

KAT6A Syndrome



This leaflet is designed to help families and healthcare professionals looking after people affected by KAT6A syndrome. It contains information about the cause of KAT6A syndrome, the ways in which it can affect people and suggestions about the help and management that can benefit people with the syndrome. It also contains information about support groups that families can access.

What is KAT6A syndrome?

KAT6A syndrome is a rare genetic condition that results from 'spelling mistakes' (aka mutations) in a gene called KAT6A. (The KAT6A gene is located on the short arm (p) of chromosome 8 within band 8p11.21).

What are genes and chromosomes?

We all have an 'instruction manual' made up of 23 chromosomes which is present in almost all of our cells. This tells cells how to behave from the moment of conception onwards. We inherit two copies of the 'instruction manual', one from our mother and one from our father, which means each person has 46 chromosomes. The chromosomes are made up of DNA which is like a string of letters that use a 4 letter code (G, A, T, C). Some of this code has instructions for cells to make proteins. The parts of the chromosomes that do this are called genes.

What does the KAT6A gene/protein do?

The KAT6A protein (made from the KAT6A gene) is involved in controlling the production of proteins from other genes. It does this in several ways. One way in which it does this is by controlling the shape of the chromosome. The 23 chromosomes contain 3 billion 'letters'. Cells are very small so the chromosomes are packed up so they can fit inside the cells. This makes it difficult for other proteins to access the code and make new proteins. The protein produced by KAT6A helps unwind specific parts of the chromosome so that specific proteins can be made. Because the KAT6A protein is involved in controlling the expression of many other genes, the syndrome can cause problems in many different parts of the body.

We do not yet know all the functions of the KAT6A gene/protein. As well as controlling the expression of other genes we know that the KAT6A protein can also modify proteins once they have been produced. This changes the way in which the proteins work. Our knowledge of KAT6A and its functions will improve over the years with further research.

What genetic changes cause KAT6A syndrome?

Several types of genetic changes can cause KAT6A syndrome. Some changes cause a shortened protein to be produced. These changes are known as **stop gains** or **frameshift** mutations. The 4 letter code that makes up chromosomes is read 3 letters at a time to choose the right building blocks (known as amino acids) to make the proteins. As well as specifying which building block to add there are 3 letter combinations that code for the start and end of the protein. If a change in the code changes the instruction from a building block to a stop code then the protein will stop being built at this point. If a letter or a few letters are added or deleted then the code will be out of frame and this will cause the wrong building blocks to be added and eventually a stop code will come along which will stop protein production.

Some people with KAT6A syndrome have a '**missense**' mutation in the gene. This causes the wrong building block to be added at a particular site. This can change the function of the gene if it is at a particularly important site in the protein. In most cases missense mutations result in milder problems.

Why did this happen and could it happen again?

KAT6A syndrome almost always arises from a new genetic change (or spelling mistake) in the KAT6A gene. This means the spelling mistake was not passed on from either parent and there is nothing either parent could have done to change this. Because this is a new spelling mistake the risk of having another child with the condition is very low. Very occasionally the change can be found in some of the cells of one of the parents, this is called 'mosaicism'. In such cases, it is possible to have further children with this condition. For this reason genetic counselling is recommended for families wanting to have more children.

Currently we are not aware of anybody with a KAT6A mutation having children but this is probably because most people that have been tested are children. If an individual with a KAT6A mutation had children they would have a 1 in 2 chance of passing the mutation on. Whatever the inheritance, it is important to emphasize that this is nobody's fault.

Sources and References – The information in this guide is drawn from about 40 people who have KAT6A syndrome. In 2016, 18 people have been reported in the medical literature in detail. Further publications are planned.

What features and symptoms do people with KAT6A syndrome have?

People with KAT6A syndrome have a lot of overlapping features.

