Alternating Hemiplegia of Childhood and *ATP1A3*-Related Diseases

Insights From a Decade of Discovery and Collaboration

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Abstract

This report presents key insights from the 2022 annual conference held in Edinburgh, commemorating the 10th anniversary of the discovery of *ATP1A3* variants in alternating hemiplegia of childhood (AHC). This milestone event marked a decade of rapid advancements in research and clinical understanding, bringing together international experts and those with lived experience to reflect on progress, identify ongoing challenges, and shape the future of *ATP1A3*-related disease research. Over the past 10 years, our knowledge of *ATP1A3*-related diseases has expanded significantly, revealing a broader clinical spectrum, complex genotype-phenotype correlations, and novel pathophysiologic mechanisms. This symposium provided new data on cardiac and respiratory involvement in AHC, the impact of Na^+, K^+-ATPase dysfunction on neurodevelopment, and the evolving understanding of progressive disease trajectories. The conference also showcased emerging therapeutic strategies, including gene therapy, antisense oligonucleotides, and small-molecule interventions. This article synthesizes these discussions, offering a comprehensive overview of a decade of progress while highlighting the urgent need for continued collaboration. By integrating research, clinical expertise, and lived experience advocacy, the *ATP1A3* community is paving the way for improved diagnosis, enhanced care, and the development of targeted treatments for these ultra-rare conditions.

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Introduction

The past decade has marked a profound journey in the understanding and management of AHC, an ultra-rare neurologic condition affecting approximately 1 in 1 million people. In 2012, the discovery of pathogenic variants in *ATP1A3* as a cause of AHC revolutionized our comprehension of the disease, sparking a decade of research, clinical advancements, and patient-centered initiatives. To commemorate this milestone, the 10th Annual *ATP1A3* in Disease Symposium was held in Edinburgh from October 19 to 21, 2022, bringing together researchers, clinicians, and individuals with lived experience. In this context, "lived experience" refers to individuals and families directly affected by ATP1A3-related diseases, whose first-hand perspectives inform research, care, and advocacy. The event, supported by a European Joint Rare Diseases grant, reflected on 10 years of progress, addressed key challenges, and established priorities for future research and clinical care. The integration of scientific expertise with patient and caregiver perspectives was central to the meeting, ensuring a collaborative, impactful approach to both its planning and delivery.

This article synthesizes conference insights, outlining advances in *ATP1A3*-related disorders, research challenges, and the need for patient-centered approaches. Rather than being a systematic

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Glossary

AHC = alternating hemiplegia of childhood; **ASO** = antisense oligonucleotide; **RECA** = recurrent episodes of cerebellar ataxia.

review, this article reflects expert-led discussions from the symposium, distilling key research updates and clinical priorities identified by the foremost specialists in the field. As rare conditions with a small but dedicated research community, AHC and other *ATP1A3*-related diseases benefit greatly from expert consensus, making this synthesis a valuable representation of the field's progress and future directions, co-created with those with lived experience. By consolidating existing knowledge while fostering global collaboration, this symposium played a crucial role in driving the field forward and ensuring that future research is guided by both scientific discovery and real-world lived experience.[1]

Background

AHC was first described as a clinical syndrome in 1971,[2] with dysfunction of sodium-potassium ATPase (Na^+, K^+-ATPase) pumps being implicated in the pathophysiology 8 years later.[3] In 1987, the first evidence for a genetic basis for these Na^+, K^+-ATPases was discovered,[4] with advances in genetic sequencing in the succeeding decades leading to the implication of *ATP1A3* in rapid-onset dystonia parkinsonism in 2004.[5] In 2012, *ATP1A3* was implicated as the genetic basis for AHC,[6] leading to an exponential growth in research into this condition. In the 40 years between the first description of the condition and the disease association of *ATP1A3*, there were 84 publications on AHC. In the 10 years since the gene was identified, there have been 342 publications on *ATP1A3*-related diseases.[7]

ATP1A3 and Sodium-Potassium ATPase

ATP1A3 encodes the α3 subunit of the sodium-potassium ATPase (Na^+, K^+-ATPase), a member of the P-type ATPase family.[8] Na^+, K^+-ATPase has a crucial role in maintaining ion gradients and potassium clearance,[8] which is essential for a variety of cellular processes.[9]

Genotype/Phenotype Matching

The relationship between *ATP1A3* variants and disease phenotypes was a key theme of the symposium's research sessions, particularly during the session chaired by Dr. Simona Balestrini. Dr. Aikaterini Vezyroglou presented findings on genotype-phenotype correlations, highlighting the predictive value of specific variants while also acknowledging considerable variability among individuals. These insights are shaping a more nuanced approach to diagnosis and disease management.

