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REVIEW

Alternating Hemiplegia of Childhood: Understanding the Genotype–Phenotype Relationship of ATP1A3 Variations

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Abstract: Alternating hemiplegia of childhood (AHC) is a rare neurological disorder affecting children with an onset before 18 months. Diagnostic clues include transient episodes of hemiplegia alternating in the laterality or quadriparesis, nystagmus and other paroxysmal attacks as tonic and dystonic spells. Epilepsy is also a common feature. In the past, a great effort has been done to understand the genetic basis of the disease leading to the discovery of mutations in the ATP1A3 gene encoding for the alpha3 subunit of Na^+/K^+ATPase, a protein already related to another disease named Rapid Onset Dystonia Parkinsonism (RDP). ATP1A3 mutations account for more than 70% of cases of AHC. In particular, three hotspot mutations account for about 60% of all cases, and these data have been confirmed in large population studies. Specifically, the p.Asp801Asn variant has been found to cause 30–43% of all cases, p.Glu815Lys is responsible for 16–35% of cases and p.Gly947Arg accounts for 8–15%. These three mutations are associated with different clinical phenotype in terms of symptoms, severity and prognosis. In vitro and in vivo models reveal that a crucial role of Na^+/K^+ATPase pump activity emerges in maintaining a correct membrane potential, survival and homeostasis of neurons. Herein, we attempt to summarize all clinical, genetic and molecular aspects of AHC considering ATP1A3 as its primary disease-causing determinant.

Keywords: ATP1A3, Na^+/K^+ATPase, AHC, genetics, animal models

Introduction

First described in 1971 by Verret and Steele in 8 children,[1] the syndrome of alternating hemiplegia of childhood (AHC, OMIM #614820) was defined only 9 years later by Krägeloh and Aicardi,[2] who described five novel cases and reviewed the previous reports discussing the nosology of this entity. Specific diagnostic criteria for AHC, named "Aicardi criteria," were first proposed in 1993.[3] Since then, the original criteria were periodically updated, in order to support clinical recognition of this peculiar neurodevelopmental disorder.[4–7]

In 2012, two independent research groups – an international consortium[8] and a German group[9] – identified de novo heterozygous mutations in the *ATP1A3* as the cause of AHC. Soon after, a Japanese study replicated this finding,[10] providing further evidence that *ATP1A3* mutations causing AHC.

Heterozygous *ATP1A3* mutations had been already reported to cause another entity previously described on a clinical basis: rapid-onset dystonia-parkinsonism (RDP, DYT12, OMIM #128235), a rare and peculiar movement disorder inherited in an

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autosomal dominant manner.[11] In 2014, *ATP1A3* have been reported to cause another neurological entity: cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss (CAPOS) syndrome (OMIM #601338).[12,13] In addition, over the recent years, two other phenotypes related to *ATP1A3* mutations have emerged: the early infantile epilepsy with encephalopathy (EIEE)[14,15] and the recurrent encephalopathy with cerebellar ataxia (RECA) phenotype.[16,17]

Most of the patients with *ATP1A3* pathogenic variants fall into one of these phenotypes,[18] which underlie a nearly non-overlapping subset of causative mutations.[19,20] Nevertheless, some individuals show atypical features or combine features of two or more of these major phenotypes.[20–24] On the other hand, some pathogenic variants have been reported to cause different phenotypes, even in the same family.[4,25–27] As a result, it has been proposed to consider *ATP1A3*-related disorders as a clinical continuum rather than distinct entities, with an age-dependent pattern of emergence and progression of different signs and symptoms.[16,18,19]

Despite the growing number of reports describing intermediate and overlapping forms between the major *ATP1A3*-related phenotypes, AHC remains a well-defined and recognizable syndrome, whose clinical identification is essential to orientate molecular investigations.

In this review, we summarize knowledge on AHC, focusing on clinical diagnostic clues, genotype–phenotype correlations and functional effect of *ATP1A3* variants of this condition.

Clinical Features

Classic AHC

AHC is a peculiar neurodevelopmental disorder characterized by a constellation of paroxysmal neurological manifestations, among which recurrent episodes of hemiplegia involving either side of the body and alternating in laterality are the hallmark of this disease.[18] Quadriplegic attacks can occur in isolation or as a generalization of a hemiplegic attack. In addition, paroxysmal manifestations include tonic or dystonic spells (either of one limb, one hemibody or generalized), oculomotor abnormalities and dysautonomic phenomena (uni- or bilateral mydriasis, flushing, pallor) may occur alone or in association with hemiplegic attacks.[19] Paroxysmal episodes usually occur before 18 months of age, with a median age of onset of 3–5 months. Nevertheless, onset may range from the neonatal period to 4 years of age.

