A HISTORY OF THE "DISCOVERY" OF VCFS (OR WHATEVER YOU CHOOSE TO CALL IT): WHY WE HAVE SO MANY NAMES FOR ONE CONDITION

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Someone in Boston gives birth to a baby who has a tetralogy of Fallot. This triggers a lot of activity, including cardiology and surgical consults, a cardiac catheterization, and blood is drawn for a genetic test to determine if there is a small deletion of DNA from chromosome 22. The test comes back positive for the deletion and the pediatric cardiologist gives the baby the diagnosis of velo-cardio-facial syndrome (VCFS). An appointment is scheduled with a genetic counselor and clinical geneticist. The next day, a baby with a tetralogy of Fallot is born in Philadelphia and after the same genetic test is given the diagnosis of either 22q11.2 deletion syndrome or DiGeorge syndrome, depending on the hospital where the baby is born. The next day in Prague, the Czech Republic, another baby is born with a tetralogy of Fallot, the genetic test is performed, and the child is given the diagnosis of Sedlačková syndrome. And finally, the next day a baby is born in Japan with the same abnormality and is diagnosed with conotruncal anomaly face syndrome (CTAFS). All four of these babies have exactly the same genetic syndrome. The difference in the label is the result of people applying different names to the same condition. Why isn't there uniformity of names? That's sort of like asking why Coca Cola is called soda in New York City, but pop in Chicago, or why the little chocolate things put on ice cream cones are called sprinkles in New York, but Jimmies in Boston. And, of course what I call a cookie is called a biscuit by someone in London.

Although New York, Chicago, Boston, and London share a common language (although people in England might argue the point), but when it comes to genetic syndromes, they may not share uniform terminology, or what is often called "nosology" in the medical world. There are, in fact, many instances where medical conditions have different names, including hundreds of genetic syndromes. Neurofibromatosis Type 1 is often called von Recklinghausen's disease, Down syndrome is often called trisomy 13 (see OMIM entry 162200)[1], and Wolf-Hirschhorn syndrome is occasionally called 4p16.3 deletion syndrome and on occasion, Pitt syndrome (see OMIM entry 194190).[2] Of interest, it is infrequent that syndromes, especially common ones, are named based on the chromosomal site of a deletion or duplication of DNA. For example, Williams syndrome is rarely ever called 7q11.23 deletion syndrome and Prader-Willi syndrome is never called 15q11-q13 deletion syndrome because the same deletion from chromosome 15q11-q13 that causes Prader-Willi syndrome also causes Angelman syndrome, a disorder that does not resemble Prader-Willi at all. This difference is caused by a genetic phenomenon known

as "imprinting," where the expression of the syndrome is determined by the absence of maternal DNA versus paternal DNA from 15q.

So, who first discovered this syndrome, who named it, and is it important if there is only one name for the syndrome?

Who first discovered this syndrome? The best evidence is that is was Eva Sedlačková.[3] Dr. Sedlačková was an ear, nose and throat physician who specialized in speech and voice disorders. This specialty, called ***phoniatry***, is a distinct type of practice in Europe, but not in the United States. There are phoniatrists in Central and South America. In fact, one of our experts, Antonio Ysunza, M.D., M.S., Ph.D. is a phoniatrist who began his career in Mexico City. In the U.S., speech and voice disorders are handled largely by a separate field of study, speech-language pathology, an area that does not require a medical degree, although some ear, nose and throat specialists focus on disorders of voice (called laryngology). Dr. Sedlačková, a phoniatrist, was a physician who focused largely on voice and resonance disorders (especially hypernasality) and was well known in Eastern Europe in the middle of the 20th Century for her work with cleft palate speech and the treatment of hypernasality. In 1955, she published a paper in a Czechoslovakian medical journal[1] describing 26 children who had deficient, hypoplastic musculature in the soft palate (also called the velum) resulting in hypernasal speech. Among these cases were a substantial number of people with what I first called velo-cardio-facial syndrome 20 years later in an article published in the American medical literature. Dr. Sedlačková published a second paper on what she called a syndrome of velo-facial hypoplasia in 1967.[4] Many of the physical problems she described were consistent with VCFS, although most of her description was focused on speech, facial appearance, and a theory of innervation of the soft palate. However, there is no doubt that she recognized a distinct condition that is the syndrome we now call VCFS. Unfortunately for Dr. Sedlačková, at the time of her report of these 26 cases, Czechoslovakia was behind the "iron curtain" and medical literature from Eastern Europe was not widely read or disseminated. Also, the fact that it was published in a foreign language did not help with wide recognition of her work. The paper she wrote preceded computers (as we know them) and hence preceded library databases like PubMed and Medline that catalogue all of the world's medical literature. Sedlačková's early publications were largely ignored in most of Western Europe and the U.S.

