Genetic Etiologies of Autism

Megan Eaker

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Josh Cannon

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Abstract:

Autism is a complex neurological disorder that hinders a child’s development and affects their behavior. Because of the complexity of this disorder, the etiology remains uncertain, but plausible theories have developed. It is now agreed that autism originates from the interaction of multiple factors. Twin and family studies, have been important in proving that autism is a hereditary disorder and is influenced by genetics. In depth studies of family genome later confirmed that chromosomal mutations make individuals more susceptible to the disorder. Other genetic disorders, like Fragile X syndrome, are also associated with autism and have thus been the subject of research in order to further determine possible genetic abnormalities that could contribute to the onset of autism.
Prior to statistical revision in 2009, the autism prevalence rate for the United States was set at one in every 150 children. Currently, in 2010, it is estimated that one in 110 children is on the autism spectrum (Hincha-Ownby, 2010). With this increase in diagnostics also comes a need to discover more about this complex disorder.

Autism was first introduced as a disorder by Dr. Leo Kanner in 1943, a time when society and professionals had little truth about the disorder. In the 1960’s, autism was thought to be childhood schizophrenia and the result of poor parenting ("History of autism"). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV), autism, along with Asperger's Syndrome, Rett Syndrome, and Childhood Disintegrative Disorder, is classified as a pervasive developmental disorder (PDD), meaning the disorder delays certain aspects of development (Rapin, & Tuchman, 2008). These pervasive developmental disorders are also classified as autism spectrum disorders (ASD).

The diagnostic procedure for autism and the other spectrum disorders does not include a medical test but instead is based on observed behaviors and psychological testing ("What is Autism"). Autism affects each individual differently with symptoms ranging from mild to severe, but there are common symptoms that the DSM IV has recognized for the diagnosis criteria, this includes: impaired social skills, such as unusual body posture, inability to hold eye contact, and lack of willingness to engage socially or emotionally; impaired communication skills, such as a delay in the development of spoken language and unwillingness to hold conversation; restrictive and repetitious behavioral patterns, such as the need to have a strict schedule and repeating motor movements. Children usually display theses characteristics around two years of age and are able to be diagnosed at this young age. Other characteristics that may arise with autism spectrum
disorders are sensory problems, seizures, or mental retardation ("Autism spectrum disorders," 2009).

Although the traits of autism are now better understood and easily diagnosable, still a lingering question remains; what causes this disorder? Despite tedious research, the answer to this question remains uncertain. As Laura Scheribman says, “When a definitive etiology for a disorder is unknown, theories of etiology proliferate” (Schreibman, 2005). Recent research shows that the etiology of autism is etiological heterogeneity, meaning the disorder’s origin is influenced by multiple factors, including heredity, chromosomal abnormalities, and genetic syndromes.

When examining the etiology of autism, it is now a plausible argument that the disorder can be associated to with heredity. This accepted theory is based on genetic and psychological studies of twins and family. Twin studies date as far back as 1977, with Michael Rutter and Susan Folstein, who studied twenty-one pair of same-sexed twins, eleven of which were monozygotic pairs, also known as identical twins because genetic material is shared between the offspring, and the other ten pairs were dizygotic, also known as fraternal twins because they developed form two separate eggs (Ronald, & Plomin, 2008). The research team observed that 4 sets of twins (36%) out of the 11 pairs of monozygotic twins were concordant for characteristics of autism. These similar characteristics of autism are known as broader phenotypes, meaning it is an expression of the disorder. This proved that genetics influence autism because these phenotypes were evident in the monozygotic twins, which share genetic information. This groundbreaking result inspired similar tests to be conducted and it is now reported that the concordant rate for autism in monozygotic twins is between approximately 60 and 90 percent while the concordant rate for dizygotic twins is only between 5 to 10 percent (Schreibman,
Throughout these twin studies, it is evident that the concordant rate for autism diagnosis increases within the family, but because this rate is not at 100%, it is still plausible to argue that other factors, like epigenetic changes or environmental influences may also influence autism (Rapin, & Tuchman, 2008).