Several clinical syndromes have been found to be associated with variants in the *ATP1A3* gene, allowing us to understand AHC within the broader context of *ATP1A3*-related diseases[7]:

- Rapid-onset dystonia parkinsonism[5]
- Alternating hemiplegia of childhood[6]
- Early infantile epileptic encephalopathy[10]
- Fever-induced paroxysmal weakness and encephalopathy[11]
- Recurrent episodes of cerebellar ataxia (RECA)[12]
- CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss)[13]
- Early profound epileptic encephalopathy with polymicrogyria[14]

Genetic sequencing advancements have led to the discovery of 168 variants in the *ATP1A3* gene.[7,15] These variants are described using transcript NM_152296.5 and protein reference NP_689509.1 (isoform 1). Despite this growing list, around half of the patients with AHC possess one of only 3 variants:

- c.2443G>A (p.E815K): associated with a severe phenotype in most of the cases
- c.2401G>A (p.D801N): typically linked to a more moderate phenotype
- c.2839G>C (p.G947R): predominantly associated with milder phenotypes[15]

However, individuals within these genotype groups do not always show consistent phenotypes. Families often report varied phenotypic expression even among those with the same genotype.

In addition to these 3 variants, there are 5 other prevalent *ATP1A3* variants that exhibit strong associations with distinct phenotypes:

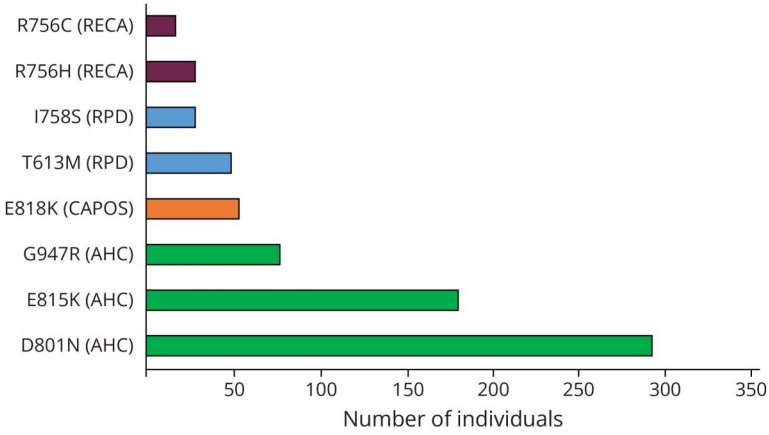
- c.2266C>T (p.R756C) and c.2267G>A (p.R756H) are linked to RECA
- c.2273T>G (p.I758S) and c.1838C>T (p.T613M) manifest predominantly in RPD
- c.2452G>A (p.E818K) correlates with CAPOS syndrome

The 8 most common *ATP1A3* variants are associated with distinct phenotypes (Figure), but rarer and benign variants complicate genotype-phenotype correlation.[15]

Mechanisms of Cellular Dysfunction

The molecular and cellular dysfunction underlying *ATP1A3*-related diseases was explored in depth during laboratory-

Figure The 8 Most Prevalent ATP1A3 Variants Associated With Disease in the 1,092 Reviewed Patients Reported in the Literature From 2004 to 2021



X-axis shows number of individuals. Used with permission from Vezyroglou et al.[15]

focused sessions chaired by Dr. Steve Clapcote. Prof. Anita Aperia (Karolinska Institutet) presented on the mechanisms driving neuronal dysfunction while Prof. Gareth Miles (University of St Andrews) discussed the impact of pathogenic *ATP1A3* variants on motor networks within the spinal cord. These discussions underscored the diverse ways in which the α3 subunit of Na^+, K^+-ATPase dysfunction manifests, influencing both clinical phenotype and potential therapeutic targets.

For example, in early infantile epileptic encephalopathy, prevalent pathogenic *ATP1A3* variants can lead to misfolded Na^+, K^+-ATPase proteins, triggering the unfolded protein response and causing endoplasmic reticulum stress and expansion. This disruption of cellular homeostasis may contribute to disease severity.[14] Conversely, fever-induced paroxysmal weakness and encephalopathy is attributed to the R756H ATP1A3 variant causing internalization of Na^+, K^+-ATPases from the plasma membrane to lysosomes. Specific *ATP1A3* variants such as c.2443G>A (p.E815K) and c.419A>T (p.Q140L) have been found to affect essential binding sites within the Na^+, K^+-ATPase, potentially elucidating disease mechanisms.[8]

Despite advances, the cellular impact of ATP pump dysfunction remains under study, including Na^+, K^+-ATPase α3 activation in neurons. Fluctuations in neuronal activity due to intracellular sodium exceeding 20 mM have been demonstrated, with afterhyperpolarization (AHP) being Na^+, K^+-ATPase–dependent.[16] This loss of AHP has been posited as a potential contributor to dystonic attacks in AHC, suggesting calcium-dependent ion channels as potential therapeutic targets.[17]

