The Virtual Center for VCFS

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Also
Do You Like Puzzles? Try One Designed by Ray!!

First Book

New Book

Second Book

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ARTICLE OF THE MONTH

What Does the Diagnosis of 22q11.21DS (Deletion Syndrome) Really Mean?

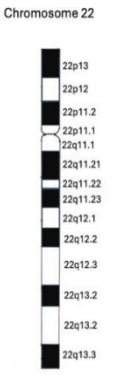
Robert J. Shprintzen, Ph.D.
Founder, President, and Director
The Virtual Center for Velo-Cardio-Facial Syndrome, Inc.

The readership of the newsletter probably already knows that the term 22q11.21ds is not a term I use and there is only one reason for my decision to avoid adopting it. It is misleading and a misnomer that can cause many treatment problems for some people who have that diagnosis. It is not a trivial matter. Because I follow thousands of cases from around the world, on the history forms we ask registrants to send us, we see many names attached to the syndrome, including velo-cardio-facial syndrome (VCFS), DiGeorge syndrome, Shprintzen syndrome, Sedlácková syndrome, Cayler syndrome, Cardiofacial syndrome, Takao syndrome, and conotruncal anomaly face syndrome (CAFS). Some names are used because they are specific to a country or region. In Japan, the syndrome was originally called CAFS and some named it for the well-known Japanese pediatric cardiologist, Atsuyoshi Takao who published many articles and texts about the syndrome dating back to the 1970s. Many people have contributed to the recognition of the syndrome and have had eponyms (having the syndrome named for them) attached to it, including myself. All people who have been following the syndrome closely deserve credit for adding a slice to the whole pie.

The naming of diseases depends on many factors and how the disease was brought to public attention. First, it is important to know what a disease is and what it is not. By definition, a disease is usually categorized as a disorder of structure or function with a known cause. To be specific, a disease needs to be differentiated from another disease by knowing the specific cause of both of them. Let's say you wake up in the morning sneezing and the sneezing is frequent, your nose tickles, you are constantly wiping your nose, your nose is running, and you may even cough a bit and have a tickly throat. You might think that you have a cold (more specifically an upper respiratory infection), or if you have pollen allergies, an allergic response you often called allergic rhinitis. The cause of these two disorders is different, the prognosis and management are different, and the planning of your next few days will be different. If you have a cold, no need to take medication except for comfort if you want to do a decongestant nasal spray for a few days. The cold with or without the spray will go away by itself usually within 3 to 7 days depending on the severity of the infection and the strength of your immune system. Such upper respiratory infections are caused by a class of viruses known as rhinoviruses. If the virus that infects you has other clinical effects, like loss of taste, weakness and fatigue, and lower airway infection, the cause may be COVID-19, RSV (Respiratory Syncytial Virus). On the other hand, if you have allergic rhinitis, the type of nasal spray is different; an antihistamine, not a decongestant. Also, as long as the pollen count is high, your sneezing could continue for weeks or months. Separate diseases, different causes, similar symptoms, different treatments.

How does this long explanation relate to VCFS and the term 22q11.21ds? Here is an example. Within the space of one week, we had two new registrants to our Center, both who had received a diagnosis of DiGeorge syndrome in one case and 22q11.21ds. Both children were given information about the syndrome we call VCFS and the genetic counselors and physicians at the institutions where they were diagnosed gave treatment options for VCFS/DiGeorge. For the first case, I immediately scheduled a video conference with o geneticist, Dr. Robert Marion, because the type

