

Understanding
chromosome
disorders

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Cantú Syndrome



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What is Cantú syndrome and how is it caused?

Cantú syndrome was first recognized in 1982 by doctor Cantú, working in Mexico (Scurr 2011). We now know that variants in two genes called *ABCC9* (Harakalova 2012) and *KCNJ8* (Cooper 2014) cause Cantú syndrome. Cantú syndrome occurs when one of a person's two copies of either of these genes carries a specific variant in the gene sequence. These small changes in the genetic code are like a spelling mistake. Gene sequences carry the instructions for making protein molecules that are the building blocks of our bodies, which have important roles in our growth and development. Genes are made of a complex chemical called DNA and are incorporated along with many other genes into organized structures called chromosomes. We all have 23 pairs of these chromosomes, and we inherit one half of each pair from each parent. Both the *ABCC9* and *KCNJ8* genes are located close together on chromosome 12. Their role is to help build a special channel, called the ATP-sensitive potassium channel, found in the cell membranes that form the outer layer of our cells. The channel controls the movement of the chemical called potassium in and out of cells. When a spelling mistake in one of the genes occurs, the channel becomes activated and is less able to control the passage of potassium through the channels. It is not fully understood why this leads to the clinical features of Cantú syndrome, but research looking into this is underway.

Most common features

The most common features of Cantú syndrome are:

- Polyhydramnios (which means excess of fluid in the uterus) in pregnancy
- High birth weight due to oedema (swelling) which disappears in infancy, muscular build later on
- Thick hair, low hair lines on the forehead and neck and excess hair growth on the limbs and other parts of the body
- Distinctive facial features
- A large heart
- Prominent blood vessels

There are a wide variety of other symptoms that can occur in some but not all people with Cantú syndrome so it is quite a variable condition.

How many people have this condition?

The population prevalence of Cantú syndrome is unknown. There are at least 50 people reported in the medical literature, but, as awareness of the condition is increasing, it is clear that there are many more people living across the world. There is no known variation in prevalence in different countries or between ethnic groups.

Where are the genes that cause Cantú syndrome?

There are two genes that cause Cantú syndrome, *ABCC9* and *KCNJ8*, which are situated on the short arm of chromosome number 12 (at the location 12p12.1) (Harakalova 2012, Cooper 2014). In some genetic conditions, the whole gene or larger sections of the chromosome containing the gene are missing (called a deletion). This does not happen in Cantú syndrome and as far as we know all affected people have tiny variations in the genetic code, usually within the *ABCC9* gene or rarely the *KCNJ8* gene.

Why did this happen?

We all have 23 pairs of chromosomes and we inherit one half of each pair from each parent. At the time of conception of a child, half of each pair is contributed as genetic material from each parent - in the egg and the sperm. When the egg and sperm join together, the two halves of each pair of chromosomes join together. The biological copying method that puts the chromosomes in the eggs and sperm is not always perfect and occasionally small changes (spelling mistakes) in the genetic code arise. If this happens in either the *ABCC9* or the *KCNJ8* genes, the child but not the parents, will be affected with Cantú syndrome.

Once someone has Cantú syndrome, they can pass the gene alteration on to their children and the chance of this happening is 1 in 2 or 50% for each child. This is called autosomal dominant inheritance. Girls and boys are equally likely to be affected. In some families, in which Cantú syndrome has been inherited from a parent, there can be one or more affected children as well as unaffected children. Although the gene alteration is the same within a given family, affected members of the same family may have slightly different clinical effects.

Can it happen again?

If neither parent is found to carry the same *ABCC9* or the *KCNJ8* gene change as their child, the most likely explanation is that the Cantú variant arose as a 'one-off' event during the generation of the egg or the sperm. In this case, the chance of having another child with the same genetic change is considered to be extremely low. Empirically, this risk would be less than 1%. The reason why there is some residual risk of recurrence is due to a rare phenomenon called 'gonadal mosaicism'. This is when a parent does in fact carry a genetic change, but only in a small cluster of their egg or sperm cells. The genetic change would not, therefore, be detected from this parent's blood test. For specific advice about the chance of this happening again, it would be ideal to talk to a clinical geneticist or genetic counsellor.

Development

■ Growth

Babies with Cantú syndrome are often large with a high birth weight, but this tends to return to the normal range quite quickly and after that children grow appropriately. They may also have a relatively large head circumference.

■ Sitting, moving, walking

Most children have normal motor development and are able to sit and walk at the normal time. Later on they are able to participate in games and sports in the usual way.

■ Speech

Some children with Cantú syndrome have mild delay in their speech development. The vast majority of children are able to read, write and talk in the normal way.

■ Learning

Most children that we know of have learning ability within the normal range. Some children may have particular areas where they require additional support with learning, but it is not absolutely clear that this is caused by Cantú syndrome, as mild learning difficulties occur independently in the general population.

■ Behaviour

Children with Cantú syndrome usually have normal behaviour. Occasionally parents have reported episodes of slightly unusual behaviour patterns but overall this is quite uncommon.

Medical concerns

Children and adults with Cantú syndrome are generally in good health and are able to participate fully in the activities they wish to. There are however some medical concerns that can arise, although these are not present in everyone with Cantú syndrome and they are of variable severity (Scurr 2011, Harakalova 2012).

