How common is Au-Kline syndrome?

Au-Kline syndrome is very rare. Currently (2021) only 13 children with this diagnosis have been reported in the medical literature (and two with Okamoto syndrome). It is known many more children have been diagnosed worldwide. It is expected that more children will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

Why did this happen?

When children are conceived, the genetic material is copied in the egg and sperm that make a new child. The biological copying method is not perfect, and random rare changes occur in the genetic code of children that are not seen in the DNA of their parents. This happens naturally and is not due to any lifestyle, dietary or environmental factors. No one is to blame and nobody is at fault. Such changes happen to everyone but it's only when a change affects an important gene that health and/or development are affected.

In all children reported with Au-Kline syndrome so far, the change in the *HNRNPK* gene occurred by chance in that child (this is known as *de novo*) and was not found in their parents.

Can it happen again?

The risk of having another child affected by a rare gene disorder depends on the genetic code of the parents. If the change in the *HNRNPK* gene has been shown to be *de novo*, that means neither parent was found to carry it, the chance of having another child with Au-Kline syndrome is low (less than 1%). The reason there is still a small chance is due to something called germline mosaicism, which is where the gene variant can be found in a few eggs or sperm, but is not found in rest of the body's cells.

To date (2021), no parent has been reported to have passed on an HNRNPK variant that causes Au-Kline syndrome to a child. Theoretically, if this were to happen, the chances of having another child with Au-Kline syndrome would be 50% for each pregnancy, or less for a parent with somatic mosaicism (which is when the variant is not found in all cells). A clinical geneticist can give you specific advice for your family.

Can Au-Kline syndrome be cured?

Au-Kline syndrome cannot be cured at the present time however, knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

Families say ...

" Having 3 neuro typical boys it has been a long road understanding our daughter and getting the advice/ services she deserves. We have two hats when it comes to B. One of being a parent which is loving and enjoying her as our daughter and the second is to be her manager. Managing her therapies, care, education, appointments and the fight for access to what she needs. The second hat is a full time job and we have had to educate ourselves in these areas. We are learning all the time but we make time to just wear our first hat and enjoy all the positives she brings to our family. We are now in a place were I can honestly say I would not change a thing about her. "

Inform Network Support

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Websites, Facebook groups and other links:

https://www.facebook.com/auklinesyndrome/

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/donate Please help us to help you!

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Charity Number 1110661
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Understanding Chromosome & Gene Disorders

Au-Kline syndrome

(HNRNPK loss of function variants and 9q21.32 microdeletions)

(may also be known as Okamoto syndrome)

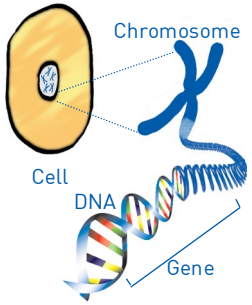
rarechromo.org

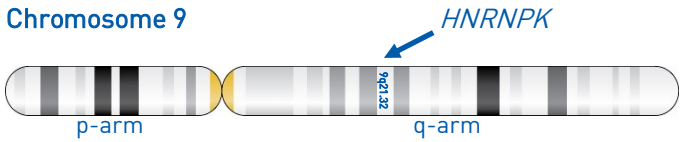
What is Au-Kline syndrome?

Au-Kline syndrome is a rare genetic condition that causes developmental delay and can affect a child's learning abilities and behaviour. As is common with genetic conditions, each person is affected differently. Au-Kline syndrome has also been associated with a number of physical differences which may require monitoring and/or medical intervention. It is important to know that the most severely affected children are likely to be the first identified so initial findings may not represent the possible spectrum of symptom severity.

What causes Au-Kline syndrome?

Au-Kline syndrome is caused by specific changes (known as pathogenic variants) to, or a deletion of, a gene called *HNRNPK* (HNRNPK is an abbreviation of the gene's full name, Heterozygous Nuclear Ribonucleoprotein K). The HNRNPK gene is located on the long 'q' arm of chromosome 9 in a region called 9q21.32 as shown in the image below.





We have two copies of chromosome 9 in our cells, so we also have two copies of the *HNRNPK* gene.

