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Developing a pathway to clinical trials for *CACNA1A*-related epilepsies: A patient organization perspective

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***Abstract*:** CACNA1A-related disorders are rare neurodevelopmental disorders linked to variants in the CACNA1A gene. This gene encodes the α1 subunit of the P/Q-type calcium channel Cav2.1, which is globally expressed in the brain and crucial for fast synaptic neurotransmission. The broad spectrum of CACNA1A-related neurological disorders includes developmental and epileptic encephalopathies, familial hemiplegic migraine type 1, episodic ataxia type 2, spinocerebellar ataxia type 6, together with unclassified presentations with developmental delay, ataxia, intellectual disability, autism spectrum disorder, and language impairment. The severity of each disorder is also highly variable. The spectrum of CACNA1A-related seizures is broad across both loss-of-function and gain-of-function variants and includes absence seizures, focal seizures with altered consciousness, generalized tonic-clonic seizures, tonic seizures, status epilepticus, and infantile spasms. Furthermore, over half of CACNA1A-related epilepsies are refractory to current therapies. To date, almost 1700 CACNA1A variants have been reported in ClinVar, with over 400 listed as Pathogenic or Likely Pathogenic, but with limited-to-no clinical or functional data. Robust genotype–phenotype studies and impacts of variants on protein structure and function have also yet to be established. As a result, there are few definitive treatment options for CACNA1A-related epilepsies. The CACNA1A Foundation has set out to change the landscape of available and effective treatments and improve the quality of life for those living with CACNA1A-related disorders, including epilepsy. Established in March 2020, the Foundation has built a robust preclinical toolbox that includes patient-derived induced pluripotent stem cells and novel disease models, launched clinical trial readiness initiatives, and organized a global CACNA1A Research Network. This Research Network is currently composed of over 60 scientists and clinicians committed to collaborating to accelerate the path to CACNA1A-specific treatments and one day, a cure.

Plain language summary

Designing a plan to find treatments for epilepsies linked to the CACNA1A gene and test them in clinical trials for FDA approval

CACNA1A-related disorders are rare conditions that affect brain development and are caused by changes in the *CACNA1A* gene. This gene provides instructions for making a protein called Cav2.1, which plays a crucial role in fast communication between nerve cells. The disorders can lead to various neurological problems such as seizures, epilepsy, developmental delays, intellectual disability, and autism. The severity of these disorders varies, and individuals may experience a broad range of seizures. More than 1700 different genetic changes in the *CACNA1A* gene have been identified, with over 400 considered likely to cause the disorders. However, there is limited information on the clinical and molecular aspects of these changes.

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Despite the significant impact on individuals' lives, there are currently no definitive treatments for *CACNA1A*-related epilepsies. To address this gap, the CACNA1A Foundation was established in March 2020. The Foundation aims to improve the lives of individuals with *CACNA1A*-related disorders, including epilepsy. It has developed a comprehensive set of tools, including patient-derived cells and new disease models, to advance research. Additionally, the Foundation has initiated initiatives to prepare for clinical trials and has formed a global CACNA1A Research Network with over 60 scientists and clinicians collaborating to develop specific treatments and, ultimately, find a cure.

Keywords: CACNA1A, developmental and epileptic encephalopathy, epilepsy, rare disorder

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Introduction

CACNA1A-related epilepsy

The *CACNA1A* gene encodes for the alpha1A pore-forming subunit of Cav2.1, the P/Q type high voltage-gated calcium ion channel that is globally expressed in the brain and enriched in areas such as the cortex, hippocampus, thalamus, striatum, and cerebellum. Cav2.1 plays a crucial role in many cellular processes, including gene regulation, and fast presynaptic neurotransmission. Variants in *CACNA1A* have been historically linked to autosomal dominant neurological disorders such as spinocerebellar ataxia type 6, familial hemiplegic migraine type 1 (FHM1), and episodic ataxia type 2 (EA2).[1,2] However, a link between *CACNA1A* and absence epilepsy was found earlier in the spontaneous *tottering* (*tg*) mouse mutant and its related alleles. The *tg* mouse was the first model to link the generalized spike and wave discharges and behavioral arrests observed in patients with childhood absence epilepsy to a single gene disorder.[3] In addition to absence seizures, ataxia, and in the case of the more severe allele *leaner (tg(ln))*, cerebellar atrophy was also observed.[4] Positional cloning eventually mapped the *tg* variant to the *CACNA1A* gene, establishing it as a key cellular component in absence epilepsy.[5,6] *CACNA1A* variants were then associated with a range of epilepsies in humans, including the more severe developmental and epileptic encephalopathies (DEEs).[7,8]