Paroxysmal abnormal ocular movements (including monocular and binocular nystagmus, strabismus, disconjugate gaze, ocular bobbing, ocular flutter) are often the first neurological manifestations, occurring in isolation before the onset of other paroxysmal spells.[28]

Paroxysmal events typically recognize emotional or environmental trigger factors (exercise, exposure to light, sounds or hot water, specific foods), while symptoms are relieved by sleep and post-awakening periods.[7] A high variability in duration and frequency of paroxysms has been reported, even in the same patient, lasting from minutes to entire days and occurring up to several times per day.[28]

Beyond paroxysmal manifestations, AHC is also characterized by persistent, interictal neurological abnormalities, whose prevalence increases with age. Developmental issues (speech and language delay, cognitive deficits, behavioral problems) with various degrees of severity are the most common finding, followed by dysarthria, ataxia, chorea, dystonia, and, less frequently, pyramidal tract signs.[7,27,29] Neurological deterioration may show a stepwise progression, with discrete motor or cognitive decline following a prolonged paroxysmal episode. Fixed neurological deficits often show a rostrocaudal gradient of severity, with severity of oro-mandibular dystonia and dysarthria overcoming upper and lower limbs dystonia severity.[7]

Up to 50% of AHC patients develop epileptic seizures.[4,5,30,31] Epilepsy can be focal or generalized, with multiple seizure types and localizations, and it is often drug-resistant. Moreover, a high frequency and recurrence rate of refractory status epilepticus has been reported.[32]

The last version of the clinical criteria for AHC recognizes major (diagnostic) and minor (supporting) criteria, and include a set of standardized definitions for a simplified description of paroxysmal episodes, in order to provide to caregivers a more accessible language to document events.[7] Particularly the criteria included 1) the onset of the symptoms before 18 months, 2) repeated episodes of hemiplegia alternating laterally or 3) repeated episodes of quadriplegia or plegia, 4) other paroxysmal episodes including dystonic attacks, 5) oculomotor abnormalities or automatic symptoms, 6) vanishing of the symptoms with sleep and 7) evidence of developmental delay and/or other neurological abnormalities as dystonia, ataxia or chorea.[7] From a pharmacological point of view, the most frequent drugs used in AHC are flunarizine, benzodiazepines, carbamazepine, barbiturates and valproic acid. It has been wildly demonstrated that flunarizine and benzodiazepines show a greater improvement in dystonic or plegic episodes.[5] Mikati et al particularly demonstrated that

flunarizine, a calcium antagonist, reduces the duration, severity, and frequency of the hemiplegic attacks in up to 80% of AHC patients.[33]

On the other hand, antipsychotics, selective serotonin reuptake inhibitors, gabapentin, and acetazolamide were invariably ineffective.[5]

Atypical AHC

Besides the classic AHC phenotype, several atypical features have been described. With regard to age at onset, a delayed occurrence of hemiplegic attacks up to 4 years of age has been described.[25] Regarding cognitive impairment, mild cases with normal development have been reported.[33] Other uncommon features include a predominantly dystonic phenotype, the absence of quadriplegic attacks,[33] or the occurrence of alternating upper limb monoplegia.[34]

In addition, some patients combine typical AHC paroxysms with the features of either early-onset encephalopathy[14,35,36] or RDP.[23,37–39]

Aside from AHC, a distinct nosological entity with milder course, characterized by episodes of unilateral or bilateral weakness arising exclusively out of sleep has been described.[40–46] Although the first report of this condition dates back to the original description of AHC by Verret and Steele,[1] its distinct nosology was recognized only in 1994, when the term benign nocturnal alternating hemiplegia of childhood (BNAHC) was proposed to differentiate this entity from AHC.[40] In BNAHC, (hemi) plegic attacks only onset from sleep, and there is no progression to neurological or intellectual impairment. In addition, other paroxysmal events such as tonic or dystonic spells and oculomotor abnormalities are lacking.[40,41] To date, 14 cases of BNAHC have been reported, all but one affecting boys.[42] Albeit rarely tested, no association between BNAHC and *ATP1A3* mutations has been described.[42] Among the 14 patients, only 2 performed a Whole Exome Sequencing (WES) analysis and in only 1 case it was disclosed a heterozygous 16p11.2 microdeletion involving, among others PRRT2 gene. PRRT2 encodes for a transmembrane protein containing a proline-rich domain and is associated with episodic kinesigenic dyskinesia-1 (OMIM #128200).[42] Although several familial cases have been reported,[40,41,45] the genetic basis (if any) of this condition is still elusive. A proper WES analysis should be performed to better investigate this condition and the role of regulatory additional genetic factors should be considered.