of heart anomaly this patient had was not consistent with what is typically seen in VCFS. There were also other anomalies present in the child that have not been reported as clinical findings in VCFS or rarely found, certainly none I had seen before in the thousands of cases I have followed. I asked the parents to send me a copy of the report from the genetic test that had been done to diagnose VCFS, a test known as microarray analysis, or CMA (Chromosomal Microarray Analysis). The test had been done by a reputable lab with which Dr. Marion and I have had a good deal of experience. The report stated at the very top line: "1.2 MB loss at 22q11.21q11.22." The second case had the same deletion as the first and had the same misguided treatments applied. The reports of the microarray analysis results show that there were deletions of DNA from chromosome 22 within the q11.21 band that also includes part of the 22q11.22 band. The deletion consisted of 1.2 Mb (megabases, meaning 1.2 million base pairs of DNA). It listed the missing genes and their location. Of the deleted genes, none were in the location of the region known as the "DiGeorge Critical Region." The microarray analysis showed that there was a deletion from 22q11.21, but that the deletion was "distal" to the region of the chromosome 22 that was known to cause VCFS/DiGeorge. Distal means further down the length of the chromosome. To explain, let's look at some pictures. Please excuse the amateurish figures...I know my genetics, but my art is another thing altogether.

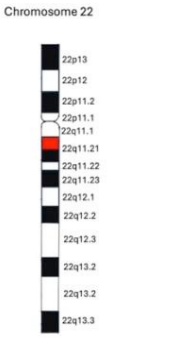


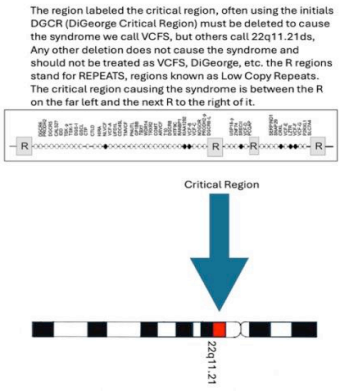
The picture to the right is a chromosome map for chromosome 22, the second smallest chromosome in the human genome. The regions that you see are labeled by a number (22) standing for the chromosome number, followed by p or q. The letter p identifies the short arm of the chromosome. When scientists met to standardize chromosome structure the letter p was chosen to identify the short arm because it is the first letter of the French word for small, petit (or petite in the female form). The long arm is labeled as q simply because q follows p in the alphabet. The two arms of the chromosome are joined by a structure known as a centromere (the indentation you see about a quarter of the way down the chromosome) and each chromosome has a different position of the centromere, but in general, it is not exactly in the middle so that one arm is longer than the other, hence the labels of short arm and long arm. The numbers of the chromosomes were originally determined by size order of the chromosomes, 1 being the largest and 22 being the smallest. This was determined in 1950s when optical microscopes were not very powerful compared to the images we get today. Also, the preparation of the chromosomes was less sophisticated. Later on we realized that chromosome 21 was smaller than 22, but too late to change the system. You will note on the picture that the numbers on the right side of the picture are all 22. That is because this is a picture of chromosome 22. Humans have 23 pairs of chromosomes in their cells except for sperm and egg cells which each have 23 chromosomes, only one chromosome of each numbered one plus an X or a Y chromosome that determine gender.

After the number 22 in the picture, you see a p or a q. That is to signify whether the region is in the short arm (p) or long arm (q). The alternating black and white bands happen when chromosomes are dyed with a substance called giemsa, a nuclear stain that helps us to see different regions of the chromosome. In the case of chromosome 22, you can see that the regions are numbered beginning at the centromere starting at 22p11.1 and going up to 22p13.3 as you go up the short arm, and as you

go down the long arm, starting at 22q11.1 and going up to 22q13.3 as you go down the long arm. OK...enough chromosome basics.