Over the next decade, the *CACNA1A* seizure spectrum itself expanded beyond generalized and absence epilepsy to encompass status epilepticus, tonic, tonic-clonic, atonic, simple motor seizures, focal seizures with altered awareness, and infantile spasms.[9–11] *De novo* variants in *CACNA1A* were linked to epileptic encephalopathies, accounting for nearly 1% of cases.[8,12,13] There are also rare cases of biallelic variants, some of which presented with severe, drug-resistant DEE and, in very rare cases, premature mortality.[14–16] Missense variants linked to DEE encompass both gain-of-function (GoF) and loss-of-function (LoF) but through different mechanisms.[17] The seizure profile of GoF and LoF missense variants does overlap, but some distinctions have emerged. Status and myoclonic seizures are more predominantly seen in individuals with GoF variants, while absence seizures are more commonly observed in those with LoF variants.[11] The spectrum of *CACNA1A*-related disorders has also grown to include congenital ataxia, hypotonia, dystonia, behavioral and cognitive impairment, global developmental delay, intellectual disability, and autism, all at varying levels of severity and reported with and without seizures.[7,10,11,18–21] While seizures are not seen in all individuals with *CACNA1A* variants, the prevalence rate has been reported as high as 60–70%[10,11] and as low as 20–25% when the patient cohort includes more adults.[22] Further studies are needed to confirm whether this is truly the natural progression of seizures as patients age, or if it is because there has only been a relatively small adult population identified. In addition, status epilepticus or seizure-like events have been seen to precede or follow hemiplegic migraines (HM).[20,23–25] Individuals diagnosed with EA2 were also shown to have a sevenfold increased risk of developing epilepsy.[26] What links ataxia and migraine to epilepsy is still

unclear, as there are distinct mechanisms underlying EA2 and HM. However, given that seizures are reported with both disorders, the relationship between them warrants further investigation and could shed new light on therapeutic approaches with a broader impact.

Limitations in developing treatments and care

Although *CACNA1A* variants have been linked to distinct disease phenotypes for over 25 years, and despite significant progress in understanding disease mechanisms using various animal and cellular models in the last few decades, translation to the clinic remains a huge challenge. The estimated incidence rate for *CACNA1A*-related disorders is 1:11,700,[27] indicating a large patient population in need of better treatment and care. Among the roadblocks identified in the quest for better therapies, a comprehensive understanding of *CACNA1A*-related disorders in humans has yet to be reached. Molecular and clinical data are available for a limited number of variants and are not always presented together. Several genotype–phenotype studies have been published with a limited number of patients, but the spectrum and overlap of symptoms among variants remain a challenge in trying to tease out robust correlations.

This is also a barrier to understanding and connecting the disease mechanisms that contribute to the spectrum of seizures in humans. Work in rodent models of the disease has revealed the complex mechanisms underlying the emergence of seizures in *CACNA1A*-related disorders. Cellular mechanisms of *CACNA1A*-induced absence epilepsy are traced back to a disruption of thalamocortical circuitry, including reduced synaptic release from layer VI pyramidal neurons projecting to the thalamus,[28] increased thalamic excitability,[29] and enhanced cortical and limbic excitability due to failure of synaptic release from GABAergic interneurons.[30–32] However, whether similar mechanisms apply to humans and how this can be tackled with more targeted therapies remain to be investigated. Functional studies of variants identified in patients with *CACNA1A*-related DEE have revealed that severe epilepsies can result both from GoF effects on channel gating properties, as well as from trafficking deficits in dominant negative LoF variants.[17] Whether other molecular mechanisms contribute to the net effects of specific variants must be further explored.

