Understanding the Pathophysiology of ATP1A3-Related Disorders

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October 9, 2024

Abstract

The *ATP1A3* gene encodes the alpha-3 subunit ($\alpha 3$ isoform) of Na^+/K^+ ATPase, a sodium-potassium pump primarily expressed in neurons and involved in maintaining neuronal membrane potential. Several genetic mutations in this gene have been identified and linked to a wide spectrum of phenotypes. These mutations and their phenotypes have been categorized into four *ATP1A3*-related disorders:

1. Alternating Hemiplegia of Childhood (AHC)
2. Rapid-Onset Dystonia Parkinsonism (RDP)
3. Cerebellar Ataxia, Areflexia, Pes Cavus, Optic Atrophy, and Sensorineural Hearing Loss (CAPOS)
4. Relapsing Encephalopathy with Cerebellar Ataxia (RECA)

This paper aims to provide a comprehensive overview of the pathophysiology of these four disorders.

1 Introduction

ATP1A3-related disorders are a rare group of neurological conditions resulting from mutations in the *ATP1A3* gene. Not much is known about *ATP1A3*-related disorders. First described in 1971 by Verret and Steele, Alternating Hemiplegia of Childhood (AHC) is the most common of these rare disorders, with an estimated prevalence of $\sim$1/1,000,000 [HCW78]. Since then, three related disorders have been identified. Rapid-Onset Dystonia Parkinsonism (RDP) was first described in 1993 by Dobyns et al., CAPOS in 1996 by Nicolaides et al., and RECA in 2015 by Dard et al.

In 2014, researchers linked the phenotypes of these four disorders to the *ATP1A3* gene [H^+14]. This finding allowed researchers to further investigate genotype-phenotype correlations and how the diverse range of clinical characteristics correspond to specific genetic mutations.

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This paper provides a detailed overview of the clinical presentations, pathophysiology, and underlying genetic mutations of AHC, RDP, CAPOS, and RECA.

2 Clinical Presentations of ATP1A3-Related Disorders

2.1 Alternating Hemiplegia of Childhood

Alternating hemiplegia of childhood (AHC) is a rare neurological disorder characterized by episodes of transient paroxysmal alternating hemiplegia, typically manifesting in children under 18 months of age [PPR+22]. These episodes of temporary paralysis can affect one side of the body (hemiplegia), both sides of the body (quadriplegia), or alternate between either side [Med23]. Episodes can last from minutes to several days, though symptoms often disappear with sleep and reappear within 30 minutes of waking [KMV13].

AHC episodes may occur independently or with other symptoms, including dystonia (involuntary muscle contractions), choreoathetosis (continuous uncontrolled movement), and ataxia (lack of muscle control and coordination) [Med23]. There may also be dysfunction of the autonomic nervous system, which regulates unconscious processes such as blood pressure and breathing. Autonomic dysfunction symptoms include changes in body temperature, irregular sweating, and abnormalities of the gastrointestinal tract [SMGV23].

Over 50% of individuals with AHC develop epilepsy. Irregular ocular movements are also frequent symptoms [KMV13]. Nystagmus (abnormal involuntary eye movements) is often attributed to seizure activity, though it is now considered one of the first defining symptoms of AHC. Additional ocular movement abnormalities include exotropia (when one eye turns outward) and esotropia (when one eye turns inward) [Med23].

Given the high variability of AHC, there is a wide range of long-term effects of hemiplegic episodes. Some affected individuals develop normally with minimal intervention, while others with more severe forms of the disorder develop severe neurological disabilities, which manifest in cognitive and behavioral delays or dysfunction.

AHC is diagnosed with the Aicardi Criteria, which was first proposed in 1993 [CGTG20]. The diagnostic criteria are as follows:

1. Onset of symptoms before 18 months
2. Repeated episodes of laterally alternating hemiplegia
3. Repeated episodes of quadriplegia or bilateral hemiplegia
4. Paroxysmal episodes including tonic/dystonic attacks and ocular abnormalities
5. Vanishing of the symptoms with sleep and reappearance within 30 minutes upon awakening

6. Evidence of developmental delay, neurological abnormalities, intellectual disability, dystonia, ataxia, or chorea

7. Symptoms not ascribable to another condition

AHC has an estimated prevalence of ∼1/1,000,000 children under the age of 16, yet due to a lack of awareness and a wide range of clinical presentations, this number could be an underestimate [AIS+17]. There is no current cure for AHC; treatment is focused on reducing the severity of episodes. Since these episodes are often triggered by overstimulating events, such as exposure to water, bright lights, and certain foods like chocolate, avoidance of these triggers is often recommended. Flunarizine, a calcium channel blocker, has been shown to have an efficacy of ∼64.5% in reducing symptoms [L+22b]. However, flunarizine has not been approved by the FDA and thus is not readily available in the U.S. Anti-convulsant medication can be used to treat individuals who have also been diagnosed with epilepsy.

