Summer-Fall 2004

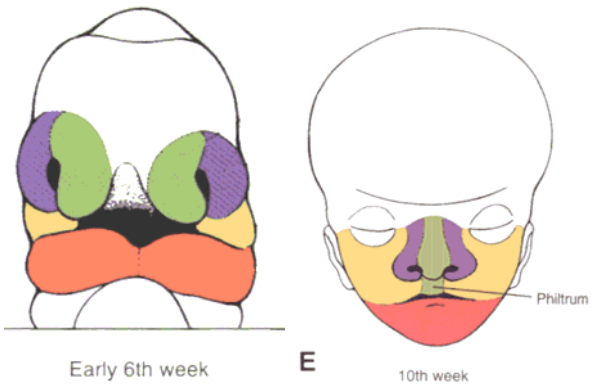
Craniofacial Genetics Research Laboratory Newsletter

The purpose of this newsletter is to provide an overview of the causes of cleft lip and cleft palate, and an update of what the lab has found so far.

Known Causes of Cleft Lip and Palate:

Craniofacial disorders involve the head and face and can include a wide range of problems. Dr. Andrew Lidral, Dr. Jeff Murray, Dr. Brian Schutte, and Dr. Paul Romitti along with their research teams, are trying to figure out the causes of some craniofacial disorders. Although most of their work focuses on cleft lip and cleft palate, they also do some research on eye disorders like myopia (or near-sightedness) and other craniofacial syndromes.

Cleft lip and palate are caused when something prevents the 2 sides of the face from growing together and fusing as they normally would in a developing baby. Changes in our genes (our body's inherited instruction code) and environmental factors (such as tobacco, alcohol, medications, or nutrition) are both known to contribute to this interruption in growth. Our research focuses on identifying the inherited factors, or genes and how genes interact with environmental factors.



Developing Face
(Figure modified from Larson, W.J *Human Embrology*, 2001.)

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Did you know? A phenotype is a characteristic that you can see, such as hair color, or blood type. There are two clefting *phenotypes:*

1. Cleft lip (which can occur with or without a cleft palate) (written CL/P)
2. Cleft palate only (written CPO)

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We can think of cleft lip and cleft palate in two ways. 1) They can occur as an isolated problem which is called an isolated cleft or 2) cleft lip and cleft palate can appear with other birth defects, called syndromic. About 30% of all people with a cleft have one of over 400 described syndromes. To date, scientists have identified mutations in specific genes, which are responsible for over 40 of these syndromic forms of clefting.

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Mutations- Mutations are changes in the DNA sequence that usually occur when the mechanism for copying the DNA makes a minor mistake as the DNA is passed from parent to child. More than three billion letters of DNA have to be copied each time a parent passes on their DNA to their child and even a single mistake can cause a problem. These mutations are what we search for in the lab. Although many people associate mutations with chemicals or radiation, these are **not** common causes of mutations in humans. (See sequence on page 2)

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Fewer mutations for isolated clefting are known. It is harder to find genes that cause isolated clefting compared to syndromic clefting. One reason for this is that there is not a clear inheritance pattern for isolated clefting. In other words how isolated clefting is passed on through a family is not clear. Most commonly (about 75% of the time), no one else in the family has had a cleft. When there is another family member with a cleft,

the relatives in between them on the family tree usually do not have a cleft.

This suggests that isolated clefting is a complex disorder. This means that a number of genes and environmental factors all play a part in the development of a cleft. The way these factors come together to cause a cleft differs between people even within a family.

It is estimated that about 10 genes may act in various combinations to cause isolated clefting. In addition, we know that there are environmental factors that play a part in clefting. Unfortunately, many of these factors are still unknown and most likely vary from person to person.

There are a few environmental factors that we know increases the risk for clefting. These include: smoking, drinking alcohol and taking some specific medications. When you look at a large group of people, those who smoke or drink alcohol during their pregnancy are more likely to have a child with a cleft. However, not every person who smokes or drinks will have a child with a cleft. In addition, we know that people who never smoke or drink during their pregnancy can still have a child with a cleft.

In order to figure out why some people have clefts and others do not, Dr. Lidral, Dr. Murray, Dr. Schutte, and Dr. Romitti's laboratories work together. They study how genetic and environment factors work together or interact to cause clefting. Their focus is to find the mutations that cause isolated clefts. To do this they need large numbers of families. This kind of study will take several years to complete.

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Did you know? Cleft lip and cleft palate are common birth defects occurring in approximately 1 out of 500–1000 live births. They are the most common birth defect of the head and face, and one of the top five birth defects found anywhere in the body.

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Description of the Research Project:

Each person has 2 complete sets of thousands of genes. One set comes from each parent. Slight changes in these genes are what cause differences seen from person to person. The Human Genome Project was a 15-year, worldwide project to make a "map" of all these genes. The completed map tells us the order of the information within the genes, and the order in which all genes are lined up. However, the map does not tell us what the information within the genes actually means to the human body. Therefore, we now have a very long list of genes, in the correct order, but most of them have an unknown purpose.

Past studies have looked at "candidate" genes, which are genes that we think might play a role in clefting. Those studies found a few specific genes that, when the instruction code is changed (mutation), might be involved. However, most of the time a mutation in one of these genes alone does not cause a cleft. These mutations may increase one's risk to have a cleft. Our research and others tells us that not everyone with a cleft has a mutation in one of these genes. Therefore, other genes must play a role. We are currently working to identify new genes.

One way of identifying new genes for clefting is to compare the genes of a large group of people who have clefts. Finding an area in the genetic code that is the same more often in people with clefts than in the general population suggests that somewhere nearby there is a gene involved in clefting. Further research can be done on each gene in that area to see if one of them has a mutation that causes clefting.