Impairment in the generation of AHP in the spinal cord may also play a role in AHC.[18] The α3 subunit of Na^+, K^+-ATPase plays an important role in generating ultraslow AHP (usAHP), critical for regulating spinal motor units. Dysfunction in these units due to pump-related issues may contribute to motor symptoms in *ATP1A3*-related diseases.[19]

Despite these advances in our understanding of the genetic and molecular mechanisms underlying *ATP1A3*-related diseases, the substantial heterogeneity makes matching phenotypes with specific genetic variants challenging. Future research aims to establish diagnostic criteria and correlations between genotypes and phenotypes.[7]

Diagnosis and Clinical Considerations

Diagnosis of AHC remains a complex challenge, requiring recognition of a constellation of clinical features. A session chaired by Dr. Aikaterini Vezyroglou featured Dr. Ailsa McLellan on diagnostic delays and prevention strategies. In addition, Prof. Mohamed Mikati (Duke University) outlined formal diagnostic criteria for AHC:

Aicardi criteria, subsequently modified,[20-22] are as follows:

1. Early onset: typically manifests before 18 months of age
2. Paroxysmal hemiplegia or quadriplegia: characterized by transient episodes of paralysis affecting one or more limbs or the entire body
3. Additional paroxysmal events: includes tonic or dystonic attacks, oculomotor abnormalities, and autonomic dysfunction
4. Developmental delay or intellectual disability: often present in affected individuals
5. Choreoathetosis or dystonia: common motor abnormalities observed in AHC
6. Genetic associations: family history of AHC or a confirmed pathogenic ATP1A3 variant in the patient
7. Exclusion of other neurologic disorders: Critical in confirming the diagnosis, ensuring that symptoms are not attributed to other conditions

However, an important caveat is the variability observed in the relationship between clinical presentation and genetic confirmation. Not all patients meeting clinical criteria carry pathogenic *ATP1A3* variants. This underscores the necessity for a unified consensus not only in diagnostic criteria but also in approaches to management, prognosis, and research across *ATP1A3*-related diseases. Consensus requires collaboration among experts and stakeholders. However, given the rarity of AHC, assembling a sufficiently powered group for this approach poses a considerable challenge.[23]

In clinical practice, significant challenges exist in the diagnosis of AHC, due to both the varied clinical manifestations of the disease and the similarity of symptoms to other disorders. This emphasizes the need for the involvement of clinicians with expertise in paroxysmal disorders for accurate diagnosis. Collaborative networks and technological aids are also crucial tools in expediting diagnoses.[24]

AHC is a condition that evolves over time, with new symptoms often emerging in adulthood.[25] Early symptoms often include neurologic issues such as movement disorders, developmental and cognitive impairment, and seizures, but a wide range of additional symptoms may arise over time. These encompass behavioral concerns, gait disturbance, mood disruption, gastrointestinal problems, sleep disturbances, and respiratory and cardiac issues.[26] Currently, little is known about adult trajectories in AHC, although there are tentative data suggesting that some aspects such as movement disorders tend to worsen in adulthood.[27] Paroxysmal episodes may decrease with time, and new issues, such as psychiatric symptoms and muscle spasms, may arise. Acute regression after triggers, such as fever, has also been noted.[28]

Multisystem Manifestations of ATP1A3 Diseases

ATP1A3-related diseases encompass a broad spectrum of clinical manifestations that extend beyond the nervous system. While neurologic symptoms remain central, cardiac, gastrointestinal, respiratory, and psychiatric issues are increasingly recognized as key aspects of disease burden. Understanding the multisystem impact is critical for comprehensive clinical care.

Polymicrogyria and Structural Brain Abnormalities

Recent reports of polymicrogyria in a subset of individuals with *ATP1A3* variants have expanded the phenotypic spectrum, although such cortical malformations are not typical features of most *ATP1A3*-related diseases. These rare associations nonetheless suggest that Na^+, K^+-ATPase dysfunction may play a role in neurodevelopment in specific contexts. Recent research has drawn parallels between *ATP1A3*, ion channel genes (*SCN1A*, *SCN3A*),[29] and cortical gyri changes rarely occurring in conditions such as Dravet syndrome.[29,30] These findings suggest that altered ion homeostasis may contribute to severe neurodevelopmental manifestations.[31]

