Why did this happen?

The KIF1A gene gives an important instruction for the health of brain cells and nerve fibres. The KIF1A gene gives an instruction for production of the KIF1A protein. This protein helps to control the transport of nutrients and other molecules within nerve cells and along nerve fibres.

We all have two copies of the KIF1A gene (one inherited from our mother and one inherited from our father). Certain changes to the code of the KIF1A gene mean that the KIF1A protein becomes sticky and binds to the protein produced by the "normal" KIF1A gene. Such changes to the KIF1A protein can be inherited from a parent or happen for the first time in the person with the KIF1A neurological condition. Given the nature of KIF1A neurological syndrome the vast majority of KIF1A gene variants have arisen for the first time (*de novo* (dn)) in the patient with the condition, rather than being inherited.

Can it happen again?

If the KIF1A variant is not found in blood tests of the parents then the chance of another child being affected by the same condition is very low. It is not zero because of something called "gonadal mosaicism". This means that a parent might carry the KIF1A variant in their sperm or eggs, which would not be detected by a blood test. This would mean that there was a chance of having another affected child. Precise advice on this issue should be sought from your local Clinical Genetics department. Please note there is a condition caused by changes in both the KIF1A gene inherited from mum and the KIF1A gene inherited from dad, which causes similar symptoms to the condition described in this leaflet but which has a higher chance of affecting other children that the couple have.

Inform Network Support

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http://www.kif1a.org/ - a patient-led foundation started by parents dedicated to finding a cure for children living with *KIF1A Associated Neurological Disorder* (KAND), a rare genetic disease.

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KIF1A syndrome

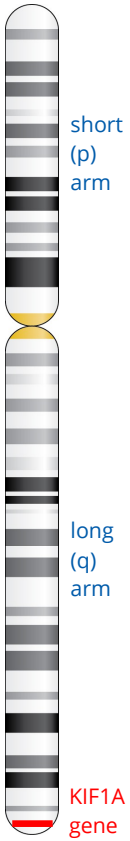
rarechromo.org

What is KIF1A Syndrome?

KIF1A syndrome is a neurological condition caused by changes in the KIF1A gene. The condition usually begins to show symptoms in childhood or early teenage years.

One of the main features of the condition is weakness and stiffness in the legs. This is called spastic paraparesis or spastic paraplegia (spastic means stiff, "para" means legs and "paresis/plegia" means weak). People with the condition also often have shaking (tremor) of their hands called ataxia.

Most people with KIF1A neurological syndrome also have developmental delay (slowness in achieving developmental milestones). This condition affects the nervous system (brain, spinal cord and peripheral nerves) but no other parts of the body. Some affected children first come to medical attention with developmental delay but then show signs of spastic paraplegia.



Chromosome 2

Medical concerns

Spastic parapelgia

Progressive weakness and stiffness of the legs leads to poor mobility. This may mean that individuals walk with an awkward gait or may need a walking aid or wheel chair in more severe cases.

Leg contracture and pressure sores

There is a possibility of leg contractures (the muscles or joints become shortened over time) and/or pressure sores (injuries to the skin and underlying tissue as a result of sustained pressure) due to poor mobility.

Most common features:

- Spastic paraplegia (stiff, weak legs) sometimes with ataxia (unsteadiness of movements or tremor)
- Those with spastic paraplegia also have intellectual disability, speech/language delay and developmental delay

Other possible features include:

- Epileptic seizures
- Thinning of the optic nerve
- Leg contracture
- Pressure sores
- Spinal curvature e.g. scoliosis or kyphosis
- Autism Spectrum Disorders (ASD)

Epilepsy

A minority of people with KIF1A neurological syndrome develop epilepsy. Several cases of epileptic fits have been reported in the medical literature, including: a boy who started to experience generalised tonic-clonic seizures at 15 years (Hotchkiss 2016); a 16-year-old boy diagnosed with generalized tonic-clonic seizures; a 6-year-old boy with refractory myoclonic, tonic and generalized tonic-clonic seizures (Nieh 2015); four cases with unspecified seizures (Lee 2015; Kun Cheon 2017).

Thinning of the optic nerve

Some people with KIF1A variants have thinning of the nerve at the back of the eye (optic nerve hypoplasia), which transmits visual signals to the brain. This can cause problems with vision.

Spinal curvature

A few children and adults have been affected by scoliosis (a sideways curve of the spine) or kyphosis (an outward curve resulting in a hump). The curvature can be treated with physiotherapy and exercises. A support brace may be needed or in severe cases spinal fusion surgery may be necessary to straighten the spine using rods.

Development

Growth

Head circumference is below the average range.

Developmental delay in children

Babies and children are typically delayed in reaching their developmental "milestones" including rolling, sitting, moving and walking.

Sitting, moving and walking

Some people with KIF1A neurological syndrome never walk independently, others require walking aids or have very limited walking ability. In a few people with KIF1A neurological syndrome walking is relatively normal.

Speech

Most people with KIF1A neurological syndrome have been reported to have delay to speech and language, with variable severity.

Learning

Most people with this condition will need to attend a special school or require additional support.

Behaviour

No clear association with autism or other behavioural problems has been reported. A single person with a KIF1A variant and autism/ADHD has been reported but it is not clear if this is due to the KIF1A variant or is a coincidence (Tomaselli 2017).

Management:

- Follow up by a Neurologist for management of spasticity or other neurological features.
- EEG (measurement of the brain's electrical activity) if seizures are suspected.
- Follow up by a Paediatrician consultant to monitor growth and development.
- Physiotherapy may help with leg stiffness.
- Speech and language therapy as needed.
- Assessment of vision and hearing.
- Genetic counselling as needed to provide support and advice about the genetic condition.