Role of *ATP1A3* Gene Disruption

Na^+/K^+-ATPase Structure and Function

ATP1A1-4 genes encode for four α subunit – respectively $\alpha_{1\text{-}4}$ – of Na^+/K^+ ATPase. Pump is ubiquitously expressed in the central nervous system (CNS) and it is constituted by almost two subunits: one alpha (α – containing the catalytic site for ATP hydrolysis and binding the ions) and one beta (β, responsible for the structural and functional asset of the α-subunit).[47] Although α1 isoform is present in whole CNS and α_2 in the astrocytes, the α_3 is expressed only in the neurons – GABAergic neurons in all nuclei of the basal ganglia (striatum, globus pallidus, subthalamic nucleus, and substantia nigra), several thalamic nuclei, cortex, cerebellum, red nucleus, and several areas of the midbrain (reticulotegmental nucleus of pons) and hippocampus;[48] while expression was not significant in the dopaminergic cells of substantia nigra.[49,50] This ion pump is essential for the maintenance of the electrogenic homeostasis of neural cells, exchanging Na^+ and K^+ ions across the plasma membrane coupled to ATP hydrolysis, setting the membrane potential both in resting potential (α_1) and after an action potential (α_2, α_3).

The α_3 isoform is encoded by the *ATP1A3* gene (OMIM #182350) on chromosome 19q13 encodes for the α_3 subunit of the Na+/K+-ATPase, an ubiquitous, electrogenic transmembrane ATPase first described in 1957[51] and located on the cytosolic side of the outer plasma membrane.[52] Exporting 3 Na^+ and importing 2 K^+ ions for every single ATP molecule hydrolyzed, the Na^+/K^+-ATPase maintains the gradient of a higher extracellular Na^+ concentration and a higher K^+ intracellular level.[53,54]

Although α_3 is the subunit predominantly expressed in neurons, some neurons express α_1 – that is predominantly expressed in glial cells. Compared to α_1, the α_3 subunit shows a lower affinity for Na^+ and K^+, and lower voltage dependence, enabling a rapid normalization of transmembrane gradient after a series of action potentials.[55]

The α subunit of the Na^+/K^+-ATPase contains 3 cytoplasmic and one transmembrane regions. The cytoplasmic domains include the phosphorylation ("P") domain, the nucleotide-binding ("N") domain and the actuator ("A") domain.[53] As in the other members of the P-type ATPase superfamily, the Na^+/K^+-ATPase forms a phosphorylated intermediate during the reaction cycle. The P domain harbors a highly conserved Asp-Lys-Thr-Gly-Lys sequence, whose aspartate residue (falling in the 366 position) is phosphorylated by transfer of the γ-phosphate group of

an ATP molecule.[56] The A domain contains a Thr-Gly-Glu -Ser motif that bonds, through the glutamate residue, the water molecule needed for aspartyl-phosphate hydrolysis in the catalytic site.[57] The transmembrane region is composed of 10 transmembrane helices (TM_{1-10}), of which helices TM_{4-6} contain the cation binding sites and TM_8 contributes to the biding of the third Na^+ ion.[57,58]

To allow ions exchange, during the reaction cycle the protein undergoes critical conformational changes, reversing the accessibility and specificity of the cation binding sites.[59] In the so-called E_1 state, the α subunit is accessible from the cytoplasmic side and is Na^+-selective. The binding of 3 Na^+ triggers the phosphorylation of the Asp^{366} residue from ATP, leading to the E_1P state. As a result, Na^+ ions are transported across the membrane and released on the extracellular side. By Na^+ release, the protein turns into the E_2P state, which is an extracellular accessible, K^+-selective conformation. The binding of 2 K^+ ions on the cytoplasmic side triggers the dephosphorylation by hydrolysis of the Asp^{366} residue, with transition to the E_2 state. The low-affinity binding of an ATP molecule to the E_2 state stimulates the transition to the E_1 state, whose low affinity for K^+ ions determines their release in the cytosol. The higher affinity for ATP and Na^+ ions of the E_1 state causes the binding of the Na^+ and the following phosphorylation of the P-domain. Rotation of the A domain and rearrangements of TM_{1-6} mediate these conformational transitions.[59–64]

The β-subunit – of which three differentially expressed isoforms (β_{1-3}) exist – acts as a molecular chaperon that facilitates the transport from the endoplasmic reticulum to the plasma membrane of the α subunit and permits its correct folding and membrane integration.[65,66]