Sleep Dysfunction and Nocturnal Events

Historically, the diagnosis of AHC relied on the observation that paroxysmal symptoms resolve during sleep.[32] However, it is now clear that sleep disturbances themselves, including nocturnal seizures and episodes of abnormal breathing patterns such as central apnea, are a core feature of *ATP1A3*-related diseases, rather than merely an incidental finding, and that not all paroxysmal manifestations of AHC resolve with sleep. Polysomnographic studies have demonstrated lateralized electrographic spectral changes that precede hemiplegic episodes.[33] Furthermore, nocturnal seizures and sudden unexpected death in epilepsy risk are areas of increasing concern, underscoring the need for systematic sleep assessments in affected individuals.[34]

Respiratory Dysfunction and Airway Vulnerability

Respiratory involvement in *ATP1A3*-related diseases is highly prevalent, with up to 91% of patients experiencing airway-related issues.[e1] These include obstructive sleep apnea, impaired airway clearance, recurrent respiratory infections, and aspiration risk. Interventions may include airway clearance techniques, physiotherapy, surgical options (e.g., adenotonsillectomy), continuous positive airway pressure (CPAP) therapy, or noninvasive ventilation, depending on disease severity.[e2]

Gastroenterology

Gastrointestinal symptoms, including dysphagia and reflux, are common in *ATP1A3*-related diseases, often correlating with motor impairment and autonomic dysfunction.[35]

Cardiac Involvement and Arrhythmias

Imbalances in concentration and flux of intracellular ions play an important role in cardiac arrhythmias.[36] The *ATP1A3* gene is expressed in both the CNS and the heart, potentially leading to cardiac dysautonomia in AHC, during hemiplegic episodes or independently.[37] The possibility of cardiac involvement suggests an additional potential cause of sudden death in these patients,[38] underscoring the need for systematic cardiac investigation in AHC.[39]

Psychiatric and Behavioral Symptoms

Genetic variants in *ATP1A3* have been identified in a small number of patients with childhood-onset schizophrenia.[e3] While psychotic symptoms are rare in *ATP1A3*-related diseases, other manifestations such as autism spectrum disorder, attention-deficit hyperactivity disorder, depression, and anxiety are more frequently observed.[e4,e5] Currently, there are no disease-specific treatments, and medications are prescribed on an individual basis following standard approaches.[e6] Given the increased prevalence of psychiatric symptoms in individuals with *ATP1A3*-related diseases, routine screening for psychiatric disorders is recommended to support timely recognition and management.[e7]

Treatment Considerations

Treatment strategies aim to address both chronic manifestations—such as dystonia, epilepsy, and neuropsychiatric symptoms—and paroxysmal attacks, including hemiplegic episodes and seizure clusters. Owing to varied presentations and treatment responses, no single standard exists. This section highlights key treatment discussions from the symposium, rather than providing a full management review, and an individualized, person-centered treatment plan.

Dystonia

Dystonia occurs in both a chronic form and as paroxysmal episodes during attacks. Chronic dystonia, which is part of the Aicardi diagnostic criteria,[20] is managed using symptomatic treatments, including baclofen, trihexyphenidyl, levodopa, and tetrabenazine. Paroxysmal dystonia, which is often associated with pain, can be particularly distressing and may require a different treatment approach. Management of dystonia in AHC follows the same principles as in other motor disorders, focusing on the avoidance of triggers. For acute episodes, benzodiazepines or sleep-inducing agents are often used to provide symptomatic relief, although prophylactic symptomatic treatments as for chronic dystonia may also be helpful. The development of novel targeted therapies is an area of ongoing research.[e8]

Paroxysmal Attacks

Flunarizine, a nonselective calcium channel blocker, is one of the most commonly used pharmacologic treatments of AHC.[e9] While anecdotal reports and clinical experience suggest that it can reduce the frequency and severity of paroxysmal attacks, there are no randomized controlled trials to confirm its efficacy.[e9] In some individuals with the E815K variant, sudden discontinuation after long-term use has been associated with irreversible deterioration, although this has not been documented in patients with the D801N variant.[10] However, families report variability in response, with some experiencing decline on withdrawal, highlighting the need for caution.[10]

The efficacy of flunarizine appears to be genotype-dependent, with the strongest rationale for use in E815K-related AHC.[10] Given the lack of targeted treatments for AHC, flunarizine is often trialed across genotypes, although its precise mechanism in preventing acute deteriorations remains unclear.[e9] Unlike in hemiplegic migraine, no formal treatment guidelines exist for flunarizine in AHC, reinforcing the importance of expert clinical oversight when prescribing or withdrawing the drug.[e11]