2.2 Rapid-Onset Dystonia Parkinsonism

Rapid-onset dystonia parkinsonism (RDP) is a rare movement disorder characterized by the sudden onset of dystonia (involuntary muscle contractions) and parkinsonism (a broad range of motor symptoms including tremors and rigidity) [Y+22]. In the U.S. population, RDP has an estimated prevalence of <1/1,000,000. It typically presents during adolescence or early adulthood.

RDP was first reported in 1993 by Dobyns et al., who discovered a family with the characteristic symptoms of abrupt onset of dystonia-parkinsonism following a trigger event. Since then, Haq et al. have proposed a diagnostic criterion for RDP [BSC+18]:

1. The presence of dystonia

2. The absence of motor symptoms before 18 months of age

3. The presence of an *ATP1A3* mutation

Affected individuals present with symptoms following inducement by a physical and/or psychological stress trigger, including an infection, prolonged exertion, and alcohol consumption [H+19]. Following the trigger event, individuals experience a sudden onset of dystonic symptoms, including oromandibular dystonia and craniofacial dystonia leading to dysphonia (speech issues) and dysphagia (swallowing issues) [L+22b]. Parkinsonism symptoms develop, most notably bradykinesia (slowness of movement) and postural instability. Symptoms may develop over hours to several days, after which they stabilize in less than four weeks, with rare improvement.

In 2015, Neurol et al. refined the RDP diagnostic criteria as follows [H+14]:

1. Onset of symptoms following a trigger

2. Rapid onset of typically permanent symptoms over the course of hours to days, and occasionally over a period of several weeks

3. Involuntary movements characterized by generalized dystonia with parkinsonian features

There is no current cure for RDP, and treatment options are extremely limited. Levodopa, commonly used as a dopamine replacement agent in individuals with Parkinson's disease, has not been proven effective in symptom management [H+19].

2.3 Cerebellar Ataxia, Areflexia, Pes Cavus, Optic Atrophy, Sensorineural Hearing Loss (CAPOS) Syndrome

CAPOS syndrome, which stands for cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss, is a rare neurological disorder with an estimated prevalence of <1/1,000,000 in the U.S. The age of onset ranges from six months to four years [BSC+18].

CAPOS syndrome was first described by Nicolaides et al. in 1996 [SKSS20]. Episodes are typically induced by a fever or febrile illness. Most affected individuals experience one to three episodes over their lifetime [DR+17]. The first symptom is usually a sudden onset of ataxia (a loss of muscle control and coordination) associated with encephalopathy (brain inflammation). Abnormal eye movements, such as nystagmus, ophthalmoplegia (paralysis of the eye muscles), and strabismus (misalignment of the eyes), also present commonly in individuals with CAPOS syndrome. While all affected individuals have cerebellar ataxia, areflexia, optic atrophy, and sensorineural hearing loss, not all patients have pes cavus (a high arch of the foot).

Following an acute episode, some symptoms, including cerebellar ataxia and myasthenia (abnormal muscle weakness), can be significantly reduced or even relieved in the following weeks. Other, more severe symptoms, such as loss of reflexes, sensorineural hearing loss, and optic nerve atrophy, persist and cannot be restored. Vision loss is also quite common due to optic atrophy and abnormal ocular movements.

Although research has been conducted into CAPOS phenotypes, no set diagnostic criteria have been proposed. Since the prevalence rate of pes cavus is only ∼10%, it has been suggested that the syndrome should be renamed to CAOS. Based on the key features of this disorder, diagnostic criteria may be as follows:

1. Early onset recurrent cerebellar ataxia

2. Optic atrophy or abnormal ocular movements

3. Mutation in the *ATP1A3* gene

There is no current cure or treatment for CAPOS syndrome, though supportive treatments and therapies may be of some benefit.

