Aicardi Goutieres Syndrome (AGS)

What is AGS?

AGS is a type of leukodystrophy.

Leukodystrophies are a group of genetic conditions that mainly affect the white matter of the brain and spinal cord. The white matter is the wiring network of the brain that connects different brain regions and links the brain to the spinal cord and rest of the body.

AGS is a congenital disorder that affects the brain, immune system, and skin. The loss of white matter and abnormal calcium deposits in the brain result in severe intellectual and physical disability.

What are the symptoms seen in AGS?

1. **Early onset AGS:** Symptoms appear during the first weeks after birth.
   Symptoms include enlarged spleen and liver, low platelet count and abnormal neurological findings including jittery behavior and feeding difficulties.
2. **Late onset AGS:** Symptoms appear after the first weeks or months of normal development.
   Symptoms include gradual decline in head growth, weak or stiffened muscles (spasticity), and cognitive and developmental delays. Irritability, inconsolable crying, puffy swelling on fingers, toes and earlobes, intermittent fever, seizures, and loss of developmental skills are some of the other noticeable symptoms.

Children with AGS may also experience episodes of severe brain dysfunction (encephalopathy), typically lasting for several months. During this phase, children develop intermittent fevers, seizures, decreased rate of growth and stop developing new skills eventually leading to loss of skills (regression). This phase can cause severe irreversible brain damage resulting in permanent neurological symptoms. Depending upon the severity of the damage caused and age of onset, life expectancy is decreased.

What causes AGS?

AGS is caused by changes in the *TREX1*, *RNASEH2A*, *RNASEH2B*, and *RNASEH2C* genes, that are responsible for the breakdown of unwanted DNA molecules produced during cell division or protein production.

Recent studies have found that changes in the *SAMHD1*, *IFIH1*, and *ADAR* genes results in faulty protein production leading to an inappropriate immune response in the body, giving rise to symptoms that resemble autoimmune conditions. Depending upon the affected gene, AGS can be inherited (autosomal recessive or autosomal dominant) or de novo (happens for the first time in the child and not inherited from either parent).

How is AGS diagnosed?

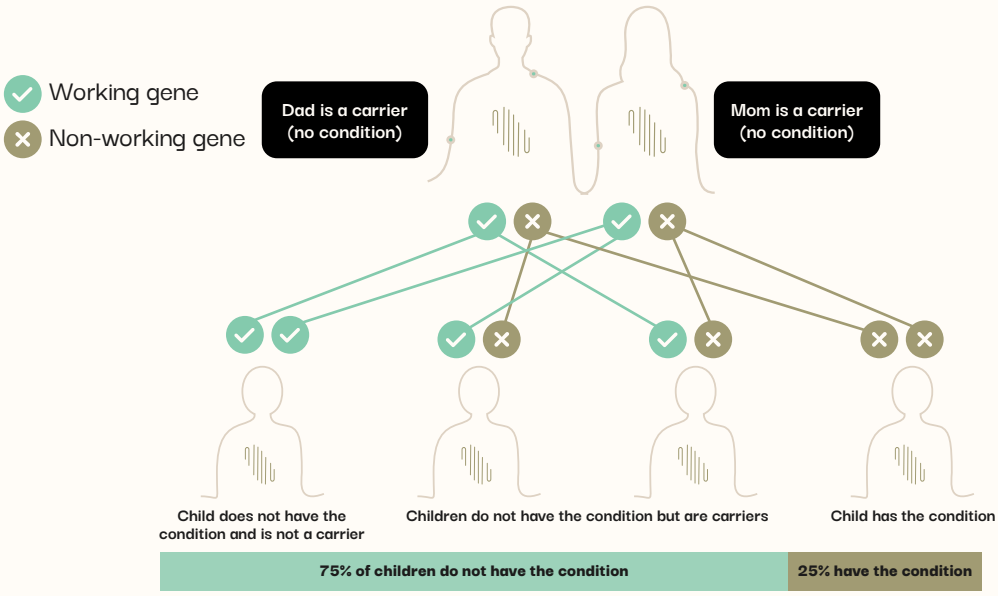
AGS is suspected in children with a combination of the listed symptoms and further studies are performed to establish the diagnosis. Testing for establishing diagnosis might include:

- MRI brain to show white matter changes and calcification of the basal ganglia and white matter.
- CT head may show calcification better than an MRI scan.
- Elevated liver enzymes, interferon (body's response to viral infections) and reduced platelet count during the encephalitic episode.
- Lumbar puncture: The fluid surrounding the brain and spinal cord may show features of inflammation without infection
- Genetic testing: identification of disease-causing changes ("pathogenic variants") in any of the above-mentioned genes confirms the clinical diagnosis.