■ Feeding Difficulties and Constipation

The majority of babies have problems with feeding including severe reflux/vomiting. Some need early tube feeding for a period of time because of these difficulties and some benefit from medications to help control reflux. If reflux is severe, a feeding tube can be inserted in to the stomach (aka PEG, aka Gastrostomy). As children get older the feeding issues improve and the reflux/vomiting resolves although a small number of children still occasionally vomit or gag. Many children have problems with constipation which may need to be medically managed.

■ Developmental Delay

All children identified with KAT6A syndrome have developmental delay. This means that they are delayed in reaching mile stones like sitting and walking and have learning difficulties. There may be some selection bias as so far cases of KAT6A syndrome have been found by testing children with developmental delay. The severity of developmental delay varies between children but tends to be mild to moderate. Many babies are noted to be more floppy than other children of the same age (this is known as hypotonia) and some have a floppy trunk but stiffer arms and legs. All children develop at different rates. All of the 11 children with KAT6A syndrome, whose walking abilities have been described in the medical literature, learnt to walk. The earliest walked at 17.5 months and the latest at 54 months (the average age was 28 months).

“ Finally we could start to piece the puzzle together and build a support network with other families in the same situation from across the globe. ”



■ **Speech and language**

All children with KAT6A syndrome have a particularly marked delay in acquiring language. This is thought to be due to poor oro-motor function (movement of muscles of the face and mouth, including the tongue). Several children have been noted to have markedly better receptive language than expressive language. This means their understanding is much better than their ability to use words. Children who have relatively good understanding but are unable to communicate can find this very frustrating. Early input from a speech and language therapist is important for children with KAT6A syndrome. Many children have benefited from using signs or alternative communication aids and this can be done in conjunction with efforts to increase verbal language. Many children with KAT6A syndrome have developed useful verbal language, this should be encouraged, but this takes time and using alternative methods can ensure they are able to communicate their needs in the short term.

■ **Seizures**

A small number of individuals with KAT6A syndrome have had seizures but this does not seem to be a very common feature.

■ **Head size and brain**

Some children with KAT6A have a smaller head than other children of the same age. In some cases this can lead to early fusion of the skull bones which may be seen as a raised bony ridge on the head. This is not uncommon in children without KAT6A syndrome and usually does not require treatment but can occasionally require surgical correction.

■ **Heart**

Of the cases currently published in the literature, over half of the 18 children described have heart defects. These are most commonly septal defects (holes between the chambers of the heart) and persistent ductus arteriosus, aka PDA, (a tube linking two major vessels from the heart, which is present normally in babies before birth, fails to close normally after birth). Some of these lesions resolve without the need for surgery but some children have received surgery. If your child has not had their heart checked this is something to discuss with the doctors looking after your child. They may wish to arrange further investigations which may include an ultrasound scan of the heart called an ECHO (aka echocardiogram) to make sure that they do not have any problems with their heart. As more children are diagnosed we will learn more about the frequency of heart problems.

■ **Facial features**

Children with KAT6A all look different but there are some features that tend to be more common. These include a prominent nose, especially at the tip and a thin upper lip. Physical features can help doctors identify other individuals with the syndrome.

■ Eye features

Some individuals with KAT6A syndrome have droopy eyelids, this is called ptosis (with a silent p). Some have eyes that look in different directions which means the eyes have difficulty focussing together, this is called strabismus (or more commonly 'cross-eyed' or 'squint') and is normal in new-born babies but should have resolved by 6 months. It is important to pick this up as it is easily correctable but can cause damaged vision in one eye if not corrected. Some children have poor vision so this should be tested. Mostly this is felt to be due to a refractive error (i.e. long or short sighted) which is easily correctable with glasses but there have been a couple of children identified as having 'cortical visual impairment' which means the brain has difficulty processing images.

