How common is *TAB2*-related syndrome?

TAB2-related syndrome is very rare. Currently (2022) about 80 individuals with this diagnosis have been reported in the medical literature; roughly half have a *TAB2* gene variant, and half have a deletion of the gene. It is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

Why did this happen?

Some children have inherited their genetic change from a (mildly) affected parent. In some individuals, the change in the *TAB2* gene or the 6q25.1 deletion occurred by chance in that person (this is known as *de novo*) and the genetic change was not found in either parent. When children are conceived, the genetic material is copied in the egg and sperm that make a new child. The biological copying method is not perfect, and random rare changes occur in the genetic code of children that are not seen in the DNA of their parents. This happens naturally and is not due to any lifestyle, dietary or environmental factors. No one is to blame and nobody is at fault. Such changes happen to everyone but it's only when a change affects an important gene that health and/or development are affected.

Can it happen again?

The chance of having another child affected by a rare gene disorder depends on the genetic code of the parents. If a parent is found to carry the genetic variant, the chances of having another child with *TAB2*-related syndrome is 50% for each pregnancy. If the change in the *TAB2* gene has been shown to be *de novo*, that means neither parent was found to carry it, the chance of having another child with *TAB2*-related syndrome is very low. There is still a very small chance if a parent has mosaicism (*Unique* publishes a separate guide to mosaicism). If a child with an altered or deleted *TAB2* gene has a child of their own, there is a 50% chance of them passing on their genetic change. A clinical geneticist or genetic counsellor can give you specific advice for your family.

Can it be cured?

TAB2-related syndrome cannot be cured at the present time however, knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

Families say .....

"When our son was diagnosed all we received was a letter telling us of the findings, with no explanation of symptoms, we just knew it was rare. We now realise our son has ALL TAB2 symptoms, which clearly was very stressful as he was growing up as we didn't know what we were dealing with. We thought that he had several separate conditions and had no idea how this would affect him getting older. Finally knowing that one condition is the cause of all of his symptoms is a relief. Despite his struggles he has grown into a very lovable and happy young man who we are very proud of." *Age 17 years.*

"Having a definitive diagnosis made the process less scary, although we know every child is different, it made us feel less alone and allowed us to explain our daughters condition with more confidence and gain access to the services she required. We also shared the Unique 6q25 deletions leaflet with our daughters nursery and healthcare providers. 8 years on and we are lucky to get updated information from Unique, such as this new information on the TAB2-related syndrome which fits exactly with our daughters 'symptoms." *Age 8 years.*

Inform Network Support

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info@rarechromo.org
www.rarechromo.org

Websites, Facebook groups and other links:

Chromosome 6 Research Project website:
https://www.chromosome6.org

Join *Unique* for family links, information and support.
Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org/donate Please help us to help you!

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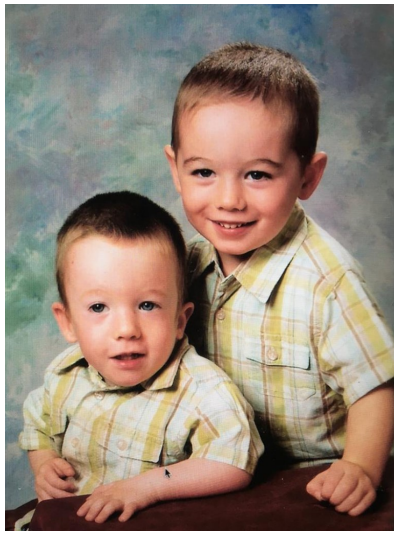
Understanding Chromosome & Gene Disorders

TAB2-related syndrome

(*TAB2* gene variants & 6q25.1 microdeletions)

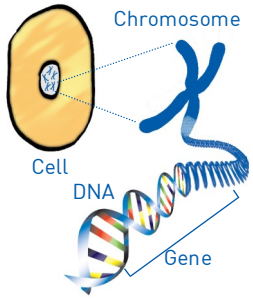


rarechromo.org

What is *TAB2*-related syndrome?

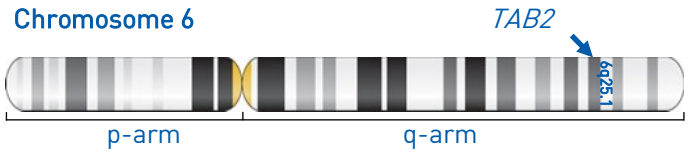
TAB2-related syndrome is a rare genetic condition associated with changes in heart structure and function, body height and connective tissue. Some children may also have developmental delay; the level of delay may vary depending on the child's genetic diagnosis. As is common with genetic conditions, each person is affected differently.

