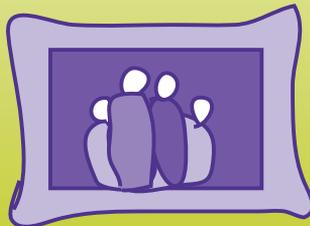




Cleft Palate FOUNDATION

Genetics and You



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Genetics and You



Second Edition
2008 Reprint

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Foreword

When a baby is born with a cleft or other craniofacial birth defect, one of the parents' immediate concerns is for their child's care. Once plans for treatment are underway, an early spoken or unspoken question is why this happened to the child and what the chances are that other children with clefts will be born into the family. As their children reach adolescence, parents may wonder what to tell the child who has a cleft, as well as other children in the family, about their own risks of having a baby with a cleft. These questions are most accurately answered by a clinical geneticist.

This pamphlet was written primarily for parents of children with clefts, although it may also be of interest to adults with clefts and to a variety of professionals who work with children and families of children who have clefts. This pamphlet will review some commonly-accepted information regarding the causes of cleft lip and palate, the risks of recurrence, and the nature and process of genetic counseling. It is through genetic counseling that families can obtain information regarding their own particular situations.

What is Cleft Lip and Palate?

Cleft lip with or without cleft palate and cleft palate alone (occurring without a cleft lip) are two common congenital birth defects. A cleft is a separation in the lip or the roof of the mouth (palate). Congenital means that the condition is present when the baby is born. Clefts can occur among all races and in both males and females. However, cleft lip and palate occurs about twice as often in boys as in girls, while cleft palate alone is slightly more common in girls. Approximately 1 in 600 babies born in the United States has some type of cleft.

What Causes This Condition?

The exact cause of clefting is unknown in most cases. For most cleft conditions, no single factor can be identified as the cause. However, it is important to distinguish between isolated clefts (in which the patient has no other related health problems) and clefts associated with other birth disorders or syndromes. A syndrome is a set of physical, developmental, and sometimes behavioral traits that occur together. Clefts have been identified as one feature in over 300 syndromes, most of which are quite rare. Syndromes account for roughly 15% of the total number of cases of cleft lip and/or palate. For information about a specific syndrome, contact a geneticist, genetic counselor, or other health professional familiar with the specific diagnosis. The remainder of this pamphlet will consider cleft lip with or without cleft palate and isolated cleft palate, not clefts that are part of syndromes.

The majority of isolated clefts appear to be caused by an interaction between an individual's genes (genetic predisposition) and certain factors in the environment that may or may not be specifically identified. Genes contain the basic substance of inheritance, DNA, which provides each person with his or her own unique human characteristics. Genes account for such factors as height, eye color, and physical appearance. Genes also determine the structure of the heart, the number of fingers on the hand, and the shape of the face. Humans have approximately 30,000 genes. The Human Genome Project (funded by the National Institutes of Health) has identified the sequence of almost all of these genes. Researchers now have the tools needed to understand how various genes work, and the basis of genetic predisposition can be better explained.

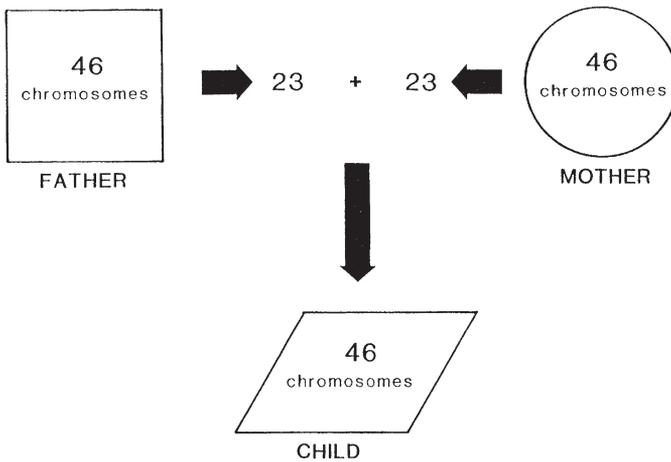


Figure 1: Each Parent contributes 23 chromosomes containing the genetic information for a particular child.

