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The Role of Genetics Mutations in Genes APP, CST3, ITM2B in Inducate Hereditary Cerebral Amyloid Angiopathy Syndrome

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Abstract

HCAA syndrome is a genetic disorder that can lead to gradual loss of intellectual function (mental decline), stroke, and other neurological problems in the middle of adulthood. The mutation in the APP gene, located in the long arm of chromosome 21 as 21q21.3, is the most common genetic cause of HCAA syndrome.

Keywords: *HCAA syndrome, APP, CST3, ITM2B genes, Brain Disorder.*

Generalization of Hereditary Cerebral Amyloid Angiopathy Syndrome

HCAA syndrome is a genetic disorder that can lead to gradual loss of intellectual function (mental decline), stroke, and other neurological problems in the middle of adulthood. Regarding the reduction of proper nerve function, this condition is usually fatal at the age of sixty, although there are variations depending on the severity of the signs and symptoms. Most people who have been affected by this syndrome die within a decade after signs and symptoms appear, however, some people with this disease are more likely to live longer[1].

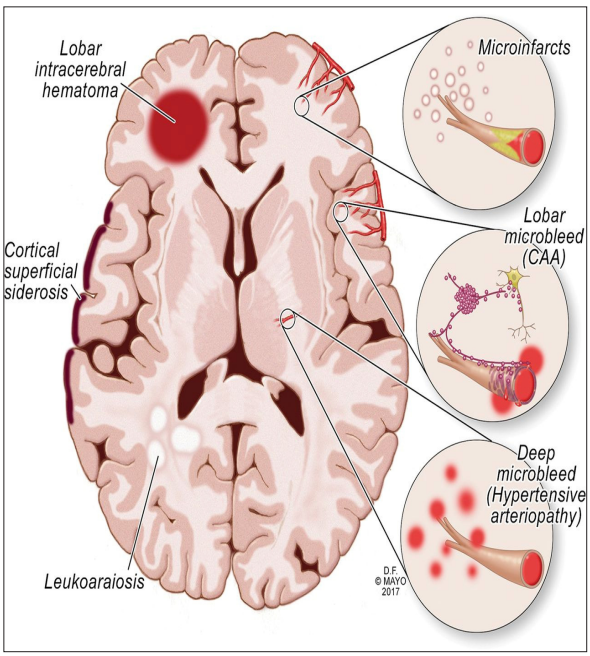
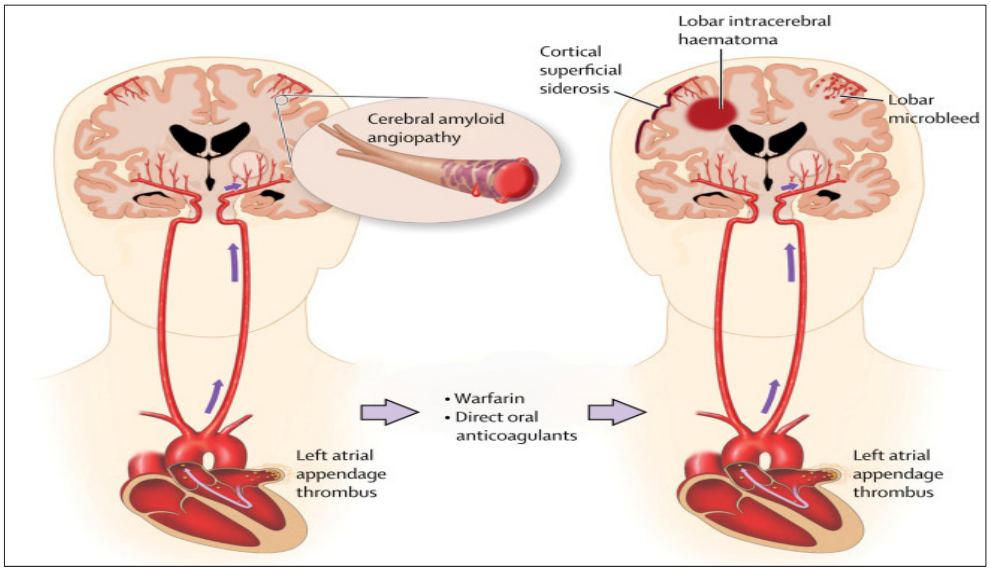