Finally, current therapies for patients with *CACNA1A*-related epilepsies are primarily symptomatic and do not target disease-specific mechanisms. Anti-seizure medications with broader mechanisms of action continue to treat only the symptoms, not the deficits induced by the variants themselves. Furthermore, more focus is needed on developing comprehensive and coordinated care pathways for individuals exhibiting the wide spectrum of *CACNA1A*-related symptoms that manifest at different stages of development.[33] This is especially true when some disorders, such as HM and DEE, require immediate medical intervention because they can become life-threatening.

The CACNA1A Foundation's programmatic areas of focus

The CACNA1A Foundation is the first and only global patient-centered organization whose mission is to find effective treatments and a cure for *CACNA1A*-related disorders. It is focused on building a collaborative network of CACNA1A patients, families, clinicians, and scientists to collectively raise awareness and accelerate the understanding, diagnosis, and treatment of *CACNA1A*-related disorders, including *CACNA1A*-related epilepsy. The Foundation is a 501(c)(3) nonprofit established in the United States in 2020 by parents of children living with *CACNA1A* disorders and is advised by a Scientific Advisory Board composed of the leading United States and international researchers and clinicians in the field. In 2021, it received a highly competitive rare capacity-building grant from the Chan Zuckerberg Initiative. The Foundation's programmatic priorities are to advance research, support families, and raise awareness.

Advancing research

The Foundation supports research that holds the promise to improve the lives of individuals with *CACNA1A*-related disorders and their families by paving the way for clinical trials of life-changing treatments. The Foundation aims to have at least one treatment for the CACNA1A community in the clinical trial pipeline within the next 5 years. In furtherance of this goal, the Foundation has focused its first 3 years of work on (a) building a preclinical 'toolbox' with a biorepository of patient-derived induced pluripotent stem cells (iPSCs), animal disease models, and a novel

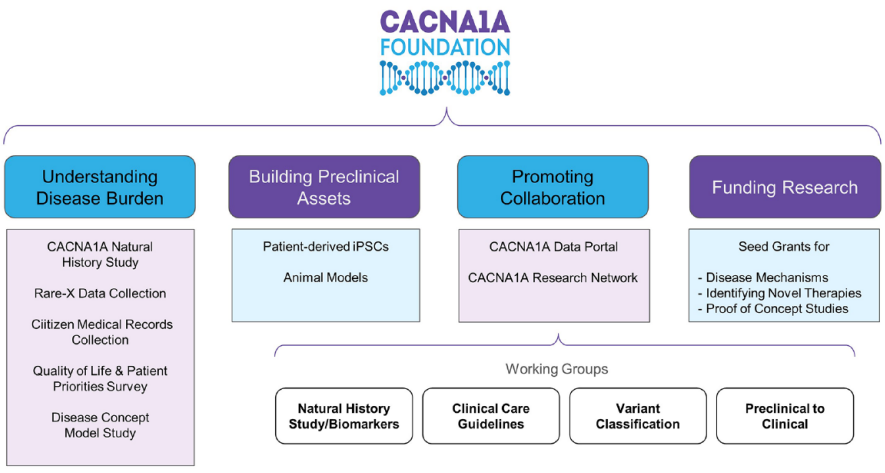

Figure 1. A summary of the CACNA1A Foundation's initiatives focused on advancing therapeutic development.

