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AUTISM AND THE GENETICIST: IS IT INHERITED OR NOT?

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Daniel was referred because his parents wanted to know if his recent diagnosis of autism might be something that could recur in future children. Then nearly 3 years old, Daniel's parents had first become concerned about him when he was 2 ½, because he lost the ability to say words he'd begun saying around his first birthday. After a multidisciplinary evaluation, Daniel had been diagnosed with an autism spectrum disorder. His parents had dealt with the news reasonably well, receiving support from the team of evaluators; when they'd asked about the risk to future children, they'd been referred for a genetic evaluation.

The parents were interested in having more children soon: the couple's first child, Daniel had been born when his mother was 36 and his father 38. "I know my biological clock is ticking!" the mother told me. "I don't want to wait too long before having another child. But I want to know what the chances are that my next child will also have autism. That's why we're here today."

I took a complete history (including information about Daniel's birth, medical problems, development, etc. Aside from his loss of speech, termed "regression," and some delay in his development, his past had been completely typical), assembled a pedigree (a diagram showing Daniel's family history; no one on either side of the family had ever been diagnosed with autism or other problems of development), and did a complete physical exam (which was also completely normal). After explaining to his parents that Daniel did not have any features that suggested the presence of a specific genetic disorder known to be associated with autism, I suggested that we perform some genetic tests looking for extra or missing bits of DNA, the genetic material, and for changes in the gene known to be associated with a condition known as Fragile X. The parents agreed, and with some fuss, I drew a sample of Daniel's blood. We made an appointment for the family to return in about six weeks, after the testing would be completed, so that we could discuss the results and their implication on the parent's risk that future children might be affected.

INTRODUCTION

More than any other disease, autism spectrum disorders (ASDs) are a group of conditions that affects families. Of course, ASDs have serious effects on the child or adult who has the condition, but the diagnosis of autism in a child also significantly changes the lives of his parents, brothers and sisters, other family members, even the community in which he lives. These effects on people other than the child with the condition are especially important to the geneticist, the specialist whose role is to identify causes of inherited conditions and provide counseling and guidance to the patient and family. Autism is a group of symptoms that include problems with social skills, problems with communicating with others, and the presence of repetitive unusual behaviors, called "stereotypies." These symptoms can result from dozens of different underlying problems, some of which are caused by changes in the genetic material, and some of which are not. The goal of performing a genetic evaluation is:

(1) To try to identify the underlying cause of the condition so that the family can learn more about what kinds of problems their child might be expected to have in the future;

(2) To provide genetic counseling, so that the family can learn what the risk to their future unborn children might be. And

(3) To provide an explanation of "why this happened."

For these reasons, a trip to the geneticist's office should be offered to every family, as part of the work-up of all individuals diagnosed with ASD.

The fact that inherited factors play a role in the cause of most cases of autism comes from many observations. For example, although we now know that an autism spectrum disorder occurs in about 1 out of every 100 children (1% of the population), it has been observed that the risk that autism will occur in a second child in a family once a first child has been diagnosed with the condition increases to between 4 and 7%, (4 to 7 times higher than in the general population). Further, if a second child has autism, the chance that a third child will also be affected rises to 25-35%. These increases point to the fact that genetic factors present in the family make it more likely that autism will recur. Other evidence suggesting that genetics plays a role in autism comes

from studies of twins. If one identical twin has autism, it is much more likely that the second twin, who has identical genetic material, will also develop autism than it is if the twins are fraternal, in which case, they share the same amount of genetic material as any brothers or sisters.

The geneticist is a medical professional, usually a pediatrician, who has received special training in conditions that are inherited, and is part of the team of professionals that make the diagnosis of autism, and provide treatment and support for the child and his family. The geneticist takes the jigsaw pieces of the child's history and physical findings and tries to solve the puzzle by finding the cause. The tests that the geneticist performs are neither "experimental" nor "research" tests; they are performed to help solve the puzzle, in order to help the child with autism and the family.

THE GENETICIST'S EVALUATION:

What can a family expect when their child is referred to the geneticist for evaluation? What does the clinical geneticist actually do? In most cases, the genetic evaluation begins with the geneticist taking a complete history, focusing on issues that might have contributed to the child's condition. Although genetic factors definitely play a role in most cases of ASD, in some cases, exposure of the fetus or baby to substances in the world around him may be responsible for his autism. For instance, we know that when a fetus is infected with German measles (Rubella) or certain other viruses (for instance, cytomegalovirus) during pregnancy, the child may have features of autism. In addition, exposure of the fetus to certain drugs and chemicals, such as Valproic Acid, a medication used by some mothers to treat seizures, or alcohol, can cause autism. So, when the geneticist asks about the mother's pregnancy, questions about these and other exposures will be asked.

Next, the geneticist will ask about the child's general health. Does the child have any chronic medical problems? Does he have seizures? Sometimes, a seizure disorder will cause a child to lose his ability to speak; in these rare cases, treating the convulsions may actually "cure" his autistic features.

A lot of attention will be focused on the child's developmental history. When did he sit up? Stand? Take his first step? When did he begin to speak? Has his speech been delayed from the beginning or, like my patient Daniel, did he just stop speaking at some point? Does he have any unusual behaviors? Answers to these questions may provide the geneticist with clues about the underlying cause of the child's condition.

Next, a complete family history is taken and written out as a picture, called a pedigree. The pedigree should include information about at least three generations (the child and his generation, his parents and their generation, and his grandparents and their generation). The family history includes details about the presence of ASDs, as well as other conditions causing developmental and behavior problems in relatives.