Fig 1. *Schematic of cerebrovascular hemorrhagic.*

Signs and Clinical Symptoms of Hereditary Cerbral Amyloid Angiopathy Syndrome

There are several types of HCAA syndrome, each of which has different genetic causes and symptoms. Dutch type of hereditary cerebral amyloid angiopathy is the most common form of HCAA syndrome. Stroke is often the first indication of Dutch type HCAA syndrome, which is lethal for 30% of people who have these conditions. Other survivors of Dutch-type HCAA syndrome often suffer from mental decline and experience repeated strokes. It should be noted that about half of Dutch-type HCAA patients who experience one or more strokes will also experience frequent seizures (epilepsy)[2].



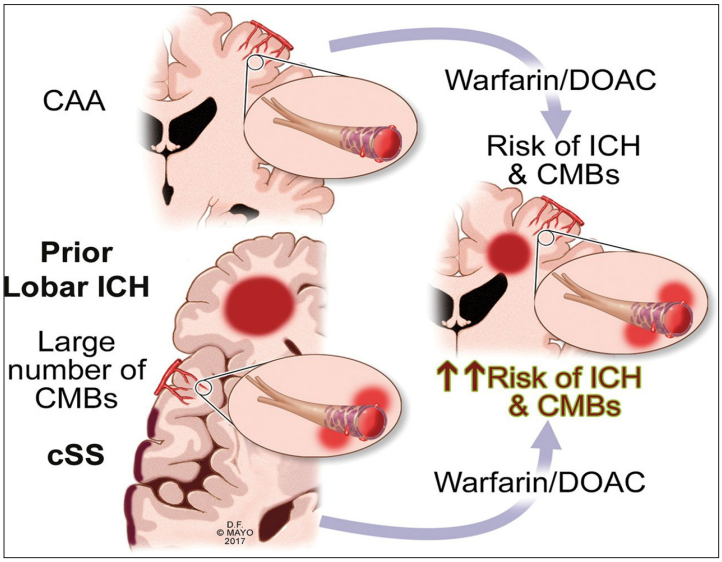


Fig 2. *Schematic of hereditary cerebral amyloid angiopathy (left) against cerebrovascular abnormalities (right side).*

Patients with HCAA syndrome type Finnish and Italian are prone to stroke and mental decline. Patients with a type of pemetone HCAA syndrome may experience one or more stroke and, as a rule, may experience motor disturbances, lethargy, tingling, dullness, or mental decline.[3]

The first symptom of the Icelandic-type HCAA syndrome is usually stroke and mental decline. An Icelandic-type HCAA syndrome stroke usually occurs more than other types of the syndrome, and people with this type of HCAA typically experience their first stroke at the age of 20 or 30 years[4].

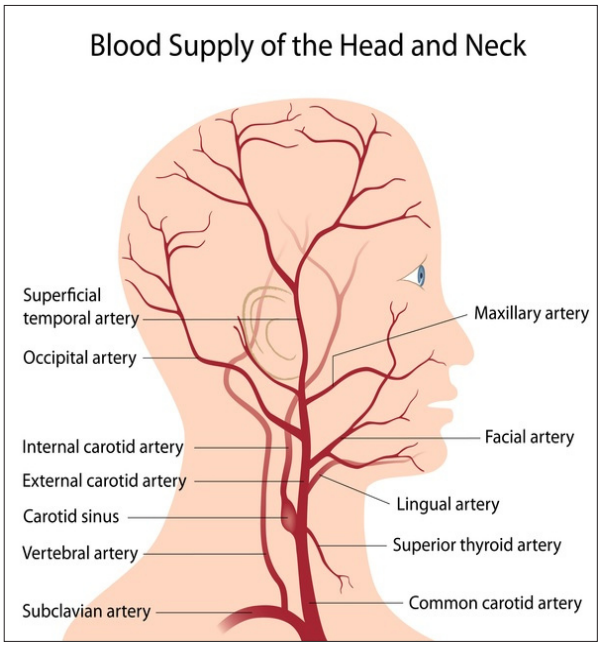


Fig 3. *A schematic of the passage of blood vessels in the head and neck.*

In people with HCAA-type syndrome (northern parts of the world), stroke occurs, where the first symptom is usually a memory loss, followed by severe mental decline. In people with HCAA-type Iowa, stroke is not common and only with loss of memory, its complications include difficulties in choosing the right words for speaking, personality changes and involuntary muscle movements (Myoclonus)[5].