The region that contains the deleted area from chromosome 22 that causes VCFS/DiGeorge/22q11.21ds is shown to the right. Its label is 22q11.21. It contains 46 protein encoding genes. The total region of 22q11.21 that is deleted in cases with VCFS/DiGeorge/22q11.21ds consists of a region of 46 genes in about 92% of people with the syndrome, with about 8% having a smaller deletion of approximately 36 genes. The entire region of 22q11.21 contains 70 protein encoding genes. Therefore, the entire region of 22q11.21 is not deleted in people who have the syndrome. Moreover, and more important, the tail end of 22q11.21 is not deleted in people with VCFS/DiGeorge/22q11.21ds so it is possible to have up to 24 protein encoding genes delete from 22q11.21 and not have the syndrome. That is why the term 22q11.21 deletion syndrome is misleading, why our two patients who had deletions that did not include the DiGeorge Critical Region were treated incorrectly for years for the wrong disease. There have been publications that have insisted that these deletions outside of the VCFS/DiGeorge/22q11.21ds region have the same syndrome as those who have deletions inside the region. The two figures below may help to understand better. On the left, 22q11.21 is shown with a red portion. That red portion is the typical deletion that causes VCFS, yet it is only a portion of the deletion that causes the syndrome. On the right, you can see a gene map showing some but not all of the genes missing in VCFS. The R in the diagram marks a genetic sequence called a low copy repeat. You will note that there are four of these in the deleted region. The typical deletion exists within from the first R to the fourth R. Some cases with VCFS have the deletion encompassing the genes that are only between the first R to the second R. The expression of the syndrome seems to be essentially the same, but when the segment between the first R and the second R are not deleted, but the rest is, the patient does NOT have VCFS and treatments will therefore not be the same.





So, now you know why we do not use the term 22q11.21ds to signify the syndrome, what some call DiGeorge syndrome, or velo-cardio-facial syndrome, or Shprintzen syndrome, or Sedlácková syndrome, etc. It is misleading to refer to it as 22q11.21 syndrome as was recently seen in the two cases we cited, and the appelation can lead to treatment errors.

NEXT PAGE: RAY GOES TO BRAZIL

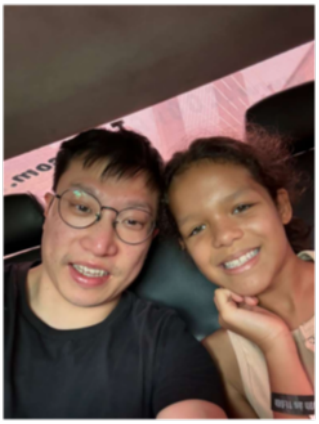
Ray Goes to Brazil 😊

I'm sitting here in the São Paulo airport, waiting to board my 9PM flight. It's nearly 7PM and I have about an hour left to kill. I was supposed to be back home already, but there was a delay at the Belo Horizonte Airport, and apparently because of that delay, my luggage wouldn't arrive on time, and I got kicked out of the original São Paulo flight to JFK scheduled yesterday. It was stressful and frustrating to try to rebook a flight on the same day. Luckily, I was with a group of people that were in the same situation as me, so they were able to help me. But unfortunately, despite tedious efforts, they could not put me on a flight on the same day, and I had to spend the night at a hotel near the airport. Because of this, I was able to explore São Paulo a little bit, which I was pleased to do.

I was in Brazil to visit my girlfriend for three weeks. Her name is Lila and she lives in a small town called Vespasiano, a suburb of Belo Horizonte. It was a place I had never heard of before. Lila and I had not seen each other since August when she was in the U.S., and it was a highly anticipated trip. I have solo traveled before, but this was the first time I was going to visit Brazil....I was definitely a bit nervous. Not because of safety, but because it was the first time I was going to see her family and friends. It was a 9-hour flight, with a transfer in Rio di Janeiro, and from there a one-hour flight to Belo Horizonte. She was going to pick me up at the airport, and her home was a fifteen-minute drive from the airport.

Lila with Ray

Ray with Ester



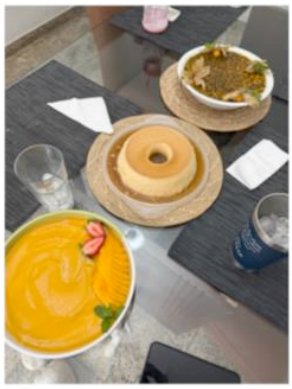
Right off the bat, the trip was an adventure. There was a delay at JFK; a long delay, and I began to get increasingly worried. The layover in Rio was 1 hour and 30 minutes and the longer the delay, the shorter the window to make my next flight. Long story short, once I arrived at Rio, I had to run to make the next flight. Because it was a different airline, I didn't realize that in Rio I had to go through security, pick up my luggage, check in my luggage again and go through customs again. What stress! Thankfully, I had a couple who was able to help me there, too, and I was sweating from running by the time I got to the gate. I thought that was it. When I got to Belo Horizonte airport, however, it turns out that my luggage was left back in Rio! There was nothing they could do but ship the luggage back in a few days. Two days later, I finally got the luggage back and sighed in relief when seeing nothing was missing. That has never happened to me before. I supposed there's a first time for everything.