Genes cannot be seen under the microscope. They are grouped like beads on a string in structures called chromosomes. Chromosomes, however, can be seen microscopically with a specialized blood test called a karyotype. Each person has 23 pairs of chromosomes (46 total). One of each pair comes from the father in the sperm and one from the mother in the egg (Figure 1). Thus, with a few specific exceptions, most people have two copies of every gene, one inherited from the father and one from the mother. Due to the large number of genes involved in inheritance, and because parents pass on to their children only one copy of each gene, no two children in the same family have exactly the same genetic make up (except identical twins). Each individual is genetically unique. Cleft conditions may be considered genetic, even if there are no other family members with clefts. Genetic disorders occur when:

- something happens to change a gene (mutation);
- an individual inherits a disordered gene from one or both parents who may or may not know they have the gene; or
- an individual inherits multiple genes which, in combination, give rise to a disorder.

When used by geneticists, the term “environmental” refers to all those factors that are not in the genes and chromosomes. It is a very broad definition that includes not only exposure to drugs, chemicals, and infectious agents, but also factors such as where the baby begins to grow in the uterus. Obviously, most of these things are not under the control of the pregnant woman or her partner. Only a few environmental factors have been

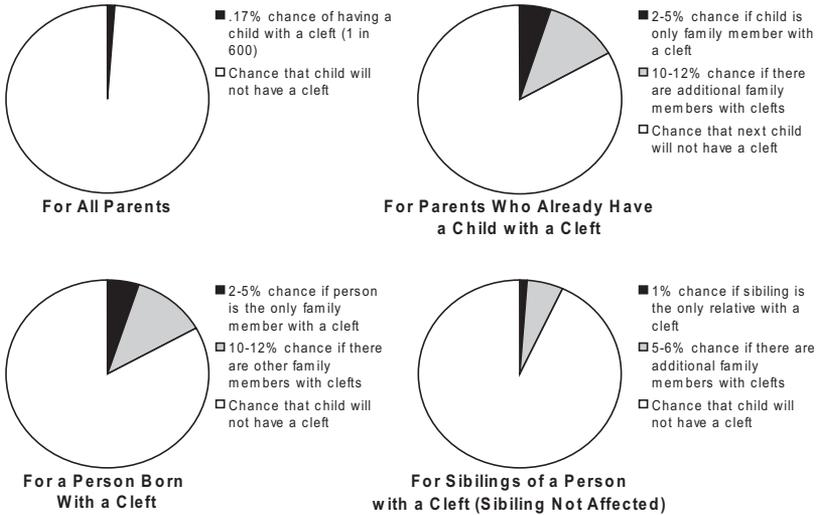
convincingly documented to increase the risk for clefting when used during pregnancy. Among these are heavy alcohol consumption, smoking, and certain prescription medications for acne, and others necessary to control epilepsy in the mother. There is little firm evidence that commonly used over-the-counter medications, trauma, or illness during pregnancy plays a significant role. The lip forms at about 7 weeks of pregnancy (counting from the last menstrual period), and the palate forms at 11 weeks using the same dating. A woman may not even know that she is pregnant at this point. To cause a cleft lip or cleft palate, an environmental exposure must have occurred before the formation of these structures. Anything that happened after this time has no bearing on the cause of the cleft.

What are the Chances that Another Family Member Will Be Born with a Cleft?

The risk for recurrence of a cleft condition is determined by a number of factors that are often unique in a particular family. These include the number of family members with clefts, how closely related these people are, the race and sex of the affected individuals, and the type of cleft each person has. After a syndrome or complex disorder is excluded, recurrence risk counseling for cleft lip and/or palate can be offered to families. There is no genetic test currently available to determine a person's individual chance of having a child with a cleft. However, information is advancing so rapidly with respect to genetic testing that couples are advised to ask whether any new tests have been developed when they are planning future pregnancies.