HCAA syndrome of the type England and Denmark are associated with rational deterioration and movement problems. Stroke is unusual in this kind of HCAA syndrome. It is worth noting that people who have a Danish-type HCAA syndrome may also experience eye and deaf cataracts[6].

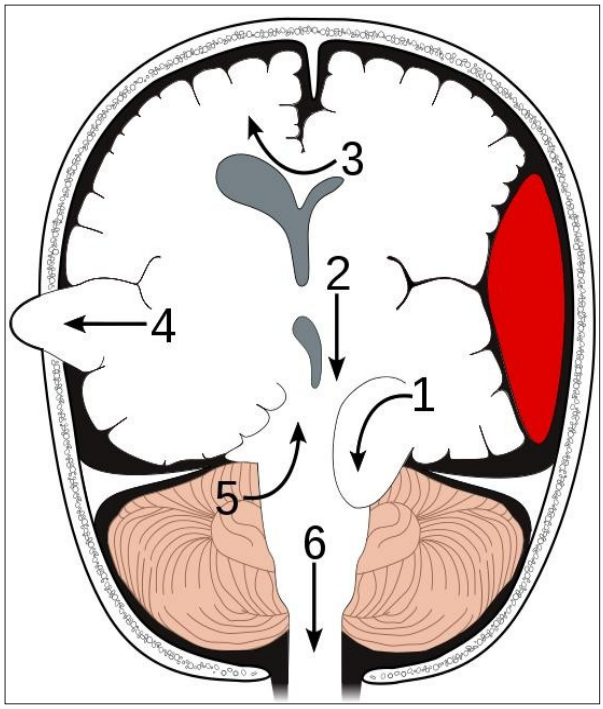


Fig 4. *A schematic of human blood in a human brain (red spots).*

Etiology of an Hereditary Cerebral Amyloid Angiopathy Syndrome

The mutation in the APP gene, located in the long arm of chromosome 21 as 21q21.3, is the most common genetic cause of HCAA syndrome. APP gene mutations cause HCAA syndrome in the peoples of the Netherlands, Iowa, Finland, Italy, Arctic and Piedmont. The mutation in the CST3 gene, based on the short arm of chromosome number 20, is 20p11.21, causing an Icelandic type of HCAA syndrome. The British and Danish intellectual decline is due to the mutation of the ITM2B gene, which is based on the long arm of chromosome 13 as 13q14.2[7].

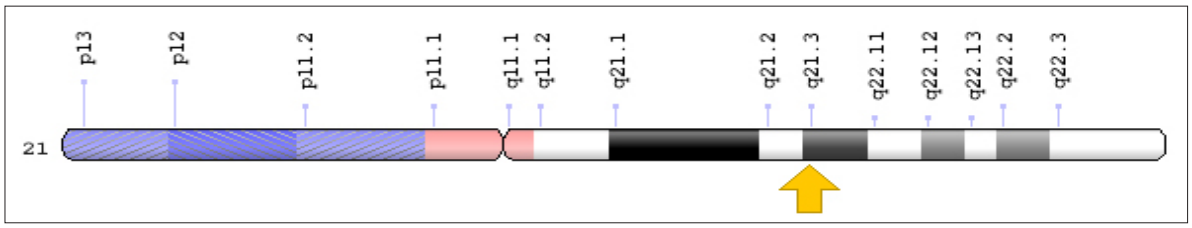


Fig 5. *Schematic view of chromosome 21, whose APP gene is located in the long arm of this chromosome 21q21.3.*

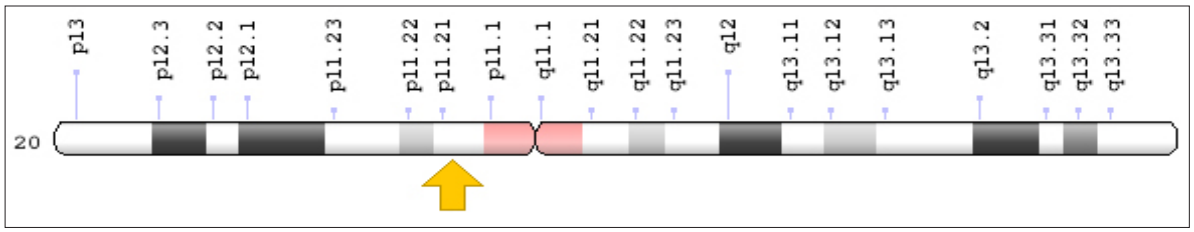


Fig 6. *Schematic view of chromosome number 20 where the CST3 gene is based on the short arm of this chromosome as 20p11.21.*