Digitalis Derivatives

Digitalis (digoxin) has long been used in the treatment of cardiac arrhythmia because of its inhibition of Na^+, K^+-ATPase activity in cardiomyocytes. It has been postulated that digitalis derivatives could be synthesized to instead enhance Na^+, K^+-ATPase activity and, therefore, play a role in the management of AHC. Recent research has involved the synthesis of digitalis derivatives to generate cardiotonic steroids with improved neuronal specificity. Rat studies of one such derivative, BD-15, have shown increased Na^+, K^+-ATPase α3 activity, neuroprotective effects, and no cardiotoxicity, highlighting its promise as a potential AHC treatment.[e10]

Epilepsy

Incidence of epilepsy within *ATP1A3*-related diseases may be as high as 75%.[12,24] As with dystonia, the management of epilepsy in AHC follows general principles as practiced in other conditions, without any consensus on disease-specific strategies. Differentiating between epileptic seizures and seizure-like events associated with AHC can be particularly challenging because both may present with overlapping features. The speed of antiseizure drug titration may be particularly important in AHC because abrupt changes may lead to an imbalance of neuronal excitation and inhibition, which may in turn exacerbate acute attacks.[e9]

Recent studies suggest that cannabidiol (CBD) may have a role in reducing seizures in *ATP1A3*-related diseases, although its efficacy remains unproven in this context.[e17]

Multidisciplinary Team Work

Given the wide-ranging symptoms of *ATP1A3*-related diseases, a multidisciplinary team approach is essential for optimizing long-term patient care. This was highlighted in a comprehensive session chaired by Prof. Helen Cross, with expert contributions from Prof. Juan Kaski (cardiology, University College London), Dr. Don Urquhart (respiratory medicine, University of Edinburgh), and Dr. Helen Aspey (community paediatrics/palliative care, Great North Children's Hospital). Discussions underscored the importance of coordinated care, particularly as patients transition from pediatric to adult services.

Given the rarity of *ATP1A3*-related diseases, multidisciplinary collaboration is crucial. Coordination between neurologists; cardiologists; gastroenterologists; respiratory physicians; psychiatrists; and allied health professionals such as physical therapists, speech-language pathologists, occupational therapists, and dietitians may help ensure individualized care. The absence of standardized, disease-specific strategies means general principles of the disciplines are applied, as in other conditions incorporating neurodisability. Similarly, palliative care, which encompasses complex disease management beyond end-of-life care alone, and pain management strategies are tailored to the specific needs of the patients. The use of anticipatory or emergency care plans can aid families and practitioners in recognizing and managing acute deteriorations, including paroxysmal attacks, dystonic episodes, seizure clusters, sleep disturbances, and respiratory complications.[e12]

Patient and Family Engagement

ATP1A3 in Disease Symposium

The *ATP1A3* in Disease Symposium is an annual meeting dedicated to advancing research and clinical understanding of

ATP1A3-related diseases.[40] The 2022 meeting marked the 10th iteration of this event, continuing its role as a forum for sharing knowledge, research updates, and patient experiences. The standing committee, established in 2016, includes clinicians, researchers, and patient advocates from across Europe and worldwide, ensuring a broad representation of expertise and lived experience.[e13]

Lived Experience

A powerful example of patient engagement at the symposium was a presentation by a young woman living with CAPOS syndrome. She described her experiences growing up with progressive visual and hearing impairments, highlighting the challenges of navigating education, social interactions, and the health care system. Her journey involved moving between mainstream and specialist educational settings, often struggling to access appropriate support. She also discussed cultural perceptions of disability and the barriers she faced—not just regarding medical symptoms but also in societal attitudes and accessibility. In addition to her current sight loss, she said that she feared losing her ability to hear more than her ability to walk. Through her story, she underscored the need for a holistic approach to *ATP1A3*-related diseases, where medical interventions are complemented by systemic and societal accommodations. Her lived experience provided invaluable insight into the everyday realities of these conditions, reinforcing the importance of patient-centered approaches in both clinical care and research.

The Good Diagnosis Project

The Good Diagnosis project, conducted by Genetic Alliance UK, focuses on understanding the diagnostic journey experiences of individuals with rare conditions. This initiative aligns with the goals outlined in the UK Rare Diseases Framework, published by the Department of Health and Social Care in January 2021. The framework emphasizes the importance of accelerating diagnosis, increasing health care professional awareness, and improving coordinated care.[e14]

Three key themes emerged from the workshops[e15]:

1. Diagnostic experiences were significantly shaped by involved health care professionals
2. Clinician knowledge about rare conditions expedites identification, acceptance, referrals, and necessary tests
3. Equipping health care professionals with reliable information and resources enhances their ability to aid individuals with rare conditions

Patient Engagement in Research and Development

The active involvement of individuals with lived experience has shaped research priorities for *ATP1A3*-related diseases, ensuring that patient and family perspectives guide both clinical and scientific directions.[e16] At the symposium, patient representatives and caregivers played a key role in discussions, particularly regarding the complexity of symptoms beyond paroxysmal attacks. Families emphasized the need for research that addresses dystonia, seizures, sleep disturbances, and autonomic dysfunction.[23]