It was not until 1968 that cases of this syndrome became evident in English language publications. Receiving the greatest amount of attention was the work of Dr. Angelo DiGeorge[5]. A pediatric endocrinologist at St. Christopher's Hospital in Philadelphia, Dr. DiGeorge described cases of babies with congenital heart disease who had an absent thymus gland, hypocalcemia, and immune deficiency. Most of these cases did not survive the newborn period because of the severity of their congenital heart disease complicated by immune issues. At that time, surgical outcomes for major heart anomalies was not what it is today. Therefore, at the time, Dr. DiGeorge did not have an opportunity to see his

patients grow into childhood, adolescence and adulthood, therefore limiting his ability to observe the development of learning disabilities, speech disorders, and other later onset disorders in VCFS. It is also true that the combination of congenital heart disease, absent thymus, immune disorders and hypocalcemia is not specific to VCFS and chromosome 22 deletions. This same combination of anomalies is also seen many other genetic and non-genetic syndromes, including Down syndrome, fetal alcohol syndrome, deletions from chromosome 10, chromosome 17, Zellweger syndrome, and kabuki syndrome (also known as Niikawa-Kuroki syndrome). For this reason, the association of congenital heart disease, hypocalcemia, and immune disorders is now known as DiGeorge sequence. A sequence is a grouping of symptoms that is not specific to a single cause, such as 22q11 deletions. Although VCFS is the most common condition to have DiGeorge sequence as part of its clinical picture, most children with VCFS do not have DiGeorge sequence. Some people mistakenly use the terms VCFS and DiGeorge interchangeably.

Also in 1968, William Strong, a pediatric cardiologist in Cleveland, Ohio who relocated to Augusta, Georgia described a family of a mother and three affected children (a boy and two girls) who had, what he called "a familial syndrome of right-sided aortic arch, mental deficiency and facial dysmorphism."[6] The article was very well documented with photographs and clinical description and review of the cases shown by Strong leave no doubt that he was, in fact, describing VCFS. Strong's article was called to my attention in 1980 by a pediatric resident, Robert W. Marion, M.D. who is currently the Executive Director of the Children's Evaluation and Rehabilitation Center at the Rose F. Kennedy Center and Chief of the Divisions of Genetics and of Development Medicine at The Children's Hospital at Montefiore, Bronx, NY. I had submitted a paper to the medical journal ***Pediatrics*** that detailed four familial cases that we were convinced was proof that VCFS was a genetic syndrome with an autosomal dominant mode of inheritance.[7] Dr. Marion, as part of a research project he was doing with me at the time, had gone to the library to do a literature search for documentation of articles involving congenital heart disease and found the article by Strong. He brought me a photocopy of the article. You can imagine that my heart sunk to my feet when I saw that Strong had clearly described the syndrome a decade before I had. Although Strong had not assigned or suggested a name for the disorder, his description of it was excellent and comprehensive. The only thing missing was information about the speech in the family he described. It took me a while to find Dr. Strong in the days before computers, the internet and search engines. Finally, after I found that Dr. Strong was in Augusta, I called him and discussed his article and the family he described. He was very gracious and openly shared information and his thoughts on his family and VCFS. I asked him if the cases he described had normal speech. He said, and this is very close to what he said word for word, "Funny you should ask. None of them had cleft palate, but they all sure sounded like they did." As a result of our conversation, I acknowledged Dr. Strong's article and his role in delineating the syndrome in an addendum to our article. Although many names have been attached to this syndrome, including my name (Shprintzen syndrome),

the truth is that the disorder should probably be called Sedlačková-Strong syndrome. Sedlačková was clearly the first person to describe cases in the medical literature, and Strong defined a broader phenotype and identified that it was a heritable disorder.