In addition to ion transport across the cellular membrane, the Na^+/K^+-ATPase has been shown to have different functions, including modulation of signal transduction via PI3K, PLC-γ and MAPK cascades, protein interactions with other transmembrane enzymes and scaffolding proteins and regulation of other transporter activity.[20,67,68]

ATP1A3 Pathogenic Variants Location and Effect

As shown in Figure 1, *ATP1A3* mutations affect the whole coding sequence. Differently from RDP causing mutations – that are distributed throughout the gene – AHC causing variants are more frequently found in exons 17 and 18.[20] With regard to the affected functional domain,

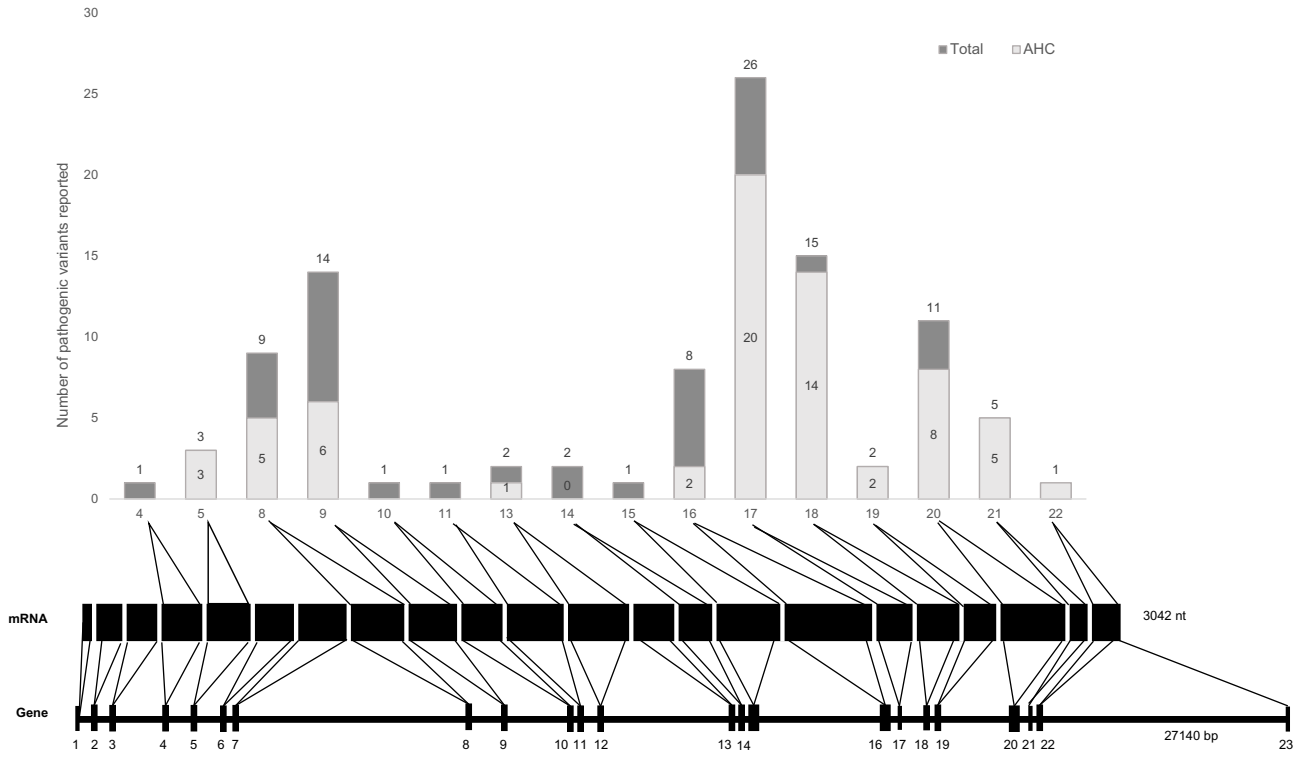

Figure 1 Distribution of AHC-causing variants along the ATP1A3 gene and mRNA.
Note: Columns show the number of AHC-causing variants (light grey bars) and the total number of pathogenic ATP1A3 variants (dark grey bars) reported in each exon.
Abbreviations: AHC, alternating hemiplegia of childhood; Nt, Nucleotides; bp, basepairs.

most AHC-causing variants affect the ions binding sites or the transmembrane segments that harbor the binding residues (Figure 2).[57] A smaller group of mutations is found in transmembrane helices other than the ion binding segments. Furthermore, several mutations affect the cytoplasmic extensions of the transmembrane helices TM_{3-5}, that connect these helices with the cytoplasmic A-, N- and P-domains (the so-called "stalk" mutations).[57] This latter cytoplasmic domain has been found to harbor several AHC-causing variants, while a small group of pathogenic variants have been found to affect the extracellular loop between TM_7 and TM_8.