What causes *TAB2*-related syndrome?



TAB2-related syndrome is caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called *TAB2* or to a deletion of this gene. (*TAB2* is an abbreviation of the gene's full name, TAK1-Binding protein 2).

The *TAB2* gene is located on the long 'q' arm of chromosome 6 in a region called 25.1 as shown in the image below.



Deletions that include the *TAB2* gene are also known as 6q25.1 deletions or microdeletions.

We have two copies of chromosome 6 in our cells, so we also have two copies of the *TAB2* gene. *TAB2*-related syndrome occurs when only one copy of the *TAB2* gene is affected, the second copy is fully functional. This is known as autosomal dominant (all numbered chromosomes are called autosomes and genetic conditions that occur when only one copy of a gene is affected are known as dominant).

The *TAB2* gene sequence is used to make the TAB2 protein. This protein has a number of different functions in different parts of the body as it forms different complex structures with other proteins. It is notably important for proper heart development and function but also plays a role in other cells at different stages of development.

TAB2-related syndrome features

Most children with *TAB2*-related syndrome have:

- A congenital heart defect and/or cardiomyopathy
- Short stature
- Connective tissue anomalies
- Slightly unusual facial features
- Some degree of developmental delay

Other possible features include:

- Weak muscle tone (hypotonia)
- Hearing loss

Development

Developmental delay

Developmental delay has been reported in about 20% of children with a *TAB2* variant but half of the people with a 6q25.1 deletion described in the medical literature. It may be that the deletion of additional genes contributes to an individual's difficulties, especially those with very large deletions. Many individuals with *TAB2*-related syndrome do not have developmental delay.

Weight and feeding

Many children with *TAB2*-related syndrome have a low birth weight and some have feeding difficulties.

Short stature

70% of children with *TAB2*-related syndrome, described in the medical literature so far (2022), are noted as having short stature, their body measurements are sometimes disproportionate with their limbs being shorter.

Management recommendations

Children with *TAB2*-related syndrome should be under the care of a multidisciplinary team including a geneticist and paediatrician. Individuals should have a cardiac evaluation, including regular follow-up. Follow-up is needed as some heart problems may develop later in life. Evaluations for overall development, hearing, vision and connective tissue anomalies are also recommended. The relevance of growth hormone therapy for short stature is not clear for children with *TAB2*-related syndrome.

Medical concerns

Heart anomalies

Heart problems have been found in most, but not all, people reported so far with *TAB2*-related syndrome. They can be present at birth or develop later in life. Surgery is required for some people. The most common change to the heart is a mitral valve defect; this is when the mitral valve does not close properly. Other heart valves can also be affected as can the internal 'walls' of the heart between the heart chambers (these are called atrial and/or ventricular septal defects). Narrowing of the main artery of the body (coarctation of the aorta) has also been identified as has the weakening of part of the aorta (thoracic aneurysm). About a third of individuals with *TAB2*-related syndrome develop a cardiomyopathy during life; this means that the heart muscle weakens, leading to heart failure. Most often this is a dilated cardiomyopathy in which the heart becomes wide and the wall of the heart chambers thins.

Hypotonia

About a third of children with a *TAB2* deletion reported so far (2022) have been found to have weak muscle tone (hypotonia), but less children with a *TAB2* gene variant have been diagnosed with hypotonia.

Connective tissue anomalies

Anomalies in connective tissue include unusually bendy joints (hypermobility), hernias, flat foot (pes planus), sunken breastbone (pectus excavatum) and other skeletal and/or skin anomalies.

Eyes and sight

Some children and adults with *TAB2*-related syndrome have droopy upper eyelids (ptosis), and some have widely spaced eyes (hypertelorism) or eyes that are slightly slanted.

Ears and hearing

Hearing loss has been reported in about one third of individuals with *TAB2*-related syndrome. Conductive, perceptive and mixed hearing loss have been diagnosed. Some children may have low set ears.

Facial features

Some children have a few shared facial features such as a broad forehead, a broad/short neck or dental crowding. Possible eye and ear features are mentioned above.