new journey with their child. The dismay of being unable to provide families with answers lead me to an interest in researching the underlying genetic causes of Autism Spectrum Disorder.

Established research states that one in every sixty-eight children in the United States are diagnosed with autism. Typically, symptoms begin to emerge around eighteen months old. It is during this time frame that typically developing children are hitting speech, gross motor, and fine motor milestones. If children appear to be delayed in one or all areas of developmental milestones, attending pediatricians will typically send them for an evaluation. Children usually get diagnosed with Autism Spectrum Disorder around two years of age, although some get diagnosed sooner and others don’t get diagnosed until four years or older (Li et al., 2015).

Best clinical practice supports early detection and diagnosis of Autism Spectrum disorder in order to begin early intervention of treatments which lead to significant improvements in language skills, intellectual capacities, day to day living, and behaviors (Li et al., 2015). Typically, children who receive a diagnosis, whether earlier or later in life, do not receive this diagnosis via genetic testing. In comparison to other genetic or

chromosomally acquired neurodevelopmental disorders/diseases, Autism Spectrum Disorder only has a 40% diagnostic yield. This low number of diagnostic yields is estimated to increase due to the rapid advancements in technology (Li et al., 2015).

Research shows that if genetic testing for Autism Spectrum Disorder was standard protocol in the diagnostic process, it would account for earlier and better diagnosis of the disorder which would facilitate better outcomes for affected children and families. Genetic testing would clarify the etiology of Autism Spectrum Disorder and help develop biological based approaches for treatment of related complications. Although research suggests genetic testing is important and effective in guiding treatment for affected individuals, families with members who have an ASD diagnosis report they received no information or guidance from medical professionals to encourage them to receive genetic testing (Li et al., 2015).

Genetic testing and findings have revealed that Autism Spectrum Disorder likely develops during pregnancy. This discovery can help clinicians eliminate myths about potential causes of Autism Spectrum Disorder. For example, many parents fault themselves or vaccinations for the development of their child’s diagnosis. This discovery provides insight into the timing of onset of ASD and can link severity to specific numbers of copies of genome variations (Jones, 2014). Specifically, genetic testing prevents families’ search for answers that are typically unproductive, not backed by research, expensive, and disruptive of the current evidence-based treatments their loved one is receiving (Vorstman et al., 2017).

Research conducted during pregnancy suggests that there is a direct link between the DUF1220 genome copy number and the increased severity of the three main symptoms of Autism Spectrum Disorder: social interaction, communication, and repetitive behaviors (Jones, 2014). This also led to the discovery of a subtype of genome DUF1200 called CON1. This subtype increases each of the three primary symptoms, making them become incrementally worsened: impaired social reciprocity, impaired communication abilities, and increased repetitive behaviors (Jones, 2014). This helped create a basis for investigation of genetics in determining risk for Autism Spectrum Disorder.

Through use of genetic testing, it has been discovered that Autism Spectrum Disorder is one of the most heritable neurodevelopmental conditions (Johannessen et al., 2017). Most of the genetic studies that have been done on Autism Spectrum Disorder compare individual cases to controls which have been used to identify risk associated variations. This linked common polygenic de novo genes and inherited rare variations to the risk of an ASD diagnosis (Robinson et al., 2016). A polygene is one whose individual effect on a phenotype is too small to be observed, but in conjunction can act with another to produce an observable variation. A de novo gene, or “ new mutation and/or variant”, is a genetic alteration that is observable for the first time as a result of sperm or egg cell mutation.

In order to understand the relationship between these rare inherited variations and de novo mutations and how they are correlated with the presentation of Autism Spectrum Disorder, researchers had to look at variations of genes within unaffected populations. Almost all genetic risk

factors for autism can be observed in unaffected people. For instance, the population contains high amounts of variation in social interaction and communication, yet none of these people received an ASD diagnosis. Studies of unaffected family members of individuals with Autism Spectrum Disorder revealed that they showed subthreshold traits of autism. This finding suggests that similarities are inherited, and traits are correlated genetically (Robinson et al., 2016).

A study of 1, 532 families with members diagnosed with ASD showed that both inherited common number variants (CNV) and rare de novo mutations contributed to the development of Autism Spectrum Disorder. The higher amount of large rare CNVs increases the inherited variants in individuals with Autism Spectrum Disorder as compared to their unaffected siblings. Research estimates that rare genetic variants and de novo mutations account for 10-30% of causation in people with ASD. This is a tremendous increase from findings which date back fifteen years, showing that genetic variants and de novo mutations only accounted for 2-3% of causation (Vorstman et al., 2017).

Similar to other psychiatric disorders, Autism Spectrum Disorder’s estimated genetic correlation to variations of social and communication traits of the unaffected population suggest that there is a strong association. As per the Social & Communication Disorders Checklist, this suggests that the millions of variations of genomes controlling social interaction and communication amongst the normal population is strongly association with variations of genes within people who present with Autism Spectrum Disorder (Robinson et al., 2016). The overall common genetic variations in the population

contribute to the risk of ASD and the contribution of common inherited variations is responsible for between 15 and 50% of causation (Vorstman et al., 2017).