2.4 Relapsing Encephalopathy with Cerebellar Ataxia

Relapsing encephalopathy with cerebellar ataxia (RECA) is an extremely rare neurological disorder that was first characterized by Dard et al. in 2015 [SMB+21]. Due to the recent discovery of this disorder, the general lack of knowledge pertaining to it, and its extreme rarity, there is no available prevalence data.

RECA is characterized by recurrent episodes of encephalopathy and cerebellar ataxia induced by fevers or febrile illness [D+15]. Other symptoms may include dysarthria (slurred speech due to damage to the cerebellum) and dysphagia [L+22b]. In the study conducted by Dard et al., symptoms of a 34-year-old female patient were completely resolved after the first RECA episode, whereas after the second episode, cerebellar symptoms persisted [PCP+21].

Cerebellar atrophy, the degeneration of the cerebellum, is one of the hallmark characteristics of RECA. In 2017, Hully et al. described two siblings with a variant of RECA. They suffered from neurodevelopmental delays, severe encephalopathy, epilepsy, nystagmus, and ataxia [SMB+21]. Brain MRIs revealed cerebellar atrophy [H+17]. Hully et al. also described an infant whose first RECA episode occurred at 22 months, and whose subsequent MRI also showed cerebellar atrophy [SMB+21].

No diagnostic criteria have been proposed for RECA due to its extreme rarity and relatively recent identification.

	AHC	RDP	CAPOS	RECA
Age of Onset	0-18 months of age	- adolescence - early adulthood	6 months of age to 4 years of age	0-5 months of age
Clinical Presentation	- transient paroxysmal alternating hemiplegia - quadriplegia - epilepsy - dystonia - choreoathetosis - ataxia - dysfunction of the autonomic nervous system - nystagmus - exotropia/esotropia - neurological disabilities - cognitive impairment - behavioral delays	- dystonia-parkinsonism - oromandibular dystonia - craniofacial dystonia - dysphonia - bradykinesia - postrula instabilities	- cerebellar ataxia - areflexia - pes cavus - optic atrophy - sensorineural hearing loss - encephalopathy - nystagmus - opthalmoplegia - strabismus - cerebellar atrophy - myasthenia - loss of reflexes	- recurrent episodes of encephalopathy and cerebellar ataxia - dysarthria - dysphagia - cerebellar atrophy - neurodevelopmental delays - epilepsy - nystagmus - ataxia
Triggers	- overstimulation - exposure to water - bright lights - chocolate	- physical stress triggers - psychological stress triggers - infection - prolonged exertion - alcohol consumption	- fever - febrile illness	- fever - febrile illness

Figure 1: This table depicts the typical age of onset, diverse clinical presentations, and triggers for AHC, RDP, CAPOS, and RECA.

3 Structure and Function of ATP1A3

ATP1A3 is a gene that encodes for the $\alpha 3$ subunit of Na^+/K^+ ATPase, an enzyme predominantly found in the nervous system. It is located on chromosome 19q13 and contains 23 exons and 22 introns. *ATP1A3* encodes a protein of 1013 amino acids [L$^+$22b]. Mutations in this gene, including those associated with AHC, RDP, CAPOS, and RECA, are collectively known as *ATP1A3*-related disorders.

4 The Importance of Na^+/K^+ ATPase in Neurons

The $\alpha 3$ isoform is highly expressed in inhibitory neurons and some cardiomyocytes [NCB23]. Na^+/K^+ ATPase is essential for neuronal activity and signaling. It restores neuronal membrane potential after depolarization, thereby maintaining neuronal excitability. It also influences burst firing—the periods of rapid action potential spikes followed by unusually long inactive periods—due to its role in action potential propagation.

The resting membrane potential of a cell is typically between -85 to -65 mV, due to a higher concentration of extracellular sodium ions and a higher concentration of intracellular potassium ions [HB18]. To maintain this negative resting membrane potential, Na^+/K^+ ATPase regulates ion movement by actively transporting them against their concentration gradients. Using 1 ATP from ATP hydrolysis, it pumps 3 Na^+ ions out of the cell in exchange for 2 K^+ ions into the cell [L$^+$22b]. Sodium and potassium ions both play essential roles in neuronal signaling. Following an action potential, the cell undergoes hyperpolarization, during which potassium channels stay open while sodium channels reset, causing the membrane potential to become more negative before returning to its resting state [HD15]. The resting membrane potential provides a baseline electrical charge, facilitating efficient signal transmission.