■ Immune and haematological features

A number of children with KAT6A syndrome are reported to have frequent infections. These are typically chest infections, urinary infections and ear infections, all of which commonly occur in childhood but may occur more frequently in some children with KAT6A syndrome. There are several reasons why this may be the case. Children with KAT6A syndrome often vomit when they are younger and this can lead to chest infections if material from the stomach enters the lungs (aka aspiration). Sometimes structural differences can lead to increased infections and a small number of children with KAT6A syndrome have an abnormally shaped urinary tract which may contribute to this. Increased numbers of infections can also result from problems with the immune system. There is some scientific evidence that the KAT6A protein is involved in some immune processes and a small number of children have problems with their immune cells. These problems include low numbers of a type of white blood cell called a neutrophil, low numbers of B cells and low numbers of antibodies. It is not yet clear whether this is directly linked to KAT6A syndrome but if your child has more infections than would be expected for their age, or they are of greater severity than would be expected, then this would be something to discuss with your doctor. They may wish to arrange further investigations. It is important to note that young children normally have frequent mild colds.

■ Behavioural difficulties

Children with KAT6A syndrome are often described as having friendly, happy and sociable personalities but some do have behavioural difficulties. These include some features that are seen in children with autism but most children do not have all the features that are required for a diagnosis of autism. These features include anxiety, repetitive behaviour and frustration. Some have sensory issues such as being more sensitive to particular sounds or textures.

■ Sleep

Some children have difficulty sleeping. Establishing sleep seems to be a particular problem. Some children take medication called melatonin to help with this. This is not helpful for all children but may be tried if children have severe difficulties sleeping. Sleeping difficulties can resolve with age.

Do KAT6A mutations cause cancer?

If you have been looking on the internet you may have seen that some genetic changes in KAT6A have been linked with cancer, especially blood cancers. These changes are different than the changes that are seen in KAT6A syndrome. These genetic changes tend to happen in cells after birth and are therefore just present in a small number of cells. Changes in KAT6A syndrome normally happens before, or shortly after conception so they are found in all cells. Many of these changes seen in cancer are caused by a 'translocation' when part of the KAT6A gene is attached to part of another gene. This can cause lots of proteins to be produced as the new fusion protein has the ability to promote the production of proteins at sites other than the specific sites where the KAT6A protein normally works. This is different to the effect of mutations in KAT6A syndrome. Currently we don't know of any cases of cancer in children with KAT6A syndrome. We cannot say for sure that people with KAT6A syndrome are not at an elevated risk but this difference in mechanism of action suggests that this is unlikely to be the case.

Medical/Educational Guidance Summary

- Children should be under the care of a general or community paediatrician to monitor their health and development.
- Monitoring weight gain in infancy is important. Feeding difficulties and reflux are common and may need significant medical support.
- Constipation is a common feature and may need medical management.
- An assessment of special educational needs should be carried out so that extra help can be put in place at school.
- Early input from a speech and language therapist is important.
- Some children have behavioural difficulties requiring support.
- Structural heart problems are common and we would suggest that a cardiology review should be considered for all children.
- Vision should be assessed, refractive errors and cortical visual impairments are seen in some children. Strabismus is common.
- Recurrent infections are common and may require further investigations.

Families say ...

“Identifying the KAT6A genetic mutation through exome sequencing was the critical step to identifying the cause of Chloe's medical and developmental challenges. Additionally, as other families gained similar results, it has allowed us to form an international family community that is interacting with doctors and researchers to identify potential therapies and treatments for the disorder.”

Inform Network Support



Rare Chromosome Disorder Support Group

The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

Tel: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.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/html/DonateNow.asp

Please help us to help you!

Websites and Facebook groups

A support group for families has been set up by Jordan Muller, father of daughter Chloe who has KAT6A syndrome. A facebook group is also available for families affected;

<https://www.facebook.com/groups/KAT6A/>

<http://www.kat6a.org>

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 Joanna Kennedy, Academic Paediatric Trainee, Severn Deanery and reviewed by Professor Ruth Newbury-Ecob, MB ChB, MD, FRCP, FRCPCH, Consultant Clinical Geneticist, Department of Clinical Genetics, University Hospitals Bristol NHS Foundation Trust.

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