The APP gene provides instructions for protein synthesis called the amyloid precursor protein. This protein is found in many tissues and organs, including the brain and the spinal cord (central nervous system). The exact function of this protein is still unclear, but researchers suspect it may bind to other proteins on the cell surface. In the brain, the amyloid precursor protein plays an important role in the development and maintenance of neurons (neurons)[8].

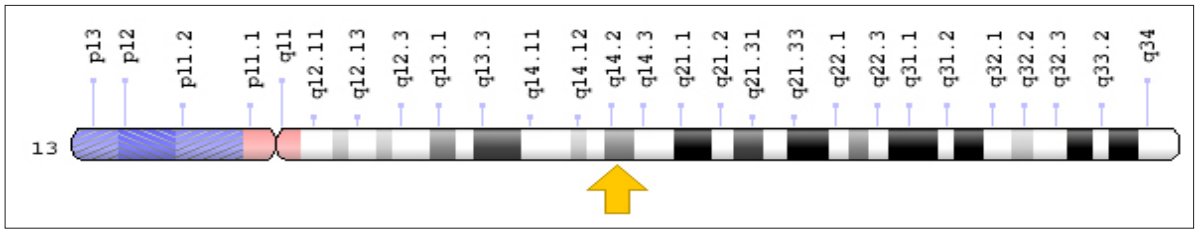


Fig 7. *Schematic view of Chromosome 13, in which the ITM2B gene is located in the long arm of this chromosome as 13q14.2.*

The CST3 gene provides instructions for protein synthesis called cystatin C. This protein stops the enzyme activity called catepsin and cuts out other proteins to decompose regularly. Cystine C protein is also found in biological fluids, such as blood, and also in the cerebrospinal fluid that protects the brain and the spinal cord[9].

The ITM2B gene provides guidelines for protein production found in all tissues. Still, the function of the ITM2B protein is unclear. It is believed that ITM2B protein plays an important role in suppressing cellular physiological death (apoptosis) and maintaining cells from overheating and uncontrolled growth and distribution. Additionally, the ITM2B protein may be involved in the processing of amyloid precursor protein[9].

The mutations in the APP, CST3, and ITM2B genes result in the production of proteins that are more stable than normal and tend to cluster together. These cumulative proteins form a massive form of protein

known as amyloid deposits and accumulate in certain regions of the brain and its blood vessels. Amyloid deposits, also known as plaque, cause damage to the brain cells and ultimately lead to cell death and various brain damage. Therefore, the destruction of brain cells in people with HCAA syndrome can lead to seizures, motor disorders and other neurological problems. In blood vessels, the amyloid plaque replaces the muscle and elastic fibers that create the flexibility of the blood vessels, and this replacement results in weakening of the muscle and elastic fibers and decomposing them. The breakdown of a blood vessel in the brain causes brain hemorrhage, which can lead to brain damage and intellectual deterioration[9].

