The Role of Genetics Mutations in Gene AR in Kennedy Syndrome

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Abstract

Kennedy syndrome affects the lower motor neurons that are responsible for the movement of many muscles in the legs, arms, mouth, and throat. Affected individuals will show signs of twitching, often in the tongue and/or hand, followed by muscle weakness and problems with facial muscles. These neurons, which connect the spinal cord to the muscles, become defective and die, so the muscles cannot contract. The destruction of these nerves is the main reason for the numbness, muscle weakness, and inability to control muscle contraction. With lack of normal neuromuscular function, a patient may experience hypertrophied calves in which the calf muscles thicken due to muscle cramps. In some cases, patients may also have one side of the body more affected than the other side. Kennedy syndrome is caused by a change (mutation) in the AR gene that encodes for a protein known as the androgen receptor on the X chromosome. The instructions within every gene consist of different arrangements of four basic chemicals (nucleotide bases) called adenine (A), cytosine (C), guanine (G), and thymine (T). Individuals with the disease have an abnormal section in the AR gene, which is due to an excessive number of CAG trinucleotide repetitions in the DNA sequence. An unaffected individual has 10-35 CAG repeats in the AR gene while a person with Kennedy disease has more than 36 CAG repeats in the gene.

Keywords: Kennedy syndrome; AR gene; CAG trinucleotide; DNA sequence; lower motor neurons

Overview of Kennedy Syndrome

Kennedy syndrome, also known as spinal cord and spinal muscular atrophy, is a genetic disorder in specialized nerve cells that controls muscle movement (motoneurons). These nerve cells are the spinal cord and part of the brain that connects to the spinal cord [1].

Clinical signs and symptoms of Kennedy Syndrome

Kennedy syndrome mainly affects men and is characterized by muscle weakness (atrophy) that usually begins in adulthood and gradually worsens over time. Loss of muscles in the arms and legs can cause low back pain, and muscle weakness in the legs can lead to hard walking and a tendency to fall. Some muscles in the face and throat (musculoskeletal muscles) are also affected by this syndrome, which causes progressive problems in swallowing (dysphagia) and speech as well as vision problems. In addition, fasciculations are also common in Kennedy syndrome (Figure 1). Some men with Kennedy’s syndrome experience unusual abnormalities in gynecomastia and may not be able to have children (infertility) [1].

Figure 1: Optological images of pupillary tissue disorder in Kennedy syndrome.
The Etiology of Kennedy Syndrome

Kennedy syndrome is caused by an AR gene mutation located on the long arm of the sex chromosome Xq12. This gene provides instructions for the synthesis of a protein called the androgen receptor. This receptor binds to a group of hormones known as androgens that are involved in male sexual development (Figure 2). Androgens and androgen receptors also play other important functions in both men and women, such as regulating hair growth and sexual development and sexual maturity [2].

The AR gene mutation that causes Kennedy’s syndrome is the abnormal expansion of a portion of DNA known as the CAG triple repeat. Typically this segment of DNA is repeated up to 36 times. In people with Kennedy Syndrome, the CAG fragment is repeated at least 38 times and may be two to three times the length of the normal fragment. Although the expanded CAG region alters the structure of the androgen receptor, it is still unclear how the altered protein disrupts the neurons of the brain and spinal cord. The researchers believe that a fragment of the androgen receptor protein containing the CAG fragment accumulates within these cells and interferes with normal cell function. The nerve cells die gradually, leading to muscle weakness and wasting (Figure 3). People with more CAG repeats develop the symptoms and symptoms of Kennedy’s syndrome earlier in life [2].

Figure 2: Schematic of brain-forming lobes.

Figure 3: Schematic overview of the sex chromosome X where the AR gene is located in the long arm of the chromosome Xq12.
Kennedy syndrome follows the X-linked inheritance pattern. In males (which have only one X chromosome), mutations in only one copy of the gene in each cell cause the disorder. In most cases, men experience more severe symptoms of the disorder than women (who have two X chromosomes). Women with mutations in one copy of the AR gene in each cell are not typically affected by the Kennedy syndrome. Several women with mutations in both versions of the gene have experienced mild features of the disease, including muscle vertigo and occasional tremors. Researchers believe that mild symptoms in women may be linked to low androgen levels. The inherited characteristic of X is that fathers cannot transfer X-related traits to their son’s offspring [3].

