

The Long Road Home

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A Parent's Guide to the Genetics of Down Syndrome

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ABSTRACT

Down syndrome is a genetic disorder, occurring when an individual has all or part of an extra copy of chromosome 21. Parents of children with Down syndrome are often confused by the term *genetic disorder* because they associate the term with inheritance but have also learned that Down syndrome is not typically inherited. These parents may have questions about the nature of chromosomes, how Down syndrome occurs, recurrence risk and more. This article attempts to address many of the common questions parents of children with Down syndrome express regarding the genetics of the disorder including the mechanisms by which Down syndrome occurs: nondisjunction, translocation and mosaicism, as well as providing information about prenatal testing options, how the diagnosis is made and where parents may go for further information.

KEY WORDS: Down syndrome, trisomy 21, chromosome, nondisjunction, translocation, mosaicism, karyotype, prenatal testing, recurrence risk

For many people, the term *genetic disorder* suggests a disorder that is inherited or passed down from parent to child in the genes. Down syndrome does not typically occur that way, so why is Down syndrome considered a genetic disorder? Down syndrome is a genetic disorder because the characteristics that make up Down syndrome occur as a result of the person having extra genetic material, either all or part of an additional copy of chromosome 21.

START WITH THE BASICS

To understand what it means to have an extra copy of a chromosome, one first needs to know what a chromosome is. Chromosomes are packages of genes, which carry all the genetic information passed down from parent to child. The genes essentially provide instructions to the cells of the body for how to function. Humans typically have 23 pairs of chromosomes in each cell of their bodies (except sperm

and egg cells) for a total of 46 chromosomes per cell.¹ At the time of conception, the mother's egg provides 23 chromosomes and the father's sperm provides the other 23.

A LITTLE DOWN SYNDROME HISTORY

Down syndrome has probably always been with us. Art and literature point to this fact. But it was not until 1866 that the set of characteristics we now refer to as Down syndrome was described in the literature and recognized as a discrete entity by John Langdon Down.² Although some of Down's theories about the reasons Down syndrome occurs were later disproved, his description and recognition of Down syndrome as a separate entity were significant. Many years later, the syndrome was renamed for Down and is now known as Down syndrome. Interestingly, Down had a grandson, also named John Langdon Down, who had Down syndrome.

Down identified the syndrome but could only speculate about why it occurred. It was not until the late 1950s that it became clear that the typical number of human chromosomes in every cell is 46. In 1959, Jerome Lejeune discovered that Down syndrome occurs as a result of an extra copy of chromosome 21.² Very soon after that, the 3 mechanisms by which Down syndrome occurs were identified. These will be described in more detail later in this article.

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What Do We Know About Chromosome 21?

Chromosomes are numbered according to size, with number 1 being very large and number 22 being very small. The 23rd pair is the sex chromosomes, labeled XX in women and XY in men. Chromosome 21 is one of the smallest of the human chromosomes, so it does not carry as much genetic material as the larger chromosomes. In part, because of its smaller size, chromosome 21 was the first of the human chromosomes to be fully mapped. Mapping involves identifying long sequences of proteins that make up the genes on each chromosome. Once the protein sequences are identified, then the proteins that make up each distinct gene must be determined. The mapping of chromosome 21 was completed in the year 2000, but the counting of the precise genes is still being studied and revised. Knowing the location and makeup of these genes does not tell us which genes or interaction between genes accounts for specific characteristics, but it does provide a wonderful map for current and future research.² As individual genes and groups of genes are identified, their role in producing the characteristics of Down syndrome can be studied.

Chromosome 21 and Down Syndrome

How does the additional genetic material present from the extra copy of chromosome 21 cause the characteristics of Down syndrome? The answer to this question is not entirely clear, but one theory is that by having an extra copy of chromosome 21, the genes present on the chromosome are present in 3 copies instead of 2, producing 50% more effect. This is called the “gene-dosage effect,” suggesting that genes work something like medications in that a different dosage causes a different result. Another theory about why the extra genetic material leads to the characteristics of Down syndrome is that entire sets of genes may have higher activity levels and together lead to the characteristics we see. These 2 possible explanations may be correct, and both mechanisms may happen simultaneously.²

Why does Down syndrome occur? This is the million-dollar question! There is much speculation about why Down syndrome occurs but no clear answers yet. We know that Down syndrome occurs once in every 733 live births, making it among the most common chromosomal disorders.³ We also know that the likelihood of having a baby with Down syndrome increases with maternal age, but knowing this risk factor and determining the cause are 2 very different things. One of the theories about why older women have an increased risk of having a child with Down syndrome is that conceptions of babies with Down syndrome may occur equally throughout women’s reproductive years but are more likely to result in miscarriage in earlier years than in later years. This

would suggest that the body somehow knows that the pregnancy may be the last one and protects it more carefully.¹ How does Down syndrome occur? Down syndrome can occur as the result of 3 different mechanisms: nondisjunction, translocation, and mosaicism. What all 3 mechanisms have in common is that the individuals have all or part of an additional copy of chromosome 21 and all have some of the characteristics associated with Down syndrome.