CACNA1A open access variant data portal, and (b) clinical trial readiness programs that include several natural history studies, a disease concept model (DCM), and a Quality-of-Life (Qol) survey (Figure 1). The Foundation also offers $50,000 seed grants to support research geared toward clinical trial readiness initiatives and treatment development. Since 2021, the Foundation has awarded over $400,000, which researchers have leveraged to apply for larger awards from the NIH and other funding sources. Through all these efforts, the Foundation has built a global CACNA1A Research Network of over 60 advocates, researchers, clinicians, and representatives from NIH and industry, encompassing over 25 different institutions, all of whom are committed to improving the quality of life for the CACNA1A community. The Foundation regularly convenes the Research Network through monthly meetings, community conferences, webinars, in-person Research Roundtables, and advocacy with the National Institute of Neurological Disorders and Stroke (NINDS).

Supporting families

One of the Foundation's fundamental purposes is to create a community for families affected by *CACNA1A*-related disorders. The Foundation has connected with over 250 families worldwide and provided resources to make their journeys easier. Its activities include hosting a community conference that brings families, researchers, and clinicians together to learn about *CACNA1A*-related research and the patient experience; virtual monthly support groups, including one devoted to families impacted by *CACNA1A*-related DEE; educational and interactive webinars, and comprehensive resources for clinicians, individuals living with *CACNA1A*-related disorders, and caregivers. The inaugural community conference was held virtually in the summer of 2021, followed by a hybrid conference in 2022. Over 100 families, researchers, and clinicians attended in person, with another 75 attending virtually. For some of the researchers, it was the first time they met an individual living with a *CACNA1A*-related disorder. For many of the families, it was their first time meeting the scientists studying the rare disease that impacts their loved ones. This historical event generated momentum among all stakeholders to work together to advance research. Through these family support efforts, the Foundation has been able to build a strong relationship with the patient community and advance research efforts around understanding the disease burden in the community.

Raising awareness

The Foundation also raises awareness about *CACNA1A*-related disorders among the general public and healthcare professionals to facilitate earlier diagnosis through genetic testing and to improve health outcomes. Every year, the Foundation leadership team attends major scientific and medical conferences, such as the American Epilepsy Society annual meeting, to disseminate CACNA1A-specific resources and meet with researchers, healthcare professionals,

and industry representatives about its efforts. Partnerships with genetic testing companies such as GeneDX and Probably Genetic have promoted awareness of the disease among newly diagnosed families and shortened the diagnostic journey. The Foundation started an annual CACNA1A Awareness Day campaign on March 19th, shares stories of individuals and families affected by *CACNA1A*-related disorders on our website, social media, and other news outlets, and hosts fundraisers to sustain our programs. The Foundation also has a Global Ambassadors program comprised of parents outside of the United States who have volunteered to help support the CACNA1A community in their geographical regions. In addition, they promote awareness of and advocacy for *CACNA1A*-related disorders and interact with local researchers and medical professionals on behalf of the Foundation.

At the heart of the Foundation's efforts is an emphasis on collaboration across similar rare disorders. The Foundation is a member of several epilepsy-focused consortia, including the Rare Epilepsy Network, DEE-P Connections, The Inchstone Project, and the Epilepsy Leadership Council. The Foundation is also a founding member of the Voltage-Gated Calcium Channel Collective (VGCCC). The VGCCC is a multi-stakeholder initiative dedicated to raising awareness and promoting collaboration across voltage-gated calcium channelopathies.

Collectively, these awareness initiatives enable the Foundation to identify additional patients, offer support, and establish connections with clinicians and researchers who may be interested in joining our Research Network.

Treatments and clinical trials for *CACNA1A*-related epilepsy and beyond – How a patient advocacy organization drives research forward

Building a patient-centric research roadmap

Advancing patient-centric research is central to the CACNA1A Foundation's mission and has been the focus of the Foundation's research initiatives since its inception. Those living with *CACNA1A*-related disorders and their families can provide crucial knowledge of how the disease presents and evolves to help inform the development of meaningful treatments to impact the full scope of disorders. The Foundation believes that its community should also have a voice at all stages of treatment development, from preclinical asset development to clinical trial readiness and the regulatory pathway, and it works to ensure that the patient community is engaged, and its perspective is reflected in all of the Foundation's efforts.