■ Polyhydramnios

Polyhydramnios is the medical term used to describe excess fluid surrounding the baby during pregnancy. Many parents have noticed that this occurred before their baby was born with Cantú syndrome. Sometimes, this required a drainage procedure because the extra fluid caused discomfort or was thought to pose a possible risk of starting labour too early. The extra fluid did not otherwise cause problems for the baby.

■ High birth weight

Studies of large numbers of babies with Cantú syndrome have shown that their average birth weight is higher than their unaffected brothers and sisters and other babies in the general population (Scurr 2011). It has been observed that affected babies can appear swollen or puffy when they are born, due to excess tissue fluid (called oedema). It is thought that this fluid causes the relatively high birth weight and as it dissipates in the first weeks of life, the weight usually drops and remains stable on the centile chart from then on. We do not yet understand why this happens.

■ Persistent swelling (oedema)

Many parents and doctors report that children with Cantú have a muscular build without any further tissue swelling. However, there is a small minority of people who continue to have swollen ankles and legs during childhood and adulthood. In some cases they find it helpful to wear compression tights as the swelling may progress during the day. Parents have also seen that children may have puffy eyes first thing in the morning, but the slight swelling goes away soon after getting up.

■ Excess hair growth (hypertrichosis)

One of the most distinctive features of Cantú syndrome is rapid hair growth and excess hair on the body. Most babies have a full head of hair at birth, which grows fast and is thick and shiny. There are usually quite low hair lines framing the face and at the back of the neck, accompanied by soft hair on the sides of the face. Parents say that excess hair growth is often visible on the body and limbs from an early stage, although this is variable and quite mild in some children.

There are various approaches to the hair, some people are happy to leave it as it is, whereas others try different ways of removing it. This can be very helpful for school-age children if their friends notice and comment on it. Cantú patients, especially female patients, report the excess hair growth as the medical concern having the most significant impact on their daily lives.

■ Distinctive facial features

Facial features are always influenced by genetic background, but there are some facial characteristics that people with Cantú syndrome may have in common, particularly having thick eyelashes, the low hairlines and very subtle features such as full lips.

■ Congenital heart disease

Children with Cantú syndrome may be born with a structural heart problem and by far the most common is patent ductus arteriosus (PDA). The ductus arteriosus is a blood vessel which connects the main blood vessel in the body (aorta) to the

pulmonary artery before the baby is born, and it usually closes at birth. Babies with Cantú syndrome may need a small operation to close the PDA.

■ **Enlarged heart**

We have known for a long time that most people with Cantú syndrome have relatively large hearts (Levin 2016), although this does not usually lead to obvious problems.

■ **Prominent blood vessels**

In people with Cantú syndrome, the blood vessels tend to be dilated (wider in diameter) than in the general population. This may occur as a direct effect of the gene change on the walls of the blood vessels. A special brain scan called a magnetic resonance angiogram (MRA) can visualize the arteries inside the brain. In people with Cantú syndrome who have had MRAs, the blood vessels look very prominent and follow a wavy path (Guerrero 2016). Some people with Cantú have dilated blood vessels elsewhere, such as the veins on their legs. Occasionally the dilated blood vessels may cause problems that need treatment.

■ **Broad ribs and skeletal changes**

Originally Cantú syndrome was described as a chondrodysplasia (meaning abnormal bone structure) because x-rays of affected people showed some changes such as broad ribs, thick skull bones and wide long bones. Although these changes can often be seen on x-rays, not everyone has them and they do not cause obvious clinical problems or constitute a specific disorder of the skeleton.

Other clinical features

There are a few more medical problems that can occasionally arise, which require attention, but overall they are quite rare in Cantú syndrome. They include:

- Gastric haemorrhage (bleeding from the lining of the stomach)
- Pulmonary hypertension (increased blood pressure in the circulation going to the lungs)
- Migraine headaches
- Seizures

Families say ...

“ Our daughter's diagnosis of Cantu Syndrome at 12 months has most certainly enabled us to have a greater understanding of the things which make her unique and has helped us to better support her as she grows up. The rarity of her condition means that when we connect with other children with Cantu Syndrome - there's a real sense of family and strength as we all take on the challenges and learn together. ”

“ Having Cantu Syndrome isn't great, but there are far worse things to have. Life is what you make it. ”

Management recommendations

At diagnosis

- Genetic testing and counselling about the implications of Cantú syndrome
- ECG (measurement of heart's electrical activity) and echocardiogram (ultrasound scan of heart)
- Respiratory tests, if any breathing problems occur
- Brain scan (MRI or MRA) if indicated by neurological symptoms or seizures

After diagnosis

- Long term follow up by a paediatrician (for children)
- Investigation of rare complications as required (such as endoscopy for gastric bleeding)
- Further eye checks may be recommended
- Referral to dermatologist for advice on hair removal if desired
- Cardiac follow up to monitor heart size

Inform Network Support



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Websites, Facebook groups

<http://cantu-syndrome.org/> - Cantu Syndrome Interest Group

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it. This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This booklet was compiled by Dr Ingrid Scurr, Clinical Genetics StR, and reviewed by Dr Sarah Smithson Clinical Geneticist, Department of Clinical Genetics, University Hospitals Bristol NHS Foundation Trust.

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