Understanding Chromosome & Gene Disorders

MYT1L syndrome

(MYT1L variants and 2p25.3 deletions)

rarechromo.org

This leaflet is based upon what is known about MYT1L syndrome (2021), from a small group of affected individuals. There are many gaps in knowledge and with time, and further research, further information will become available.

What is MYT1L syndrome?

"Syndrome" is a medical term which means a combination of symptoms and physical features which are found together in a person and are all due to the same underlying cause. Not every person with the syndrome will have identical combinations of symptoms and physical features, but there will be shared features.

MYT1L syndrome is the medical term used to describe the medical condition which affects a person who has a change in one of the two copies of their MYT1L gene. This change can be a deletion of the part of chromosome 2 which contains the MYT1L gene, known as a chromosome 2p25.3 deletion, or a change to the MYT1L gene sequence, known as a single nucleotide variant (SNV).

People with MYT1L syndrome have combinations of slowness in reaching developmental milestones, learning difficulties and neurological conditions such as autism or epilepsy.

How common is MYT1L syndrome?

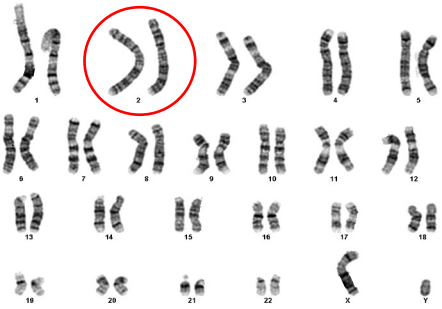
MYT1L-syndrome was only recognised in 2017 when the first research paper describing a group of affected children was published. It is a very rare medical condition with only very few known affected people. This leaflet is based upon what we know about MYT1L-syndrome, but we recognise that there are many gaps in our knowledge and with time, and further research, we will be able to provide better information.

What are genes and proteins?

Genes are the instructions that tell our bodies how to develop and function. We all have about 20 000 genes. Our genes are arranged in pairs, one of each pair is inherited from our mother and the other is inherited from our father. Genes are biological instructions and are made of a biological alphabet that contains four letters (A, C, T, G). This is called the genetic code. Long combinations of these biological letters code for detailed instructions (genes) on how to make proteins.

Proteins carry out specific tasks in our bodies and are used to make our cells, tissues and organs. Changes to gene 'letters' can alter the function of the protein they produce, or even stop it working altogether. However, when we think how much variety there is in people (for example height, eye colour, voice, etc.) we can appreciate that the genetic code of each person varies a great deal. Because of this, it can be difficult sometimes to work out if a change to the lettering of a gene will cause a medical condition or if the change is just part of the natural variation we see from one person to the next.

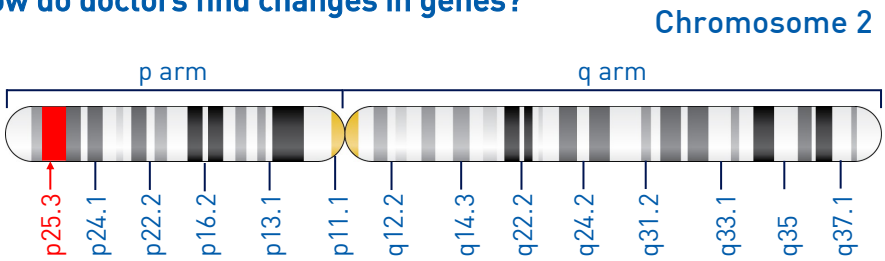
What are chromosomes?



Chromosome pairs 1-22, X and Y (genetic male).

