The X Factor in Autism

Researchers study how the X chromosome may play a role in causing autism

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Autism doesn't strike everyone equally - it's a male-dominated disease. Boys are four times more likely to have autism than girls. About 80 percent of the millions of people with autism are male.

So why is autism so discriminating? One theory is that some genes that predispose a person to autism are located on the X chromosome. While females have two X chromosomes, only one is active at any one time in a cell. If one X chromosome contains normal genes and remains active, it may protect against the X-chromosome-linked autism. Males have only one X chromosome which remains active at all times.

This gender factor might be a clue in unlocking one of the causes of the disease, according to Merlin G. Butler, Ph.D., professor of pediatrics and William R. Brown/Missouri Chair in Medical Genetics and Molecular Medicine at Children's Mercy Hospital and UMKC. In particular, he speculated that a condition called X-inactivation skewness in women might help them narrow down which genes cause autism.

X-inactivation skewness reflects the pattern of activity in the female's X chromosomes. Usually, one X is active 50 percent of the time, and the other X is active the other 50 percent. In females with X-inactivation skewness, one X chromosome is more active than the other, usually about 80 percent of the time, while the other is active only 20 percent.

Dr. Butler wondered if this condition might be a factor in whether or not autism is present in females.

"We know there are probably several different genes that cause autism, as well as some environmental factors," says Dr. Butler. "But we don't know where to start looking for the genes in a particular subject. Looking at the X chromosome inactivation pattern in females might be a place to start in females. If there is skewness, we could start looking for the abnormal gene on the X chromosome."

Dr. Butler began a research study to find out whether X-inactivation skewness was more common in female patients with autism. Along with Zohreh Talebizadeh, Ph.D., an instructor at the School of Medicine, they obtained DNA samples from the Autism Genetics Research Exchange Program, which keeps DNA and cell lines from patients and families with autism. They obtained DNA from families with autistic females and their sisters who didn't have autism. They then looked at whether or not there was a difference in X-inactivation in the females with autism as opposed to their unaffected sisters.

The results showed that the patients with autism did have a higher incidence of X-inactivation skewness. Of the 30 patients with autism, 33 percent showed an X-chromosome skewness pattern. In the group of unaffected sisters, only 10 percent showed X-inactivation skewness, which is about the same percentage as the general population.

These results show that X chromosome genes may contribute to some cases of autism, say Drs. Butler and Talebizadeh.

"For autistic females with X-inactivation skewness, it's likely that some, if not all of them, have a gene that predisposes them to autism on the X chromosome," says Dr. Talebizadeh. "And the combination of skewness and having that mutated gene on the X chromosome predisposes them to autism."

The females probably received the mutated X-chromosome gene from their mother, according to Dr. Butler. The mother was probably a carrier for the gene for autism, but was unaffected, because she had 50/50 X-inactivation. The mother passed on the X chromosome to her daughter, who also received a normal one from the dad. If the daughter's normal X-chromosome gene was inactivated, she would have autism.

Dr. Butler says the results provide a way for the researchers to start looking for the abnormal gene. If the patient has X-chromosome skewness, the abnormal gene would probably be on the X chromosome.

"There are probably at least 15 different genes that cause autism," he says. "So this could be one screening tool to help categorize patients with autism and what gene may be affecting them."

The next step for researchers is to find out which gene on the X

Photograph by John Carmody

chromosome is responsible. Currently the researchers are focusing on three candidate genes on the X chromosome. They will use the same group of DNA samples to look at those candidate genes and screen for mutations in the females with autism and X-chromosome skewness.

The researchers are also comparing the behavior patterns of the two groups of autistic patients, those with and without X-inactivation skewness. In the original sample, they found that the two groups seemed to exhibit different behavior abnormalities. For instance, in the highly skewed group, the researchers found less stereotyped body movements than in the females without skewness. Stereotyped movements include movements of the whole body, such as spinning or repeatedly bouncing up and down or arm waving while rocking. However, because of the small sample size, these clinical results are still preliminary. The researchers hope to expand their study to include more subjects in order to verify these clinical differences.

Dr. Butler says that studying these behavior abnormalities may help identify other genes that cause autism.

"For example if our preliminary data on stereotyped body movements hold true, we could look at the genes on the X chromosome that deal with mannerisms or motion activity," says Dr. Butler. "It might be a further way for us to look at the candidate genes that could be causing the abnormal behavior present in those patients."

Dr. Butler and Dr. Talebizadeh have applied for further funding through the Cure Autism Now Foundation to expand their research in X inactivation. After finding the responsible genes on the X chromosome, they plan to apply their results to a larger sample size of females with autism.

"Once we find these genes for autism, they can be researched in the male group as well," says Dr. Talebizadeh. "Hopefully, this will someday lead to future screening, disease management or treatment for these patients."■

Merlin Butler, Ph.D., and Zohreh Talebizadeh, Ph.D., are studying DNA in females with autism to help identify the abnormal genes on the X chromosome.