Building a preclinical 'Toolbox'

An early initiative of the Foundation has been to build a comprehensive preclinical 'toolbox' that includes patient-derived iPSCs and animal disease models carrying patient variants. The Foundation partnered with COMBINEDBrain, a consortium for developing outcome measures and biomarkers for neurodevelopmental diseases, to create a biorepository of patient-derived iPSCs. Cells from patient blood samples are reprogrammed into stem cells with the capability of differentiating into specific cell types, such as neurons, in which a disease can be studied. These lines are accessible through COMBINEDBrain and the Foundation to researchers in academia and industry to further *CACNA1A*-related research. To date, the Foundation's biorepository offers three completed iPSC lines, spanning LoF, GoF, and mixed-function variants, with several more in development. The V1393M line represents a recurrent pathogenic variant with HM and DEE.[10,11,17] Additional lines of variants linked to DEE are in development including R1349Q and A713T (Table 1).[17,34]

Animal models for *CACNA1A*-related diseases also exist in mice, *Drosophila melanogaster* (fruit fly), and *Danio rerio* (zebrafish; Table 1), many of which were established before the Foundation was formed. R192Q and S218L are variants that have been well characterized in mice and fruit

Table 1. Existing CACNA1A preclinical models and associated clinical phenotypes.

Cell models	Animal models		
Patient-derived iPSCs[a]	**Mouse**	**Fruit fly**	**Zebrafish**
V1393M (HM, DEE)[10,17] *R1667P* (ataxia, DD)[11,35] *Q1674SfsX* (ataxia, DD)[36] *A713T* (HM, DEE) – in progress[11,17] *R1349Q* (HM, DEE) – in progress[11,34]	*S218L* (FHM1, epilepsy, ataxia)[37] *R192Q* (FHM1)[38] *R1349Q* (HM, DEE)[b] *C1844X* (EA2)[b] *Tottering* series (absence epilepsy, ataxia, EA2)[b,5,6,39]	*S218L* (FHM1, epilepsy, ataxia)[40] *R192Q* (FHM1)[40] *R1673P* (ataxia, DD)[41] *R1664Q* (ataxia, DD)[41]	*L356V/fakir*[42] *Y1662N/tb204a*[43]

Variants are listed in reference to *CACNA1A* transcript NM_001127221.2.
[a]iPSC lines are available through the CACNA1A Foundation Biorepository at COMBINEDBrain.
[b]Mouse models are available through The Jackson Laboratory Catalog.
DD, developmental delay; DEE, developmental and epileptic encephalopathy; EA2, episodic ataxia type 2; FHM1, familial hemiplegic migraine type 1; HM, hemiplegic migraine; iPSCs, induced pluripotent stem cells.

flies as models of FHM1.[37,38,40] S218L mice also have ataxia and express one of the more severe GoF variants linked to Sudden Unexpected Death in Epilepsy (SUDEP).[44,45] The *tottering* series in mice, including *Rolling Nagoya* and *Leaner*, are used as LoF models for ataxia (including EA2) and absence and generalized epilepsy.[4,5,39,46,47] Other available mouse models include the R1349Q variant (Jackson Laboratory), which is linked to clinical phenotypes such as HM and DEE.[34] The Foundation has funded the development of novel animal models carrying human pathogenic variants, including a truncation variant C1844X linked to EA2 (Jackson Laboratory). Zebrafish models for locomotor deficits and epilepsy have also been published.[48,49] In addition, *Caenorhabditis elegans* (nematode) has proven to be an effective model for studying the biophysical properties of Cav2.1.[50,51] The impact of pathogenic human variants in this system is currently being explored. These animal models and patient-derived iPSCs are available through COMBINEDBrain, Jackson Laboratory, or academic labs (Table 1) to researchers interested in identifying disease mechanisms and developing and testing candidate therapeutics for proof-of-concept studies.