This is followed by a complete physical exam. When examining the child, the geneticist looks for more clues that might lead to the diagnosis of a condition known to be associated with autism. For instance, we look for the presence of dark spots on the skin that are known to occur in neurofibromatosis, a condition in which autism can occur. We check for facial features, such as a prominent forehead or jaw, or large ears that might point to a diagnosis of the condition known as fragile X syndrome. These, and many other findings will lead the geneticist to perform specific tests in an attempt to solve the mystery of whether there is a genetic cause for the child's condition.

THE GENETIC WORK-UP

Following the history and physical exam, a decision is made about the likely cause of the child's autism. It comes down to this: does the child have autism because of some underlying condition, such as Fragile X syndrome or due to exposure to a drug or chemical or maternal illness like German measles? Or is the child's autism not associated with any underlying physical problems?

The first of these situations is called ***secondary autism*** (that is, autism that is secondary to some other condition); secondary autism accounts for only 10 to 20% of all cases of autism. The latter situation is called ***primary autism***; this is responsible for 80 to 90% of all cases of autism. The genetic testing that will be ordered will depend on which of these situations in actually the case.

If the child is believed to have secondary autism, we gear the testing to trying to confirm the diagnosis we believe the child might have. For instance, if the child has features that make us think he has fragile X syndrome, we will order specific testing for this condition. Results of these tests will allow us to provide counseling for the family.

Most children will be judged to have primary autism. Following recommendations made by the American College of Medical Genetics, testing in these cases follows a three-tiered approach (that is, a second set of tests are done if the results of the first set do not identify a cause; if the second set of tests do not identify a cause, a third set is performed). This is described in detail in: Schaefer GB, Mendelsohn NJ. Genetics evaluation for the etiologic diagnosis of ASDs. Genet Med 2008;10:4–12. Although in most cases, an underlying genetic cause will not be identified, new and very powerful genetic tests have recently been developed that offer new hope for the identification of the cause of autism in many cases. Slowly, the mysteries of the cause of autism are being unlocked.

Among these new tools is microarray comparative genomic hybridization (array CGH for short). This test can identify very small abnormalities in the amount of genetic material. Autism may result from too much genetic material, called a duplication, or too little

genetic material, called a deletion. Identifying these problems will be important not just in caring for the child, but in counseling the parents as well. Such abnormalities are seen in 10 to 20% of children with autism.

Although array CGH can identify very subtle duplications or deletions in the DNA, it cannot identify specific changes in genes, changes that lead to the presence of specific genetic diseases. So, even when clinical features of the condition are not obvious, because it is so common and the significance of the diagnosis is so great, all children with autism should be tested for fragile X syndrome.

The medical literature (Schaefer and Mendelsohn) shows that the total result of tier 1 testing is that between 22 and 33% of children with primary autism will have an identifiable cause of their condition. This includes between 10 and 15% with either duplications or deletions in their DNA, as well as children found to have mutations in specific genes that cause fragile X or other conditions.

Based on results received, if the first tier of testing is normal, a second tier of testing should be performed. And if the second tier tests are also normal, there is a possibility of performing a third tier of tests.

COUNSELING

Following completion of genetic testing, the family is invited back to discuss the results and their implications. If a specific cause of autism, such as fragile X, has been found, genetic counseling is provided for that condition. If the child with primary autism has been found, on array CGH, to have a duplication or deletion of genetic material, the parents need to be tested to rule out the possibility that one of them is either also carrying this duplication or deletion (unlikely) or that he or she is carrying a genetic rearrangement that may predispose them to have other affected children. If this is ruled out (as it is in most cases), the family can be told that there is a very small chance that this problem will happen again in future children (less than 1%).

If the testing has failed to identify a genetic cause for the child's autism, we counsel the family that the risk that their future children might have autism is between 4 and 7%. If it has been found that two children in the family have autism, the risk that future children will also be affected rises to between 25 and 35%. This visit is also an opportunity for the family to ask questions of the geneticist.

Follow-up visits with the geneticist are necessary, especially when no underlying etiology has been identified. Because technology in the field of clinical genetics is advancing so quickly, it is possible that new tests will become available that will identify a cause for autism in children in whom currently no etiology is identifiable. For this reason, periodic reevaluation on an annual or biannual basis is important.

Six weeks after their first visit, Daniel and his parents returned to my office. Array CGH testing revealed that Daniel had a rare chromosomal abnormality, called mosaic trisomy 8 (that is, he has an extra copy of one of his chromosomes, the structures that carry the genetic material from parent to child, in some of the cells that formed his body; in other cells, his genetic material is normal). In addition to telling the parents that this chromosome abnormality was definitely the cause of Daniel's autism, I explained that this problem had occurred at the time of Daniel's conception; a tiny error had taken place when the sperm or the egg had formed. I also explained that because this problem was present so early, nothing that either parent did or did not do either before or after Daniel's conception would have in any way changed the outcome (i.e., this was not their fault!). I told the family that since this is an accident that occurs at the time of conception and not something that runs in the family, the chance of it happening again in future pregnancies was extremely small; in fact, less than 1%. Finally, I told them that testing performed prior to the birth of their next child would help us in guaranteeing that such an outcome would not happen again.

Though they were upset that we had found a cause for Daniel's problem, the parents were happy that their risk of having another affected child was so small. A few months later, Daniel's mother became pregnant; an amniocentesis, a test done during the pregnancy in which a small amount of amniotic fluid is removed from the womb and the fetus's genetic material is analyzed, revealed that Daniel's new sibling was a healthy girl. Six months later, Arabella was born. Healthy and happy, she shows no signs of autism.