Na^+/K^+ ATPase is ubiquitously expressed in the plasma membrane of eukaryotic cells. It is critical not only for neuronal function, but also for skeletal, smooth, and cardiac muscle. In skeletal muscle, Na^+/K^+ ATPase activity can increase beyond resting levels when there is a higher demand for ion transport, such as during exercise [PC16]. In smooth muscle cells, particularly in vascular smooth muscle, Na^+/K^+ ATPase helps maintain ion homeostasis. Inhibition of Na^+/K^+ ATPase causes depolarization, whereas stimulation induces hyperpolarization [SMLSH96]. In cardiac muscle, Na^+/K^+ ATPase influences calcium homeostasis and contractility. When Na^+/K^+ ATPase is inhibited, cytoplasmic sodium levels rise, which activates the sodium-calcium exchanger, increasing intracellular calcium and enhancing the force of cardiac contractions [MVS$^+$02]. The $\alpha 1$ isoform is highly expressed in the basolateral membrane of renal epithelial cells in the renal tubules, where Na^+/K^+ ATPase regulates sodium ion balance and contributes to blood pressure regulation [XLX13, LYNS17].

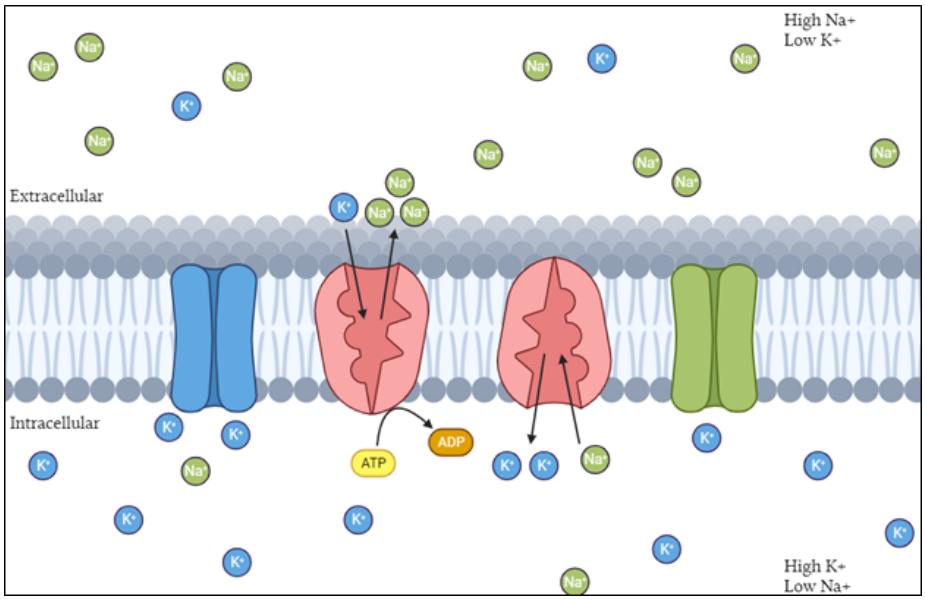

Figure 2: The sodium-potassium pump uses 1 ATP to pump 3 Na+ ions against their concentration gradients from outside the cell to inside the cell in exchange for 2 K+ ions.

5 Mutations in ATP1A3-Related Disorders

Five types of mutations in ATP1A3 have been identified: missense mutations, splice-site mutations, complex rearrangements, small deletions, and small insertions [L$^+$22b]. In a study conducted by Li et al., it was found that 868 out of 902 ATP1A3-related disorder cases (96.2%) were a result of missense mutations [L$^+$22b]. Missense mutations occur when a point mutation—a change in a nucleotide base in a DNA sequence—results in a different codon that codes for a different amino acid. These different amino acids are encoded in the resulting protein, altering its structure and function. In the same study, the second most prevalent type of mutation was small deletions, accounting for approximately 2% (22 out of the 902 patients) [L$^+$22b]. Small deletions occur when a section of a DNA sequence, ranging from a single nucleotide base to a substantial section, is omitted during DNA replication. The resulting incomplete DNA sequence may affect the structure and function of the protein.