As a result, a vast proportion of AHC-causing variants are expected to affect the ion binding and transport, while another consistent group of mutations is expected to affect enzyme phosphorylation.[57]

For some of the ion-binding sites mutations (Asp801Asn, Asp923Asn, Ser137Tyr, Phe780Leu, Ile810Asn), experimental evidence of defective Na^+ binding has been provided,[69–71] while for other variants impaired Na^+ binding has been shown with mutations affecting the corresponding residue in the α_1 paralog.[57] Of note, few mutations have been reported in the transmembrane helices far from the ion-binding sites (such as TM_{1-2} and TM_{9-10}). Interestingly, variants affecting the N-cytoplasmic domain or the C-terminus domain have been described only in RDP.

Genotype–Phenotype Correlation

Emergence and Frequency of Different AHC-Causing Variants

Although AHC is a sporadic disorder due to de novo variants, few autosomal dominant inherited cases have been reported.[4,25,26,72] Germline mosaicism has been reported in familial cases of other *ATP1A3*-related disorders,[73] but it has not been described in AHC so far.

Despite the growing number of pathogenic variants reported, the largest cohort studies conducted in different populations (European, North American and Chinese cohorts) demonstrated that three variants account for about 60% of all cases.[4,30,74] Specifically, the p.Asp801Asn variant has been found to cause 30–43% of all cases, p.Glu815Lys is responsible for 16–35% of cases and p.Gly947Arg accounts for 8–15% (Figure 3).

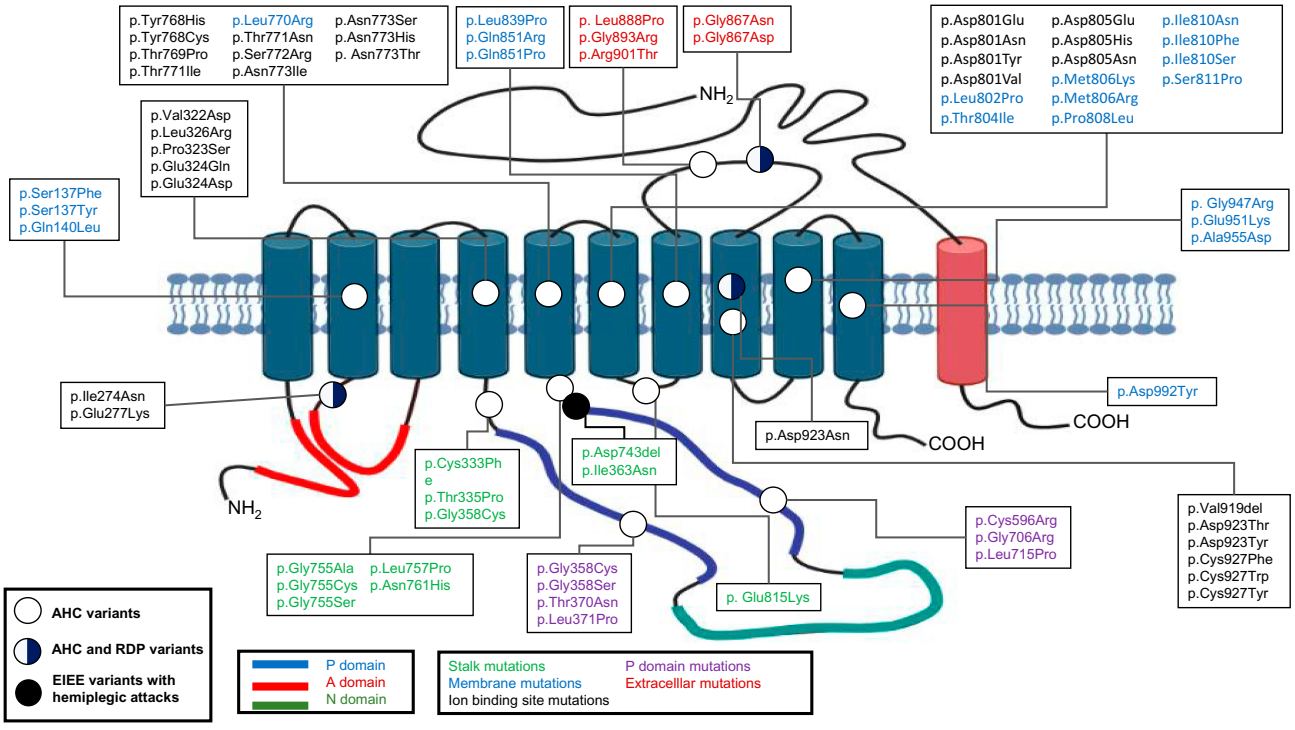

Figure 2 Location of AHC-causing variants in the ATP1A3 protein.

