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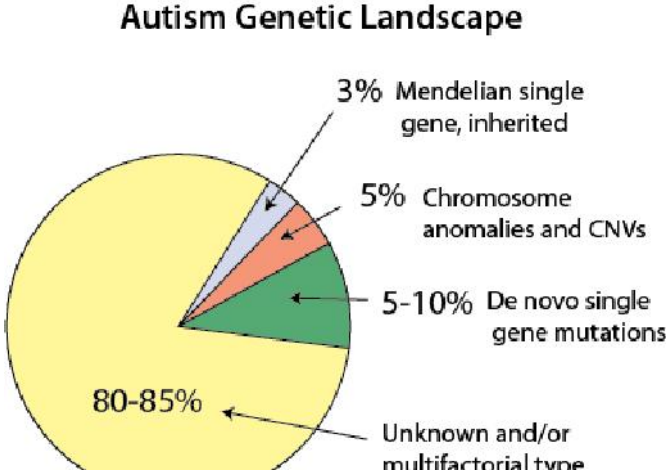
The Genetics of Autism

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 1/150 children. This prevalence number includes the spectrum of different types of autism, as listed.

Chilldhood Autism Spectrum

- Incidence: 1/150
- 4:1 male: 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)

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 conditions that usually requires specialized genetic testing in order to identify them. The pie diagram below illustrates the general categories of genetic causation of autism.

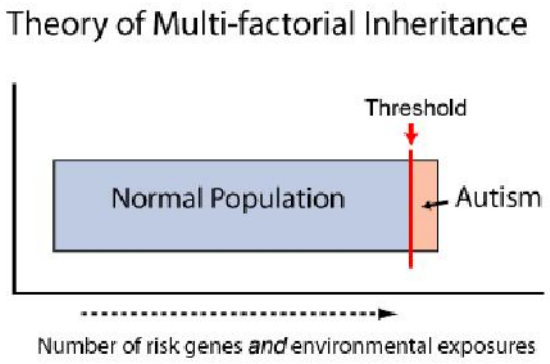


A small percentage of autistic individuals have an identifiable Mendelian single gene disorder such as Fragile X, and also a small percentage will have a chromosome disorder such as Down or Klinefelter syndrome (extra X chromosome). Molecular chromosome studies such as microarray testing are now identifying 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 suprising 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 10% of autism cases.

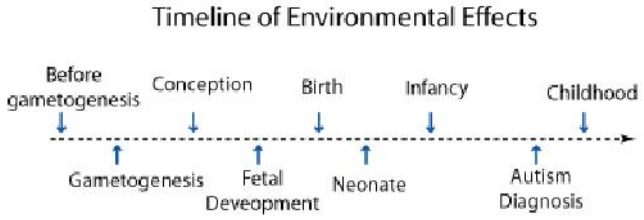
The majority of children with autism however will have normal genetic and metabolic studies. Yet, we know that there is a genetic basis for autism because, for example, identical twins have a high concordance for autism, sometimes as high as 90%. This indicates a genetic component that is relatively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

Other features about autism tell us that there is a genetic basis for it, such as a relatively high recurrence risk of 3-6% in first degree relatives of an individual with autism. 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 contributing to autism. 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 multiple environmental forces that interact in some complex way to ultimately create the problem of autism. A simplistic way of thinking about this is that these genetic and environmental risk factors push he child over a "threshold" and then autism become manifest.

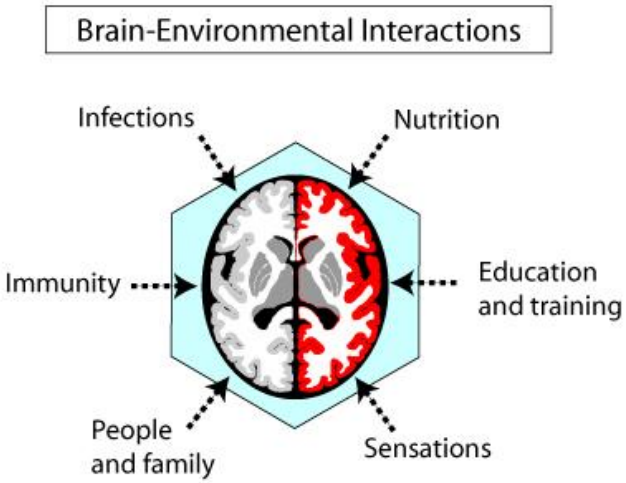


At present, it is not known what these genes or environmental influences are. Environmental influences could begin very early, during the period of egg or fetal development, and could extend into the postnatal period as indicated below.



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 in some way prove critical to either the onset of autism or the prevention of this condition. 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. Of course, these neuronal abnormalities may have strong genetic underpinnings.



Edited 11-10-2012