Nondisjunction

Nondisjunction is by far the most prevalent mechanism by which Down syndrome occurs, accounting for about 94% of all cases.¹ In simple terms, it refers to an error in cell division at the time either the egg or the sperm was formed. The newly formed egg or sperm has 24 chromosomes, instead of the usual 23. At conception the egg or sperm from each parent join, resulting in a zygote, the bundle of cells just following fertilization of the egg with a sperm, with 47 total chromosomes.

When a newborn is suspected of having Down syndrome, a blood sample can be taken and tests done to count, sort, and display the chromosomes in each cell. This is called a karyotype.¹

Nondisjunction appears to occur as something of a fluke of nature with a cause that is not yet known. It does not usually occur as a result of an inherited likelihood, although it does appear that some families seem to be prone to errors of nondisjunction raising their risk slightly.^{4,5} This family tendency is not something that can be tested at this time, so when a couple has already had a child with Down syndrome and is expecting another child, they will most likely be told that their risk of having a second child with Down syndrome is approximately 1% plus the risk associated with the mother’s age.^{1,6} There is some disagreement in the literature about this risk and how to calculate it in part because the conception of a second child with Down syndrome as a result of nondisjunction to the same parents is very uncommon.

Translocation

Translocation occurs far less frequently than nondisjunction, accounting for about 3% to 4% of all cases of Down syndrome.^{1,6} Translocation means that all or part of an extra copy of chromosome 21 is present in every cell of the individual with Down syndrome, but it is attached to another chromosome. Both nondisjunction and translocation can be diagnosed by doing a karyotype, which is a study of the chromosomes, using a blood sample from the individual with Down syndrome.¹ It is important to determine which mechanism is at play in causing the Down syndrome because translocation can have an inherited risk. Approximately one-third of the cases of translocation Down syndrome occur as a result of a parent being a carrier for the translocation. The parent is unaffected

and shows no signs of Down syndrome. The other two-thirds of the time translocation occurs as an isolated event and is not inherited.¹ Parents who learn that their baby's Down syndrome occurred as a translocation should be offered genetic counseling, even if they do not plan future children. The possibility of inherited risk could impact the baby's siblings as well as other relatives. These possible risks can be explained in greater detail as part of genetic counseling.

Mosaicism

Mosaic Down syndrome occurs very infrequently and accounts for only 1% to 2% of all cases of Down syndrome.⁶ People with mosaic Down syndrome have the extra copy of chromosome 21 in some cells of the body, whereas other cells have the typical 2 copies of chromosome 21. This can happen in 2 different ways. The first mechanism for mosaic Down syndrome is that initially the zygote, the bundle of cells just following fertilization of the egg with a sperm, has 3 copies of chromosome 21 in every cell but at some point in cell division, at least 1 cell line somehow drops the extra copy of chromosome 21. The other mechanism for mosaic Down syndrome is that the zygote has the typical 2 copies of chromosome 21 but as cell division continues, one of the cells has a duplication of chromosome 21, again, for reasons unknown.⁷

Mosaic Down syndrome may be more difficult to diagnose than either nondisjunction or translocation because the characteristics of Down syndrome may not be as evident right at birth. However, once Down syndrome is suspected, the blood test for the karyotype should be done. If the blood karyotype does not show trisomy 21 but suspicion of Down syndrome persists because of characteristics, low muscle tone, and/or health issues consistent with Down syndrome, further testing can be done. Usually cells of a different type than blood will be tested, such as skin or bone marrow to see whether they have 3 copies of chromosome 21. If some cell lines, such as skin cells, have 3 copies of chromosome 21, whereas other cell lines, such as blood cells, have just 2 copies of chromosome 21, mosaic Down syndrome has been identified.⁷ Mosaic Down syndrome does not typically occur as a result of any inherited risk, but, as mentioned above, some families may be prone to errors of nondisjunction and so may have a slightly increased risk of having a child with Down syndrome as a result of typical nondisjunction or mosaicism.

Do the different mechanisms causing Down syndrome have different effects? In other words, does it matter to my child if his or her Down syndrome occurred as a result of nondisjunction, translocation, or mosaicism?

The effects of Down syndrome vary widely from one individual to the next. Not everyone has all the

characteristics, health issues, or learning differences. There is a huge range of talents, abilities, and interests among people with Down syndrome. On average, the effects of Down syndrome on people who have nondisjunction or translocation are not noticeably different. People with mosaic Down syndrome may have fewer characteristics or health and learning challenges than those with either nondisjunction or translocation because not every cell line is affected by extra genetic material.⁷

PRENATAL TESTING

There are 2 major categories of prenatal testing: risk assessment tests and diagnostic tests. Risk assessment tests include maternal age, tests of the expectant mother's blood to measure various hormone levels, and special ultrasound tests that look for markers of Down syndrome. Risk assessment tests can use all or some of these mechanisms at specific times during the pregnancy.

The advantages to risk assessment tests are that they can begin in the first trimester, they can provide some information to help in a decision regarding the need for diagnostic testing, and they are generally seen as very safe and less invasive than diagnostic testing.

The disadvantages of risk assessment tests include both false positives and false negatives. In other words, risk assessment tests, no matter how comprehensive, can never provide a definite yes or no answer to the question, "Will my baby have Down syndrome?" Some expectant parents who choose risk assessment tests will be told that the risk is high when, in fact, the baby will not have Down syndrome. This could be called a false positive. Some parents will be told that the risk is low when in fact the baby will have Down syndrome. This is called a false negative. The likelihood of false positives and false negatives varies with the specific test or tests chosen.

Diagnostic testing involves collecting fetal cells or in some cases, placenta cells, to actually count chromosomes.⁸⁻¹⁰ The most common form of diagnostic testing is amniocentesis in which amniotic fluid is collected from the mother's uterus using a needle while guided by ultrasound. There are other less commonly used tests such as chorionic villus sampling (CVS) that also involve actual chromosome counts. This test can be done earlier in the pregnancy, during the first trimester.¹¹ The advantage to diagnostic testing is that it can provide a definite yes or no answer to the question, "Will my baby have Down syndrome?" with greater than 99% accuracy.^{8,9}

The disadvantages of diagnostic testing are that in most cases, it is not done until the second trimester as well as the fear and discomfort some people feel about the procedures themselves. Concerns about the safety of diagnostic testing and risk of miscarriage

have led some expectant parents to forego this. The safety of amniocentesis in terms of risk of miscarriage has now been shown to be much lower than previously thought (0.06% or 1 in 1600).¹² Risk of miscarriage with CVS is slightly higher at 1 in 100 to 1 in 200.^{9,13} There is a very small risk of limb abnormalities in the fetus associated with CVS, approximately 1 in 3000.¹¹

The variety of risk assessment options is wide and very complex, so many expectant parents do not understand the range of options facing them should they choose to do risk assessment. Before any option is chosen, the distinctions between risk assessment and diagnostic testing options should first be clear to the expectant parents. Decisions about prenatal testing should begin with some discussion about the pros and cons of risk assessment as well as diagnostic testing and how important it is to the expectant parents to know whether the baby will have Down syndrome or not. Some will want a definitive diagnosis to weigh their options to end or continue the pregnancy, whereas some will want to know in order to educate and prepare themselves to welcome and raise their baby with Down syndrome. Others may choose no prenatal testing feeling that the information it would provide would not affect their decisions and would cause stress that may detract from the joy of pregnancy. This is a highly personal decision impacted by belief systems, resources, dreams, and fears as well as comfort with uncertainty. Many expectant parents benefit from the information they can learn from their prenatal care provider, genetic counselors, and Down syndrome parent groups.

What If I Still Have Questions?

Many parents, after learning that their child has Down syndrome, have questions about the diagnosis, testing, causes, and other implications of the diagnosis. Some of these questions can be answered by the child's primary care provider. Others may be best handled by a genetic professional, either a medical geneticist

(MD) or a genetic counselor. The cost of these services is often covered by insurance carriers or Medicaid. Health maintenance organizations also usually cover these costs but may first require a referral by the primary care provider. Sometimes parents of children with Down syndrome do not feel the need for this consultation right away but may wish to do so later if contemplating a subsequent pregnancy, and again these costs are usually covered for parents who already have a child with Down syndrome. Information about the availability of genetic professionals in the parents' area and coverage of costs for the services should be directed to the health insurance provider. In addition, university-based health science centers may be able to direct interested individuals as well as regional genetic service collaboratives.

For more information about Down syndrome or available services, please contact Mile High Down Syndrome Association at (303)797-1699 or www.mhdsa.org.

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