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The Role of Mutations on Genes TWNK, CLPP, HARS2, LARS2, HSD17B4 in Perrault Syndrome

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Abstract

Perrault syndrome was first reported by Dr. M. Perrault, a physician from Paris, in 1951. Perrault syndrome is a rare genetic disease that causes various signs and symptoms in men and women affected by this syndrome. One of the key features of this syndrome is hearing loss, which occurs in both men and women. In perrault syndrome, hearing problems occur due to changes in the inner ear, known as hearing loss. This disorder usually affects both ears of the patient and the first symptoms can start at birth or in infancy. Perrault syndrome has several genetic causes. However, researchers believe that perrault syndrome is caused by mutations in the TWNK, CLPP, HARS2, LARS2, and HSD17B4 genes.

Keywords: perrault syndrome; genetic mutations; infertility

Introduction

Generalities of Perrault Syndrome

Perrault syndrome is a rare genetic disease that causes various signs and symptoms in men and women affected by this syndrome. One of the key features of this syndrome is hearing loss, which occurs in both men and women. Women with perrault syndrome are also affected by ovarian disorders. In addition, neurological problems occur in some men and women with perrault syndrome [1].

Signs and Symptoms of Perrault Syndrome

In perrault syndrome, hearing problems occur due to changes in the inner ear, known as hearing loss. This disorder usually affects both ears of the patient and the first symptoms can start at birth or in infancy. It is worth noting that if the sense of hearing is completely damaged at birth, then hearing problems will worsen over [1,2]. It is worth noting that women with perrault syndrome have abnormal or damaged ovaries, however the fetuses born from these women are normal and healthy. Girls are severely affected by perrault syndrome, for example the menstrual cycle in most of these girls does not begin before the age of 16 (primary amenorrhea) and most of these girls do not experience the menstrual cycle. As mentioned, women are so affected by perrault syndrome that they experience early ovarian failure, the onset of menstruation during adolescence over the age of 15, and finally the cessation of the menstrual cycle at the age of 40. Women with perrault syndrome may have difficulty having a biological (infertile) child [1,3].

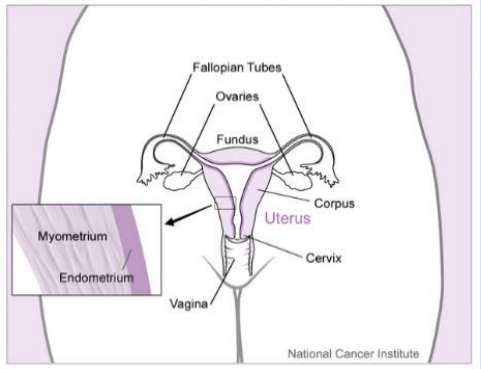

Figure 1: Schematic view of the structure of the female reproductive system.

Neurological problems in people with perrault syndrome can include: mental disorder, imbalance in coordination of hand or foot movements (ataxia) and loss of sense of nerve and weakness of organs (peripheral neuropathy). However, not all people with perrault syndrome have neurological problems [1,4].

Etiology of Perrault Syndrome

Perrault syndrome has several genetic causes. However, researchers believe that perrault syndrome is caused by mutations in the TWNK, CLPP, HARS2, LARS2, and HSD17B4 genes. The TWNK gene is located on the long arm of chromosome 10 at 10q24.31. The CLPP gene is located on the short arm of chromosome 19 as 19p13.3. The HARS2 gene is located on the long arm of chromosome 5 as 5q31.3. The LARS2 gene is located on the short arm of chromosome 3 at 3p21.31. The HSD17B4 gene is located on the long arm of chromosome 5 as 5q23.1 [1,5].

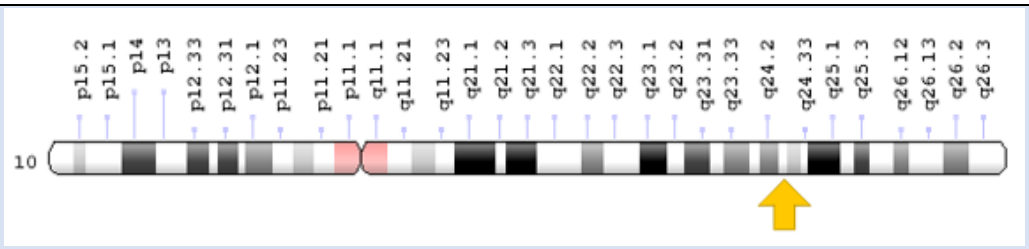

Figure 2: Schematic view of chromosome 10 where the TWNK gene is located in the long arm of this chromosome at 10q24.31.

TWNK, CLPP, HARS2, LARS2 genes contain instructions for the synthesis of proteins that act in the cellular structure like mitochondrial organs and convert energy from food into a usable cell form, ATP (adenosine triphosphate). Although the effect of these mutated genes on mitochondrial function is still unknown, researchers suspect that impaired mitochondrial energy production could affect the signs and symptoms of perrault syndrome [1,6].

