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National Institute of Child Health and Human Development

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Autism Research at the NICHD

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Autism and Genes

What is autism?

Autism is a complex biological disorder of development that lasts throughout a person's life. People with autism have problems with social interaction and communication, so they may have trouble holding a conversation with you, or they may not look you in the eye. They sometimes have behaviors that they *have* to do or that they do over and over, like not being able to listen until their pencils are lined up or saying the same sentence again and again. They may flap their arms to tell you they are happy, or they might hurt themselves to tell you they are not.

One person with autism may have different symptoms, show different behaviors, and come from different environments than other people with autism. Because of these differences, doctors now think of autism as a "spectrum" disorder, or a group of disorders with a range of similar features. Doctors classify people with autism spectrum disorder (ASD) based on their autistic symptoms. A person with mild autistic symptoms is at one end of the spectrum. A person with more serious symptoms of autism is at the other end of the spectrum. But they both have a form of ASD.

What causes autism?

No one knows for sure what causes autism. It's a complex biological disorder, and no two people with autism are the same. These differences lead scientists to believe that autism is the result of a mixture of causes. They aren't looking for just one cause for all cases of autism.

At this point, scientists believe that the underlying cause of autism is genetic. Researchers from the Network on the Neurobiology and Genetics of Autism: Collaborative Programs of Excellence in Autism (CPEA), a network of scientists supported by the National Institute of Child Health and Human Development (NICHD) and the National Institute on Deafness and Other Communications Disorders (NIDCD), as well as other NICHD, NIH, and non-NIH scientists, are looking into how genes might be involved in autism. This worldwide research effort hopes to solve the mysteries of autism by understanding its causes.

What are genes?

Genes are very small pieces of hereditary material, which means that parents pass them on to their children. Every person gets half their genes from their mother and half from their father.

The pattern, or sequence, of your genes is like a blueprint that tells your body how to build its different parts. Your gene sequence controls how tall you are, what color your hair and eyes are, and other features of your body and mind. Changes in that blueprint can cause changes in how your body or mind develops.

Genes are found on chromosomes. Almost every cell in your body contains 23 pairs of chromosomes, 46 in all. Genes and chromosomes give the body all the information it needs to "build" a person.

Why study genes?

Past research hints at a link between autism and genes. For example:

- When autism occurs in *identical* twins, both members of the set have the condition 60 percent of the time. When autism occurs in *fraternal* twins, both members of the set have the condition only 3-to-6 percent of the time. Identical twins come from a single egg that splits in two, so they share 100 percent of their genes; fraternal twins come from two separate eggs, so they are genetically different. If autism was not caused in part by genes, then the number of identical twins with autism would not be any higher than the number of fraternal twins with the condition. But, since both identical twins have autism more often than both fraternal twins do, researchers think that genes play a role in autism. (Folstein & Rutter 1977; Bailey et al 1995; Smalley et al 1988, as cited in Ingram 2000)

- Family histories and family studies show that some of the autism-like symptoms, such as delays in language development, occur more often in parents and adult brothers and sisters of people with autism, than in families who have no autistic members or relatives. Because members of the same family have similar gene sequences, these studies suggest that something about gene sequences is linked to autism. Autism is a spectrum disorder, meaning people with autism can have a range of symptoms. A certain change in the gene sequence may make the

condition very mild, so that a person doesn't have autism, but has one of its symptoms instead. A different change in that sequence could make the symptoms of autism more serious. (Landa et al 1991; Landa et al 1992; Volkmar et al 1998; MacLean et al 1999 as cited in Ingram 2000)

Based on these findings, doctors have long felt that a link between genes and autism was a strong possibility.

But researchers don't expect to find that just one gene causes autism. Because of differences in peoples' symptoms, researchers believe that autism is the result of many genes interacting with each other. At this point, it seems that some children are born with a genetic susceptibility to autism. What makes some susceptible individuals develop autism and others not is an important research question.

What have CPEA researchers found by studying genes and autism?

Genetic studies of autism conducted by the CPEA Network highlight some of the ways genes may be involved in autism.

Chromosomes where defective genes are likely to be found

CPEA investigators, working with researchers from around the world, are using a process called linkage analysis to identify genetic "hotspots," or chromosome areas where defective genes related to autism may be found. So far the most promising leads seem to be on Chromosome 7, where genes for other language disorders are known to exist, and Chromosome 15 where genes for other developmental disorders have already been identified.

A missing piece of a chromosome could be tied to autism

A group of researchers at the University of California, Irvine, found that one of their seven-year-old patients with autism was missing a certain section of Chromosome 15 (Smith 2000). Why is this such a great discovery? It's important because this is one of the first times that a specific genetic problem has actually been found in a person with autism.

In the past, studies looked at groups of people with autism and some of the more general features of their genes, like which chromosomes might have problem genes, and whether they had one, two, or three copies of a chromosome. But in this study, researchers looked at one person at a time, to carefully focus on that person's genes. This slow and complex process allowed researchers to create a detailed catalog of all 46 chromosomes for each autistic person, to find any missing blocks of these chromosomes.