Notes: White dots show AHC-causing variants, black dots indicate variants causing EIEE with the presence of hemiplegic attacks, blue-and-white dots show variants causing both RDP and AHC. According to functional domains localization, variants are divided into ion binding site variants (black), membrane variants (blue), stalk variants (green), P domain variants (purple) and extracellular variants (red). The three-different cytosolic domains of the *ATP1A3* protein are indicated in red (A domain), green (N domain) and blue (P domain).

Abbreviations: AHC, alternating hemiplegia of childhood; EIEE, early infantile epileptic encephalopathy; RDP, rapid-onset dystonia-parkinsonism.

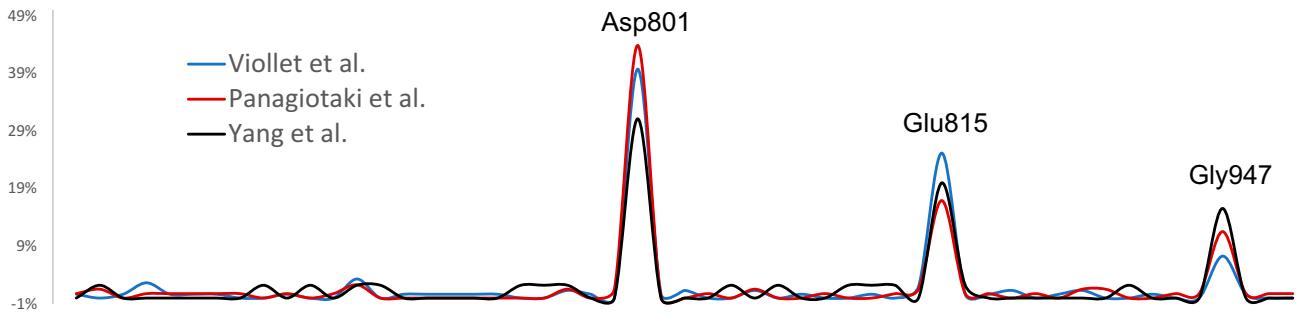

Figure 3 Frequency of AHC-causing variants in different cohorts.
Notes: The graph shows the relative frequency of variants affecting each specific *ATP1A3* residue in a North American (blue line, N= 151), European (red line, N= 130) and a Chinese (black line, N= 45) cohort. The peaks are expressed as the percentage of the total number of AHC patients in each cohort. The three hotspots for AHC-causing variants (Asp801, Glu915 and Gly947) are indicated above the corresponding peak.
Abbreviation: AHC, alternating hemiplegia of childhood.

As previously stated, the location of ATP1A3 mutations along the coding sequence shows a genotype–phenotype correlation of the ATP1A3 clinical spectrum. Only specific mutation – particularly near the transmembrane domains – and consequently protein alterations result in AHC (Rosewich H. Neurology 2014).[27]

Three recurrent missense mutations count for 60% of all AHC cases. Fifteen percent of AHC have no mutation identified but meet the clinical criteria. In a recent report by Panagiotakaki al. clinical data of a large cohort of 155 patients from the international Consortium of AHC were deeply reviewed and an attempt to discretely genotype–phenotype correlation was done.[30] First, interestingly, ATP1A3 mutations were detected in 85% of patients, confirming that a small group of patients met the criteria for AHC without any molecular genetic diagnosis. The study also confirmed the relative incidence of the three most common mutations: p.Asp801Asn, p.Glu815Lys and p.Gly947Arg. Of these, Glu815Lys was associated with a more severe phenotype, with drug-resistant epilepsy, profound intellectual disability and severe dystonia as neurological main findings. p.Asp801Asn appears to be associated with a milder phenotype with later onset of the paroxysmal events and less frequent plegic attacks; the majority of patients present moderate intellectual disability with a higher rate of behavioral problems. p.Gly947Arg seems to correlate with a positive prognosis; the onset of the paroxysmal event is the latest when compared with other two mutations, moreover no severe intellectual disability has been reported. In conclusion, the three mutations show a gradient of severity of the symptoms: p.Glu815Lys > p.Asp801Asn > p.Gly947Arg. Table 1 summarizes the clinical spectrum associated with the three most common mutations.