The first week consisted of meeting and spending time with Lila's family – her daughter, Ester, her four dogs and her mom and dad. I also met her best friend. I met her brother and his family the next day. They lived in a town nearby called Nova Lima. He made me a churrasco, which was unforgettable. Unlike her mom, Ester and father, her brother was able to speak a little bit of English,

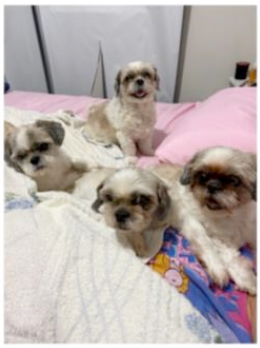
which made communication easier. He was super cool, and I loved being with them. I met her dad, and toured the cacao factory that he owned, about an hour and a half away from where she lived. It was an incredible place, and his story of hard work and starting everything from scratch was truly inspirational. Lila translated my English into Portuguese. They loved me immediately, and I loved them as well. Her four dogs—Julia, Jackie, Daniels and Leffe—were so cute, and (I hope) they loved me right away, too.

Lila made me a Brazilian carrot cake, (which was different than the carrot cakes in New York), along with Pudim (Brazilian flan), and her cooking was incredible. The Pudim was easily my favorite. Along with that, a mango and passionfruit dessert. I try local foods, such as pão de queijo, empadas, the local fruits and Brazilian pizza. I tried feijão tropeiro. Personally, the fruits were my favorite. In Brazil, they have mangos and bananas that aren't capable of growing in America. The mango and papaya were out of this world, simply melt-in-your-mouth. Honestly, I've never tasted sweeter fruit. The pão de queijo, which are basically cheese balls, were a unique taste, and I fell in love with the cheese called catupiry. Shrimp or chicken with catupiry cheese quickly became one of my favorites. Simply, everything was delicious.






Pão De Queijo and Empadas
Brazilian Carrot Cake
Mango Cake, Pudim, Passionfruit Cake
Fruits of Brazil

Feijão Tropeiro *Lila's dogs: Daniels, Jackie, Julia and Leffe*

Lila drove me around neighboring towns, such as São José Da Lapa, where her mom does Pilates, and the small village of Taquaraçu De Minas. One thing I love about traveling is to see how the other world lives; it never ceases to amaze me how hard people work to make a living.

The first weekend rolled around, and we were to take a trip to Rio de Janeiro. I was excited. We were to visit the very famous statue, “Christ the Redeemer”, and the beaches. Her aunt lives in Rio, and I heard some crazy (but fun) things about her.

Unfortunately, it was going to rain the whole weekend. This meant that the activities on the beaches would be closed. We were bummed, but we were not going to let a little rain ruin our trip. The six-hour drive from her home to the hotel in Rio was so much fun, taking silly pictures with her mom and Ester and listening to Brazilian music. We made a pit stop to grab something to eat, and we were there before we knew it.
Although I did not understand a word of Portuguese, her aunt was hilarious and so much fun to be with. We decided to stay one more day—and boy were we glad we did. We were planning on going to the statue on Sunday, but when we arrived it was very foggy and we couldn’t see a thing. Thankfully, the next morning it was clear, and we were able to see it! It was absolutely packed, very hot, but the views were breathtaking. So we stayed one more day in Rio, with her aunt. I met a friend of theirs, who lived in a favela, or a slum. He gave us free pizza and was fun and chill to be around. And it’s moments like these that make me feel more grateful about my life. If people can survive and be happy in situations like that, what do I have to complain about?

