Aarskog-Scott syndrome

Subjects: Genetics & Heredity
Contributor: Catherine Yang

Aarskog-Scott syndrome is a genetic disorder that affects the development of many parts of the body. This condition mainly affects males, although females may have mild features of the syndrome.

Keywords: genetic conditions

1. Introduction

People with Aarskog-Scott syndrome often have distinctive facial features, such as widely spaced eyes (hypertelorism), a small nose, a long area between the nose and mouth (philtrum), and a widow's peak hairline. They frequently have mild to moderate short stature during childhood, but their growth usually catches up with that of their peers during puberty. Hand abnormalities are common in this syndrome and include short fingers (brachydactyly), curved pinky fingers (fifth finger clinodactyly), webbing of the skin between some fingers (cutaneous syndactyly), and a single crease across the palm. Other abnormalities in people with Aarskog-Scott syndrome include heart defects and a split in the upper lip (cleft lip) with or without an opening in the roof of the mouth (cleft palate).

Most males with Aarskog-Scott syndrome have a shawl scrotum, in which the scrotum surrounds the penis instead of hanging below. Less often, they have undescended testes (cryptorchidism) or a soft out-pouching around the belly-button (umbilical hernia) or in the lower abdomen (inguinal hernia).

The intellectual development of people with Aarskog-Scott syndrome varies widely. Some may have mild learning and behavior problems, while others have normal intelligence. In rare cases, severe intellectual disability has been reported.

2. Frequency

Aarskog-Scott syndrome is believed to be a rare disorder; however, its prevalence is unknown because mildly affected people may not be diagnosed.

3. Causes

Mutations in the *FGD1* gene are the only known genetic cause of Aarskog-Scott syndrome. The *FGD1* gene provides instructions for making a protein that turns on (activates) another protein called Cdc42, which transmits signals that are important for various aspects of development before and after birth.

Mutations in the *FGD1* gene lead to the production of an abnormally functioning protein. These mutations disrupt Cdc42 signaling, leading to the wide variety of abnormalities that occur in people with Aarskog-Scott syndrome.

Only about 20 percent of people with this disorder have identifiable mutations in the *FGD1* gene. The cause of Aarskog-Scott syndrome in other affected individuals is unknown.

3.1. the gene associated with Aarskog-Scott syndrome

- FGD1

4. Inheritance

When caused by *FGD1* gene mutations, Aarskog-Scott syndrome is inherited in an X-linked recessive pattern. The *FGD1* gene is located on the X chromosome, which is one of the two sex chromosomes. 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 X chromosomes), a mutation would have to occur in both copies of the gene to cause Aarskog-Scott syndrome. Because it

is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. Females who carry one altered copy of the *FGD1* gene may show mild signs of the condition, such as hypertelorism, short stature, or a widow's peak hairline. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Evidence suggests that Aarskog-Scott syndrome is inherited in an autosomal dominant or autosomal recessive pattern in some families, although the genetic cause of these cases is unknown. In autosomal dominant inheritance, one copy of the altered gene in each cell is sufficient to cause the disorder. In autosomal recessive inheritance, both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- Aarskog syndrome
- AAS
- facio-digito-genital dysplasia
- faciodigitogenital syndrome
- faciogenital dysplasia
- FGDY

References

1. Daubon T, Buccione R, Génot E. The Aarskog-Scott syndrome protein Fgd1regulates podosome formation and extracellular matrix remodeling in transforming growth factor β-stimulated aortic endothelial cells. Mol Cell Biol. 2011Nov;31(22):4430-41. doi: 10.1128/MCB.05474-11.
2. Estrada L, Caron E, Gorski JL. Fgd1, the Cdc42 guanine nucleotide exchangefactor responsible for faciogenital dysplasia, is localized to the subcorticalactin cytoskeleton and Golgi membrane. Hum Mol Genet. 2001 Mar 1;10(5):485-95.
3. Gao L, Gorski JL, Chen CS. The Cdc42 guanine nucleotide exchange factor FGD1regulates osteogenesis in human mesenchymal stem cells. Am J Pathol. 2011Mar;178(3):969-74. doi: 10.1016/j.ajpath.2010.11.051.
4. Hou P, Estrada L, Kinley AW, Parsons JT, Vojtek AB, Gorski JL. Fgd1, the Cdc42GEF responsible for Faciogenital Dysplasia, directly interacts with cortactin andmAbp1 to modulate cell shape. Hum Mol Genet. 2003 Aug 15;12(16):1981-93.
5. Orrico A, Galli L, Buoni S, Hayek G, Luchetti A, Lorenzini S, Zappella M,Pomponi MG, Sorrentino V. Attention-deficit/hyperactivity disorder (ADHD) andvariable clinical expression of Aarskog-Scott syndrome due to a novel FGD1 genemutation (R408Q). Am J Med Genet A. 2005 May 15;135(1):99-102.
6. Orrico A, Galli L, Cavaliere ML, Garavelli L, Fryns JP, Crushell E, RinaldiMM, Medeira A, Sorrentino V. Phenotypic and molecular characterisation of theAarskog-Scott syndrome: a survey of the clinical variability in light of FGD1mutation analysis in 46 patients. Eur J Hum Genet. 2004 Jan;12(1):16-23.
7. Orrico A, Galli L, Faivre L, Clayton-Smith J, Azzarello-Burri SM, Hertz JM,Jacquemont S, Taurisano R, Arroyo Carrera I, Tarantino E, Devriendt K, Melis D,Thelle T, Meinhardt U, Sorrentino V. Aarskog-Scott syndrome: clinical update and report of nine novel mutations of the FGD1 gene. Am J Med Genet A. 2010Feb;152A(2):313-8. doi: 10.1002/ajmg.a.33199.
8. Oshima T, Fujino T, Ando K, Hayakawa M. Role of FGD1, a Cdc42 guaninenucleotide exchange factor, in epidermal growth factor-stimulated c-JunNH2-terminal kinase activation and cell migration. Biol Pharm Bull.2011;34(1):54-60.