Chromosomes are the structures which contain our genes. We have 46 chromosomes in each cell. These are arranged in pairs (as shown in the image opposite), from pair number 1 (the longest) to pair number 22 (the shortest) and two X chromosomes in a genetic female and an X and a Y in a genetic male. If a piece of chromosome is missing it is called a deletion. If a deletion removes a gene, or part of a gene which gives an important instruction for development it can cause a medical condition. MYT1L syndrome can be caused by a deletion called a 2p25.3 deletion. The number 2 denotes chromosome 2, p denotes the short arm of chromosome 2 and 25.3 refers to a more precise position on the chromosome which is missing the piece of genetic material as shown in the image below. A duplication of 2p25.3 can also cause a medical condition, this is somewhat different to the deletion and will be described briefly at the end of this leaflet.

How do doctors find changes in genes?



Our genetic code can be read by a test called sequencing. There are two main types of this test that are used to identify changes in the sequence of gene lettering. One is called exome sequencing, this reads the code of all of our genes. The other is called genome sequencing, which reads the code of our entire genome, which includes all 20 000 genes and the parts of the genetic code that control the activity of genes.

Once a change to the lettering of a gene is identified it is looked at in great detail and doctors and genetics laboratory staff try to work out if it is likely to be causing a person's symptoms or not. For example, if a computer program identifies that the genetic change is likely to stop the gene and its protein from working properly this would indicate that the gene change might be causing symptoms. On the other hand, if the genetic change is found in lots of unaffected people then it would indicate that this genetic change is just a natural variation in the genetic code.

When a gene change is identified as causing specific symptoms, it is called a pathogenic variant, when professionals are unsure whether the change could be causing these symptoms, it is named a variant of uncertain significance (also known as a VOUS or VUS).

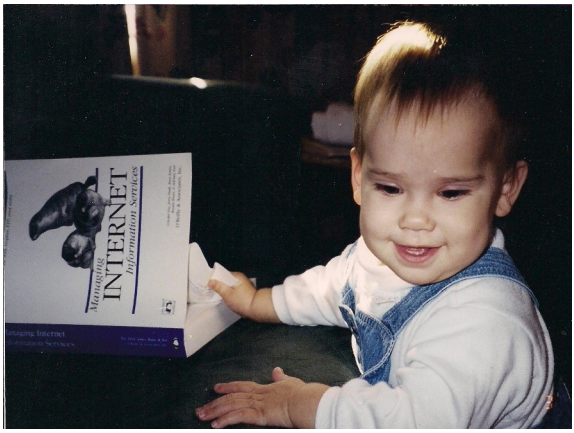
It is routine practice to sequence the genes of the parents of a child who has a genetic change. If the sequencing shows that the genetic change has been inherited from an unaffected parent, then this normally suggests that the genetic change is a natural gene variant found in that family, and is not causing the difficulties their child is experiencing. However, if the genetic change has not been inherited from either parent, then this suggests that it could be causing the child's symptoms. If a genetic variant is not inherited, it is known as de novo.

Pieces of missing chromosomes can be identified using a test called a microarray, which is also known as comparative genomic hybridization or aCGH. This type of test can detect very small pieces of missing chromosome known as deletions, microdeletions or copy number variants (since a single copy of a piece of chromosome is now present instead of two copies). Again, sophisticated computer programs need to be used to work out if the chromosome change is possibly causing a medical condition or is just a natural chromosome variation.

What is the MYT1L gene?

The MYT1L gene provides the instructions necessary to make a protein called a transcription factor. This type of protein switches other genes on and off during development and is particularly important in the brain. The activity of this protein makes sure that the correct genes (instructions) are active during brain development so that the brain forms as expected.

In the developing brain (when the baby's brain is growing in the womb), MYT1L helps control the production of brain cells (neurons). MYT1L stimulates cells to divide to produce more cells, and so increase the number of neurons. MYT1L also helps guide brain cells to the correct parts of the brain for their appropriate and specific function. We need two working copies of the MYT1L gene for our brains to develop as expected, so a deletion or change to the sequence of one of the two MYT1L genes causes MYT1L syndrome.



Why has this happened?