5.1 General ATP1A3 Mutations

The molecular mechanisms influencing the severity of ATP1A3-related disorders are not yet fully understood [L$^+$20]. Most mutations affect ion-binding sites, ion pump transport, or enzyme phosphorylation [L$^+$22b]. While pathogenic variants of ATP1A3 affect ion transport, the rate of ion transport does not influence the

severity of AHC/RDP variants [C$^+$23]. Additionally, while the locations of most mutations have not been proven to correlate with clinical phenotypes, Lazarov et al. found that AHC and RDP mutations are both associated with reduced Na^+/K^+ ATPase activity [L$^+$20].

The Pro775Leu (P775L) ATP1A3 variant is associated with developmental delay (DD) and intellectual disability (ID) [C$^+$23]. P775L is a missense mutation located at position 775 in ATP1A3. In a case study conducted by Calame et al., nine patients who did not meet the diagnostic criteria for ATP1A3-related disorders yet tested positive for Pro775Leu were studied for a molecular explanation of phenotypic variability in ion transport diseases, particularly AHC and RDP [C$^+$23]. All nine patients presented with spasticity (abnormal muscle stiffness or muscle spasms), DD, and ID. To identify the changes in Na^+/K^+ ATPase, Calame et al. injected Xenopus oocytes with human ouabain-resistant ATP1A3 coding RNAs [C$^+$23]. Na^+/K^+ ATPase currents were then measured with two-electrode voltage clamps and cut-open vaseline gap voltage clamps (COVG) [C$^+$23].

P775L causes α3 Na^+/K^+ ATPase dysfunction and a leakage of intracellular sodium ions and protons [C$^+$23]. Calame et al. found that this inward current leak through the sodium-potassium pump is associated with the impairment of Na^+ binding and the favoring of states with bound ions [C$^+$23]. Ouabain, a cardiac glycoside (cardiac steroid), binds to the extracellular region of the α-subunit of Na^+/K^+ ATPase, inhibiting Na^+/K^+ ATPase from pumping sodium to extracellular regions [OPZVDH17]. This increased intracellular sodium concentration causes an increased intracellular build-up of calcium, which, when released, increases cardiac contractility [OPZVDH17]. In the brain, this ouabain binding also inhibits Na^+/K^+ ATPase from effectively transporting ions, increasing the concentrations of intracellular sodium and calcium [L$^+$22a]. Calame et al. found that, during extracellular sodium binding, P775L impaired conformational changes in the enzyme which then triggered protein kinase signaling [C$^+$23]. During signal transduction, protein kinases—specifically Protein Kinase C (PKC)—send signals from the cell membrane to inside the cell and are also involved in the phosphorylation of protein substrates [FKN$^+$04]. This phosphorylation of signaling proteins and neuron receptors allows for neurotransmitters to respond to stimuli [DDB15].

5.2 Mutations in AHC

Over 87 mutations have been identified in AHC, though the three most frequent variants make up the majority (60%) of all AHC cases: p.Asp801Asn (D801N), p.Glu815Lys (E815K), and p.Gly947Arg (G947R). [L$^+$22b] Amino acid position 801 is considered a mutational hotspot, as the four currently known mutations on that position make up 30-43% of all AHC cases [C$^+$21]. The D801N, D801E, and D801V mutations are associated with AHC, while D801Y is associated with both AHC and RDP [DCA$^+$04].

D801N is the most common pathogenic variant in AHC, occurring when aspartic acid is changed to asparagine [C$^+$23]. Li et al. measured Na^+/K^+

ATPase function in *Xenopus laevis* oocytes, which were modified to express human D801N mutations. They found that loss of ion transport correlated with the severity of AHC [L$^+$15]. In another study, it was found that, since the D801N mutation site is near cation binding sites, D801N, E815K, and G947R mutations cluster around ion binding pockets, resulting in disrupted Na^+/K^+ binding [S$^+$20]. This decreased pump function leads to the depolarization of the resting membrane potential, wherein the membrane potential becomes more positive.

The D801E variant, also part of the mutational hotspot at position 801, results from aspartic acid being replaced by glutamic acid. D801V is a novel mutation linked to a milder phenotype. It was found in a patient who presented with late onset, no intellectual disability, and no characteristic AHC episodes [P$^+$15].

