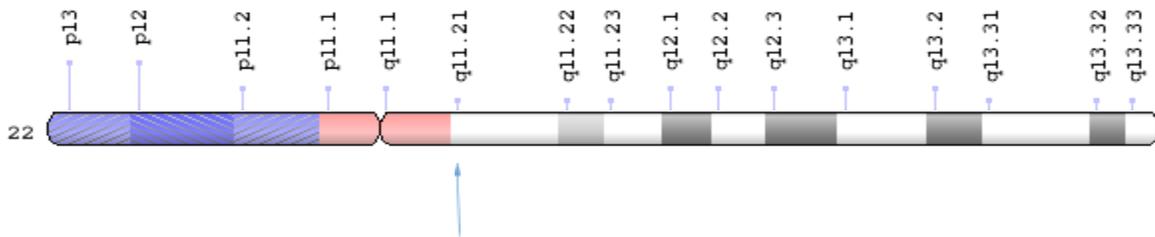


Inheritance of *TANGO2* Disease

The inheritance of *TANGO2* disease is complicated. We recommend that you meet with a genetic counselor in order to have your child's specific genetic result explained in detail.

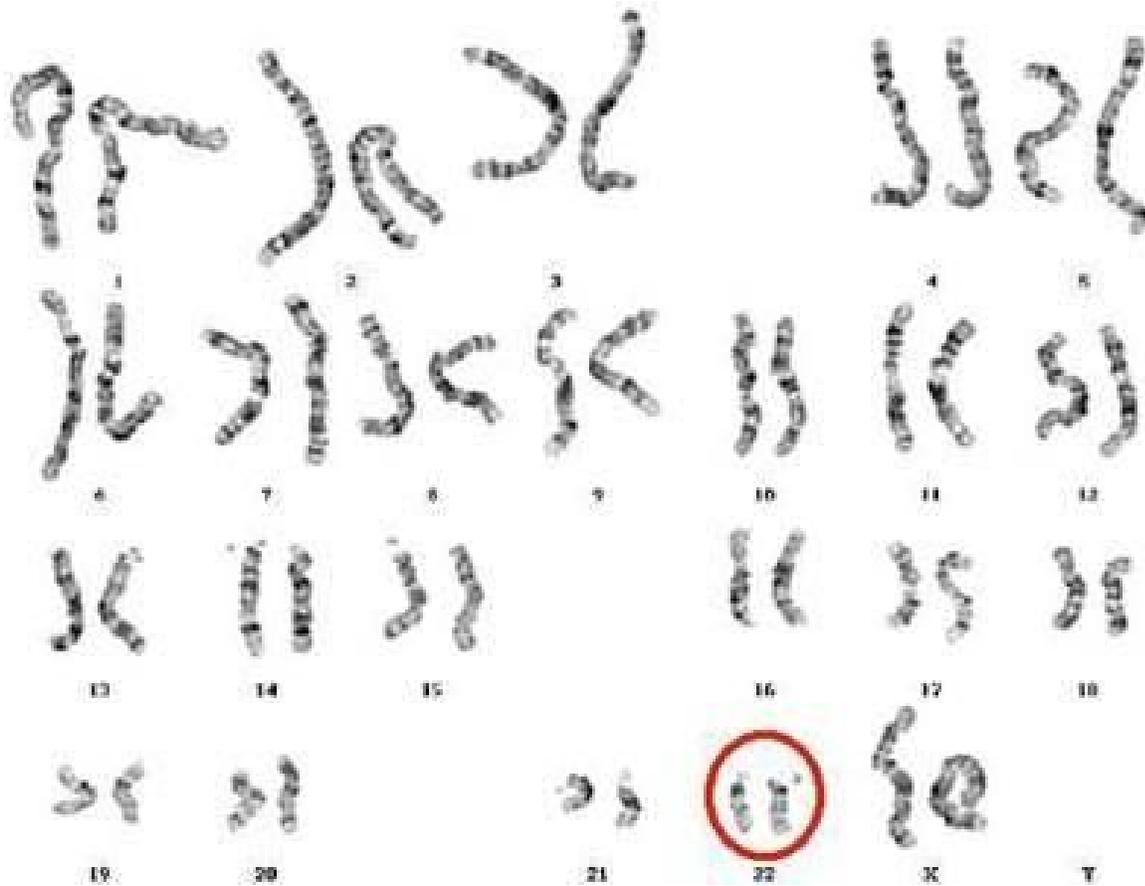
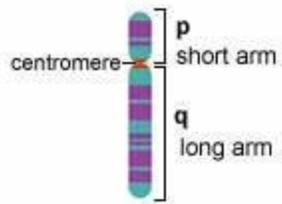
TANGO2 disease is a genetic condition that is present at birth. It is an autosomal recessive condition. This means that it is inherited when a child receives two *TANGO2* genetic changes (mutations)-one from each parent. A mutation in *TANGO2* will prevent that copy of the gene from working correctly. We all should have two working copies of *TANGO2* gene, one that we inherit from our mother and one that we inherit from our father. If we have one copy of *TANGO2* that is not working we are considered a carrier for *TANGO2* disease but are not affected and will not show symptoms of *TANGO2* disease. The *TANGO2* gene is located at 22q11.21. This means that it is located on chromosome 22 on the q (long) arm at band position 11.21. This tells us precisely where the gene is located.