Christ the Redeemer

The last day of Rio consisted of touring Copacabana, trying the famous Brazilian hot dog (my god, I will never look at a hot dog in the states the same way again), having her taxi friend drive us around, and her helping out a foreign couple because they did not understand Portuguese. We tried the most fresh, amazing seafood I’ve ever tasted in my life *(including this local restaurant where apparently no tourists go—only locals)*, shrimp pastel, and we took many photos and bought souvenirs. It was Ester’s first visit to the Christ, and her expression of joy upon seeing it was priceless. At the end, we were sad to go, but I was glad to have made many memories from it.

The second week consisted of bonding more with her mom, her daughter, her dogs and trying local foods. One day, her mom made me a local Brazilian dish called feijoada, a soup made of beans and meat. Lots of meat. It wasn’t a dish with which I was familiar, but the more I ate, the more I liked it. Lila also drove me around to nearby towns Lagoa Santa and Santa Luzia. I noticed that there are many stray dogs in the towns, and I feel sad seeing them. In Lagoa Santa, we spot a capybara family; we shriek with joy and comment on how cute the babies are. It is my first time seeing capybara except in pictures.

Coxinha and Itabaína soda

Lila took me to this local shop in São José Da Lapa that sells coxinhas, a soda that's only found in their state, Itabaína (it's so local you can't even find it anywhere else in Brazil). It was delicious. She made me a Brigadeiro cake; it's a chocolate lover's dream and hands down one of the best things I've ever eaten in my life. She had worked at the restaurant business for over 19 years, and she knows a thing or two about baking.

Lila took me to a local Churrascaria, and I completely underestimate the amount of food they would serve. Picanha became my favorite meat (I had tried picanha at her brother's place, but this was different). I had learned that Brazilians do not take kindly to people throwing away food, and Lila has the same sentiment. She gets upset whenever I throw away leftovers, stating that there are poor people who don't have any food and struggle daily I suppose she's right and once again it makes me see life in a different way.

We met another one of her best friends and had unique pizzas, visited her dad's ranch about two hours away, and tried an açaí bowl in downtown Belo Horizonte. Did you know that açaí was from Brazil? It was incredible; nothing compared to the açaí bowls you can get in New York. The same goes for the poke bowl: the seafood and fruits are so fresh! It was absolutely unbelievable. I couldn't get enough of it, and, like the Brazilian hot dog, I'd never look at açaí bowls and poke bowls the same way ever again.

Week number three arrived and I can't believe it's going by so quickly. I wish time would just slow down. We go to a fine dining restaurant in downtown Belo Horizonte called Per Lui, and have the most amazing three-hour dinner, with unique dishes, laughs, wine-tasting, story-telling and plans for the future. She will come to the U.S. to visit me in July, and then again in January. I plan to go back again next September and Christmas. I'm sad it will be months at a time that I won't be with her, but I suppose it could be worse.

Watching a Football Game

The last night I went to my first football game *(what we in the U.S. call soccer)*. Her brother had made and bought me my very own football jersey, which I wear proudly at the game. Her best friend and boyfriend came with us, and the vibes and the energy of the stadium were almost nothing like that I had ever seen. Unfortunately, the Belo Horizonte hometown team Cruzeiro lost, but it was a great time, nonetheless.

The last day arrived. The trip flew by—gone in the blink of an eye. Goodbyes are always so bittersweet. Ester wouldn't let me go; her mom tells me how much I had enriched their lives; her dad wanted to say goodbye to me one last time. I think it's funny and cute how they already call me their son-in-law. Saying goodbye to Lila at the airport is always the hardest thing to do. I can't wait to see her again.

Brazil had changed my way of thinking. I loved every second of it. I will be more grateful for my life; seeing how people lived in favelas made me realize that. I loved meeting her friends and family. Everyone was so nice to me, and while there were stressful moments, I didn't have a single bad experience. It was without a doubt one of the best trips I have ever taken. And I can't wait to go back. 😊

Artwork from the talented and multimedia hands of
***Aici Button** … from Utah.*


Aqours

A *maze* puzzle from Ray for you to solve.

You can print out the page or contact Ray Cheng at raymond.cheng@vcfscenter.org … and he will send you a copy in the mail.