



My46 Trait Profile

Kallmann syndrome

Other Names: Isolated GnRH Deficiency with anosmia, Idiopathic Hypogonadotropic Hypogonadism

Kallmann syndrome is a rare genetic condition characterized by the failure to go through puberty, reproductive difficulties, and the inability to smell (anosmia). It is caused by mutations in one of many different genes.

Characteristics of Kallmann syndrome

People with Kallmann syndrome have low levels of certain hormones (e.g., gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH)). Having low levels of LH and FSH prevent people from going through puberty or getting pregnant without medication. Males with Kallmann syndrome are often born with a small penis (microphallus) or undescended testes (cryptorchidism), and have low levels of testosterone. They do not show signs of sexual maturation (deepening of their voice, growth of their testes, growth of facial hair, or increased muscle mass) nor do they experience a puberty related growth spurt. Females with Kallmann syndrome generally have low levels of estradiol which causes little to no breast development and the absence of their period (amenorrhea). People with Kallmann also have a diminished to absent sense of smell (hyposmia/anosmia) due to the underdevelopment or absence of their olfactory bulbs in the brain.

Other symptoms that affect some people with Kallmann syndrome include mirror movements (synkinesia), having only one kidney (renal agenesis), cleft lip or cleft palate, missing teeth (dental agenesis), and hearing loss.

Diagnosis/Testing

The diagnosis of Kallmann syndrome is generally based upon clinical findings: anosmia, the absence of sexual maturation, and low sex hormones. Genetic testing for changes or mutations in the *KAL1*, *PROK2*, *PROKR2*, *FGFR1*, *FGF8*, and *CHD7* genes can be useful for providing genetic counseling about risks for other family members or future pregnancies. These genes are thought to be involved in the growth of cells that process smells, as well as directing the movement of cells that make GnRH. Mutations in these genes result in the characteristic features seen in Kallmann syndrome.

Management/Surveillance

The management of Kallmann syndrome depends on the goals of treatment. People with Kallmann syndrome need medication to start puberty or to get pregnant and have a child. Males with Kallmann syndrome not seeking fertility are usually treated with testosterone therapy. Females with Kallmann syndrome not seeking fertility are usually treated with estrogen and progestin therapy. Without hormone treatment, individuals with Kallmann syndrome have a high chance of developing osteoporosis.

When fertility is desired, other hormone medications are used to produce eggs in females or sperm in males. If a couple is not able to get pregnant using traditional medications, adoption or in vitro fertilization (IVF) – a process where the egg and sperm are put together outside of the body in a laboratory and then placed inside the woman to grow, can be considered.

Beginning around 11 years of age, children with features suggestive of Kallmann syndrome or at an increased risk of having inherited Kallmann syndrome based on family history, should be monitored regularly for signs of puberty. As

part of these evaluations, doctors should check a child's sexual maturation (by Tanner staging on physical examination), gonadotropin and sex hormone levels (by blood testing), and bone age (through x-ray) to determine whether a child should be started on hormones to induce puberty. In people with confirmed Kallmann syndrome, bone mineral density should be monitored.

Mode of inheritance

Kallmann syndrome may be inherited in one of three patterns of inheritance: X-linked recessive, autosomal dominant, and autosomal recessive. They are explained below.

X-linked recessive inheritance:

Up to 10% of Kallmann syndrome is caused by changes or mutations in the KAL1 gene, which is located on the X-chromosome. This inheritance pattern means that in females, both copies of the KAL1 gene (i.e., one on each X chromosome) must have a change or mutation, whereas in males, only one copy of the KAL1 gene must have a mutation to be affected. A female with a mutation in one copy of the KAL1 gene is said to be a carrier, and is typically not affected.

Autosomal dominant inheritance:

Some individuals with Kallmann syndrome have mutations in the FGFR1, FGF8 or CHD7 genes. This inheritance pattern means inheriting one mutation is enough for an individual to be affected and show signs of Kallmann syndrome.

Autosomal recessive inheritance:

Some individuals with Kallmann syndrome have mutations in the PROK2 or PROKR2 genes. This inheritance pattern means that an individual has to inherit two mutations (i.e., one from each parent) to be affected. If both parents are carriers of a mutation they have a 1 in 4 (25%) chance with each pregnancy of having a child with the condition.

Risk to family members

The risk to family members depends on the pattern of inheritance.

X-linked recessive inheritance:

If a father is affected with Kallmann syndrome, his daughters will be carriers and his sons will be unaffected. If a mother is a carrier of Kallmann syndrome, each daughter has a 1 in 2 (50%) chance of being a carrier and each son has a 1 in 2 (50%) chance of being affected with KS.

Autosomal dominant inheritance:

The risk to family members depends on whether or not the individual with Kallmann syndrome has a parent affected with the condition. If a parent also has Kallmann syndrome, the risk of having a child with Kallmann syndrome is 50% with each pregnancy. If a parent does not have Kallmann syndrome, the risk of other siblings being affected is very low.

Autosomal recessive inheritance:

Parents of a child with Kallmann syndrome are carriers of Kallmann syndrome. If a sibling of a person with Kallmann syndrome is unaffected, he/she has a 2 in 3 (66%) chance of being a carrier of Kallmann syndrome.

Special considerations

Kallmann syndrome is part of a group of conditions known as Isolated GnRH Deficiency (IGD). People with IGD have the same hormone deficiencies as Kallmann syndrome, but only individuals with Kallmann syndrome have a decreased or absent sense of smell. The genetic cause of IGD and Kallmann syndrome has been identified in about half of patients. Research is underway to identify additional genes that contribute to both conditions.

Resources

Genetics Home Reference: Kallmann syndrome

<http://ghr.nlm.nih.gov/condition/kallmann-syndrome>

Pituitary Network Association: Hypogonadism

<http://www.pituitary.org/knowledge-base/disorders/hypogonadism>

References

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