Who Did Name the Syndrome?

The short answer to this question is lots of people did. Sedlačková labeled this disorder "velofacial hypoplasia," a descriptive term for the symptoms she described.[8] The first appearance of the term Sedlačková syndrome I have found was in a publication in 1975, an article by Loós and Mártha in ***Folia Phoniatrica***, a Swiss journal.[9] The title of the article, "Bronchus Anomalies Associated with Sedlačková Syndrome" is the first appearance of that eponym I can find in the literature. The label "DiGeorge syndrome" came from a Fellow of Dr. DiGeorge, Roberto Kretschmer, a pediatric endocrinologist from Mexico City who published a single case in 1968 that clearly had the syndrome we call VCFS. The title of that article, "Congenital Aplasia of the Thymus Gland (DiGeorge's Syndrome)" was in the ***New England Journal of Medicine*** in 1968. The term "Shprintzen syndrome" first appeared in medical literature in 1978 in an article describing syndromes with cleft palate by my primary mentor in clinical genetics, M. Michael Cohen, Jr.[11] Afterwards, the term was used in "Recognizable Patterns of Human Malformation," one of the definitive source books on genetic syndromes written by another of my mentors, David W. Smith of the University of Washington in Seattle.[12] The use of a person's name attached to a syndrome is known as an "eponym" such as Down syndrome after John Langdon Down from Great Britain, or Turner syndrome named after Henry Turner, an Illinois endocrinologist who described the condition in 1938. Eponyms are common in all walks of life for naming streets, parks, mountains, cities, and diseases. Although many scientists dislike the practice, it continues to this day for everything from an Apgar score (Virginia Apgar) to the Heimlich maneuver. The continuous argument over the name of the disorder will probably continue for a long time and, in my opinion, is not a very good use of time or thought. People know that a car and an automobile are the same thing and that VCFS and 22q11 deletion syndrome is also the same thing. It is no secret that I am not in favor of the use of the label 22q11 deletion syndrome, and the reason for not preferring that label is very simple. Not everyone with a deletion from chromosome 22 at the q11 band has the same syndrome.

Deletions from chromosome 22 and VCFS

It is now well understood that the syndrome that brings people to this web site, what I prefer to call VCFS, is cause by a deletion from chromosome 22 in a region called the q11.2 band. The term "band" refers to the appearance of a chromosome after it has been stained with a chemical called giemsa, and the application of giemsa to chromosomes creates alternating dark and light bands (called G-banding) that are assigned number labels when counted from the centromere of the chromosome (see Figure 1). The chromosome

number is 22, q signifies the long arm of the chromosome (the short arm is labeled the p arm), and q11.2 refers to the region within a particular stained band. More specifically, the segment of 22q11.2 labeled as q11.21 is the region from which the deletion for VCFS occurs. This is a region large enough to contain approximately 40 genes, and the region is divided into 3 different segments see Figure 2). The divisions within 22q11.2 are caused by 4 area of DNA known as Low Copy Repeats (LCRs). These LCR segments are labeled as A, B, C, and D and have been shown to be responsible for the process of the deletion of DNA that causes VCFS (Edelmann et al., 1999). The first segment from LCR A to LCR B is approximately 1.5 million base pairs of DNA and contains approximately 30 genes. Deletion of the portion of chromosome 22 causes a multiple anomaly syndrome that we recognize as VCFS, DiGeorge, Conotruncal Anomalies Face Syndrome, Sedlačková syndrome, and what people are often calling 22q11 deletion syndrome. This region contains the important genes *TBX1*, *COMT*, *DGCR6*, *GP1BB*, *CTLD* and *PRODH*. The segment from LCR B to LCR C contains only four genes and their significance in terms of how their deletion may result in problems for people with VCFS is not yet known for certain. The regions from C to D contains approximately 10 genes and their significance in terms of the expression of the syndrome is also not fully understood. What we do understand is that the only cases that have the "classic" expression of VCFS (DiGeorge, CTAF, Sedlačková syndrome, 22q11DS, etc.) are those in whom the segment from A to B is missing. In a recent article, Mikhail et al. (2013) reported a series of cases with deletions that did not include the region from A to B.[13] I have also seen a number of these cases, as have others. At the annual meeting of the Velo-cardio-Facial Syndrome Educational Foundation in 2012, Graf et al. reported these cases. This presentation is available on the web site of the Educational Foundation.[14] Mikhail et al. suggested that depending on the location of the deletion, the expression of the anomalies