Evidence from in vitro and in vivo Studies

A great contribution to explaining the clinical heterogeneity associated with ATP1A3 mutations as well as to improve our knowledge and develop new therapeutic strategies, arises from cellular and animal models.

Cellular Studies

In the neuron presenting the α_3 allele mutation, Na^+/K^+ ATPase shows reduced sodium affinity, leading to an elevated intracellular Na^+ concentration with many possible dramatic events such as increased influx Ca^{++} ions into the cell with toxic effects and liberation of excitatory aminoacids.[50] Moreover, it has been supposed that an altered uptake of dopamine secondary to the abnormal Na^+ gradient is partially responsible for the ATPase related syndrome.[4,75] This alteration leads to dystonia and/or parkinsonism without degeneration of the nigrostriatal pathway,[54,75] but it has not been demonstrated by PET and DAT-SCAN study in RDP patient, which explains lack of response to levodopa in these patients.[76]

Heterogeneity in the phenotypic spectrum shown by AHC patients and by patients with RDP suggests different underlying cellular consequences relevant to the pathological mechanisms. In general, from the first description and characterization of ATP1A3 mutations associated with AHC,[8] the activity of Na^+/K^+ pump seems to be responsible of pathogenicity in AHC. Thus, it was reasonable that in RDP, most mutations affected protein expression and cell surface expressions, and in the AHC, an altered activity of the pump could explain the phenotype.[8] Several studies have been conducted to clarify that issue[71,77] and one useful approach was by using induced Pluripotent Stem (iPS) cells. Recently, in a model of

Table 1 Clinical Features of Most Common ATP1A3 Variants Causing AHC

Genotype AA Variation	Frequency	Severity	Prognosis	Plegic Attacks	Paroxysmal Manifestation	Epilepsy	Psychomotor Delay	Intellectual Disability	Baseline Movement Disorder
c.2443G>A pGlu815Lys	43% 57/132	Severe	Less favorable	Early onset (neonatal) Frequent - short duration	Early onset	More frequent Early onset	Severe	50% IQ<40 33% IQ 40–55	Dystonia >Ataxia
c.2401G>A pAsp801Asn	16% 22/132	Intermediate	Intermediate	Intermediate onset Less frequent long duration	Intermediate onset	Less frequent Late onset	Mild	70% IQ 40–55	Ataxia > Dystonia
c.2839G>A pGly947Arg	11% 15/132	Mild	More favorable	Late onset Less frequent long duration	Late onset	Less frequent Early onset	Mild	63% IQ 55–63%	Rare

Note: Data from Panagiotakaki et al.[30]
Abbreviations: AHC, alternating hemiplegia of childhood; AA, amino acids; IQ, intelligence quotient.

iPS cells derived neurons from AHC patients carrying the missense mutation p.Gly947Arg, lower levels of ouabain-sensitive outward current (a net outward transport of a Na^+ ions) have been demonstrated compared to controls.[77] Furthermore, as it may be predicted by a lower intracellular K^+ ion concentration, neurons exhibit a resting membrane potential similar to resting cell with altered excitability, dealing with the hypothesis of a loss of function mechanism.[77]

Moreover, in a very recent study (2019), Arystarkhova et al point out that severity of phenotype cannot be explained solely by reduction of pump activity and other cellular mechanisms are hypothesized from experimental data, including misfolding protein at Golgi apparatus level and consequent ratio between good and bad alleles, by competition.[78]

Animal in vivo Studies

Several mouse models have been developed to study in vivo consequences of α3 isoform variants. There are five main models which have been exhaustively studied, summarized in Table 2. The first model was characterized by Moseley et al (2007).[79] Introducing a single base pair mutation in intron 4 ($\alpha_3^{+/KOI4}$), with aberrant splicing knocking out the allele ($Atp1a^{3tm1/Ling/+}$), replicated by other authors,[80,81] these mice displayed both maniacal-like phenotype, increased by methamphetamine response, and seizures with an increased motor activity. In 2013, Ikeda et al[49] proposed another mouse model with the large deletion from 2 to 6 exons ($\alpha_3^{+/}\Delta^{E2-6}$): for the first time, affected mice disclosed dystonia induced by intracerebellar kainite injections. Because of the large deletion and the sequential aberrant product, the clinical pattern of the above two models was very severe and far from the human ATP1A3 phenotype. Clapcote et al[71] were the first to develop a mouse model with single nucleotide substitution causing a single aminoacid substitution (I810N, Myshkin $\alpha_3^{+/I810N}$). In his work, he described mice with severe seizures both spontaneous and evoked by vestibular stress (running, leaping), behavioural arrest (freezing-like) and death after partial complex seizures with secondary generalization. Another similar mutant model has been described by Hunayan et al in 2015, modelling the pAsp801Asn variant, called Mashl +/- ($\alpha_3^{+/D801N}$). The model recalls many features of AHC such as dystonia and hemiplegia, with cerebellar involvement (ataxia and tremor). Recently another mouse model of AHC has been reported. This novel knock-in mouse model ($Atp1a3^{E815K+/-}$, Matoub, $Matb^{+/-}$) expresses the E815K mutation of the Atp1a3 gene (the