In most people with MYT1L syndrome, the gene change or chromosome deletion has happened for the first time in them and has not been inherited from either of their parents (de novo).

Nothing that either parent did, or did not do, caused this to happen. There are no known drugs, environmental or occupational factors which cause MYT1L gene changes. It is no one's fault.

Could this happen again?

If neither parent is found to have this chromosomal or gene change, it is unlikely that they will have another child with MYT1L syndrome. Very rarely, parents are identified as having unaffected chromosomes by a blood test, but a few of their egg or sperm cells carry the genetic change. This is called germline (or gonadal) mosaicism and it means that such parents can have more than one child with the same chromosome/gene disorder. If they wish, parents can discuss their specific recurrence risks with a genetic counsellor at their local Clinical Genetics department (your GP can refer you).

What are the most likely features of MYT1L syndrome?

There is a lot of variability in the symptoms people with MYT1L syndrome have. It is not fully understood why symptoms are so variable.

People with MYT1L syndrome can have combinations of:

- **Delayed motor development**
  (sitting and walking)
- **Delayed speech development**
- **Epileptic seizures**
  (altered electrical activity in the brain)
- **Intellectual disability**
  (children will need extra help at school or may attend a special school)
- **Autism**
  (an unusual pattern of behaviour with impaired social interaction)
- **Increased appetite and weight**
- **(which could lead to obesity)**

Appearance

Unlike many other genetic conditions, children and adults with MYT1L syndrome do not have any distinctive alterations to their facial appearance. Clinical geneticists can usually identify unusual facial features that may not be obvious to a lay person, to help identify suspected diagnoses, but this is not the case for MYT1L syndrome. However, people with MYT1L syndrome might have a head circumference (head size) smaller than average.

Growth

People with MYT1L syndrome tend to be within the average range for height, but towards the lower end of average, and have a tendency to have a high body mass index (BMI). This means that their weight is greater than it should be, on average, for their height. This can lead to the development of obesity. It is not clear if people with MYT1L syndrome are any more, or less likely to have an increased BMI than people with other causes of intellectual disability. Obesity can affect health: for example by increasing the chance of developing diabetes.

It is not clear if people with MYT1L syndrome have an increased chance of developing any of the health effects of being obese. But it would be sensible to be aware of the potential for this to happen.

Sitting and moving (Gross motor skills)

All people with MYT1L syndrome have some problems with gross motor skills. Many babies with MYT1L syndrome are floppy at birth (hypotonia). It is difficult to give much information because of the small number of people, but delayed walking is common. More research is needed to define the full range of movement abilities in people with MYT1L syndrome. In one person with MYT1L syndrome, walking problems were linked to spina bifida (a problem with development of the spinal cord). It is not clear if this was a chance association or if MYT1L syndrome increases the chance of spina bifida.

Seizures

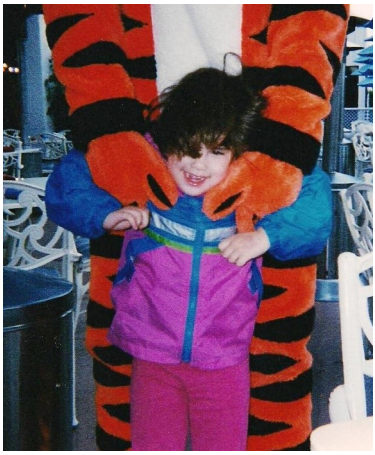
A seizure is an uncontrolled and unexpected electrical disturbance in the brain that can affect levels of consciousness, movement, behaviour and feelings. A few children with MYT1L syndrome have been reported as having partial seizures or absence seizures.