The p.Glu815Lys (E815K) mutation accounts for 16-35% of AHC cases, occurring when the original amino acid glutamic acid is changed to lysine [C$^+$21]. E815K is linked to the most severe phenotype of AHC cases. It is characterized by an earlier onset of characteristic AHC symptoms, including seizures, hemiplegic attacks, and both cognitive and motor impairment [K$^+$20]. The E815K mutation significantly reduces proton transport, leading to intracellular alkalosis—when there is a higher concentration of extracellular potassium [Pub]. Potassium causes a decrease in pH, thereby inhibiting Na^+/K^+ ATPase function. Given the importance of maintaining balanced intracellular and extracellular concentrations for the purpose of maintaining neuronal excitability, increased intracellular alkalosis has severe effects on neuronal function [K$^+$20].

p.Gly947Arg (G947R) is a missense mutation that accounts for 8-15% of AHC cases and occurs when glycine is changed to arginine [C$^+$21]. It is characterized by a later onset as compared to D801N and E815K and is not associated with severe intellectual disabilities. G947R is considered to have one of the mildest phenotypes in AHC. In a study that examined the electrophysiological properties of Na^+/K^+ ATPase in AHC, neurons were generated from the iPSCs of AHC patients with the G947R mutation [S$^+$18]. It was found that these neurons were less sensitive to ouabain outward current (the outward transport of Na^+) [CGTG20]. These neurons also exhibited a significant decrease in intracellular K^+ concentration and depolarized resting membrane potential [CGTG20]. There was impaired neuronal excitability and, in response to a stimulus, there was a lower evoked action potential firing frequency [S$^+$18].

The p.Gly755Ser (G755S) mutation is one of the less prevalent AHC mutations, with a milder phenotype. Because of a lack of long-term follow-up and the rarity of this mutation variant, not much is currently known about its progression [I$^+$18].

5.3 Mutations in RDP

D801Y is part of the mutational hotspot at position 801 on chromosome 19. A knock-in mouse (a genetically modified mouse with a DNA sequence inserted into a specific locus in its genome) with the D801Y mutation was created

to further explain the genotype-phenotype correlation of AHC and RDP. The $\alpha 3^+$/D801Y mice were more sensitive to induced epileptic seizures and displayed cognitive delay [I^+18, H^+16].

Isaksen et al. found that, in the D801Y mouse model, the Na^+/K^+ ATPase pumps did not carry out ion exchange but were still able to bind Na^+ [I^+17]. They also found that the expression of $\alpha 3$ in the cerebellum was 20% lower than in the wild-type mice (the normal form) [L^+20].

p.Glu277Lys (E277K) is a missense mutation resulting from a nucleotide substitution in the ATP1A3 gene in exon 8 of chromosome 19, which causes the original amino acid glutamic acid to change to lysine at position 277 [L^+16].

5.4 Mutations in CAPOS

p.Glu818Lys (E818K) is the most prevalent mutation in patients diagnosed with CAPOS. It is located in the cytoplasmic loop connecting M6 and M7 of Na^+/K^+ ATPase [R^+19]. The substitution of lysine for glutamic acid reduces Na^+ affinity at the extracellular-facing sites in the CAPOS mutation [R^+19]. An increased affinity for K^+ activation of Na^+/K^+ ATPase has been linked to less dependence on the pumping rate of Na^+/K^+ ATPase [R^+19]. Under normal circumstances, Na^+ binds to the E1 form of the phosphoenzyme, which activates phosphorylation (important in protein function regulation) [R^+19]. K^+ then binds to the E2P form, which activates dephosphorylation. In the E818K mutation, an increased affinity for K^+ leads to competition between K^+ and Na^+ in binding to E1. When K^+ binds to E1, it inhibits phosphorylation and the function of Na^+/K^+ ATPase. Competition between the ions also causes Na^+ to abnormally bind to E2P, thereby inhibiting Na^+/K^+ ATPase [R^+19]. The function of Na^+/K^+ ATPase is thus impaired.

5.5 Mutations in RECA

Due to the rarity and lack of information about RECA, only three mutations have been linked to this ATP1A3-related disorder: Arg756His (R756H), Arg756Cys (R756C), and Arg756Leu (R756L) [A^+23]. All three mutations are substitutions for the amino acid arginine at position 756 on chromosome 19 and are associated with encephalopathy during fever or febrile illness [A^+23].

