Genetics: Diagnosis and Genetic Counseling

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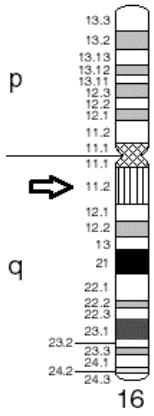
Velocardiofacial syndrome (VCFS) is the most common microdeletion syndrome in humans and affects all ethnicities, yet many people have never heard of it. One reason for this is that many different names have been used to describe the same disorder, depending on *which part of the body* is studied, *who* studied the condition, or *where* the studies took place. These names include Conotruncal Anomaly Face Syndrome, DiGeorge Syndrome, Cayler Syndrome, Takao Syndrome, Sedlackova Syndrome, Shprintzen Syndrome, and 22q11.2 deletion syndrome. In 1992, this confusion began to clear when Pete Scambler and colleagues published their discovery of the microdeletion on chromosome 22q11.2, which proved to be the underlying cause of all of these syndromes.

What does “22q11.2” mean? This is how cytogeneticists describe the change they see on chromosome 22 individuals with VCFS. A brief biology review will help explain this. Our bodies are made up of millions of tiny cells, and within these cells are our chromosomes containing genetic information. There are 46 chromosomes present in each cell, and they come in 23 pairs - one chromosome of each pair is inherited from the mother and one chromosome of each pair is inherited from the father. In



VCFS, one of the 22nd chromosomes is affected. Chromosomes are said to have two "arms", a short arm called the "p" arm and a long arm called the "q" arm. These arms are separated by a centromere which is like a belt for the chromosome. The "q" in "22q11.2" refers to the long arm of chromosome 22, and the "11.2" refers to the specific location on this long arm. It is pronounced "one-one-point-two".

Chromosomes contain genes which can be thought of as chemical instructions that tell our bodies how to develop, grow and function. The genes are arranged along the chromosomes like beads on a string. If a piece of a chromosome is missing, the genes along that piece of the chromosome are missing. Genes on the other chromosome are normal, resulting in "haploinsufficiency" or reduced copy number of genes. If those copy number sensitive genes contain instructions that direct the formation of the brain or other organs, then these structures may not develop and function correctly. There are about 60 genes in the most common 3 million base pair deletion causing VCFS. These genes are being researched thoroughly, to understand how they cause the features seen in VCFS.

When VCFS is suspected, a specific test to analyze this region of chromosome 22 may be performed. Fluorescence In Situ Hybridization (FISH) is a technique which uses fluorescent probes to attach to specific areas of a chromosome and "light up" when viewed with a special microscope. Instead of seeing two probes for the 22q11.2 region, individuals with VCFS only have one probe light up because the other copy has a microdeletion. Within the past few years, another test has become available called a chromosome microarray which identifies microdeletions or microduplications throughout the genome; sometimes VCFS is detected with this methodology and then confirmed with FISH.

The initial diagnosis of VCFS depends on the age of the individual, the types of manifestations present, and the types of specialists they are seeing. A diagnosis may be made prenatally if certain ultrasound findings are present including specific heart

defects or absence of a thymus. During infancy, reasons to test include conotruncal heart defects, low calcium or parathyroid hormone levels, absent or small thymus, specific immunological findings (T-Cell deficiency), nasal regurgitation (when milk comes up through the baby's nose during feedings), or subtle facial features. School-age children may be tested because of nasal speech (due to velopharyngeal insufficiency), facial features, or cognitive difficulties. Adults may be diagnosed after the diagnosis of their child, or if they develop mental health problems and also had other diagnostic clues from their childhood.

When an individual is diagnosed with VCFS, about 93% of the time it is the first diagnosis in the family. The deletion occurs during the formation of the egg or sperm that after fertilization, goes on to make the child. Since we do not know enough about these processes, there is nothing parents can do to cause or prevent this deletion. In the other 7% of cases, the deletion is passed down from a parent to the child. Sometimes the parent is mildly affected and does not know he or she has the deletion until testing is done. Since the signs and symptoms of VCFS can vary greatly among individuals, even within families, it is recommended that both parents of affected individuals be tested. A diagnosis of VCFS in a parent would implications for their health care too.

VCFS follows a dominant pattern of inheritance, which means that having the deletion on one copy of chromosome 22 will cause VCFS. (There are other genetic conditions that require genetic changes on both copies of the chromosome in order to have the condition) When a person has VCFS, there is a 50%, or 1 in 2 chance, with each pregnancy that the child will inherit the deletion and be affected. It is currently impossible to predict to what extent the child would be affected, because clinical features vary greatly even within a family. For example, just because a parent has a heart defect, this doesn't mean his or her child would have a heart defect. Likewise, just because a parent does *not* have a heart defect doesn't mean his or her child would be

free of it. Genetic counseling is recommended for individuals with VCFS so that these issues may be explored.

Prenatal testing options are available for individuals with VCFS. Some parents decide to pursue prenatal diagnosis so that they can plan for the birth of a baby that may require extra medical attention. Chorionic villus sampling (CVS) or an amniocentesis can be performed during the first or second trimesters of pregnancy, respectively, and sent to a lab for FISH testing. Another option growing in availability is Preimplantation Genetic Diagnosis (PGD) which involves In-Vitro Fertilization (IVF) followed by testing of each embryo to determine which ones do not have the deletion. Then these embryos are implanted in the woman. Although this testing is expensive, it is an option to consider if someone with VCFS wanted to be assured that their baby would not inherit it.

Currently, much research is in progress to gain more knowledge about the genetics of VCFS. This information will hopefully lead to a better understanding of the reasons for the various manifestations of VCFS, and why there is such variability between individuals.