Every parent has approximately a 1 in 600 risk of having a child with a cleft (Figure 2). Once parents have a child with a cleft, the risk that the next child (and each succeeding child) will be affected is 2-5% (2 to 5 chances in 100). If there is more than one person in the immediate family with a cleft, the risk rises to 10-12% (roughly 1 chance in 10). An individual with a cleft who is the only one in his/her family with a cleft has a 2-5% chance that his or her child will have a cleft (2 to 5 chances in 100). If the individual with the cleft also has a close relative with a cleft, the risk increases to 10-12% (roughly 1 in 10) that a child will have a cleft. Finally, the unaffected siblings of an individual with a cleft have a roughly 1% (1 chance in 100) risk of having a baby with a cleft. This risk may rise to 5-6% (5 to 6 chances in 100) if more than one close family member has a cleft. If a syndrome is involved, the risk for recurrence within the family could be as high as 50% (1 chance in 2). A genetic evaluation will help identify such syndromes.

Figure 2: Recurrence Rates for Cleft Conditions



With respect to recurrence, cleft lip and/or palate is believed to have a different cause from cleft palate alone. Recurrence for cleft lip with or without cleft palate implies a risk for any condition ranging from incomplete cleft lip alone to bilateral complete cleft lip and palate. Recurrence for cleft palate (without cleft lip) implies a risk for cleft palate alone. These families are not at increased risk for cleft lip.

This very general information is based upon studies of different populations from around the world. Individuals with clefts, parents of affected children, and other family members usually require more specific information about the recurrence risks in their own family. This type of information is available from a genetic evaluation.

What is Involved in a Genetic Evaluation?

A genetic evaluation provides specific information for a particular family. Most evaluations involve several steps, including a detailed family history, a medical history, a physical examination of the individual with the cleft, and, where appropriate, laboratory testing. Once the information is collected, the findings are discussed with the family. Although this evaluation can often be accomplished in one visit, several sessions may be necessary if laboratory testing is involved or if extended family members need to be evaluated either in person or through review of medical records.

1. The most essential part of a genetic evaluation is verifying that the cleft is isolated, not part of a syndrome. The geneticist will take a family history, medical history, and physical examination to determine whether the cleft is part of a broader problem in development (syndrome). The presence of a syndrome often changes the risk for recurrence. **It is important to recognize, however, that most children who have clefts do not have any other genetic problems.**
2. The evaluation will consider whether other relatives have similar conditions, and if so, how many relatives and how closely related they are. Usually this information is provided by the individual requesting the evaluation. Occasionally medical records of relatives will be requested. The geneticist will often ask to evaluate immediate relatives if they are available and, rarely, extended family members. Evaluation of immediate and extended relatives is usually pursued if the clinician suspects a specific genetic cause of the cleft. Even photographs of family members may help. In general, for isolated clefts, the greater the number of relatives in the family known to have clefts and the more closely they are biologically related to the affected individual, the greater the risk for recurrence.
3. The type and severity of the cleft must be considered. In general, the type of cleft tends to be consistent within families, although the severity of the cleft may vary among the individuals in the family. This trend is understandable if one remembers that family members share many genes in common and are likely to share a predisposition to the same type of cleft.
4. Laboratory testing may be required. Chromosome tests (karyotypes) are generally requested when there is a suspicion that the cleft may be part of a syndrome. Chromosome testing looks at the packaging of the genetic information, not the genes themselves. It requires a small sample of blood. X-rays may be requested if there appear to be problems in bone formation that might help the geneticist understand the cause of the cleft. Increasingly, molecular testing is available for specific genetic conditions known to cause clefts. These tests are not used as screening tools but rather to confirm or disprove a specific diagnosis. Lastly, clinical photographs may be taken. Syndrome identification is still largely a matter of matching physical characteristics with photographs and descriptions in the literature, and in computer databases that have been developed for this purpose. Since the process is highly visual, photographic records are extremely helpful.