**Frequency of Kennedy Syndrome**

Kennedy syndrome is a rare genetic disorder with an estimated incidence of 1 in 350,000 men. This syndrome is very rare among families (especially women). Kennedy syndrome has been diagnosed in the USA, Europe, Asia, South America, and Australia. The Japanese population appears to have a very high prevalence of Kennedy Disease because of a founder effect [3].

**Diagnosis of Kennedy Syndrome**

Kennedy syndrome is diagnosed based on clinical and clinical findings of patients and some pathological and neurological tests. The most accurate method for detecting this syndrome is molecular genetic testing for the AR gene to detect possible mutations. A diagnosis of Kennedy disease is suspected based on physical signs and symptoms, and sometimes family history. Diagnosis can be confirmed by molecular genetic testing on a blood sample for CAG trinucleotide repeat expansion in the AR gene (Figure 4). Individuals with greater than 36 CAG trinucleotide repeats in the AR gene are diagnosed with the condition [4].

**Standard Therapies for Kennedy Syndrome**

The treatment and management strategy for Kennedy syndrome is symptomatic and supportive. Treatment may be provided with the efforts and coordination of a team of specialists, including a neurologist, a brain surgeon, and other healthcare professionals. Breast reduction surgery is used when needed in patients with gynecomastia. Testosterone is not a good treatment because it can make the disease worse. There is no effective treatment for this syndrome and all clinical measures are to alleviate the suffering of the patients. Genetic counseling is also needed for all parents who want a healthy child [5, 6, 7, 8].

**Related disorders**

Symptoms of the following diseases can be similar to those of Kennedy’s disease. Comparison may be useful for differential diagnosis:

- **Adrenoleukodystrophy (ALD)** is one of many different leuko odystrophies. The primary form of adults or adults with
this disorder is called adrenomilonuropathy (AMN) and the symptoms of this type of ALD may be similar to the symptoms of a sluggish illness. Symptoms usually appear between the ages of 21 and 35 years. These may include progressive stiffness of the legs, partial paralysis of the lower extremity spasms, and ataxia. There may be a decrease in gonalad function. Adult onset ALD progresses slowly, but can eventually lead to deteriorating brain function [1-9].

**Amyotrophic lateral sclerosis (ALS)** is one of a group of disorders known as motor neurological diseases. The disease is characterized by progressive destruction and eventual death of nerve cells (motor neurons) in the brain, brainstem and spinal cord, which facilitate the connection between the nervous system and the voluntary muscles of the body. Typically, motor neurons in the brain (upper motor neurons) send motor neurons to the spinal cord (lower motor neurons) and then to different muscles. ALS affects the upper and lower motor neurons, so that the transmission of the message is interrupted and the muscles gradually weaken and disappear. As a result, the ability to initiate and control voluntary movement disappears. Ultimately, ALS results in respiratory failure as people lose the ability to control the chest and diaphragm muscles. ALS is often called Lou Gehrig’s disease [1-9].

**Kugelberg-Welander** syndrome is a type of spinal muscular atrophy and is inherited as an autosomal recessive genetic feature. Major symptoms may include wasting and weakening of the arm muscles and legs, torsion, clumsy walking and eventually reflexes. The Kugelberg-Welander syndrome at birth is not obvious, but it usually occurs within the first ten to twenty years of life [1-9].