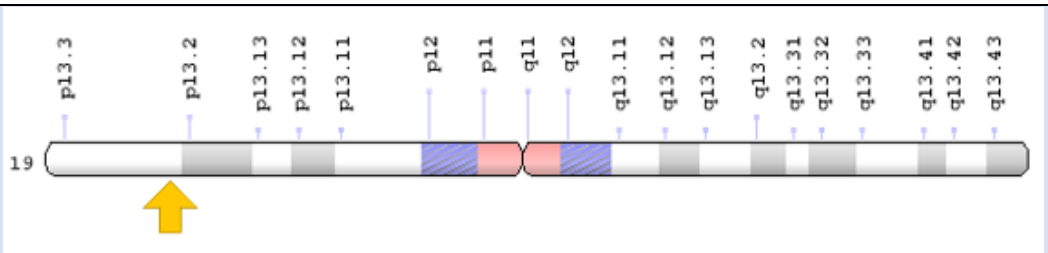

Figure 3: Schematic view of chromosome 19 where the CLPP gene is located in the short arm of this chromosome as 19p13.3.

The HSD17B4 gene contains instructions for the synthesis of proteins that are active in cellular structures called peroxisomes, and contains a variety of enzymes that break down many different substances in cells. It is not yet fully understood how mutations in this gene affect peroxisome function, but researchers believe that mutations in the HSD17B4 gene could affect hearing loss in men and women and ovarian disorders in women with perrault syndrome [1,7]. Therefore, it is possible that other genes may be involved in the development of perrault syndrome that have not yet been identified [1,7].

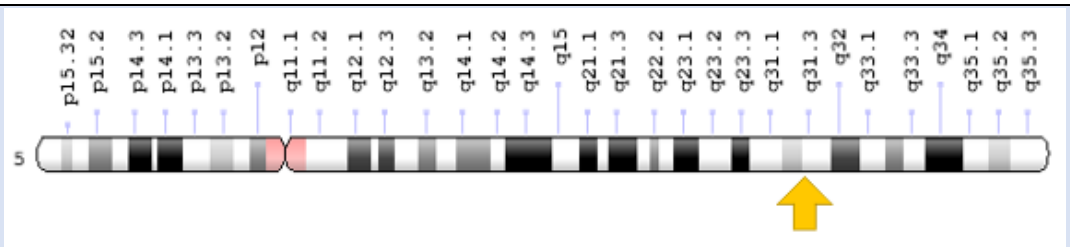

Figure 4: Schematic view of chromosome 5 where the HARS2 gene is located in the long arm of this chromosome as 5q31.3.

Perrault syndrome follows an autosomal recessive inherited pattern. Therefore, two copies of the mutated genes TWNK, CLPP, HARS2, LARS2, HSD17B4 (one from the father and the other from the mother) are required to cause this syndrome, and the chance of having a child with perrault syndrome in this case is 25%. It is possible for any pregnancy.[1,8]

Frequency of Perrault Syndrome

Perrault syndrome is a rare genetic disorder that has been reported in less than 100 cases in the medical literature. In most cases, perrault syndrome is not properly diagnosed in men with hearing loss. Therefore, it is difficult to determine the exact frequency of perrault syndrome in the general population [1,9].

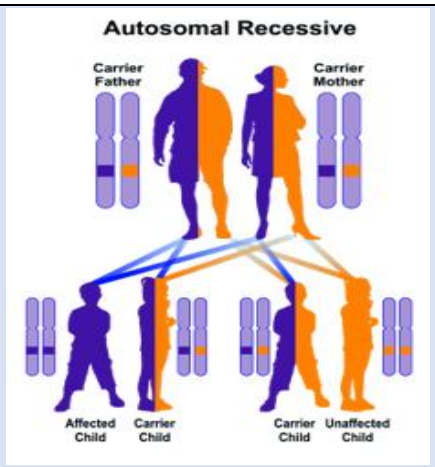

Figure 5: Schematic view of the autosomal recessive inherited pattern, which is followed by perrault syndrome.

Diagnosis of Perrault Syndrome

Perrault syndrome is diagnosed based on the clinical signs and symptoms of each affected person, both men and women. Evaluation of hearing, observation of ataxia, evaluation of mental disorder and evaluation of menstrual cycle in girls and premature ovarian failure in women are the diagnostic factors of Perrault syndrome. However, the most definitive way to diagnose perrault syndrome is to test molecular genetics for these genes to check for possible mutations. Prenatal diagnosis is also possible using amniocentesis fluid or chorionic villi of the fetal placenta.

Treatments for Perrault Syndrome

The treatment and management strategy for perrault syndrome is based on the signs and symptoms that each person has. Treatment may be performed with the efforts and coordination of a team of specialists including: gynecologist, endocrinologist, ear specialist, audiometrist, neurologist and orthopedist. Genetic counseling is also necessary for families who want a healthy child [1,10].

Discussion and Conclusion

In perrault syndrome, hearing problems occur due to changes in the inner ear, known as hearing loss. This disorder usually affects both ears of the patient and the first symptoms can start at birth or in infancy. Neurological problems in people with perrault syndrome can include: mental disorder, imbalance in coordination of hand or foot movements (ataxia) and loss of sense of nerve and weakness of organs (peripheral neuropathy). The treatment and management strategy for perrault syndrome is based on the signs and symptoms that each person has [1,10].

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