Understanding Chromosome & Gene Disorders

SLC12A2 syndrome & SLC12A2-related deafness

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The information in this leaflet is based on Dr Alisdair McNeill's experience of people affected by changes to the SLC12A2 gene. Further detailed information is published in a scientific paper (McNeill 2020). Since so few people with *SLC12A2* gene changes have been identified, the information we have is limited and may change in the future when more research is done.

What is SLC12A2 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 same syndrome will have identical combinations of symptoms and physical features, but there will be shared features.

SLC12A2 syndrome is the medical term used to describe the medical condition which affects a person who has a change in one copy of their SLC12A2 gene. People with SLC12A2 syndrome have combinations of slowness in reaching developmental milestones, learning difficulties and neurological conditions such as movement problems.

How common is SLC12A2 syndrome?

SLC12A2 syndrome was recognised in August 2020, when the first research paper describing a group of affected children was published. It is a very rare medical condition with very few known affected people to date (Feb 2021). This leaflet is based upon what we currently know about SLC12A2 syndrome, but we recognise that there are many gaps in our knowledge and with time, and further research, we will be able to provide more information.

What is SLC12A2-related deafness?

In SLC12A2-related deafness the person has deafness due to altered function of the auditory nerve and part of the inner ear called the cochlea. They may also have balance problems. They do not have the wider medical problems associated with SCL12A2 syndrome.

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 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 (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.

How do doctors find changes in genes?

The 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 which control the activity of the 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 and 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, otherwise known as a VOUS or VUS.

What is the SLC12A2 gene?

The SLC12A2 gene gives an instruction to make a protein called NKCC1 that helps form an ion channel. This ion channel controls the movement of salts (ion is another word for salts) called potassium and sodium in and out of cells. The carefully regulated movement of ions is important for proper functioning of many organs.

The SLC12A2 gene is found in lots of different parts of the body, this is why changes in the SLC12A2 gene can cause so many different symptoms.

In the developing brain (when the baby's brain is growing in the womb), SLC12A2 helps control the production of brain cells (neurons). SLC12A2 stimulates cells to divide to produce more cells, and so increase the number of brain cells (neurons). SLC12A2 also helps guide brain cells to the correct parts of the brain for their appropriate function.

SLC12A2 is also found in the cochlea, the cochlea is found in the inner ear inside the skull. It detects sound waves transmitted along the nerve from the ear drum and plays a very important role in hearing and balance.

SLC12A2 is also found in the lining of the intestine and bronchi (tubes in the lungs which carry air). It plays a role in producing mucous in these areas to keep these tissues healthy.

How can changes in the SLC12A2 gene cause such different symptoms?

There are two parts to the SLC12A2 gene, one part is important for brain development and the other for development of the inner ear (cochlea). If a person has a change in the part of the SLC12A2 gene which is important for development of the cochlea they will have SLC12A2-related deafness. If a person has a change in the part of the SCL12A2 gene giving instructions for brain development they will have SLC12A2 syndrome. It is currently thought that if both copies of the SLC12A2 gene carry a pathogenic variant, this will lead to a different syndrome and the lungs and/or intestines may be affected.

Why has this happened?

In all people with SCL12A2 syndrome, the gene change has happened for the first time in them and not been inherited from either of their parents. This is called a de novo genetic change.

Nothing that either parent did, or did not do, caused this to happen. There are no known drugs, environmental or occupational factors which cause SLC12A2 gene changes. It is no one's fault. We are all thought to carry new genetic changes that are not found in either of our parents but we don't usually notice them unless they affect an important gene.

Could this happen again?

If a de novo genetic change in the SLC12A2 gene has been found, then the chances of another child being affected are very low (<1/200). This is because it is possible that the gene change may be found in the sperm or eggs, which would not be detectable in blood tests. This is known as germline or gonadal mosaicism. If you wish, you should be able to seek advice from your local Clinical Genetics department (your GP could refer you) if you want to discuss this further.

What are the most likely features of SLC12A2 syndrome?

There is a lot of variability in the symptoms people with SLC12A2 syndrome have. Although it is not understood why it is so variable. People with SLC12A2 syndrome can have combinations of the following symptoms:

- Delayed motor development (sitting and walking)
- Delayed speech development
- Epileptic seizures
- Intellectual disability
  (needing extra help at school or attending a special school)
- Autism
- Stiffness of limbs (the medical term is spasticity)
- Deafness

People with SCL12A2-related deafness have sensorineural deafness (this means nerve deafness) and sometimes balance problems (which can cause delayed walking in children) but not a wider medical condition causing learning disorders or limb weakness. However, people with SLC12A2 syndrome can have deafness as part of their wider neurological condition.

