4H syndrome: Hypomyelination with Hypogonadotropic Hypogonadism and Hypodontia (also known as Pol III-related Leukodystrophy)

What is 4H syndrome?
4H syndrome is a form of leukodystrophy, also known as Pol III or POLR3-related leukodystrophy. 4H syndrome stands for Hypomyelination Hypogonadotropic Hypogonadism and Hypodontia.

Hypomyelination – this means there is a lack of myelin in the central nervous system.
Hypogonadotropic Hypogonadism – this occurs when normal puberty development is absent because the central nervous system is not able to initiate it properly.
Hypodontia – this means that not all teeth are present.

4H syndrome is inherited and passed on through either the POLR3A or POLR3B genes.

What are the POLR3A and POLR3B genes?
These genes provide instructions for making the two largest parts of an enzyme called RNA polymerase III. This enzyme is involved in the production of ribonucleic acid (RNA).
Reduced function of the RNA polymerase III molecule is thought to affect the development and function of many parts of the body, including the nervous system and the teeth. The relationship between changes in the POLR3A and POLR3B genes, and the specific symptoms of 4H syndrome are still mostly unknown.

What are the symptoms of 4H syndrome?
The age of onset of 4H syndrome is typically in early childhood, usually the second year of life, but later onset cases have been reported. Individuals with 4H syndrome may have different combinations of its symptoms. Symptoms include;

- Late walking
- Problems with balance and fine motor skills (ataxia).
- Difficulties with speech (dysarthria)
- Eruption of teeth is delayed, and not in the typical order.
- Some of the teeth may be missing, or have an unusual shape (hypodontia).
- Normal puberty development is absent.
- Short stature may become evident during childhood.
- Short sightedness is common.

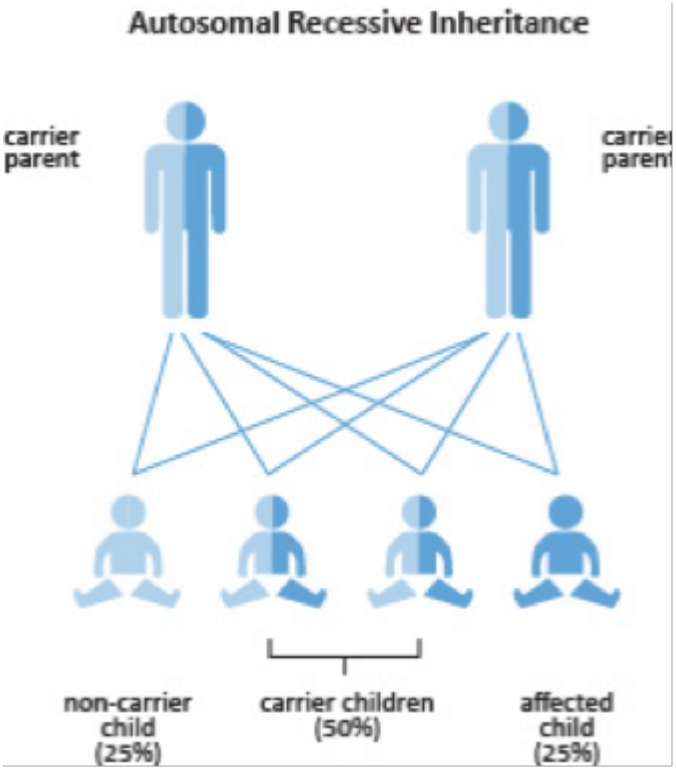
Hypomyelination underlies most of the neurological issues associated with 4H syndrome. Affected individuals usually have intellectual disability, in varying severity, which will gradually worsen over time.

Individuals with changes in the POLR3B gene have earlier disease onset than those with changes in the POLR3A gene, but the disease progresses more slowly.

How is 4H syndrome diagnosed?

4H syndrome is diagnosed when there is a combination of symptoms in an individual, and further investigations such as a brain MRI show typical characteristics of 4H syndrome. Genetic testing for 4H syndrome will look for changes (or mutations) on both copies of the POLR3A or POLR3B genes.

Are family members at risk of 4H syndrome?
4H syndrome is an autosomal recessive disorder. Individuals who have one copy of the gene change on either POLR3A or POLR3B do not typically shown any signs or symptoms, and are considered as carriers of the 4H syndrome. Both parents must be carriers of the condition for it to be passed on and for symptoms to be present in their child. Each pregnancy has a 1 in 4 chance of inheriting the condition.



Can 4H syndrome be treated?
While there is no cure for 4H syndrome, management and therapies for individual symptoms is recommended. This may include; paediatric neurologist, clinical geneticist, physiotherapist, occupational therapist, speech and language pathologist, dentist, endocrinologist and ophthalmologist.

Other names for 4H syndrome
4H syndrome is also known as POLR3- related Leukodystrophy and Pol III-related Leukodystrophy.

Contact Us
Ph: 1800 141 400 | M: 0418 755 994 | info@leuko.org.au | www.leuko.org.au |
PO Box 850 Mornington VIC 3931 | Facebook or Twitter @leukodystrophyaustralia

References
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