Clinical trial readiness

The Foundation has also focused on several clinical trial readiness initiatives, including the first CACNA1A Natural History study led by Dr. Wendy Chung, the Chief of the Department of Pediatrics at Boston Children's Hospital. This ongoing study has just over 100 patients enrolled. A publication on the first 47 patients in the cohort provided insight into the spectrum of seizures in *CACNA1A*-related disorders.[10] The Foundation has also partnered with RARE-X to mine its rare disease data collection platform for nearly 100 patients. A collaboration with Ciitizen's Rare Patient Network was launched in 2023 to utilize its platform to collect electronic medical records from the CACNA1A patient community. This platform has been successful in constructing comprehensive seizure profiles for other rare epilepsies.[52,53] Collaborations with COMBINEDBrain have also been launched to identify molecular biomarkers for *CACNA1A*-related disorders.

Recent projects have focused on extracting a clearer understanding of the patient perspectives and disease burden for those living with *CACNA1A*-related disorders and their caregivers. A DCM study in collaboration with the University of Pennsylvania Master of Science in Genetic Counseling Program, the Orphan Disease Center, and COMBINEDBrain was launched in the Fall of 2022. This project is structured around interviews with caregivers and clinicians that are systematically coded to identify the disease burden on families and meaningful endpoints for clinical trials. These data are often used during Patient-Focused Drug Development (PFDD) meetings with the FDA. The Foundation also developed and disseminated a QoL survey to the CACNA1A community to identify treatment priorities from the patient perspective: what symptoms impact patients and their families the most, what

improvements would be the most beneficial to improve QoL, and which symptoms or disorders should be priority targets for therapeutic development. The Foundation also aims to organize a patient listening session with the FDA in the next year and a PFDD meeting within 2–3 years, using data from the DCM and QoL studies. These events will also require a strong partnership with caregivers and patients to ensure that the perspectives of the CACNA1A patient community inform regulatory evaluation and decision-making.

CACNA1A data portal

Another collaborative research initiative spearheaded by the Foundation was the creation of an online CACNA1A Data Portal. This open science tool is the first to aggregate and curate a comprehensive database of existing clinical and molecular data for *CACNA1A* variants from the literature, CACNA1A Natural History Study, and patient cohorts from Children's Hospital of Philadelphia, the Cleveland Clinic, and Boston Children's Hospital. Through a seed grant to Dennis Lal, PhD at the University of Texas Health Sciences Center-Houston, the Foundation brought together researchers and clinicians from different institutions to create tools tailored for various stakeholders, including patients and families, physicians and genetic counselors, researchers, and industry members. A steering committee composed of Foundation leadership and its scientific advisors led this project over the last 2 years, along with molecular and clinical working groups that met monthly. Many of the researchers who helped with this effort were collaborators from the NIH-funded Channelopathy-Associated Epilepsy Research Center. The two working groups were eventually combined to finalize the portal. Resources include educational information and videos, variant analysis and interpretation, and access to existing and new data. The portal can be accessed through the following link: https://cacna1a-portal.broadinstitute.org/

Building a collaborative CACNA1A Research Network

The CACNA1A Portal has played a pivotal role in the formation of the global CACNA1A Research Network. Presently, the network comprises more than 60 clinicians, researchers, and representatives from the NIH and industry, actively participating in various events organized by the Foundation. This collaborative engagement with the Foundation, families, and among members ensures the Research Network remains abreast of ongoing research and maintains focus on patient-centric agendas.

The inaugural hosting of the annual, in-person CACNA1A Research Roundtable by the Foundation in the Fall of 2022 marked a significant milestone for the Research Network. The roundtable focused on identifying gaps in the CACNA1A field and developing approaches to accelerate the pathway to clinical trials for *CACNA1A*-related disorders. It also marked the start of the Foundation's work on developing a strategic research plan focused on getting treatment in the clinical trial pipeline within 5 years. In addition, it highlighted the need to develop clinical care guidelines for *CACNA1A*-related disorders, none of which existed. This collaborative initiative between the Foundation, families, and clinicians was launched in the Spring of 2023 to publish comprehensive care and treatment guidelines in the next 2 years.