Studies have also been conducted on families who have a member with autism, in order to further determine the heritability of the disorder. Although autism is influenced by genetic factors, most individuals, about 80 to 90 percent, are the only ones diagnosed with autism in their family (Rapin, & Tuchman, 2008). Recently, in 2008, a whole-genome search was conducted in over 700 multiplex families who had at least one member with autism. With the use of a genotyping platform containing single-nucleotide polymorphism technology, researchers were able to detect copy-number variation (CNP) and identify chromosomal abnormalities in individuals with autism (Weiss, Shen, & Korn, 2008). The gene variations found were dominantly hereditary, but other variations arose from de novo mutations, meaning the alteration was only present in the one affected family member (Rapin, & Tuchman, 2008). In multiple family case studies, it was found that chromosome region 16p11.2 carried de novo deletions, meaning the mutation was not found in the mother or father. This finding raised questions as to the cause of the mutation. The research also uncovered cases in which either a deletion or duplication had occurred on this same chromosome region due to genes from the mother and father, confirming that heretics do play a role in the etiology of autism (Weiss, Shen, & Korn, 2008). Although this genetic deletion or duplication only occurs in a small population of individuals with autism, this finding is important because it proves that specific chromosomal variations influences susceptibility to autism.
Genetic syndromes and known chromosomal anomalies also play a role in the development of autism and about ten percent of the autism population have etiologies that can be traced back to these forms of genetic mutations (Weiss, Shen, & Korn, 2008). The most common of these genetic syndromes associated with autism is Fragile X syndrome (Hagerman, 2009). It is estimated that between two to six percent of children with autism have Fragile X, which is known to cause autism (Hagerman, 2006) Fragile X is a genetic disorder, like autism, and is caused by a trinucleotide repeat at the bottom end of the X chromosome. This mutated gene on the X chromosome normally produces the Fragile X Mental Retardation Protein (FMRP), which is necessary for normal brain development. FMRP is an RNA binder and carrier protein and carries messages produced from various genes to the synapse, which passes this information to various cells. Fragile X mutations have the potential to cause autism because the lack of FMRP hinders synaptic development. FMRP also influences the expression of multiple other genes, some of which may also be linked to the development of autism. (Hagerman, 2006).

There are multiple other genetic disorders associated with autism. Tuberous sclerosis complex (TSC) is an inherited genetic disorder generally associated with neuropsychiatric difficulties. This genetic disorder accounts for an estimated one to four percent of the autistic population. Although the pathogenesis between autism and TSC is uncertain, it has been found that people with autism and TSC are more likely to have temporal tubers, which affects the temporal-lobe of the brain thus increasing abnormalities that could lead to behavioral disorders, like autism (Korthur, Ray, & Mailhi, 2007).

Another genetic disorder associated with autism is Smith-Lemli-Opitz syndrome (SLOS). This inherited disorder occurs when there is a mutation in the DHCR7 gene, which provides instructions for producing an enzyme called 7-dehydrocholesterol reductase ("Smith-
lemli-opitz syndrome," 2010). When there is a mutation in this gene, the amount of enzyme being produced is reduced or eliminated which prevents cells from producing enough cholesterol. The fact that SLOS, a disorder affecting cholesterol and metabolism, is associated with autism, a disorder affecting behavior, could potentially give insight to the understanding of the biochemical basis of some forms of autism (Tierney, Nwokoro, & Porter, 2000).

Potocki–Lupski syndrome is yet another genetic syndrome that can be connected with the etiology of autism. This recently discovered and rare disorder is linked to a duplication of chromosome 17p11.2 which causes developmental delays and autistic phenotypes. Cognitive and behavior evaluations of fifteen patients with Potocki–Lupski syndrome revealed that ten out of fifteen people met diagnostic criteria for an autistic spectrum disorder (Treadwell-Deering, Powell, & Potocki, 2010). Research has proven that there is no association between autism susceptibility and 17p11.2, the short arm of the chromosome, but instead the locus could be in 17q11.2, the long arm of the chromosome (Potocki, Bi, Treadwell-Deering, & Lupski, 2007).

Although Fragile X, Tuberous Sclerosis Complex, Smith-Lemli-Opitz syndrome, and Potocki–Lupski syndrome each contribute insight to the etiology of autism, these chromosomal and genetic disorders only accounts for a minute autistic population. Because genetics and heredity are not the only etiological factors of such a complex disease, environmental and other non-genetic factors must also be considered. An estimated 10% to 20% of the autistic population has a plausible non-genetic cause, including viral infections such as intrauterine rubella or cytomegalovirus (Rapin, & Tuchman, 2008), but the largest amount of the autistic population’s etiology is deemed idiopathic, meaning the cause is unknown. Often, these unknown causes are associated with environmental factors. These possible environmental elements include elevated levels of certain cytokines in the cord blood of infants (Rapin, & Tuchman, 2008), valproic acid
exposure during pregnancy (London & Etzel, 2000), exposure to environmental toxins such as heavy metals and mercury, and many more plausible theories. Generally, it is supported that these environmental factors interact with genetics, to form a multi-dimensional etiological perspective of autism.

To conclude, theories of the etiology of autism are influenced by multiple factors, and are thus called etiological heterogeneity. Through twin and family studies, it has been determined that genetics and heredity increase susceptibility to this disorder. Certain genetic disorders are also associated with autism and give insight into what mutations and abnormalities can potentially cause autism. Research has come a long way in the understanding of autism and the search for a cause, but there is still more to go, in hopes of being able to treat autism at its source.
Work Cited:


