

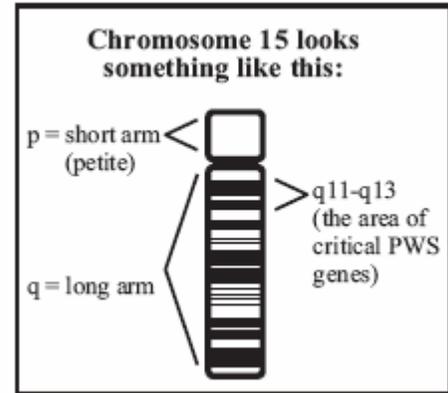
The Genetics of Prader-Willi Syndrome: An Explanation for the Rest of Us

(Originally published in PWSA-USA's The Gathered View by Linda Keder, former editor, March-May 2000. Revised and updated in July 2004 with the assistance of Merlin G. Butler, M.D. Ph.D., Chair, PWSA-USA Scientific Advisory Board.)

When the medical world first learned about Prader-Willi syndrome in 1956, doctors had no idea what caused people to have this collection of features and problems that we now know as PWS. In 1981, Dr. David Ledbetter and his colleagues reported a first breakthrough discovery: Many people with PWS that they studied had the same segment of genes missing from one of their chromosomes. They had discovered the deletion on chromosome 15 that accounts for about 70 percent of the cases of PWS. Since then, researchers have made a series of other important discoveries about the genes involved in Prader-Willi syndrome. Thanks to their perseverance, we now know much more about the several genetic forms of this complex disorder, and we have genetic tests that can confirm nearly every case.

Chromosomes and Genes: The Basics

To understand the genetics of PWS, it helps to have a basic understanding of chromosomes and genes. Chromosomes are tiny structures that are present in nearly every cell of our bodies. They are the packages of genes we inherit from our parents. Genes contain all the detailed instructions our bodies need to grow, develop, and function properly—our DNA. Specific genes direct our cells to produce proteins, enzymes, and other essential substances. Each of our many genes is located on a specific chromosome. Most of our body's cells contain 46 chromosomes—23 inherited from our mother and 23 from our father. (Egg and sperm cells normally contain just 23 chromosomes, because those are the cells that join in conception and provide the baby the right number of chromosomes.) Twenty-two of the chromosome pairs are labeled with a number based on their size (chromosome 1 is the largest pair, and chromosome 22 is nearly the smallest), and the two chromosomes in each numbered pair contain the same genes (one set from mother and one from father). The changes that cause Prader-Willi syndrome occur on the



pair known as chromosome 15. The 23rd chromosome pair is designated as the sex chromosome pair. This pair determines the baby's sex: XX for a girl, XY for a boy.

Changes or errors in genes and chromosomes are common in the formation of egg and sperm cells. Some of these genetic changes will have no effect when a baby is conceived; some will cause a miscarriage; and some, like those in Prader-Willi syndrome, will cause significant differences in how the baby develops and functions. While many genetic disorders are caused by a change in a single gene and can be passed down from parent to child, PWS is more complicated.

Some of the important genetic characteristics of PWS identified through research are:

- **More than one gene is involved** in PWS, and these genes are near each other in a small area of what is called the "long arm" of chromosome 15—in a region labeled 15q11-q13. Scientists still don't know exactly how many genes and which specific ones are involved.
- **The critical genes must come from the baby's father in order to function properly;** the mother's genes in this area are "turned off" through a rare phenomenon called "genomic imprinting."
- **There are at least three different chromosome**

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errors that can keep these key genes from working normally, and all result in the child having Prader-Willi syndrome.

- The two most common errors that cause PWS **can occur in any conception**—in other words, PWS is not usually an inherited condition; it just happens. In very rare cases, however, parents may have a 50-percent chance of having another child with PWS.

The Role of Genomic Imprinting

During the early 1980s, scientists puzzled over why some people who seemed to have PWS did not have the chromosome 15 deletion, and why some people with the chromosome 15 deletion seemed to have a different condition from PWS. Dr. Merlin Butler and colleagues began unraveling the puzzle when they reported in 1983 that the chromosome 15 deletion in PWS was on the father's chromosome.

The next breakthrough came in 1989, when Dr. Robert Nicholls and fellow researchers announced their discovery that PWS is an example of genetic or genomic imprinting, a process well known in plant genetics but not previously identified in humans. This means that some of our genes have to come from a particular parent to work normally. These rare genes are said to be “imprinted,” or have the ability to be turned off or on, depending on which parent contributed the gene. In what scientists call the “Prader-Willi region” of chromosome 15 (the area where the deletion occurs), there are genes that must come from the baby's father that are active, or “expressed,” in order to work. These genes are not active or expressed on the chromosome 15 inherited from the mother because the mother's imprint turns them off. In Prader-Willi syndrome, these critical genes are either missing (deleted) from the father's chromosome 15, functioning improperly because of an imprinting defect, or the entire chromosome 15 from the father is missing and both chromosome 15s come from the mother. (See The Three Genetic Forms of PWS for more detail on each of these errors.)

When a deletion of chromosome 15q11-q13 region is found on the mother's chromosome 15, the result is an

entirely different syndrome called Angelman syndrome (AS). That is because there is also one gene in the Prader-Willi region that is imprinted, or turned off, on the father's chromosome 15; people who lack this gene from their mother have AS rather than PWS. This discovery explained the mysterious cases of people who had a chromosome 15 deletion but did not have the characteristics of PWS—their deletion was on the chromosome 15 that came from the mother. Because the genetic errors happen in the same section of chromosome 15, PWS and AS are sometimes called “sister” syndromes even though the disorders have few features in common.

The Three Genetic Forms of PWS

Although every case of Prader-Willi syndrome is due to the baby failing to receive active genes from a specific section of the father's chromosome 15, there are three different ways that this can happen:

- **Paternal deletion — about 70% of all cases of PWS**

In the most common form of PWS, part of the chromosome 15 inherited from the child's father—the part containing the PWS critical genes—is missing. In some cases, the section that has disappeared (called a “deletion” or sometimes a “microdeletion”) is large enough to be identified with high resolution chromosome studies done with a microscope; in other cases, it is too small but it can be detected with another chromosome test called FISH (see Tests Used To Diagnose Prader-Willi Syndrome). Typical or common deletions are now classified as Class/Type 1 or Class/Type 2, based on the size of the deletion. Usually a deletion happens for no known reason, and it is not likely to happen again in another pregnancy (less than 1% chance of recurrence). There is nothing the father did (or did not do) to cause it and no way to prevent it.

Note: In rare cases of atypical deletions, imprinting defects (see below), or when a chromosome change such as a “translocation” caused the PWS genes to not function normally, the family could have another

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child with the same condition. (In a translocation, part of one chromosome is broken off and attached to a different chromosome.) It is especially important for these families to have further testing and genetic counseling.

- **Maternal uniparental disomy (UPD) — about 25% of cases**

In this less common form of PWS, the baby inherits both copies of chromosome 15 from one parent—the mother. (Maternal means mother; uniparental means one parent; and disomy means two chromosome bodies). In these cases, the developing baby usually starts out with three copies of chromosome 15 (a condition called trisomy 15) because there was an extra chromosome 15 in the mother's egg. Later, one of the three is lost—the chromosome 15 that came from the father's sperm. The result has the same effect as a deletion. The child does not have active genes on chromosome 15 that must come from the father in order to be expressed (to function). Even though there are two complete copies of the mother's chromosome 15, the key genes in the PWS region are imprinted, or turned off, in the mother's copies. Because the error in this form of PWS starts with an extra chromosome in the mother's egg, and older eggs are more likely to have errors of this type, older mothers are more likely than younger mothers to have a baby with this form of PWS. Even so, it is not likely to happen (and hasn't yet) to a second child in the same family. When a baby inherits two identical chromosome 15s from the mother (isodisomy, or two copies of the same one rather than one of each of the mother's own chromosomes), there is a chance of having additional genetic problems or conditions.

- **Imprinting defect — less than 5% of cases**

In very rare cases, the PWS genes on the father's chromosome are present but do not work because the imprinting process is faulty. The activity of the genes is controlled by a tiny imprinting center on chromosome 15 in the same area as the PWS critical genes. Normally, when genes are passed down to a

child, the prior imprints are cleared away, and new imprints are made according to the sex of the parent. When there is a microdeletion or other defect in the imprinting control center, gene function on the father's chromosome 15 may not be set to work normally. An imprinting defect can appear suddenly, or it can be present in the father's chromosome that he received from his mother. If he received the defect from his mother, the father would not have PWS himself (because it's on his maternal chromosome 15), but he could pass it on to his child (it would be the child's paternal chromosome 15). There is a 50-50 chance that any child he has will receive the chromosome with the defect instead of the one that's working correctly. Likewise, the father's siblings could carry and pass on the mutation to their children. *Further testing and genetic counseling are especially important for families who have a child with an imprinting defect.*

Genetic Tests for PWS

Because the genetics of PWS is so complicated, it usually takes more than one test to be certain whether someone has PWS and what form of it they have. The major tests that are used in the diagnosis of PWS are shown in the table below. Which genetic tests are used, and in what order, will depend on a number of considerations for each individual case (see Testing Considerations). Genetic testing usually requires a blood sample from the child and possibly from the parents as well.

Families should consider genetic testing for PWS if they have:

- a baby with low muscle tone (hypotonia), poor sucking ability, and — if a boy — undescended testicles;
- a child or adult who has a number of the characteristics of Prader-Willi syndrome as listed in the Diagnostic Criteria for PWS (www.pwsausa.org/syndrome/Diagnos.htm); or
- an undiagnosed child who was tested for PWS using older tests than those available today.