The second CACNA1A Research Roundtable was held in the Fall of 2023, with over 50 attendees from the clinical and research community, program managers from NINDS, and representatives from industry. The Research Roundtable was preceded by a virtual CACNA1A Think Tank meeting through the Foundation's participation in a pilot Research Readiness program developed by RARE-X and the Orphan Disease Center. The Think Tank focused on understanding the nature of episodic *CACNA1A*-related disorders and highlighted the need for expanding studies on genotype–phenotype correlations, disease mechanisms, biomarkers, and outcome measures. The 2023 Research Roundtable continued the discussion, focusing on how to (a) best design clinical trials for disorders that are episodic and as broad as *CACNA1A*-related epilepsies and (b) how to build a strong proof-of-concept package to advance therapeutics through the regulatory pathway.

A concrete outcome from the Research Roundtable was the establishment of three working groups composed of members of the Research Network: Natural History/Biomarkers, Variant Classification, and Preclinical-to-Clinical. The

Natural History Study/Biomarkers group focuses on refining the CACNA1A Natural History Study to identify outcome measures and endpoints and build a potential placebo arm for clinical trials. In addition, the group aims to identify and validate seizure and non-seizure endpoints that are currently being used for other rare neurodevelopmental diseases including epilepsies. The Variant Classification group concentrates on developing a more comprehensive framework for classifying the large spectrum of *CACNA1A* variants. This will occur in three phases. Phase I focuses on identifying recurrent variants with homogeneous clinical phenotypes from the literature and current patient cohorts, as well as variants with unique manifestations. Phase II will involve expert curation by a group of clinical CACNA1A experts, and in phase III, molecular researchers will functionally characterize each representative variant. The preclinical-to-clinical group consists of basic and translational researchers and industry advisors working together to identify pivotal studies needed for approval of an Investigational New Drug IND application. Early discussion has centered on building on the existing pharmacology of calcium channel modulators to identify compounds that could treat the more severe GoF disorders, such as DEE and HM. The Foundation coordinates monthly meetings for each group and actively participates in discussions to ensure that the patient's voice and priorities guide the projects. Progress updates will be reported regularly through Research Network meetings and upcoming Research Roundtables.

Conclusion

Pathogenic variants in the *CACNA1A* gene are associated with a broad range of neurological and developmental disorders, including a range of epilepsies, from milder forms such as absence epilepsy, to the severe form of developmental epileptic encephalopathy. Despite *CACNA1A* being linked to disease phenotypes for over two decades and the surge of gene-targeted programs directed at rare epilepsy syndromes, there are few definitive symptomatic treatment options for *CACNA1A*-related epilepsies and disorders in general, and no treatments that target the underlying genetic cause. The CACNA1A Foundation set out to change that.

Though the CACNA1A Foundation was only formed in 2020, it has moved quickly toward accomplishing its programmatic priorities. The CACNA1A Foundation plays more than just the role of a patient advocacy and support group. In its first 3 years, the Foundation has formulated a patient-centric research agenda, developed a robust global CACNA1A Research Network, and established a comprehensive preclinical research portfolio to support therapeutic development. It has recognized the need to break down silos that have existed within the scientific community and promote an open science culture to advance research toward treatments for CACNA1A-related disorders. Through its community conferences, CACNA1A Research Roundtables, and regular working group meetings, the Foundation has provided a platform to freely exchange ideas, build collaborations, and share data and reagents across different fields and institutions. This platform has also presented meaningful opportunities for researchers to hear from and engage with CACNA1A patients and families who are living with the burdens of this rare disease and who are the Foundation's North Star. Collectively, the Foundation's efforts are focused on accelerating progress toward therapeutic development that will have the greatest impact on the CACNA1A patient community.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Pangkong M. Fox: Conceptualization; Writing – original draft; Writing – review & editing.

Sunitha Malepati: Conceptualization; Writing – original draft; Writing – review & editing.

Lisa Manaster: Conceptualization; Writing – review & editing.

Elsa Rossignol: Conceptualization; Writing – review & editing.

Jeffrey L. Noebels: Conceptualization; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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