

## The Genetics of Autism

Despite several decades of intense genetic research, we still do not know the primary genetic causes for autism. However, we are sure that autism has a strong genetic basis even though we have identified only a few genes that contribute to this genetic basis. The figure below lists some basic aspects about autism including its high population prevalence, now estimated at 1/90 children. This prevalence number includes the spectrum of different types of autism, as listed.

### Childhood Autism



Incidence 1/90

4:1 male to female

Criteria

Aloof social Interaction

Delayed language

Stereotypical behavior

Types

Classical infantile, severe

Onset before 30 months age

High functioning autism

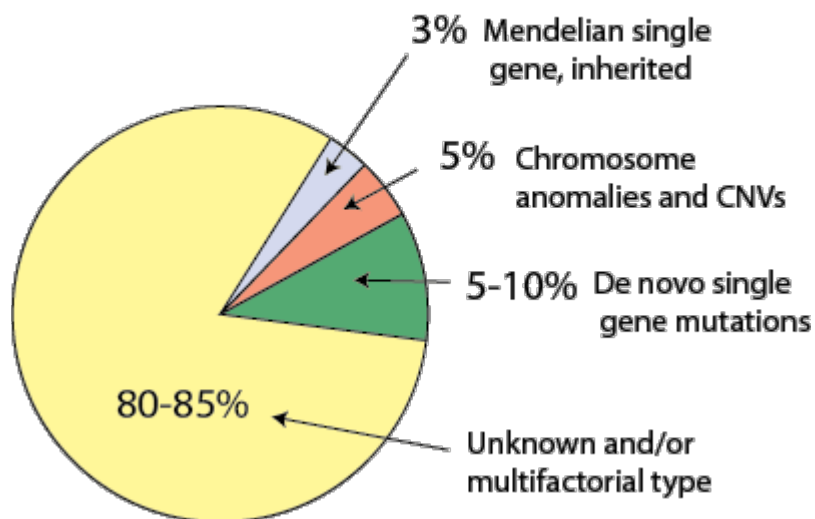
Asperger syndrome

Pervasive Developmental Disorder,  
Not Otherwise Specified (PDD, NOS)

Autism Spectrum Disorder

Children with autism are often evaluated by pediatricians or neurologists in an attempt to find a genetic or medical causation for the problem but about 85-90% of children with autism have no identifiable causation. In fact, these children are physically well developed and do not have any known medical or metabolic problems. As many as 10-20% of autistic children however may have identifiable genetic contributors that usually requires specialized genetic testing in order to identify them. The pie diagram below illustrates the general categories of genetic causation of autism.

### Autism Genetic Landscape



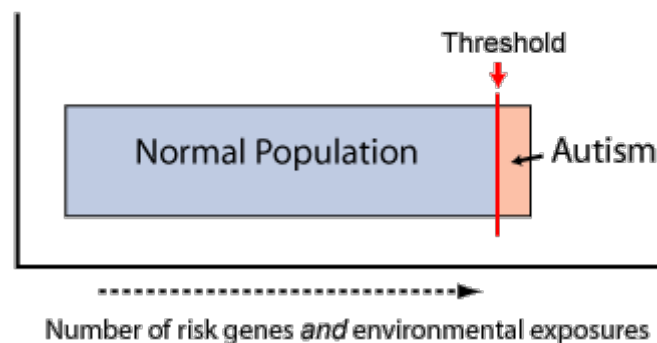
A small percentage of autistic individuals have an identifiable Mendelian single gene disorder such as Fragile X, and also a small percentage will have a chromosome disorder such as Down or Klinefelter syndrome (extra X chromosome). Molecular chromosome studies such as microarray testing are now identifying variations in chromosome microregions (e.g., copy number variants, CNVs) that are main contributors to the autism phenotype. Finally, recent next generation sequencing of all genes, such as in whole exome sequencing, has disclosed a surprising number of de novo mutations that appear causative of the autism problem in those studied. These de novo events may account for as much as 5-10% of autism cases.

The majority of children with autism however will have normal genetic and metabolic studies. Yet, we know that there is a genetic basis for autism because, for example, identical twins have a high concordance for autism, sometimes as high as 90%. This indicates a genetic component that is relatively strong since non-identical twins typically do not have concordance rates that exceed 10%.

Other features about autism tell us that there is a genetic basis for it, such as a relatively high recurrence risk of 5-15% in first degree relatives of an individual with autism (depending on which study is used to determine this risk). Also, the excess male prevalence suggests an influence from the genetic makeup but we do not have evidence for a major gene on the X-chromosome that might account for this excess. Additionally, close relatives have an increased risk for certain comorbid conditions (e.g., Obsessive-Compulsive Disorder), and from these observations, we presume that some heritable influence may be operative.

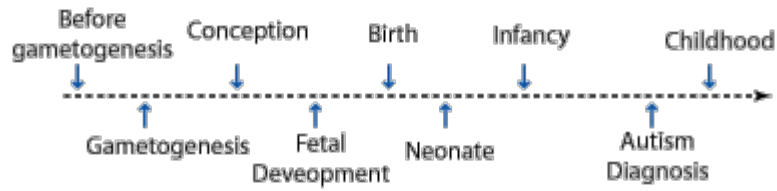
The prevailing theory for autism is that it is a polygenic or multi-factorial genetic disorder. This model, which is a hypothetical one, presumes that there are multiple genes and environmental forces interacting to create the autism. A simplistic way of thinking about this is that these genetic and environmental risk factors push the child over a "threshold" and then autism becomes manifest.

### Theory of Multi-factorial Inheritance



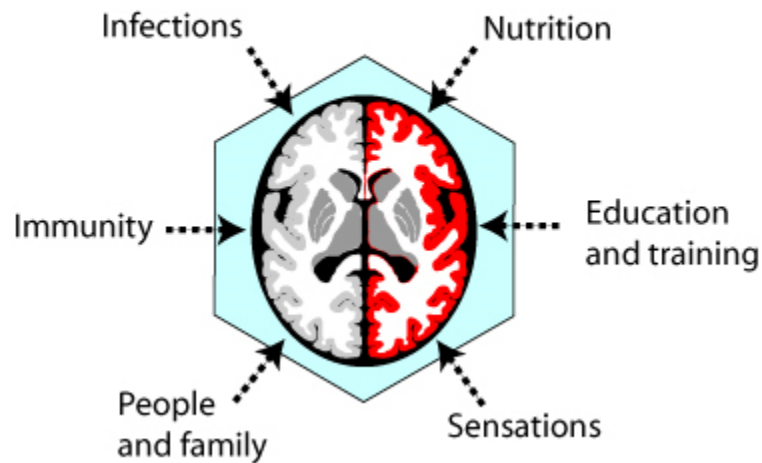
At present, it is not known what these environmental influences are. Environmental influences could begin very early, during the period of egg or fetal development, and could extend into the postnatal period as indicated below.

## Timeline of Environmental Effects



The environmental influences could also be factors related to socialization and behavioral issues. The diagram below illustrates that nurturing elements such as the family environment and educational background may be critical to either the onset of autism. Attempts to manipulate environmental factors, particularly oriented around nutritional issues, are made in the hope that these manipulations may in some way change the neuronal abnormalities associated with autism.

## Brain-Environmental Interactions



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