After taking a close look at the autistic boy's chromosomes, the scientists found that he was missing nearly 1,000 pieces of the genetic sequence on Chromosome 15. Missing pieces of chromosomes mean that some of the instructions for building the body or mind are missing. Without these instructions, the body or mind may not be built correctly.

Using this discovery, scientists will try to match the missing chromosome piece to some of the genes they think play a role in autism. If they can match a gene to the missing section of the chromosome, they may be able to uncover how the gene changes the body to cause autism. These findings may also lead to treatments that correct the changes caused by the missing chromosome piece.

A genetic change found in many patients with autism

Researchers at the University of Rochester School of Medicine and Dentistry in Rochester, New York, found that nearly 40 percent of people with autism in their study had a change in their gene linkage that could be a factor in causing their autism (Ingram 2000). The sequence or pattern of your genes controls how your body builds its parts. An alteration in that sequence changes how your body and mind are built, which may lead to autism.

Specifically, 39 percent of the people with autism in the study had a change in one of the two copies of the HOXA1 gene, which is located on Chromosome 7. (Remember that chromosomes come in pairs, which means your cells have two copies of every gene.) The percentage of people who had the change in one of their genes, but did not have autism and were not related to anyone with autism, was much lower (only 22 percent). Because twice as many people with autism had the gene change when compared with people who did not have autism but had the gene change, the HOXA1 gene could play a role in causing autism.

In addition, 33 percent of people in the study, who did not have autism, but were related to someone with autism, also had the change in their gene, which supports the idea that the HOXA1 gene plays a role in causing autism. These findings suggest that the genetic sequence of these families is linked to autism and autism-like symptoms in some way. Scientists need to do more studies to find out just what that link is.

But scientists don't think that the change in the HOXA1 gene by itself causes autism. If the gene change was the only cause, then everyone who had that change would be diagnosed with autism. Because this is not the case, scientists think that the HOXA1 gene is only one of many genes that may contribute to the autism.

Fast Facts on HOX Genes

HOX is short for homeobox, a word that scientists use to describe the group of genes that control growth and development very early in life. HOX genes act like the director of a movie in that they tell other genes when to act and when to stop during development. For example, when a certain HOX gene says, "ACTION," your body's other genes start building your ears. Once your ears have developed that same HOX gene says, "CUT" and your ear genes stop building.

You have 38 different HOX genes spread out among your chromosomes that direct the action of your other genes to form your body. These genes are active very early in human growth, before a baby is born.

From studies on growing infants, doctors know that the HOXA1 gene does its directing very early in human development—between the 20th and 24th day of conception. Most women don't even know they are pregnant when the HOXA1 gene is working. HOXA1 controls the genes that make the building blocks for the central nervous system, which includes the brain and the spinal cord. A change in this gene could also change the way the body builds its nervous system, which in turn could lead to autism.

References

Ingram JL, Stodgell CJ, Hyman SL, Figlewicz DA, Weitkamp LR, and Rodier PM. Discovery of allelic variants of HOXA1 and HOXB1: genetic susceptibility to autism spectrum disorders. Teratology, 62:393-405, 2000.

Smith M, Filipek PA, Wu C, Bocian M, Hakim S, Modahl C, and Spence MA. Analysis of a 1-megabase deletion i9n 15q22-q23 in an autistic patient: identification of candidate genes for autism and of homologous DNA segments in 15q22-q23 and 15q11-q13. American Journal of Medical Genetics (Neuropsychiatric Genetics), 96:765-770, 2000.

What does the future hold for studies of genes and autism?

The CPEA Network is looking at other genetic mechanisms that may account for why different genetic defects related to autism seem to be found across different studies. Researchers in the Network will share their information and their methods to see if other researchers get the same results in other people with autism. Having several scientists get the same results "confirms" that discovery. They will see if these and other new genetic findings can be "replicated" or confirmed in other persons with autism. Once confirmed, a discovery becomes the stepping stone to other discoveries. Researchers in the Network hope that the latest findings on genes and autism are just the beginning. By understanding both genetic and environmental causes of autism, scientists may be able to understand how to treat it and maybe even how to prevent it.

While some researchers focus on confirming the findings reported here, other researchers are doing their own studies on different features of autism and genes. Doctors and scientists will keep looking at genes and environment and how they interact with each other until they solve the mysteries of autism.

Where can I go for more information about autism?

The NICHD Clearinghouse provides information on autism and autism research, and on other topics related to the health of children, adults, and families. The information specialists at the NICHD Clearinghouse are available at:

Mail: PO Box 3006, Rockville, MD 20847
Phone: 1-800-370-2943
Fax: 301-984-1473
Email: NICHDClearinghouse@mail.nih.gov

The NICHD Autism Web Page, www.nichd.nih.gov/autism, offers information on NICHD autism research, including the CPEA Network, current grants and funding mechanisms, ongoing clinical trials, and the NIH Autism Coordinating Committee. With a variety of information on topics related to autism, the NICHD Autism Web site is a good place to start your search for information. You can also comment on the *Autism Research at the NICHD* fact sheets through the Autism Web site.

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