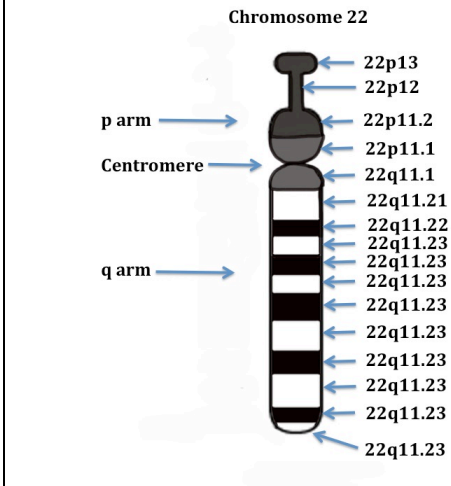

Figure 1: Drawing of chromosome 22 after banding.

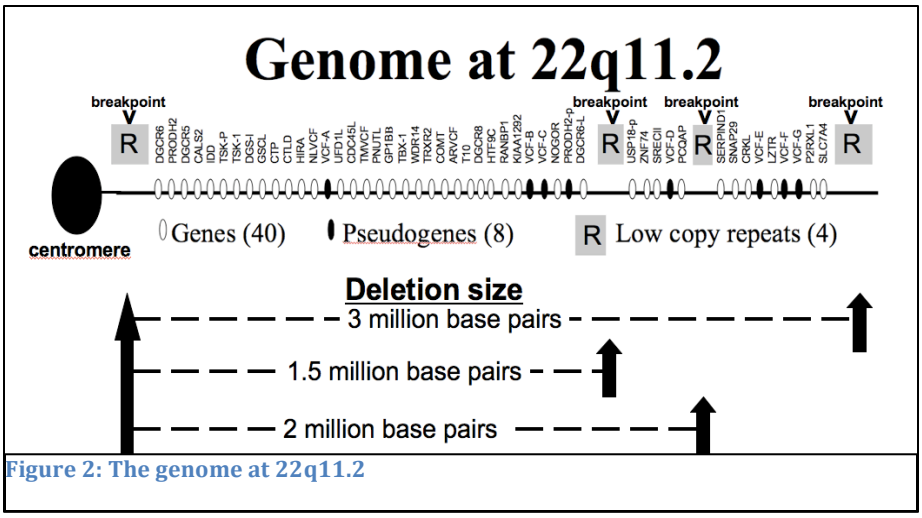

Figure 2: The genome at 22q11.2

was different from that seen in classic VCFS cases. My own experience is that the clinical expression of deletions that do not include the region from A to B are very different from cases of VCFS in most ways and cannot be confused . Therefore, not everyone who has a deletion within the 22q11 region has the same syndrome. There are number of different clinical conditions that can be caused by deletions within 22q11. Therefore, calling VCFS "22q11 deletion syndrome" is misleading because people with deletions that do not include the region from A to B do not have VCFS. While this may seem like an academic argument, it is not. Many treatments applied to people with VCFS are syndrome specific. In other words, the treatments applied to VCFS would not be applied to people who do not have the syndrome. These treatments would range from medications and surgery to behavioral therapies and education. Therefore the distinction is important.

So, What Should I Call It?

Whatever you want. In my opinion, the entire issue of name and label is irrelevant compared to what is important. The important thing is knowing what to do once the syndrome is recognized. Would a health care professional do something different for Down syndrome than they would for trisomy 21? Not here in the United States, or America, or the USA. Not sure how it would work in England, Great Britain, or the United Kingdom.

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