Even though evidence supports the causation of common inherited genetic variations in Autism Spectrum Disorder, rare and de novo variants typically confer a higher risk than common variants. This has led to the discovery of novel gene risks in ASD (Vorstman et al., 2017). Autism Spectrum Disorder implicated genes have been used to identify risk modules or units of risk on certain genes. This revealed genes that are associated with ASD based on co-expression. Co-expressed genes are associated with different phenotypes, including intellectual disability, epilepsy, schizophrenia and attention deficit hyperactivity disorder (ADHD). These genes are considered " guilty by association" with Autism Spectrum Disorder risk variants (Vorstman et al., 2017). Genetic correlation between ASD and other social communication disorders is estimated to be similar to the genetic correlation between Type II Diabetes and obesity (Robinson et al., 2016). Additional somatic symptoms have been identified through early clinical observations of individuals with Autism Spectrum Disorder, including gastrointestinal problems, sleep disorders, and immunological disorders (Vorstman et al., 2017). These somatic symptoms are typically observed in relation to severity of the diagnosis. Autism Spectrum Disorder is one that is known for the high amount of diversity in presentation between affected individuals.

A discovery called intermediate phenotypes, or phenotypes of an offspring expressing a mixture of the parents' phenotypes, helped researchers understand recurrence rates within families. The highest recurrence rates

were observed in monozygotic twins at 88%, then in dizygotic twins at 31%, and in siblings at 18. 7%. A syndromic autism diagnosis only accounts for 10% of individuals with Autism Spectrum Disorder (Fakhoury, 2018). These intermediate phenotypes must fulfill a certain number of criteria to be reliably measurable, heritable, stable over time, related to the disorder and its symptoms, and show an increased expression in unaffected relatives to have common genetic influence with the disorder. Intermediate phenotypes discovery is important because it represents a step beyond well-defined behavioral phenotypes and are more closely linked to the neurobiological pathway of risk genes (Fakhoury, 2018).

Another hypothesis that families question is the relationship between gender and risk for ASD. Common research suggests that males are at higher risk for developing autism, but new findings do not support this idea. An alternative approach to the concept of penetrance examined how much a proband on continuous traits deviates from what is expected based on parents (Vorstman et al., 2017). This approach allows for a more accurate investigation into additional modifiers that may be both genetically or environmentally influenced. Using this approach led to the discovery that the female gender has a higher resistance to penetrance of ASD linked mutational loads (Vorstman et al., 2017). These findings suggest that it is either less likely for a female to develop Autism Spectrum Disorder, or the threshold for penetrance of mutational loads in females is higher than in males. This can lead to a more severe presentation in girls diagnosed with ASD (Vorstman et al., 2017).

Although striking differences were found between males and females, the differences were found only to suggest similar reflections of gender differences found in children without an Autism Spectrum Disorder diagnosis. This is thought to be because males exhibit more externalizing symptoms, including aggression and hyperactivity. Females typically present with more internalized symptoms like mood disorders, anxiety, and depression. Usually, females with Autism Spectrum Disorder tend to show higher cognitive impairments than males, most likely linked to the higher level of mutational loads needed for penetrance (Vorstman et al., 2017). Other research suggests these differences might be attributed to the substantial differences in gender cognitive and behavioral styles rather than to their ability. Awareness of presentation that gender differences cause is crucial in correct screening and management of comorbidities and in therapeutically targeting debilitating symptoms associated (Jeste & Geschwind, 2014).

All of these findings have been revealed, yet so few families with children with Autism Spectrum Disorder are educated about receiving genetic testing for their child. It is atypical to find parents or caregivers who do not want to know the cause of their child's diagnosis, regardless of any potential benefits regarding treatment or prognosis (Vorstman et al., 2017). More than 80% of families with children with Autism Spectrum Disorder report never having received any information regarding genetic testing and its benefits. Most of the United States' well-funded healthcare systems do not propose implementing genetic testing for all people with Autism Spectrum Disorder.

The amount of genetic testing done on individuals with Autism Spectrum Disorder has only increased within the last 15 years (Vorstman et al., 2017).

The use of what is called chromosomal microarray analysis (CMA) technology has helped enable investigation of chromosome deletions, duplications, and mutations which defines an important role of smaller chromosomal structural variation in human diseases. Implementing the use of neuroimaging of individuals with Autism Spectrum Disorder during implicit language-learning tasks demonstrated immature neuronal network connectivity patterns and differences in the frontostriatal activity (Jeste & Geschwind, 2014). For example, genetic testing translated a known genetic and biological mechanism to develop informed treatments applied to several genes, including the CNTNAP2 variant, which is associated with neurodevelopmental disorders specifically associated with abnormal language development (Jeste & Geschwind, 2014).

