X-linked lissencephaly with abnormal genitalia

X-linked lissencephaly with abnormal genitalia (XLAG) is a condition that affects the development of the brain and genitalia. It occurs most often in males.

XLAG is characterized by abnormal brain development that results in the brain having a smooth appearance (lissencephaly) instead of its normal folds and grooves. Individuals without any folds in the brain (agyria) typically have more severe symptoms than people with reduced folds and grooves (pachygyria). Individuals with XLAG may also have a lack of development (agenesis) of the tissue connecting the left and right halves of the brain (corpus callosum). The brain abnormalities can cause severe intellectual disability and developmental delay, abnormal muscle stiffness (spasticity), weak muscle tone (hypotonia), and feeding difficulties. Starting soon after birth, babies with XLAG have frequent and recurrent seizures (epilepsy). Most children with XLAG do not survive past early childhood.

Another key feature of XLAG in males is abnormal genitalia that can include an unusually small penis (micropenis), undescended testes (cryptorchidism), or external genitalia that do not look clearly male or clearly female (ambiguous genitalia).

Additional signs and symptoms of XLAG include chronic diarrhea, periods of increased blood sugar (transient hyperglycemia), and problems with body temperature regulation.

Frequency

The incidence of XLAG is unknown; approximately 30 affected families have been described in the medical literature.

Causes

Mutations in the ARX gene cause XLAG. The ARX gene provides instructions for producing a protein that is involved in the development of several organs, including the brain, testes, and pancreas. In the developing brain, the ARX protein is involved with movement and communication in nerve cells (neurons). The ARX protein regulates genes that play a role in the migration of specialized neurons (interneurons) to their proper location. Interneurons relay signals between neurons. In the pancreas and testes, the ARX protein helps to regulate the process by which cells mature to carry out specific functions (differentiation).

ARX gene mutations lead to the production of a nonfunctional ARX protein or to the complete absence of ARX protein. As a result, the ARX protein cannot perform its role regulating the activity of genes important for interneuron migration. In addition to impairing normal brain development, a lack of functional ARX protein disrupts cell differentiation during the formation of the testes, leading to abnormal genitalia. It is
thought that the disruption of ARX protein function in the pancreas plays a role in the chronic diarrhea and hyperglycemia experienced by individuals with XLAG.

Inheritance Pattern

This condition is inherited in an X-linked pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females, who have two copies of the X chromosome, one altered copy of the gene in each cell can lead to less severe brain malformations or may cause no symptoms at all. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Other Names for This Condition

- LISX2
- X-linked lissencephaly 2
- X-linked lissencephaly with ambiguous genitalia
- XLAG
- XLISG

Diagnosis & Management

Genetic Testing Information

- What is genetic testing? /primer/testing/genetictesting

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov https://clinicaltrials.gov/ct2/results?cond=%22X-linked+lissencephaly+with+abnormal+genitalia%22+OR+%22X-linked+lissencephaly%22+OR+%22neuronal+migration+disorder%22

Additional Information & Resources

Health Information from MedlinePlus

Genetic and Rare Diseases Information Center

- X-linked lissencephaly with abnormal genitalia

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Epilepsy Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page
- National Institute of Neurological Disorders and Stroke: Lissencephaly Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Lissencephaly-Information-Page

Educational Resources

- Kennedy Krieger Institute: Brain Malformations
  https://www.kennedykrieger.org/patient-care/conditions/brain-malformations
- MalaCards: x-linked lissencephaly with abnormal genitalia
  https://www.malacards.org/card/x_linked_lissencephaly_with_abnormal_genitalia
- Orphanet: X-linked lissencephaly with abnormal genitalia
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=452

Patient Support and Advocacy Resources

- American Association on Intellectual and Developmental Disabilities (AAIDD)
  http://aaidd.org/
- American Epilepsy Society
  https://www.aesnet.org/
- National Organization for Rare Disorders (NORD): Lissencephaly
  https://rarediseases.org/rare-diseases/lissencephaly/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28x-linked+lissencephaly%5BTIAB%5D%29+AND+%28abnormal+genitalia%5BTIAB%5D%29+OR+%28XLAG%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- LISSENCEPHALY, X-LINKED, 2
  http://omim.org/entry/300215
Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11891829
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15921244
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18842366
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