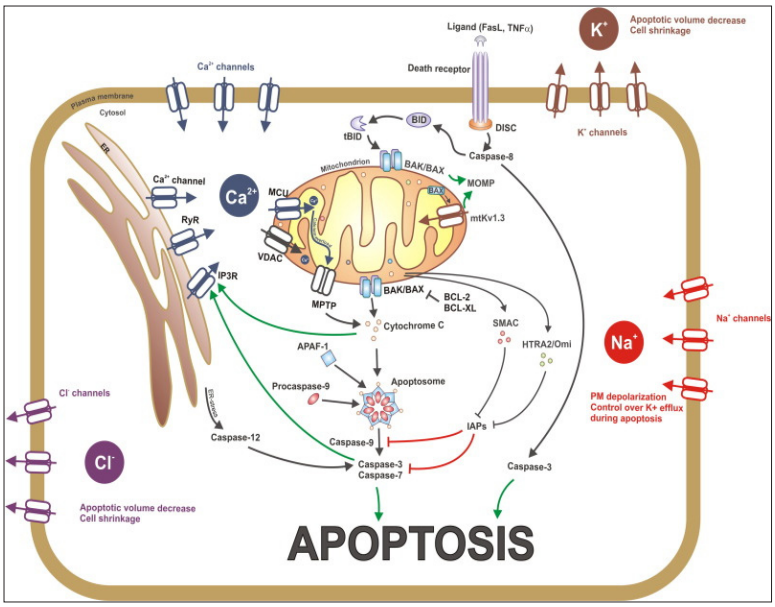


Fig 8. *Schematic representation of Apoptosis in the cell.*

HCAA syndrome follows the dominant autosomal inheritance pattern. Therefore, to produce this syndrome, an APP, CST3, and ITM2B (parent or parent) gene mutation version is required and the chance of having a child with HCAA syndrome in the dominant autosomal state is 50% for each pregnancy[9].

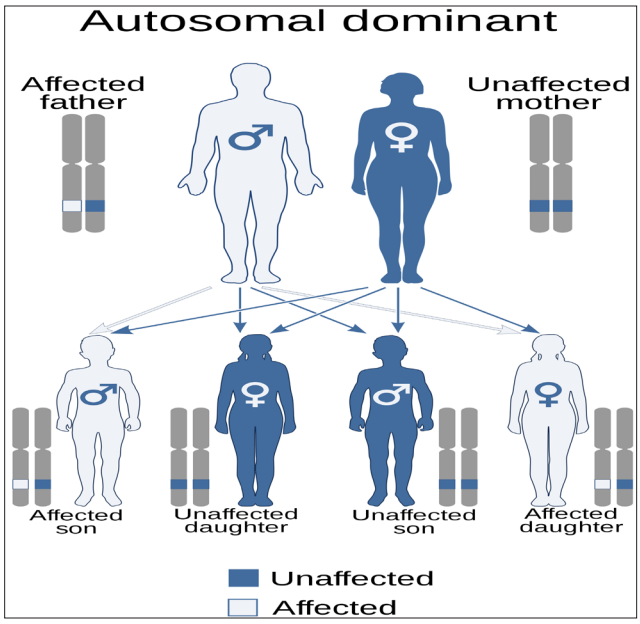


Fig 9. *Schematic view of the dominant autosomal inheritance pattern that inherits the hereditary cerebral amyloid angiopathy syndrome follows this pattern.*

Frequency of Hereditary Cerebral Amyloid Angiopathy Syndrome

HCAA syndrome is a rare genetic disorder whose frequency is not known in the world. The Dutch type is the most common syndrome. So far, over 200 cases of HCAA syndrome have been reported from around the world in medical literature[9].

Detection of Hereditary Cerebral Amyloid Angiopathy Syndrome

HCAA syndrome is diagnosed based on the clinical and physical findings of the patients and some pathological and neurological tests, such as the brain electroencephalogram. The most accurate method for detecting this syndrome is the molecular genetic testing for APP, CST3, and ITM2B genes to investigate the presence of possible mutations[9].

Therapeutic Traits of Hereditary Cerebral Amyloid Angiopathy Syndrome

The strategy for treatment and management of HCAA syndrome is symptomatic and supportive. Treatment may be done by a team of experts, including adult neurologists, brain surgeons, psychiatrists, physiotherapists, and other healthcare professionals. The use of antiepileptic drugs such as phenytoin or sodium valproate and phenobarbital can also be effective in reducing the frequency of seizure of HCAA syndrome. There is no decisive treatment for HCAA syndrome and all clinical interventions are designed to reduce the suffering of the sufferers. Genetic counseling is also needed for all parents who want a healthy baby[9].

Discussion and Conclusion

HCAA syndrome is a genetic disorder that can lead to gradual loss of intellectual function (mental decline), stroke, and other neurological problems in the middle of adulthood. The mutation in the APP gene, located in the long arm of chromosome 21 as 21q21.3, is the most common genetic cause of HCAA syndrome. The mutation in the CST3 gene, based on the short arm of chromosome number 20, is 20p11.21, causing an Icelandic type of HCAA syndrome. The British and Danish intellectual decline is due to the mutation of the ITM2B gene, which is based on the long arm of chromosome 13 as 13q14.2. There is no decisive treatment for HCAA syndrome and all clinical interventions are designed to reduce the suffering of the sufferers.

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