Another recurring theme was the transition from pediatric to adult care. Given the lifelong nature of *ATP1A3*-related diseases, families highlighted the significant challenges in securing appropriate adult health care once pediatric services are no longer accessible.[e16] Improving quality of life, including interventions that enhance daily living, communication accessibility, and psychosocial support, was also a priority for families.[e3] These patient-driven insights have played a central role in shaping the research agenda, ensuring that future studies reflect the needs of those most affected.[e16]

Beyond research priorities, patients and caregivers have also influenced clinical trial design, ensuring that outcomes measured in studies are meaningful to those living with *ATP1A3*-related diseases. The focus has expanded beyond standard clinical markers to include functional abilities, independence, and overall well-being.[e16]

Patient involvement has also improved recruitment strategies, with families helping to develop more inclusive trial designs that acknowledge the challenges of participation faced by individuals with AHC.[e19] Furthermore, accessibility remains a critical factor, and lived experience feedback has influenced trial methodologies to accommodate physical limitations, reduce participation burden, and incorporate remote monitoring where possible.[e19] These collaborative efforts have led to a more patient-centered research approach, increasing the likelihood of studies delivering impactful clinical results.

Global Collaboration and the International Bureau for Epilepsy

An established model of structured patient engagement is the International Bureau for Epilepsy, which has developed a global epilepsy advocates program aimed at empowering communities, educating health care professionals and researchers, and involving patients and families earlier in research.[e16] Discussions at the symposium highlighted this approach as a potential framework for enhancing patient engagement in *ATP1A3*-related diseases, advocating for early and sustained patient involvement in research and health care planning.

The successes observed in epilepsy research, largely driven by patient-led initiatives, illustrate the broader impact of integrating lived experience into rare disease research. Lessons from the epilepsy model reinforce the importance of patient-driven advocacy in shaping research priorities, accelerating clinical translation, and improving health care outcomes.[e19]

Lessons for Other Rare Disease Communities

The AHC community's approach to patient engagement offers a valuable example of how rare disease groups can help shape research and clinical care. A key strategy has been the

development of natural history registries, supporting the collection of longitudinal data to better understand disease progression and identify potential therapeutic targets.[e17] Collaborative networks have also emerged, bringing together patients, caregivers, researchers, and clinicians to share knowledge; enhance research coordination; and develop community-led initiatives.[e18]

In addition, the advocacy efforts of the AHC community have contributed to policy discussions, helping to inform health care strategies, influence research-funding priorities, and improve access to emerging treatments. The approaches used by the AHC community provide helpful insights into how structured patient engagement can contribute to progress in research and care.[e16]

Future Directions for Patient Engagement

The active role of patients and caregivers in *ATP1A3*-related research and clinical advancements underscores the importance of sustained collaboration between families, scientists, and health care professionals. By ensuring that scientific progress remains aligned with the real-world needs of those most affected, the *ATP1A3* community continues to advance patient-centered research, policy, and clinical care models.[e16]

What Is in a Name?

The debate over renaming "alternating hemiplegia of childhood" was one of the most impassioned conference discussions, with family members and carers particularly vocal. While the name has historical significance and has helped raise awareness, many argued that it does not fully reflect the condition's complexity.

Families and adult patients argued that "childhood" in the name is misleading and stigmatizing, contributing to barriers when transitioning to adult care. Many described their adult children being excluded from services because of the misconception that AHC is solely a childhood disorder. The distinction between "starts in childhood" and "only in childhood" was repeatedly emphasized.

In addition, families questioned the focus on "alternating hemiplegia," highlighting that the name overlooks key symptoms such as dystonia, seizures, and autonomic dysfunction. Some felt that this narrow focus risks misdiagnosis and under-recognition of nonmotor symptoms. Proposed alternatives, such as "alternating hemiplegia complex," aim to better reflect the disease's breadth while retaining the familiar AHC abbreviation for advocacy purposes.

However, some clinicians, researchers, and families were cautious, concerned that a name change could disrupt existing awareness and recognition in medical literature. The debate reflected necessary tension between accuracy and continuity. What was clear is that patient and family voices must be central in any renaming decision. The condition, once seen as non–life-threatening, has proven life-limiting for some. Recent patient losses have heightened the urgency for continued research and consensus, ensuring that any change is shaped by lived experience.