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Genetic Tests Used To Diagnose Prader-Willi Syndrome

TEST	WHAT THIS TEST DETECTS	WHAT IT CAN'T DETECT	TEST AVAILABILITY
High resolution Chromosomal Analysis (examination under a microscope)	Large deletions and other chromosome abnormalities such as translocations and extra chromosomes	Small deletions, Uniparental disomy (UPD) Imprinting defects	Widely available
FISH (stands for <i>fluorescence in situ hybridization</i> , often done at the same time as a chromosome analysis)	All common or typical deletions	UPD, Imprinting defects, Which parent each chromosome 15 came from (A deletion could mean either Prader-Willi or Angelman syndrome.)	Widely available
<i>The following are classified as "molecular" tests:</i>			
DNA methylation test (confirms or rules out PWS as a diagnosis, with over 99% accuracy)	The imprinting pattern in region 15q11-q13 (Normal results show both paternal and maternal DNA pattern. In PWS there is only a maternal pattern, whether there is a deletion, UPD, or imprinting defect.)	Which form (molecular class) of PWS the child has: deletion, UPD, or imprinting defect	Not widely available
DNA polymorphism studies (done to detect UPD, requires blood samples from both parents and child for best accuracy)	Which parent each chromosome 15 came from (If both chromosomes are from the mother, the child has PWS; if both are from the father, it's Angelman.); can also detect some deletions	Imprinting defects, Some deletions	Not widely available

Testing Considerations

Which genetic tests should be done and in what order?

The approach to testing for PWS in any given case will depend on a number of considerations—what tests have already been done, what expertise and laboratories are available, whether both parents are available for blood samples, and so forth. Chromosome studies are typically done in any case, but the order of the other tests—and their results—will determine how many need to be done. In 1996, two national genetics groups worked together to develop guidelines on testing for Prader-Willi and Angelman syndromes. Their recommendations have been published and are available on the Internet at www.faseb.org/genetics/acmg/pol-22htm. In most cases, they recommend

continued testing until the genetic cause of PWS is known.

Some testing scenarios:

If an experienced diagnostician suspects Prader-Willi syndrome in an older child or adult who meets the Diagnostic Criteria for PWS, the FISH test might be the first test of choice because it is widely available and will detect the majority of cases of PWS. If the FISH test is positive (a deletion is found), the diagnosis of PWS is confirmed and no further testing is needed. If the FISH test comes back negative (detecting no deletion), the next step would be the DNA methylation test. A relatively new test, DNA methylation can diagnose more than 99 percent of people with PWS, but it does not tell whether the cause of PWS is deletion, uniparental disomy (UPD), or an imprinting defect. If,

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after the negative FISH test, the methylation test confirms that the person has PWS, more testing is needed to find out whether the cause is UPD or an imprinting defect. If the UPD test is negative in this case, the cause must be an imprinting defect. At this time, imprinting defects are diagnosed by process of elimination—positive methylation test, but negative FISH and UPD tests—However, to confirm a suspected defect may require testing in genetics laboratories specializing in PWS research.

In cases where the suspicion of PWS is not as strong, or where the diagnosing physician is not as familiar with PWS, the DNA methylation test might be the best place to start. The test is becoming more widely available and can confirm or rule out PWS at the first step. If the methylation test is positive, then additional testing can be done at the same lab to determine the specific form of PWS. Even experienced diagnosticians have sometimes misdiagnosed infants as having PWS when in fact they had Angelman syndrome. (Both syndromes can cause hypotonia in the newborn baby, and both will show a chromosome 15 deletion on the FISH test.) Starting with the methylation test avoids this problem.

In cases of an imprinting defect or other rare test findings, families may need further testing through a research laboratory, both to get an accurate diagnosis and to learn about their risks of having another child with PWS.

What about prenatal testing?

Prenatal testing for PWS is now available. An expectant family might wonder whether to have testing done if they have had a child with PWS previously. Although the risk of having a second baby with PWS is very low in most cases, prenatal testing can provide important reassurance to the family that the new baby will not be affected. Counseling by a genetics professional can help a family understand their specific risks and whether testing of the fetus is important in their situation.

Prenatal testing for PWS might also be done in cases where a genetic study of the fetus (through chorionic villus sampling—CVS—or amniocentesis) shows abnormalities that raise suspicion of PWS. In one case, for example, a routine chromosome test done through CVS early in a woman's pregnancy found that some of the baby's cells had three chromosome 15s (called

mosaic trisomy 15). This led the doctor to order a molecular test for maternal uniparental disomy (UPD) in the remaining cells. The test results showed that the baby would have PWS due to UPD.

Who should do the testing?

Families who are seeking a diagnosis or who have concerns about their risks should work with a genetics specialist who is knowledgeable about PWS and the latest in testing. The geneticist will arrange to have blood samples sent to an appropriate laboratory for testing.

There is available on the Internet a free, searchable database of genetics laboratories and the tests they offer for specific conditions such as PWS. GeneTests Laboratory Directory (formerly called Helix) is sponsored by the Children's Health Care System, Seattle, Washington, and can be found on the Internet at www.genetests.org. Note, however, that not every laboratory that performs these tests is included in the database.

Those who need help in locating a geneticist or a testing center may contact the PWSA (USA) national office at 1-800-926-4797 or through its Website, www.pwsausa.org.

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The author wishes to thank Drs. Suzanne Cassidy, Dan Driscoll, and David Ledbetter for editing the original article, and Dr. Merlin Butler for assisting with this latest revision, so that families and other non-geneticists might better understand this complex and evolving subject.