During the counseling summary, the geneticist and/or genetic counselor provides information to the patient about what the evaluation revealed. The diagnosis of a syndrome may indicate that future treatment will be needed.

Information regarding the risk for recurrence is conveyed to the individual, the family, or extended family members. For families interested in options for managing this risk in future pregnancies, strategies for prenatal (before birth) diagnosis may be discussed.

Prenatal Diagnosis and Prevention

The purpose of prenatal diagnosis is to provide information that will allow individuals and/or couples to make decisions about childbearing. Individuals who work in the field of reproductive counseling provide factual information. The individuals seeking the information make their own reproductive choices.

Cleft Lip With or Without Cleft Palate:

Between 85 and 90% of individuals with this type of cleft have no other physical problems. When seen in isolation, this condition is believed to result from an interaction between genes and the environment.

Prenatal diagnosis for cleft lip with or without cleft palate depends on the ability of ultrasound to see the baby's face in the womb. Many factors influence the accuracy of ultrasound studies, including the following:

- the sophistication of the scanning equipment;
- the experience and skill of the sonographer;
- the number of weeks into the pregnancy (optimum time is 18-20 weeks or later);
- the baby's position in the womb;
- maternal body structure (it is much harder to see fetal anatomy in overweight women);
- the presence or absence of amniotic fluid, which is the liquid surrounding the baby in the womb (reduced amounts of amniotic fluid limit visualization).

A procedure called targeted Level II ultrasound is designed to check the baby's anatomy and is therefore the best method for prenatal diagnosis of cleft lip with or without cleft palate. With current technology and a fetus that happens to be in the perfect position for scanning, the chances for prenatal diagnosis of cleft lip are reasonably good. The cleft palate that is seen on ultrasonography, however, is actually the alveolar ridge, or gumline. Current technology does not routinely visualize most of the hard palate or the soft palate of a developing baby.

Families need to know that guidelines for routine obstetrical ultrasound

scanning do not require an examination of the baby's anatomy. If an ultrasound is requested for the purposes of prenatal diagnosis, it is critical that this study be done at a center with the equipment and experience to produce the best possible images. Even so, ultrasound is not 100% accurate.

There are currently no treatments for unborn babies with clefts. The condition cannot be repaired before birth. However, babies can have surgical treatment and cleft care in their early years of life.

There is some evidence that taking folic acid before becoming pregnant may reduce the risk for isolated clefts. The Centers for Disease Control and Prevention and the American College of Medical Genetics already recommend a daily vitamin supplement of 400mg of folic acid for all pregnant women, which is intended to reduce the baby's risk for spina bifida, other neural tube defects, and possibly cleft lip and palate. This dose is provided by most over-the-counter multivitamins. If you have a history of clefts in your family, your prenatal care provider may recommend an additional supplement of folic acid.

Isolated Cleft Palate:

Between 50 and 60% of individuals with cleft palate (without cleft lip) have the cleft as their only structural difference. When seen in isolation, cleft palate alone is felt to result from the interaction between genes and the environment. The risk for recurrence represents the risk for cleft palate alone, not for cleft lip.

Unfortunately, prenatal diagnosis is not yet reliable for diagnosing cleft palate alone. Although ultrasound sees the outside surface of the baby's face, the palate is not readily seen with the equipment currently in use. Imaging with new 3-D machines is not likely to change this.

Although folic acid supplements have not been shown to reduce the risk of cleft palate alone, this vitamin is recommended as a general preventive measure for all women contemplating pregnancy (see above).

Clefts That Occur as Part of a Syndrome:

Approximately 10-15% of individuals with cleft lip with or without cleft palate also have a related syndrome, while about 40-50% of individuals with cleft palate alone do. Most of these syndromes include other physical problems that are obvious at or before birth. Recurrence risk counseling for these individuals can be complicated, and genetic counseling is highly recommended. If the cleft is believed to be the result of exposure to a specific "teratogen" (environmental agent known to increase the risk of birth defects), then avoiding that exposure in subsequent pregnancies is the best approach, if possible.