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Normal DNA sequence - ATCGGCCTACAGT

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Mutated DNA sequence – ATCGGACTACAGT

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Populations Involved:

We receive samples from individuals and families in the Philippines, Denmark, South America, Australia and from all over the United States. The variety of populations and large numbers of samples we have to work with helps us to identify candidate genes more quickly and confidently.

Long Term Goals of the Research:

The Human Genome Project has made it possible to identify genes for complex diseases such as isolated cleft lip and palate. An understanding of these genes will give us a better picture of how the head and face develops in humans. This information will help determine when and how many genes interact in facial development. This may also lead to identification of specific environmental factors that interact with certain forms of these genes. We hope that an overall understanding of head and face formation will lead to prevention and better treatment for clefting and other disorders of the head and face.

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Did you know? Environmental factors that are **known** to cause an increased risk for a cleft include **smoking** and **drinking alcohol** during pregnancy and specific medications. It is not clear if a lack of certain vitamins increases the risk. Nor is it clear if taking extra B-vitamins, especially folic acid, will prevent clefts.

However, it is clear that folic acid (B_9) taken in the months before and during early pregnancy can prevent *neural tube defects* (NTD). NTDs are another type of common birth defect. Neural tube defects, such as *spina bifida,* occur when the covering on the 2 sides of the spine are prevented from growing together and fusing as they normally do in a developing baby. This incomplete closure can leave an opening to the spine, nerves, or brain that can be very damaging. Thus the U.S. Public Health Service recommends that ALL women of childbearing age should take 0.4 mg of folic acid through diet or vitamin supplementation, *even if they are not planning a pregnancy*. Your health care provider can discuss how to get enough folic acid and reduce other exposures that may increase the risk of clefting.

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Progress

A number of exciting discoveries have been made in our laboratories recently. Dr. Lidral, Dr. Murray, Dr. Schutte, Dr. Romitti and other people who work in their labs have published more than 100 articles in the past 10 years in national academic journals. Here are a few of our recent articles.

(The full text of these articles can be accessed from either of our websites - See page 4)

Environment/Gene Interactions or Environmental Risks

Maternal age and oral clefts: a reappraisal – 2002 Vieira, A.

We reviewed 8 studies that had extensive birth records of many families, including the age of the mothers and whether or not the children had any birth defects (such as a cleft). We found that isolated oral clefts are not related to the age of the child's mother.

Candidate Genes

TGFA, TGFB3, and MSX1 are the names of three "candidate genes" or genes that we suspect play a role in the cause of facial clefts. These studies looked at the interaction between these three genes and various environmental factors as well as their role in clefting in general.

Candidate Genes for Isolated Cleft Lip and Palate and Maternal Cigarette Smoking and Alcohol Consumption – 1999 Romitti, P.

This study looked at the interaction between these three genes and two exposures during pregnancy (smoking during pregnancy and drinking alcohol during pregnancy). Although different versions of these genes don't seem to increase clefting by themselves, the combinations of some of the gene variations with exposure to alcohol or smoking do seem to increase the risk of facial clefts.

Analysis of the p63 gene in classical EEC syndrome, related syndromes, and isolated orofacial clefts – 2002 Barrow, L. et. al.

Families with EEC (ectrodactyly-ectodermal dysplasia-clefting) syndrome (a syndrome that includes clefting and hand problems) have been found to have mutations in a part of a chromosome called p63. Three unrelated patients with EEC that we studied also had mutations in p63. This supports the data that p63 plays a role in EEC syndrome, but not in other related or isolated forms of orofacial clefts.

Mutations in MSX1 are associated with Isolated Orofacial Clefting – 2003 Jezewski, P. et. al.

Changes in the MSX1 gene have been previously reported to cause a syndrome consisting of missing teeth and cleft lip and/or palate. This paper showed that changes in the MSX1 gene may also be responsible for isolated clefts.

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Syndromes Vs Isolated Cases

Sometimes it can be difficult to distinguish whether a person with a cleft has a syndrome or not. Some of the features associated with syndromes don't show up in every person with the syndrome or may be minor or unusual enough that you might not think that they are important. Examples of this include missing teeth or the inability to smell. Both of these findings along with clefts can be found in some syndromes where the genes have been identified and mutations in those genes found. However, since some people are not even aware that they can't smell or certain missing teeth are relatively common, these may be overlooked. If you have either of these present in your family, it would be worth discussing this the next time you visit your craniofacial clinic.

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MSX1 and TGFB3 contribute to clefting in South America – 2003
Vieira, A. et. al.

Other Studies

Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes – 2002 Kondo, S. et. al.

Approximately 2% of people who have clefts have Van der Woude Syndrome (VWS). VWS is diagnosed when an individual or multiple family members have mounds or depressions (pits) on their lower lip in addition to cleft lip and/or cleft palate. VWS is passed in an autosomal dominant fashion meaning that a person with VWS has a 50% chance of passing it on each time they have a child. Our lab found that changes in the IRF6 gene causes VWS and popliteal pterygium syndrome, a syndrome similar to VWS.

Individual and Family Resources

March of Dimes
www.modimes.org
888-MODIMES (663-4637)

American Cleft Palate - Craniofacial Association / Cleft Palate Foundation
www.cleftline.org
1-800-24-CLEFT

Wide Smiles
www.widesmiles.org

Thank You!

Since multiple genes and environmental factors complicate isolated clefting, a very large number of families are needed to detect common regions within the genome. The participation of every individual and family is greatly appreciated, as your participation increases the likelihood for success of the project. Each person brings us one step closer to finding ways to prevent clefts in future generations.

Questions/Concerns contact:

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For Future Updates Check:
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www.uiowa.edu/~didr

If would like to receive updates by mail please contact Amy Mach at 1-866-520-8982

Craniofacial Genetics Research Lab