Research Considerations

Natural History Studies

Natural history studies are crucial for understanding rare diseases. International collaborations and workshops dedicated to natural history, as has happened in other rare conditions such as Dravet syndrome, are key steps in advancing research methodology and treatment planning in AHC.[e17] OBSERV-AHC,[e18] a prospective observational natural history and therapy study on AHC, was launched in September 2018 and will collect data on over 100 patients, aiming to elucidate adult trajectories, identify relevant clinical scales and biomarkers,[25] and improve understanding of long-term outcomes. While no definitive data currently exist on life expectancy in AHC, retrospective reviews suggest that AHC may increase risk of premature mortality from epilepsy-related sudden death respiratory complications and cardiac dysfunction. The OBSERV-AHC study may provide crucial insights into these risks and help guide long-term management strategies.

Designing Clinical Trials

Designing clinical trials in AHC and other *ATP1A3*-related diseases presents significant challenges.[e19] First, the rarity of the condition can make patient identification and recruitment difficult. Clinical registers and patient databases, such as those that have been effectively used in Dravet syndrome, may provide a way forward.[e20] Collaborative networks using natural history studies aim to enhance scientific research, monitor treatment efficacy, and pave the way for precision therapies.[e21] Second, the absence of disease-specific clinical outcome measures for AHC can make trial design problematic. Ongoing efforts involve collaboration between clinicians, researchers, and families with lived experience to develop an AHC-specific scale aimed at evaluating disease severity, treatment effectiveness, and genotype-phenotype correlations. Involvement of patient advocacy organizations in the validation process, ensuring comprehensive input from all stakeholders, is important.[e22] Defining measurable outcomes in AHC trials presents challenges akin to those seen in Lennox-Gastaut syndrome, such as heterogeneity of symptoms and lack of established biomarkers. This necessitates compromises for meaningful research outcomes. Future trials in AHC must attempt to mitigate bias, advocate for patient involvement, and have well-defined research questions and reliable end points.[e19]

Animal Studies

Animal studies have been pivotal in comprehending *ATP1A3*-related diseases. Studies conducted on less complex organisms such as *Drosophila* demonstrated reduced motor function,

increased recovery time to mechanical stress, and occurrences of seizures/paralysis due to specific variants.[e23] Subsequent studies involving increasingly complex animals have offered further insights. Mutant zebrafish have shown deficits in locomotion and EEG patterns, as well as structural changes in the brain,[e24] with mouse models revealing deficits in motor function, altered seizure thresholds, and impaired social interaction.[e25] Indeed, mouse models have been pivotal in deciphering the pathophysiology and mechanisms underlying *ATP1A3*-related diseases. Given the limited number of patients, lack of comprehensive natural history studies, and sparse postmortem data, mouse models are instrumental in bridging the knowledge gap.[e26] The Jackson Laboratory Rare Disease Translational Center serves as a repository for existing mouse models and collaborates with rare disease foundations to develop new models and conduct preclinical therapeutic tests. Understanding the impact of therapeutics in the context of the entire organism becomes crucial for FDA-required safety and efficacy assessments before clinical trials. A mammalian model allows for in vivo exploration, offering insights into systemic effects and therapeutic responses essential for translational research.[e27] The advent of clustered regularly interspaced short palindromic repeats (CRISPR) gene editing broadens the scope for genetically modifying various species, enhancing the spectrum of animal models available for study.[e26]

The Future

The final sessions of the symposium, chaired by Prof. Arn Van Den Maagdenberg, focused on emerging treatment strategies. Prof. Cat Lutz (The Jackson Laboratory) presented an update on AAV9-mediated *ATP1A3* gene therapy while Mr. Alexander Sousa (Broad Institute of MIT and Harvard) explored the potential of CRISPR-based gene editing. In addition, Prof. Alfred George (Feinberg School of Medicine) introduced antisense oligonucleotide (ASO) as a potentially transformative approach for *ATP1A3*-related diseases.

Cellular Modeling

Ongoing research uses cell models to identify compounds that can reduce abnormal ion levels seen in *ATP1A3*-related disorders. A commonly used model is the SH-SY5Y cell line, originally derived from a neuroblastoma in a 4-year-old girl. These cells can differentiate into neuron-like cells, making them useful for studying neuronal function and disease mechanisms. When pathogenic *ATP1A3* variants—such as the D801N variant—are introduced into SH-SY5Y cells, researchers observe changes including abnormal intracellular sodium levels, increased acidity, and increased rates of cell death. These cellular features are thought to mimic key aspects of disease pathology in AHC.[e28] Transcriptome analysis of these modified cells suggests that *ATP1A3* expression may be reduced over time, potentially due to epigenetic silencing mechanisms. However, it is also possible that the observed reduction is simply due to the presence of null variants that fail to express functional protein, and this has not yet been ruled out.[e28]