The R756C mutation occurs when arginine is replaced by histidine. This mutation has a higher affinity for K^+ and a reduced affinity for Na^+. This reduction in Na^+ affinity reduces the physiological activity of Na^+/K^+ ATPase at the normal cytoplasmic concentrations of Na^+, thereby inhibiting its expression [A^+23]. A higher affinity for K^+ and subsequent increase in K^+ activation results in competition between Na^+ and K^+ at Na^+ activation sites. This competition leads to an inhibition of Na^+/K^+ ATPase activity at high K^+ levels [A^+23].

In the R756H mutation, the original amino acid arginine is substituted for histidine. It is the most common RECA mutation. Arystarkhova et al. conducted research to test the capacity of R756H to elicit RECA-associated phe-

notypes in isogenic mammalian cells and to examine the relationship between temperature and RECA phenotypes [A$^+$23]. The R756 mutation caused reduced expression of Na^+/K^+ ATPase activity. It was also found that the severity of RECA phenotypes correlated with the temperature that the cells were in. Lower temperatures corresponded to milder phenotypes while higher temperatures corresponded to more severely abnormal Na^+/K^+ ATPase functions.

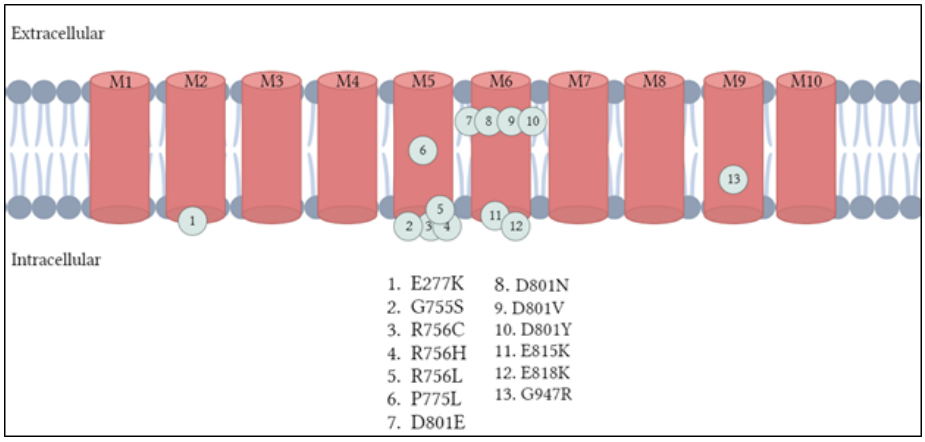

Figure 3: This figure depicts the locations of the thirteen ATP1A3 mutations discussed in this paper.

6 Future Directions

6.1 Treatment

Treatments for ATP1A3-related disorders are largely symptomatic and do not address the underlying genetic root causes of the disorders. These symptomatic treatments vary depending on the disorder and its severity, mostly focusing on controlling episodes of hemiplegia, seizures, and dystonia. Symptomatic treatment options include flunarizine, anti-convulsant medications, anti-epileptic drugs, dopaminergic agents, and physical, occupational, or speech therapy.

In the future, advancements in gene-editing technologies may be the path to treatment or a potential cure. The success of gene therapies like Zolgensma, a novel gene therapy that treats spinal muscle atrophy (SMA), has demonstrated the potential of gene therapy in treating these genetic-based ATP1A3-related disorders [Nov21]. With the increasing capabilities of Next-Generation Sequencing (NGS), individuals with the rarer, more intermediate phenotypes of ATP1A3-related disorders will be able to be diagnosed. NGS will enable researchers and scientists to identify the expanding range of genotype-phenotype correlations, making it possible to recognize lesser-known or previously unknown

genetic variations. Advancements in gene-editing technologies like CRISPR-Cas9 offer the potential to treat ATP1A3-related disorders at their source.

6.2 Conclusion

While there has been significant progress in more fully understanding ATP1A3-related disorders, there is still much to uncover regarding genotype-phenotype correlation and the genetic basis and pathophysiology of these disorders. Despite challenges and uncertainties, there is a growing body of research. Efforts should be made to increase awareness among the medical and scientific communities and the public alike to further refine diagnostic criteria and catalyze the development of potential treatments. While current symptomatic treatments do not target the genetic causes of these disorders, advancements in research techniques and gene-editing technologies like NGS and CRISPR-Cas9 bring the possibility of effective treatments closer, one step at a time.

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