Of fifty parents studied who received genetic testing results, two thirds of them reported feeling the results were helpful for their child and family (Vorstman et al., 2017). Approximately 65% of parents of children with an Autism Spectrum Disorder diagnosis feel that genetic testing should be offered to someone having a child with ASD, 36% feel it should be offered after the child deviates from the norms of development, and 36% feel it should be offered during pregnancy. A large majority of these parents were in favor of genetic testing to discover possible etiological explanations (Johannessen et al., 2017). The use of genetic testing has led to active surveillance of early intervention for conditions before they develop in at risk

individuals due to known risk associations with genetic abnormalities (Vorstman et al., 2017).

Genetic counselling is the process which deals with predicting occurrence or risk of occurrence of a genetic disorder within a family. Genetic counselling can help families understand genetics associated with autism as well patterns in inheritance (Hens et al., 2016). With reward comes risk, and advocates for individuals with Autism Spectrum Disorder must always consider the risks associated with any procedure or testing. Families and advocates want to know if the gains outweigh the risks. For some individuals, genetic testing would not be beneficial based on presentation. For example, genetic testing is most beneficial for individuals who also present with another syndrome or physical abnormality. Currently, researchers claim genetic testing can offer partial explanations for the cause of autism in 40% of people diagnosed whose genetics contain a variant (Hens et al., 2016).

Parents must consider the fact that genetic testing may induce some guilt or blame if a genetic variant can be linked back to a specific carrier. In turn, this raises questions regarding future pregnancies and other options. Parents are faced with moral dilemmas regarding the difficulty of caring for another child with autism and whether or not this is a strong enough reason to discontinue having children or to terminate a pregnancy. Options for families include preimplantation genetic diagnosis or prenatal diagnosis (Hens et al., 2016).

Chances of genetic testing producing informative and helpful results for families are higher in children with coexisting disabilities, including intellectual disability or syndromes, or for individuals with a strong familial component. One geneticist stated, " children for whom this is very meaningful are those with an additional intellectual disability or physical problem, if you suspect it might be a syndrome. And then the other group, those with an obvious familial component" (Hens et al., 2016). Another geneticist disagreed, stating:

I think that each child that has a diagnosis of autism should be genetically tested, because you want to rule out certain things. Especially those genetic things that convey a heightened risk of comorbidities next to autism, and you can only effectively do so by starting up those tests (Hens et al., 2016).

Geneticists and families are beginning to shed light on the importance of genetic testing and counselling for individuals and families of those with Autism Spectrum Disorder. Discoveries from genotype-phenotype correlations can greatly inform prognosis and treatment targets for people with ASD (Jeste & Geschwind, 2014). Despite some genetic testing not changing or impacting course of treatment, the discovery of specific diagnostic criteria can simplify the focus of management and anticipate future care needs for the child (Li et al., 2015). In fact, genetic testing has since led to idiopathic autism becoming obsolete. The contributory mutations in more than 20% of individuals with ASD have been identified in several hundred major mutation predictions (Jeste & Geschwind, 2014).

Advances in genetics have helped develop an understanding of developmental trajectories, comorbidities and underlying biological mechanism deficits which will help develop mechanism-based phenotype specified treatments. The goal is to use genetic testing to guide choice of pharmacological intervention therapies and identify predictors of treatment response (Jeste & Geschwind, 2016). Having knowledge of these genetic causes can influence involvement of specific pharmacological interventions targeted to treat somatic comorbidities. Rare genetic causes of Autism Spectrum Disorder are beginning to highlight possible developments of targeted therapies to influence clinical outcomes and improve the individual's quality of life (Vorstman et al., 2017).

The increase of identified phenotypes affected by ASD or genetic variations can be crucial in enhancing clinical management of coexisting symptoms. This affords clinicians the opportunity to improve quality of life, overall health, and lifespan of people with ASD. Based on recent studies showing premature mortality rates of people affected by autism, improving treatment specificity and effectivity is imperative. Specific cognitive and behavioral profiles from genetic testing can direct behavioral treatments as well (Vorstman et al., 2017).

Recent studies found that out of 1, 780 subjects followed over three years, 55% of 187 genetic findings provoked changes in the clinical management of the disorder. For families, finding a genetic cause can provide them an opportunity to connect with other families and create a supportive networking system (Vorstman et al., 2017). Serving the families of affected persons will help clinicians ensure good involvement and carryover of clinical

management (Johannessen et al., 2017). For families who are unsure about genetic testing or counselling, it is important to provide them with education regarding cost, benefits, accuracy, potential physical harm, type of procedure conducted, and confidentiality of the results found (Li et al., 2015).

There are many consequences if healthcare professionals do not advocate for the genetic testing of people diagnosed with autism. Naturally, without testing or research, there will be no novel information discovered regarding identifying or underlying traits of the disorder. Also, there will be a lack of accumulated genotype-phenotype information, which will slow down any discoveries regarding the etiology or causation of autism (Vorstman et al., 2017). Genetic testing is essential in pioneering extinction of myths and treatment fallacies regarding Autism Spectrum Disorder.

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