Physical appearance

People with SLC12A2 syndrome do not have distinctive alterations to their facial appearance. They might have a head circumference (head size) smaller than average. There is no known association with cleft lip or cleft palate as is sometimes seen with other genetic changes.

Growth

So far, people identified with SLC12A2 syndrome are found to be within the average range for weight and height, but towards the lower end of average. People with SLC12A2-related deafness have growth within the average range for height and weight.

Sitting and moving (Gross motor skills)

All people with SLC12A2 syndrome have some problems with gross motor skills. Many babies with SLC12A2 syndrome are floppy at birth due to low muscle tone (this is called hypotonia). It is difficult to give much information because of the small number of people with SLC12A2 syndrome, but all have delayed walking.

Children with SLC12A2 syndrome may also have stiffness of their limbs associated with delayed walking (the medical term for this is spasticity). More research is needed to define the full range of movement abilities in people with SLC12A2 syndrome.

Children with SLC12A2-related deafness can also have delayed walking. This is due to problems with balance. Once again more research is required to define the full range of walking abilities for these children.

Communication abilities

People with SLC12A2 syndrome have markedly affected communication abilities. Most have only a few or no spoken words.

Hearing problems at important stages of language development may worsen speech delay. Language abilities may also be linked to the level of learning disability for each child.

Speech and language therapists can help by assessing communication skills. They can help with speech development and introduce communication devices. They can also help to ensure that whatever your child's ability, they are supported in achieving their full communication potential. Children with limited or no speech may be able to learn other ways to communicate their feelings and needs.

Hearing

Some people who have a change in a specific part of the SLC12A2 gene develop deafness without other neurological features. This deafness can be associated with balance problems and delay in learning to walk. The deafness is likely to be due to altered development of the cochlea, since the part of the SCL12A2 gene affected by the variant has been shown to be crucial for development of the cochlea in mice.

People with SLC12A2 syndrome can also have nerve deafness as part of a more widespread neurological condition.

Seizures

Some children with SLC12A2 syndrome have experienced seizures (a sudden change in electrical activity of the brain that causes momentary brain dysfunction), or have had a seizure but there is currently very little information regarding seizure activity.

Children who experience seizures may have investigations to check the activity of their brain. This may include an 'EEG' (electroencephalogram) that looks at the electrical activity in the brain. This is done by attaching stickers to the scalp, that are connected by wires, to the machine used for analysis.

Some children may be offered an MRI (magnetic resonance imaging) scan of their brain, to look for structural changes.

Learning difficulties and intellectual disability

Children with SLC12A2 syndrome are expected to experience learning difficulties, some will be given a diagnosis of intellectual disability (ID). Intellectual disability (ID) is a term used to describe significant limitations in intellectual functioning (measured by IQ scores) and adaptive behaviour (types of behaviour used to adjust to other behaviours or situations).

As infants become older, schooling can be a concern for some parents. While some children may attend a mainstream primary school with extra help, the extra demands of mainstream secondary school may prove challenging. Some children will transfer to special schooling and others may remain in a mainstream school with an Educational Health Care Plan (EHCP).

Autism

Children with rare gene variants often have behavioural, social and/or communication difficulties and vulnerability in these areas means that children should be monitored and families offered early support. Some children with SLC12A2 syndrome have been identified as having autism or autistic like behaviours.

There is not a 'medical test' that can diagnose autism. Children undergo an autism-specific behavioural evaluation usually carried out by a specially trained paediatrician and psychologist. Evaluations will vary according to the age of the child and may be multidisciplinary. A child may be assessed by a speech and

language therapist as well as an occupational therapist. Depending on the outcome, further evaluation by a specialist such as a developmental paediatrician, neurologist, psychiatrist or psychologist may be offered or recommended.

Eyesight

There is no consistent association of SLC12A2 syndrome with eye or vision problems. However, when we have more information on this condition, eye or vision problems may become apparent.

Therapies

People with SLC12A2 syndrome would benefit from multidisciplinary care. Standard therapies should include the following:

- speech and language (to help with communication)
- physiotherapy (to help with motor development)
- occupational (to help with adaptations in the home)
- People with hearing impairment should be assessed by an ear, nose and throat doctor (ENT). Based on limited evidence, cochlear implants may help people with SLC12A2-related deafness, but further research and information is needed.

Currently there is no specific treatment for SLC12A2 syndrome, and there is no cure, but knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

Families may benefit from referral to Clinical Genetics to discuss the chances of other family members being affected by SLC12A2 syndrome.

Inform Network Support

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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 written by Dr. Alisdair McNeill (Honorary Consultant Clinical Geneticist), University of Sheffield, UK and compiled by Unique (AP).

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