Table 2 Summary of Pre-Clinical Mouse Models of ATP1A3 Mutations Related to AHC

Model and Gene Mutation	Phenotype	Study
Atp1a$^{3tm1/Ling/+}$ ($\alpha_3^{+/KO14}$)	Motor hyperactivity Mania-like behaviour Seizures Sleep cycle abnormalities	Kirshenbaum et al[81]
$\alpha_3^{+/\Delta E2-6}$	Motor hyperactivity Intracerebellar kainate injection related dystonia Enhanced inhibitory neurotransmission	Ikeda et al[49]
Myshkin $\alpha_3^{+/I810N}$	Motor hyperactivity Spontaneous and induced by vestibular stress epilepsy Hippocampal hyperexcitation Memory and learning reduction	Clapcote et al[71] and Kirshenbaum et al[81]
Mashl +/- ($\alpha_3^{+/D801N}$)	Small size Hyperactivity Ataxia and tremor Hind-limb clasping (tail suspension) Spontaneous seizures and SUDEP Reversible Hemiplegia, quadriplegia, and dystonia Avoidant and anxiety-like behaviors	Hunanyan et al[82]
Matb+/-, Atp1a3$^{E815K+/-}$	Small size Hemiplegia/dystonia/seizures spontaneously and upon stimulation; Abnormal episodic memory; Abnormal motor performance and coordination; Less activity and freezing; High mortality	Helseth et al[83]

Abbreviation: SUDEP, sudden unexpected death in epilepsy.

most severe common phenotype of AHC).[83] In their elegant study, authors clearly demonstrated that mutated mice expressed behavioural and neurophysiological features, resembling the most severe form of AHC. In particular, the motor initiative was poor, the motor performance was deeply impaired (e.g. coordination, balance, abnormal gait), and interestingly, other than epilepsy, many mice were observed to pass during spontaneous seizure or provoked seizures for sudden unexpected death in epilepsy (SUDEP).[83] Of note, the hemiplegia and dystonia episodes were both spontaneous and induced by high level of stress (e.g. water contact or cage change), likely in the human phenotype. It's noteworthy to underlie that although differences among the proposed models exist, some features are common including the brain hyperexcitability, motor abnormalities (spontaneous or provoked) and behaviour alterations, according to a pivotal role of ATP1A3 in brain functioning.

Conclusion

With the growing emergence of new phenotypes related to ATP1A3 along together with the high accessibility to genetic tests in this new era, clinicians and scientists have renewed their interest in ATP1A3-related disorders. In particular, since the discovery that ATP1A3 mutations are causative of AHC, great efforts have been made to understand how disruption of normal functions of ATPase activity may lead to different phenotypes of the disease. Although many pathogenic mechanisms contributing to AHC and RDP are still unknown, AHC phenotypes have been better understood and delineated, thus, in the last years, a genotype–phenotype correlation has been attempted in order to classify main discrete phenotypes. AHC is a complex condition where clinical picture includes paroxysmal events fluctuating over time, dystonia, epilepsy, ataxia as well as intellectual disability and behavioral disorders; consequently, understanding the natural course, prognosis and expectance is very crucial for

patients' care, clinicians, and care-givers. For the three most frequent and recurrent mutations in the population (as shown in Figure 3), we are reasonably able to know what clinical course will be, what conditions we have to treat, and maybe, predict the prognosis. Unfortunately, a relatively small percentage of patients remains without diagnosis or does not fall in one of these three discrete phenotypic categories; most of them present neurological signs and symptoms variably associated revealing the nature of continuum spectrum of ATP1A3 disease. Nevertheless, for all patients, understanding the ultimate molecular mechanisms underlying the disruptions of ATP1A3 protein function is the goal to achieve new therapeutic approaches. In vitro modelling as well as animal models of disease increasingly phenotyping the human clinical condition are the promising framework where new effective treatment can be developed.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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