

Genetics of Autism

Autism is the most common disorder in a group of neurodevelopmental disorders called the Autism Spectrum Disorders (ASD).¹ It is characterized by impairments in social interaction, deficits in verbal and non-verbal communication, and restricted repetitive patterns of behavior and interests. ASDs also include Asperger syndrome and pervasive developmental disorder not otherwise specified (PDD-nos).¹ Autism is estimated to affect 15-20 in 10,000 children, while all ASDs combined affect approximately 60 in 10,000 children.² Autism is strongly genetically determined, as demonstrated by its increased prevalence in siblings.² Monozygotic twins show 60%-90% concordance, meaning that in 60%-90% of cases in which one twin has autism, the other twin does also.² Concordance in dizygotic twins and siblings is 5%-10%.² Males are affected with ASDs four times as often as females.²

The genetic control of autism is an extremely active area of research. A rich source of data is available to researchers from the Autism Genetic Research Exchange (AGRE), a collection of DNA and clinical data from families with at least one affected individual. Combined with rapidly advancing technology, an enormous amount of genetic data attempting to explain autism has emerged. Several different genetic abnormalities have been found in autistic individuals, and affected individuals in the same family tend to carry the same genetic abnormality.

Among the genes most-strongly linked to autism are *Engrailed 2* and the *Serotonin Transporter*. *Engrailed 2* (*EN2*) encodes a protein involved in the development of the cerebellum. Mice that improperly express *EN2* exhibit abnormalities in cerebellar circuits and cell numbers.³ Cerebellar abnormalities are one of the most common histopathological findings in humans affected with ASDs, and the human *EN2* gene is located in a chromosomal region that is frequently abnormal in individuals affected with ASDs.³ *SLC6A4*, the gene encoding the serotonin transporter, is also implicated in ASDs. There has long been interest in this gene because approximately one-third of patients with ASD have platelet hyperserotonemia, a condition thought to be caused by variations in *SLC6A4*.³ Recent cloning studies identified four *SLC6A4* sequence variants that correlated with increased severity of rigid-compulsive behaviors.³ Much work remains to conclusively link *EN2*, *SLC6A4*, and other candidate genes to autism, but research uncovering the genetic control of autism is ongoing and promising.

The large number of genetic abnormalities found in families with at least one autistic individual has led to a theory that there are several genetic loci that contribute to the autism phenotype.^{2,3} Patterns of inheritance in families and the observation that some individuals show subtle symptoms, suggest that common forms of ASDs are the result of multiple genes, which when abnormal in an individual, contribute small increments of risk to that individual.^{2,3} Those individuals who inherit many of the abnormal genes will exhibit more serious ASD symptoms, yet will probably not pass on the large number of abnormal genes that they carry because of low reproductive fitness.³ Those individuals who inherit fewer of the abnormal genes will be only slightly affected for ASDs, but will be reproductively fit enough to pass on the few abnormal genes that they carry, perpetuating the frequency of the abnormal genes in the population.³

An alternate theory explains the inheritance of autism as a result of *de novo* mutations, i.e. mutations that happen sporadically, in the parental germ line (the cells that eventually produce sperm and egg).⁴ The *de novo* mutations could happen in any of the genes critical for autism. Offspring of parents with affected germ lines are at risk for autism, but for unknown reasons, females are more resistant to the abnormal gene, and show less serious symptoms, explaining the increased incidence of autism in males.⁴ Females carrying the abnormal gene who show few symptoms are reproductively fit enough to pass the abnormality to their children, who in turn are at risk for developing autism.⁴

Diagnoses of autism have increased in the past few decades, but it is important to note that the increase is attributed to a broadened definition of ASDs and better recognition on the part of physicians of autism

symptoms.⁵ There is no scientific evidence that a link exists between incidence of autism and vaccinations.⁵ Funding for autism research has grown dramatically over the last five years, and it is supporting promising research projects that continue to make strides into discovering the cause and the genetic control of autism.⁶

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