

Genes, Heredity and CVID: *What Are the Odds?*

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When I became pregnant with my first child four years ago, one of my biggest concerns was the chance that my child could also have common variable immune deficiency (CVID), as do I. As a genetic counselor, I know there is likely a genetic component to the development of CVID, but we don't know what it is, so it was difficult to determine how likely it would be that my child would develop CVID. I truly understood what my patients must have gone through when I would provide them genetic counseling on diseases that ran in their families but couldn't identify for them the genes associated with the diseases.

Unfortunately, this is still true today for the majority of patients with CVID considering parenthood. However, in the last five years, there has been some progress made in deciphering the genetic basis of CVID (the genes associated with CVID).

To understand how genetics plays a role in CVID, we will review some of the basic genetic concepts and the progress that has been made in genetic research of CVID, and we will discuss genetic testing and whether it may be an option for families.

Genetics 101: Basic Training

According to the Immune Deficiency Foundation, genes are the messages that determine the physical and chemical characteristics of an individual. They are the instructions that communicate to the body how to work and run efficiently. Typically, a human has two copies of every gene within each cell of his body. One copy of the gene is inherited from the mother and the other copy is inherited from the father. The immune system is made up of numerous genes to tell the body how to make the substances that will react to and fight infections. When a gene is

damaged or mutated, it doesn't work properly and this can ultimately affect the function of a whole system in the body, such as the immune system.

Chromosomes are long string-like structures that contain our genes. Humans have a total of 46 chromosomes, which come in 23 pairs. Half of these chromosomes come from the mother and half from the father. The first 22 pairs of chromosomes, called autosomes, are numbered. They are the same in both males and females. The 23rd pair is the sex chromosomes. Females have two X chromosomes and males have an X and a Y chromosome.

Inheritance Patterns

Genetic diseases follow different patterns of inheritance, how the disease is passed on in a family. Each pattern is determined by the gene defect that causes the disease and the chromosome on which the gene is located. The three most common patterns of inheritance for primary immune deficiency diseases are autosomal dominant, autosomal recessive and X-linked recessive. Autosomal dominant (AD) diseases can affect either gender because they are caused by a defect in a gene on one of the numbered chromosomes (those that males and females have in common). These diseases may appear to be passed on through a family from generation to generation. However, they may also occur for the first time in one individual as the result of a new genetic mutation that can happen by chance in anyone. A person affected by a known AD disease has a 50 percent chance of passing the gene mutation on to his or her children.

Autosomal recessive (AR) diseases can also affect either gender because they too are caused by gene defects on autosomes. However, these diseases occur only when both parents are carriers of the gene defect and both have passed

the defective gene on to their child. Typically, carriers of an AR gene defect do not show symptoms of disease. Couples who have a child with an AR disease have a 25 percent chance (1 in 4) of having another affected child. Siblings of an affected individual have a 25 percent chance of also being affected with the disease and a 50 percent chance of being a carrier, but not likely affected.

X-linked recessive (XLR) diseases typically affect males and are caused by gene defects on the X chromosome. Since males have only one copy of the X chromosome, they do not have another copy of the gene to balance out the damaged copy. Affected males have either inherited the gene defect from their mothers, who are carriers, or the gene defect occurred as a new mutation for the first time in the affected male. Regardless, the daughters of affected males will be carriers of the defective gene because they inherit their father's X chromosome. The sons of affected males inherit their father's Y chromosome, so they will likely be unaffected, depending on their mother's carrier status.

Female carriers of XLR diseases do not usually show symptoms of the disease. However, each of their sons has a 50 percent chance of being affected and each of their daughters has a 50 percent chance of being a carrier. For XLR diseases, it is important to determine whether the gene defect is inherited or is a new mutation, because this will affect the recurrence risk to other family members, including the couple's children, siblings and even more distant relatives. Families with inherited XLR defects typically show multiple generations of affected males, passing through unaffected female carriers. When the first affected person is a male with a new XLR mutation, family members may be negative.

Some primary immune deficiency diseases such as CVID and selective IgA deficiency may follow multifactorial inheritance, rather than a single gene inheritance pattern as those described above. Multifactorial inheritance is less defined and does not show the clear patterns when looking at the family history. In multifactorial diseases, it is thought that a person inherits a genetic predisposition to developing a disease that could be caused by one or more genetic components. However, the environment also plays a role in disease development and may act like a trigger. If a person has the genetic predisposition but is not in the right environment, he or she may never develop the disease. It has been difficult to determine the genetic components and

environmental factors for multifactorial diseases, and it is therefore difficult to determine actual recurrence risks for family members.