Communication abilities

Most people with MYT1L syndrome have delayed expressive language during early childhood. However, there is a wide range of communication abilities with this syndrome, with some children saying their first words before the age of 2 years, and others not speaking their first words until much later. The vast majority of individuals with MYT1L syndrome eventually develop speech, and a few develop average verbal communication skills by adulthood. Some children with MYT1L syndrome have been diagnosed with verbal dyspraxia (also known as verbal apraxia), which is when a child has difficulties saying words and sounds due to difficulties coordinating the appropriate muscle movements. Further research is needed to better understand the specific reasons behind this speech delay and to characterize the range of speech abilities in adults with MYT1L syndrome.

Hearing

It is not uncommon for people with genetic conditions to have ear anomalies or hearing deficits. However, there is no increased chance of deafness or ear anomalies in people with MYT1L syndrome.



Eyesight

There is no consistent association of MYT1L syndrome with eye or vision problems. However, when we have more information on this condition, eye or vision problems may become apparent.

Education and learning

Based upon the information we have so far (2021), it seems that people with MYT1L syndrome will need additional help with education and schooling. Most often a special educational needs school is attended. Detailed information on the strengths and weaknesses in learning of people with MYT1L syndrome is needed.

There is little information on the level of independence of adults with MYT1L syndrome. It is likely that an adult with MYT1L syndrome will not be able to live completely independently. For example, they may need to live in sheltered housing.

Therapies

People with MYT1L syndrome would benefit from multidisciplinary care. Standard therapies would be speech and language (to help with communication), physiotherapy (to help with motor development) and occupational therapy (to help with adaptations in the home). This could be delivered via a child development clinic or community paediatrics.

Treatment from a specialist neurologist may be needed for seizures.

Weight management and diet advice from a qualified dietician may be beneficial.

There is no specific treatment or cure for MYT1L syndrome since a lot of the effects of this genetic change take place during a baby's development (meaning while the baby is developing in the womb). However, knowing this diagnosis means that appropriate monitoring and therapies can be put in place.

Research

Scientists are continuously researching the MYT1L gene, it's functions and the possible effects of changes to this gene. Some research groups use animal models in which the gene or it's activity have been altered. Studies in an experimental fish, in which MYT1L gene function is blocked during development, have shown that these fish have a reduction in a chemical called oxytocin in specific parts of the brain (the neuroendocrine hypothalamus). This part of the brain is known to be important for regulating bodily functions such as releasing hormones and regulating behaviour, appetite, and body temperature. The importance of reduced oxytocin is not understood, or if it happens in people with MYT1L syndrome. Oxytocin is not recommended as a treatment for MYT1L syndrome. Recent studies in an experimental mouse have shown that a MYT1L mutation, that is similar to one found in people, causes the mice to have neurons that mature earlier than expected. Scientists think this may help explain the autistic features observed in some people with MYT1L syndrome.

2p25.3 Duplications

As mentioned at the beginning of this guide, MYT1L syndrome is caused by a change to the MYT1L gene, or a *deletion* of the section of chromosome 2 that contains the MYT1L gene (2p25.3). If this region of chromosome 2 is duplicated, meaning there would be three copies of this section of genetic material instead of the expected two, then people have a 2p25.3 *duplication*. This is not the same as MYT1L syndrome but having an extra MYT1L gene also seems to cause alterations to development and brain function.

People with the chromosome 2p25.3 duplication are likely to have mental health issues. Autism, attention deficit hyperactivity disorder (ADHD) and depression seem to be common in people with a 2p25.3 duplication containing MYT1L. People with this duplication also have intellectual disability, we do not know if this is more or less marked than for people with MYT1L gene changes or the 2p25.3 deletion. It is not yet clear if people with a 2p25.3 duplication have an increased chance of being overweight.

Inform Network Support

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Understanding Chromosome & Gene Disorders

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This leaflet was made possible by a contribution from the Sir Halley Stewart Trust.

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.

This booklet was written and updated by Dr Alisdair McNeill, Senior Clinical Lecturer in Neurogenetics (University of Sheffield) and consultant in clinical genetics (Sheffield Children's Hospital) together with Unique (AP).

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