To understand the inheritance, it helps to first understand how our genes are inherited on our chromosomes. Chromosomes, which are present in most cells in our bodies, are made up of smaller structures — called genes — which are, in turn, made up of DNA.

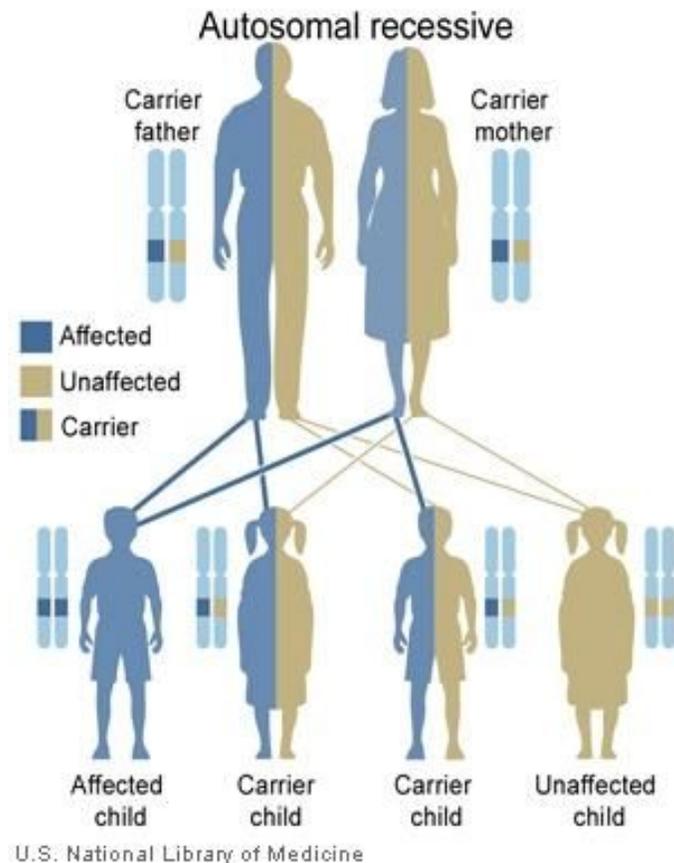
Most people have 23 pairs of chromosomes (46 total), with one of each pair coming from their mother and the other from their father. Chromosomes are numbered 1 through 22; the 23rd pair are called sex chromosomes (X and Y) because they determine a person's sex — typically male (XY) or female (XX). Chromosomes are also divided into two parts called "arms." The top half is the short or "p" arm and the bottom half is called the long or "q" arm. Our genes are packaged up on our chromosomes and control how our bodies grow, develop, and function by producing proteins.

Short and Long Arms of a Chromosome



TANGO2 disease is inherited in an autosomal recessive manner.

- If both parents carry a *TANGO2* genetic change, there is a 1 in 4 (25%) chance that any child of theirs will have *TANGO2* disease.
- There is a 1 in 2 (50%) chance that any child of a carrier couple would be a carrier for *TANGO2* disease. The children that are carriers are not at risk to have *TANGO2* disease but they could be at risk to have an affected child.
- There is also a 1 in 4 (25%) chance that any child of a carrier couple will not have *TANGO2* disease and will not be a carrier for *TANGO2* disease.



Some individuals with 22q11.2 deletion syndrome (DiGeorge syndrome) also have a mutation on their other copy of *TANGO2* on chromosome 22. 22q11 deletion syndrome means that someone has one full copy of chromosome 22 and the other copy of chromosome 22 has a deletion at 22q11.2. The deletion of one copy of 22q11.2 region results in 22q11 deletion syndrome (22q11DS). The 22q11.2 deletion is associated with a wide variety of symptoms and features. The 22q11DS affects many organs and systems. The most common features include the following: Congenital heart defects (74% of individuals), palatal abnormalities (69%), learning difficulties (70%-90%), and immune deficiency (77%). About 93% of individuals with 22q11DS have a *de novo* deletion (deletion that occurred in the egg or sperm cell that created that individual) of 22q11.2 and 7% have inherited the 22q11.2 deletion from an affected parent.

22q11DS is diagnosed in individuals with a submicroscopic (too small to see just looking under the microscope at that chromosomes) deletion of chromosome 22 detected by fluorescence in situ hybridization (FISH) or chromosomal microarray (CMA). The 22q11DS region contains several genes including *TANGO2* gene. That means that an individual with 22q11DS always has

one deleted copy of *TANGO2*. If, by chance, a person with 22q11DS also has a mutation in their other copy of *TANGO2* gene then that individual would have no working copies of *TANGO2* and would also have *TANGO2* disease. FISH and microarray for 22q11DS would not typically be able to evaluate the *TANGO2* gene alone. This means that if we suspect an individual with 22q11 DS also has *TANGO2* disease we would need to do *TANGO2* gene studies to confirm or rule out *TANGO2* disease. It is probably quite rare to have both 22q11DS and *TANGO2* disease but we do not know enough about the carrier frequency of *TANGO2* disease to predict this.

TANGO2 disease mutations can typically only be identified by molecular studies such as single gene analysis or whole exome analysis. This means that an individual's *TANGO2* genes need to be sequenced and/or undergo deletion and duplication studies to identify the mutations at the gene level.

This diagram below shows the typical 3Mb pair deletion that causes 22q11DS. As you can see *TANGO2* gene is just one of several genes deleted.

