



Understanding ATP1A3 & AHC



The AHC Foundation is proud to provide families & friends of patients with AHC an easy way to understand recent research on ATP1A3 mutations and their relationship to AHC. This document has been created with the assistance of researchers and members of our Medical Advisory Board.

How Does ATP1A3 Relate to AHC?

- The ATP1A3 gene is located on chromosome 19 and mutations in this gene were identified as the primary cause of AHC in 2012.
- ATP1A3 is **highly intolerant to genetic variation**, meaning that it is so important and sensitive that mutations are likely to be disease-associated.
- Mutations in ATP1A3 are found in approximately 85 % of AHC cases.
- For any particular trait, you inherit one copy from your mother and another from your father. When inherited, AHC is transmitted as an autosomal dominant trait (meaning you only need one bad copy to get the disease). However, in AHC, mutations are more commonly de novo (new), meaning neither parent has the mutation. Every child born has many new DNA changes; having one in this gene is just a matter of chance.
- An AHC patient with an ATP1A3 mutation has a 50% chance of passing on the ATP1A3 mutation.

What is ATP1A3?

The ATP1A3 gene provides instructions for making **one part (the alpha-3 subunit)** of a protein known as Na⁺/K⁺ ATPase or the sodium pump. This protein uses energy from a molecule called ATP to **transport charged atoms (ions) into and out of cells**. Specifically, it pumps sodium ions (Na⁺) out of cells and potassium ions (K⁺) into cells.

- ATP (adenosine triphosphate) is a high-energy molecule found in every cell.
- Its job is to store & supply the cell with needed energy.
- The alpha-3 subunit has been found mainly in neurons and cardiac muscle.

How Does ATP1A3 Normally Function?

ATP1A3 is expressed in almost all central nervous system neurons, including in the cerebellum and basal ganglia, key structures in the **regulation of motor activity and behavior**.

The movement of sodium and potassium ions helps **regulate the electrical activity** of these cells and plays an important **role in how the brain controls movement**.

Additionally, Na⁺/K⁺ ATPase helps regulate a process called neurotransmitter reuptake. Neurotransmitters are chemicals that **transmit signals from one neuron to another**. After a neurotransmitter has had its effect, it must be removed quickly from the space between the neurons. The reuptake of neurotransmitters is carefully controlled to ensure that **signals are sent and received accurately throughout the nervous system**.

What are the Main ATP1A3 Mutations in AHC?

- D801N (43%) appears to confer a milder phenotypic expression.
- E815K (16%) is associated with a more severe phenotype (more severe intellectual and motor disability).
- G947R (11%) appears to correlate with the most favorable prognosis.



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Why are AHC patients so Different? Is there a Spectrum in AHC?

- There is a wide range of neurobehavioral deficits exhibited by AHC patients.
- Multiple parts of the sensory system appear to be unusually or excessively excitable. An investigation of AHC patients showed that the brain's immediate response to a standardized sensory stimulus did not differ, but that the recovery phase was prolonged in AHC.
- As of 2016, 59 different ATP1A3 mutations were associated with AHC, but the list continues to expand.
- Patients have also been identified with intermediate, non-classical, symptoms.
- Modeling of different mutations suggests different mutational consequences.
- Specific mutations cause more severe phenotypes of ATP1A3-related disorders, creating a spectrum that include catastrophic early life epilepsy, episodic apnea, and postnatal microcephaly.

What has been learned from animal models about ATPase Mutations?

- ATPase is fundamental for **optimizing central synaptic functioning**.
- ATP1A3 plays a critical role in **neural function during development and at birth** in mice.
- Reduction of Na, K-ATPase activity by an inhibitory drug has long been known to increase **sensitivity to seizures** in animals.
- ATPase mutations are associated **with impairments in spatial memory, spatial habituation, locomotor habituation, object recognition, social recognition, and trace fear conditioning**.
- Motor dysfunction, ataxia, dystonia, unsteady gait, and tip-toeing are reflected in **motor function, balance problems, and gait disturbances** in mice. These defects are caused by discoordination rather than lack of muscle strength.
- ATP1A3 dysfunction has a **damaging effect on social behavior** in mice.
- **Stress causes a deterioration of motor performance** and a significant drop in ATPase activity in mice.
- ATP1A3 mutations may increase vulnerability to **stress symptoms of anxiety and attention deficits**.
- **Poor memory performance** can be displayed and may be dependent on stress.
- **Symptoms resembling mania** in mice were found in anxiety tests which revealed increased impulsivity and risk-taking and a diminishing of a physiological or emotional response to a frequently repeated stimulus.
- ATPase activity loss resembles AHC patients in that the **mice tend to be smaller & weigh less, possibly due to problems eating**.
- **Changes in circadian rhythm** have been shown in mice.
- In fruit flies, mutations affecting the ATP alpha gene family have dramatic phenotypes including altered longevity, neural dysfunction, neurodegeneration, myodegeneration, and striking locomotor impairment (**including temperature-sensitive paralysis**).

The research that has funded these discoveries is expensive and time consuming to conduct. We wish to thank all of the researchers and organizations that have participated in these efforts along with us. We look forward to raising additional funds for the all-important work of achieving our One Mission: End AHC!