CVID Genetics Research

What does all of this jargon have to do with CVID? Current research shows that somewhere between 10 percent and 20 percent of individuals with CVID have an identified gene associated with their disease. These genes may follow autosomal recessive, autosomal dominant and even X-linked recessive inheritance, depending on the gene. Still, for the majority of patients with CVID, "there is not one single gene defect associated with the disease," says Hans Ochs, MD, professor of pediatrics and director of the Immunodeficiency Molecular Diagnostics Laboratory at the University of Washington in Seattle. Dr. Ochs explains that CVID is likely to be a group of disorders caused by multiple gene defects. Once certain genes are identified, this group of individuals will be pulled out of the CVID category and given a new diagnosis, even though they may still have the same clinical symptoms as others in the CVID category.

Recurrence risks for family members of CVID patients are most clearly defined for the following genes that have been identified with CVID:

- The ICOS gene is located on chromosome 2 and follows autosomal recessive inheritance. Therefore, carrier parents of a child with an ICOS gene defect have a 25 percent chance of having another affected child. Although this gene was an exciting discovery back in 2003, it has since been identified in only four families in the Black Forest region of Germany and Lienz, Austria. Moreover, the ICOS gene probably accounts for less than 1 percent of patients with CVID.¹
- The TACI gene is located on chromosome 17 and follows autosomal dominant inheritance. The original studies in 2005 suggested that defects in this gene may account for as many as 10 percent to 15 percent of patients with CVID in their study. However, additional studies have suggested that not all of the reported changes in the gene are associated with clinical symptoms of CVID and may be due to normal variation in the gene. Caution should be used when trying to predict risk in families with TACI gene alterations.² ➤

- The CD19 gene is located on chromosome 16 and follows autosomal recessive inheritance. Discovered by a group in the Netherlands, the CD19 gene is thought to account for less than 1 percent of patients with CVID.³
- The BAFF-R gene is located on chromosome 22 and follows autosomal recessive inheritance. It is thought to account for less than 1 percent of patients with CVID.⁴

Genetic Testing

Until the last couple of years, much of the genetic testing for primary immune deficiency diseases was done in the research laboratories that identified the genes. This is starting to change. Now, specialty commercial laboratories, along with university-based laboratories, are starting to offer clinical genetic testing. Many of these specialty labs also offer prenatal testing once a gene defect is identified in a family. However, health practitioners are not commonly familiar with such labs.

Two of the main reasons to consider genetic testing are to more clearly define a person's diagnosis and to help predict recurrence risks for other family members.

Dr. Ochs suggests that "many patients never get a genetic workup and may be misdiagnosed." For example, it is very

important that a male with CVID has a clinical laboratory workup or genetic testing to rule out X-linked and autosomal conditions that can be clinically similar to CVID, such as X-linked agammaglobulinemia, X-linked lymphoproliferative disease and hyper-IgM syndrome. Recurrence risks for someone with an X-linked primary immune deficiency will be much higher than for someone with standard CVID. Dr. Ochs believes that it is important for a patient to discuss his or her clinical and family history with an immunologist to determine if genetic testing is warranted. If so, the patient's immunologist or specialist can send a sample of the patient's blood to the appropriate genetic laboratory for analysis of the suspected genes.

It is worth noting that once a gene defect is identified in an individual, other at-risk family members can be offered this testing. In addition, prenatal testing may be an option through chorionic villus sampling (CVS) or amniocentesis, two procedures that can be performed on a fetus. However, there are risks of miscarriage associated with both procedures, and, if they are being considered, the risks should be addressed in genetic counseling. Genetic counseling is available in most hospitals and medical centers that offer high-risk obstetric services.

What Are the Odds?

Now, let's get back to the question: What is the chance my children might be affected?

The odds are all over the board. The bottom line is this: If a specific gene has been identified and is thought to be the cause of CVID in an individual, the odds will be based on the inheritance pattern of that gene. However, for the majority of us with CVID, we still don't have the definite answer to that question. And for those contemplating having children, it is a very personal choice that should be discussed with your spouse and your physicians.

Conclusion

If you have CVID and you are willing to take a chance that your child might also have it, keep in mind that any couple takes myriad chances when having a child. Despite the unknown, I go on about my life as I always have, thankful for a diagnosis and an effective treatment that allows me to enjoy every day with the wonderful children I am fortunate to have. ■



^{1,2,3,4} Gene Reviews: Common Variable Immune Deficiency Overview www.genetests.org/profiles/cvid.