For individuals or families with a confirmed diagnosis of a chromosomal or molecular genetic condition, invasive prenatal testing may be a consideration. The most common tests of this type are amniocentesis and Chorionic Villus Sampling (CVS). Amniocentesis is currently the best method for obtaining fetal cells. It is performed at 15-20 weeks of pregnancy (ideally at 16-18 weeks) and carries a risk of miscarriage of 0.5% (1 in 200 procedures). To perform this test a needle is inserted through the abdominal wall of a pregnant woman into the fetal cavity. The procedure is done under ultrasound guidance so that the baby is not touched. The fluid that is removed contains cells from the baby as well as amniotic fluid, which is mostly fetal urine. Both can be sent for testing to answer a specific genetic question with respect to recurrence risk. Amniocentesis does not screen for all birth defects or for isolated (non-syndromic) clefts.

CVS takes advantage of the fact that the placenta develops from the first cell that is the baby. By taking a piece of placental tissue, various genetic tests may be performed. CVS is performed at 11 weeks into a pregnancy, either through the abdomen or through the vagina and cervix. CVS carries a miscarriage risk of 1% (1 in 100 procedures). The trade-off for earlier results is a slightly higher rate of miscarriage. CVS does not screen for all birth defects or for isolated clefts. **For this reason, neither CVS nor amniocentesis is recommended for individuals or couples for whom the only question is recurrence of isolated cleft lip and/or palate.**

Because the field of genetic diagnosis and genetic testing is advancing rapidly in response to the information provided by the Human Genome Project, new tests may be developed to diagnose conditions that are not currently identifiable before birth. For this reason, families may wish to contact a geneticist or genetic counselor whenever a pregnancy is discovered or contemplated.

For those individuals in whom the cleft represents one feature of a broader pattern and the diagnosis is not known, accurate genetic counseling is not possible. In addition, prenatal diagnosis depends upon the ability of ultrasound to see the structural abnormalities believed to be part of the suspected condition.

Although folic acid supplementation is not believed to reduce the risk of clefts associated with syndromes, it is recommended as a general preventive measure for all women contemplating pregnancy (see above).

Finding a Geneticist or Genetic Counselor

Clinical geneticists are often physicians (MD) with specialty training in genetics, although some geneticists may have a dental degree (DDS or DMD) or a doctoral degree in the field of genetics (PhD). Genetic counselors typically have a master's degree. Although geneticists/genetic counselors are integral members in only a minority of cleft palate treatment programs in the United States, most teams can refer families to appropriate providers. Ask your team director or coordinator for a referral.

Contact the Cleft Palate Foundation or these genetic organizations:

- American College of Medical Genetics: www.acmg.net
- Genetic Alliance: www.geneticalliance.org
- National Society of Genetic Counselors: www.nsgc.org

For More Information

Las publicaciones de la Fundación del Paladar Hendido también se ofrecen en español. Favor de llamarnos para recibir copias en español.

This publication and many others have been produced by:

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The Cleft Palate Foundation (CPF) maintains a growing collection of booklets and fact sheets that present an introduction to and explanation of many elements of cleft and craniofacial care and treatment. All publications are authored and regularly revised by representatives of professional disciplines serving the field of cleft and craniofacial care and treatment.

A publications order form for institutions including current pricing, bulk order rates and shipping and handling fees may be accessed at the CPF website or by calling the **Cleftline** at 1.800.24.CLEFT. All fact sheets are available at the website as open-access, PDF documents. Families, patients, students and other individuals may request complimentary packets of publications by emailing info@cleftline.org or by calling the **Cleftline**.

To date, the Cleft Palate Foundation has shared over 7,000 Gund Teddy Bears with repaired cleft lips with children and families all over the world. Please visit www.cleftline.org or call the **Cleftline** for more information about our bears.

If you are interested in helping us continue in our mission, please contribute to the CPF Cleftline Fund. Visit www.cleftline.org or call the **Cleftline** to make your donation today! Thank you.

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