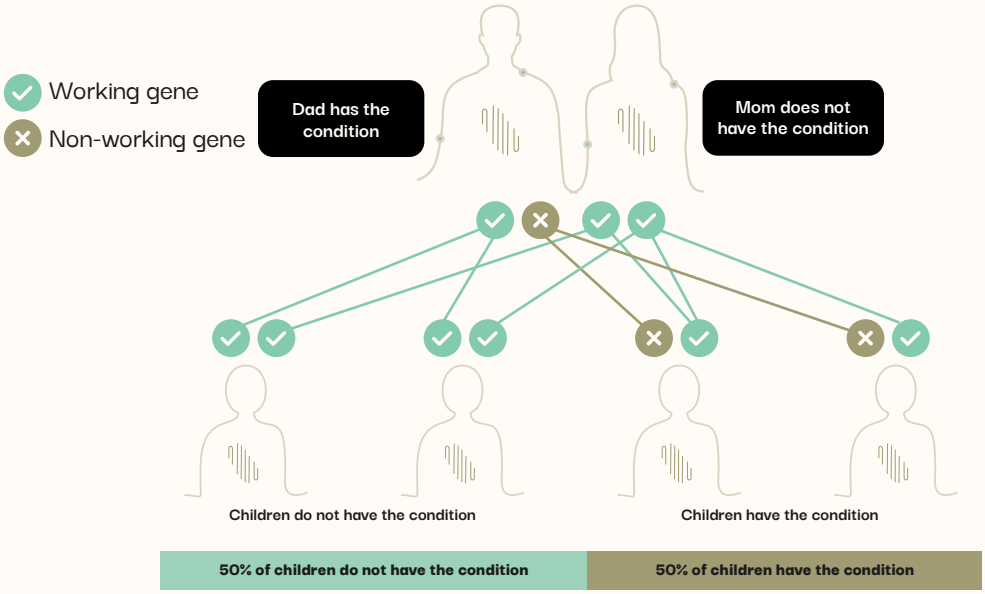
How is AGS inherited?

AGS follows different inheritance patterns depending on the gene involved:

1. **De novo:** the gene change is present for the first time in the affected individual. This can result from a change in an egg or sperm cell from one of the parents (without being present in other cells of the parent) or a change in the fertilized egg.
2. **Autosomal recessive inheritance:** this is where two copies of the altered gene change causes AGS. Each parent passes on one copy of the altered gene change. This inheritance pattern is observed in the *ADAR*, *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, and *SAMHD1* genes.



3. **Autosomal dominant inheritance:** this is where one copy of the altered gene change is sufficient to cause AGS. This inheritance pattern is observed in the *IFIH1*, *TREX1* or *ADAR* genes.



Can AGS be treated?

- There is currently no cure or specific treatments for AGS.
- Treatment is aimed at management of symptoms.
- Researchers are trialing immune therapies in some patients with AGS.

Support and resources:

- **International Aicardi-Goutieres Syndrome Association** aicardi-goutieres.org/index.jsp?lingua=ENG
- **Leukodystrophy Australia** leuko.org.au
- **Mission Massimo Foundation** missionmassimo.com
- **United Leukodystrophy Foundation** ulf.org/leukodystrophies
- **Hunter's Hope** huntershope.org/familycare/leukodystrophies

Research:

- **Australian Leukodystrophy Clinical and Research Program** leukonet.org.au
- **Clinical trials** clinicaltrials.gov/ct2/results?cond=Aicardi+Goutieres+Syndrome&term=&cntry=&state=&city=&dist=
- **Global Leukodystrophy Initiative** theglia.org

References:

- rarediseases.info.nih.gov/diseases/575/aicardi-goutieres-syndrome
- huntershope.org/family-care/leukodystrophies/aicardi-goutieres-syndrome
- chop.edu/conditions-diseases/aicardi-goutieres-syndrome-ags