**Myasthenia gravis** is a neuromuscular disorder characterized primarily by muscle weakness and muscle fatigue. Although this disorder usually manifests itself in adulthood, symptoms can occur at any age. The disease may be confined to certain muscle groups, especially the eye (myasthenia gravis), or it may become more general (myasthenia gravis), which includes several muscle groups. Most people with myasthenia gravis develop eyelid weakness (ptosis). Ocular muscle weakness resulting in bilateral vision (diplopia); and excessive muscle fatigue following activity. Extra features usually include facial muscle weakness. Speech disorder (speech disorder). Difficulty chewing and swallowing (dysphagia); and weakness of the arms and legs (proximal limb weakness). In addition, in about 10% of cases, people with severe muscular dysfunction (respiratory distress) can have potentially life-threatening complications. Myasthenia gravis results from an abnormal immune response in which the body’s immune system (i.e., antibodies) attacks the body inappropriately and gradually receives specific receptors in the muscles that stimulate the nerve [1-9].

**Discussion**

Kennedy disease is a rare, X-linked slowly progressive neuromuscular disorder. Kennedy disease is typically an adult-onset disease, where symptoms occur mainly between the ages of 20 and 50. The disease is characterized by symptoms such as muscle weakness and cramps in the arms, legs, and facial area, enlarged breasts, and difficulty with speaking and swallowing (dysphagia). Kennedy disease affects fewer than 1 in 350,000 males and does not typically occur in females, who are protected by their low levels of circulating testosterone, accounting for the sex-limited inheritance pattern in this disorder. Treatment is symptomatic and supportive, and life expectancy is normal, though a small percentage of patients (~ 10%) succumb to the disease in their 60’s or 70’s due to swallowing complications (aspiration pneumonia, asphyxiation) resulting from the bulbar weakness. Kennedy disease is named after William R. Kennedy, MD, who described this condition in an abstract in 1966 and a full report in 1968. The disease also affects nerves that control the bulbar muscles, which are important for breathing, speaking, and swallowing. Androgen insensitivity can also occur, sometimes beginning in adolescence and continuing through adulthood, characterized by enlarged breasts, decreased masculine appearance, and infertility. Patients may experience problems such as low sperm count and erectile dysfunction.

Symptoms of the following disorders can be similar to those of Kennedy disease [6]. Comparisons may be useful for a differential diagnosis:

Adrenoleukodystrophy (ALD) is one of many different leukodystrophies. The adolescent or adult onset form of the disorder is called adrenomyeloneuropathy (AMN), and symptoms of this form of ALD may be similar to those of Kennedy disease. Symptoms typically appear between the ages of 21 and 35. They may include progressive leg stiffness, spastic partial paralysis of the lower extremities and ataxia (clumsiness in walking). Decreased function of the sex glands may be present. Adult onset ALD progresses slowly, however, it can ultimately result in deterioration of brain function. (For more information on this disorder, choose “adrenoleukodystrophy” as your search term in the Rare Disease Database [8].)

**Conclusion**

Amyotrophic lateral sclerosis (ALS) is one of a group of disorders known as motor neuron diseases. It is characterized by the progressive degeneration and eventual death of nerve cells (motor neurons) in the brain, brainstem and spinal cord that facilitate communication between the nervous system and voluntary muscles of the body. Ordinarily, motor neurons in the brain (upper motor neurons) send messages to motor neurons in the spinal cord (lower motor neurons) and then to various muscles. ALS affects both the upper and lower motor neurons, so that the transmission of messages is interrupted, and muscles gradually weaken and waste away. As a result, the ability to initiate and control voluntary movement is lost. Ultimately, ALS leads to respiratory failure because affected individuals lose the ability to control muscles in the chest and diaphragm. ALS is often called Lou Gehrig’s disease. (For more information on this disorder, choose “amyotrophic lateral sclerosis” as your search term in the Rare Disease Database.) As it turns out, as many as 10% of Kennedy disease patients may be misdiagnosed with ALS prior to determining that they really have Kennedy disease. Currently, there is no known treatment or cure for Kennedy disease.

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Physical therapy, occupational therapy, and speech therapy are commonly used to adapt to the progressing disease and maintain an individual's skills. Braces, walkers, and wheelchairs are used for ambulation. Breast reduction surgery is sometimes used as needed in patients with gynecomastia (Figure 5). Testosterone is not an appropriate treatment, as it can make the disease worse [9].

Figure 5: Schematic overview of recessive and predominant X-linked inheritance patterns that Kennedy’s syndrome can follow.
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References