Au-Kline syndrome occurs when only one copy of the *HNRNPK* gene is affected, this is known as autosomal dominant since the change occurred on an autosome (any of the chromosomes numbered 1-22) and features are apparent when only one copy of the gene is altered (this is known as dominant).

The *HNRNPK* gene sequence is used to make the HNRNPK protein. This protein is involved in many processes that are essential in creating other proteins. This gene is active in many different parts of the body so absence of HNRNPK can lead to a wide number of physical and developmental differences.

Au-Kline syndrome features

Most children with Au-Kline syndrome have:

- Developmental delay
- Learning difficulties or intellectual disability (ID)
- Weak muscle tone (hypotonia)
- Antenatal increased nuchal translucency
- Common facial features with a long face, upper eyelid drooping (ptosis) a deeply grooved tongue, a down-turned and open mouth and a broad nose
- Gastrointestinal dysmotility, high pain threshold, recurrent fevers, abnormal sweating (autonomic dysfunction)

Other possible features include:

- Heart anomalies
- Genitourinary anomalies
- Brain anomaly identified by MRI
- Neonatal feeding and breathing difficulties
- Hypothyroidism
- Skeletal and teeth anomalies
- Ear, nose and throat anomalies
- Vision and hearing problems

Medical concerns

Hypotonia

All children reported so far with Au-Kline syndrome have weak muscle tone (hypotonia) which can be severe.

Heart anomalies

Ten children with Au-Kline syndrome described so far have been reported to have congenital heart anomalies with ventricular septal defect (VSD) being the most common. One child with ascending aortic dilatation has been reported.

Genitourinary anomalies

About half of the children identified so far (2021) have urine blockage (hydronephrosis) and backward flow of urine (vesicoureteral reflux) as a new-born. Some have recurrent urinary tract infections. Two children have been reported to have a weak bladder tone requiring medication with oxytocin. A few boys were found to have undescended testes (cryptorchidism).

Brain anomaly

Some children diagnosed with Au-Kline syndrome have had a brain MRI. Anomalies of the nerve bundle connecting the left and right sides of the brain (corpus callosum), reduced myelin sheath surrounding nerves (hypomyelination) altered nerve cell migration (periventricular heterotopia) have been found.

Hypothyroidism

An underactive thyroid gland has been reported in some children, most resolved but one child required treatment with thyroxine.

Skeletal and dental anomalies

In a third of children, premature fusion of the skull bones has been identified (craniosynostosis), club foot (talipes), curvature of the spine (scoliosis) and hip dysplasia have also been reported. Some children have missing or misaligned teeth.

Ear, nose and throat anomalies (ENT)

A cleft palate (bifid uvula and submucous) has been reported in some children with Au-Kline syndrome.

Vision

A variable spectrum of vision related difficulties have been reported including refractive errors and optic nerve anomalies.

Hearing

About a third of children reported so far with Au-Kline syndrome have been found to have a hearing problem, both conductive and sensorineural hearing loss have been reported.

Development

Physical Development

Developmental delay of motor function has been reported in all children diagnosed with Au-Kline syndrome so far (2021). Walking is typically markedly delayed, however, most children continue to improve their motor skills into adolescence.

Intellectual Development and Learning

Children with Au-Kline syndrome usually have some level of learning difficulty or intellectual disability, although one child has an intelligence test score within the low average range.

Speech and language

Some form of language developmental delay has been reported in all children diagnosed with Au-Kline syndrome to date (2021). There can be severe difficulties with speech abilities requiring supportive communication strategies.

Height

About half of children with Au-Kline syndrome reported so far, have short stature (below the third centile).

Management recommendations

Following diagnosis and advice from Clinical Genetics, children with Au-Kline syndrome would benefit from an assessment with a paediatrician for surveillance for scoliosis, hearing and vision, and thyroid function. Investigations should include a heart scan (Echo) and kidney scan, a brain MRI should also be considered.

A referral should be made to the child development team for a neurodevelopmental paediatrician, physiotherapy, speech and language therapy and occupational therapy as required. Audiology and ophthalmology review is recommended. Referral to a specialist Dentist, ENT (ear, nose and throat), kidney or heart specialist may be required depending on clinical findings.