Of interest, these transcriptomic studies also show upregulation of genes involved in DNA repair pathways, although the mechanism behind this is still unclear. One advantage of the SH-SY5Y model is its suitability for high-throughput drug screening. Using this system, researchers screened a large compound library and identified 27 drugs that reduced excessive intracellular sodium, specifically in cells carrying the D801N variant. Of these, 3 compounds have demonstrated therapeutic promise in a subsequent animal model, and a Phase I clinical trial is now being planned to assess their safety in humans.[e28]

CRISPR-Based Gene Editing

Gene therapies offer promising prospects for the future treatment of AHC and *ATP1A3*-related diseases. Research is currently ongoing in the use of CRISPR-based precision gene editing, specifically prime editing, for correcting disease-associated genetic variants. CRISPR is a sequence found in the genomes of bacteria and other microorganisms. This system has been adapted for targeted gene editing in various organisms, including humans. The CRISPR-Cas9 system allows researchers to precisely modify or edit specific genes by introducing changes to the DNA sequence. Cas9, an enzyme associated with CRISPR, splices the DNA at the desired location. Subsequent cellular repair processes can then be harnessed to introduce changes, deletions, or insertions in the targeted gene.[e29] Work is currently ongoing in developing a prime editing strategy to correct the ATP1A3 D801N variant in a mouse model of AHC. Using cell-based experiments, researchers have developed an optimized prime editing strategy that efficiently corrects the c.2401G>A (p.D801N) variant while minimizing undesired editing by-products.[e30] This is a key step toward using prime editing in AHC animal models to assess survival and symptom reduction.[e31]

Antisense Oligonucleotides

Furthermore, the potential of antisense oligonucleotides (ASOs) as a therapeutic approach for treating AHC has been explored. An ASO is a single-stranded RNA molecule that pairs to a messenger RNA (mRNA) molecule. In doing so, the ASO blocks the mRNA's translation into a given protein. ASOs can be used to reduce the levels of mRNA carrying disease-causing variants, thereby preventing their expression. This strategy has been successful in genetic disorders of the nervous system. In the case of AHC, there is evidence suggesting a dominant-negative mechanism. An ongoing proof-of-concept study aims to investigate whether selectively suppressing the expression of the mutant *ATP1A3* allele using ASOs is feasible, and whether it affects protein levels and function. At present, no specific pathogenic variants have been designated as primary targets for ASO therapy, and ongoing research aims to determine whether variant-specific or general allele suppression would be the most effective approach.[e32]

Summary and Future Directions

The 10th Alternating Hemiplegia of Childhood and *ATP1A3*-Related Diseases Symposium highlighted the significant advancements in understanding and developing treatment

strategies for *ATP1A3*-related diseases since the identification of pathogenic variants in the *ATP1A3* gene and their role in disease pathogenesis. The spectrum of *ATP1A3*-related diseases has expanded from 3 to 7 distinct conditions, with AHC being the most prevalent. However, the complexity of AHC is further compounded by the fact that not all individuals with AHC have *ATP1A3* variants, adding to the challenges in deciphering the genotype-phenotype relationship in this ultra-rare disease.

The conference was pivotal not only in presenting cutting-edge research but also in bringing together families and patients—who are, in fact, the true experts in their lived experience. Their insights were not only shared but also actively co-created research priorities, influencing discussions on treatment approaches, clinical trial design, and long-term care strategies. A major theme emerging from the symposium was the need for improved symptom management beyond hemiplegic episodes, with growing recognition of the impact of dystonia, sleep disturbances, autonomic dysfunction, and psychiatric manifestations on patients' quality of life. The importance of ensuring seamless transition from pediatric to adult health care services was also emphasized because *ATP1A3*-related diseases are lifelong conditions that require sustained, multidisciplinary support.

Therapeutic discussions focused on emerging gene-targeting treatments such as ASO and CRISPR, alongside refining symptomatic treatments including flunarizine and benzodiazepines. Although promising, these therapeutic strategies remain in early stages and the field is now moving toward rigorous preclinical validation and patient-centered clinical trial design. The symposium reinforced that progress in *ATP1A3* research will depend on international collaboration, improved natural history data collection, and integration of patient perspectives into research frameworks to ensure that future developments align with real-world patient needs.

Despite significant strides made in the decade since the gene's discovery, the ongoing reality for those living with AHC remains challenging. As Dominique Poncelin, former President of the French AHC Family Group (AFHA), poignantly observed, "One year is almost nothing for research—12 years between the first blood bank and gene discovery for AHC. But one year means 365 days of stressful or worrying situations for families due to daily life."

This underscores the critical need for targeted treatments, the urgency of continued research, and the importance of a sustained, collaborative approach that integrates scientific progress with patient-led priorities. The next decade will hopefully see refinement of therapeutic targets, advanced gene-based interventions, and strengthened multidisciplinary care to improve clinical outcomes and quality of life.

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