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A Longitudinal Exploration of *CACNA1A*-Related Hemiplegic Migraine in Children Using Electronic Medical Records

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Abstract

Background and Objectives

Since the initial description of *CACNA1A*-related hemiplegic migraine (HM), the phenotypic spectrum has expanded from mild episodes in neurotypical individuals to potentially life-threatening events frequently seen in individuals with developmental and epileptic encephalopathies. However, the overall longitudinal course throughout childhood remains unknown.

Methods

We analyzed HM and seizure history from electronic medical records in individuals with *CACNA1A*-related HM, delineating frequency and severity of events in monthly increments through a standardized approach. Combining these data with medication prescription information, we assessed the response of HM to different agents.

Results

Our cohort involved 15 individuals between 3 and 29 years (163 patient years) and included 11 unique and 2 recurrent variants (p.R1349Q and p.V1393M; both n = 2). The age of first confirmed HM ranged from 14 months to 13 years (average 3 years). 25% of all HM events were severe (lasting >3 days), and 73% of individuals had at least 1 severe occurrence. Spacing of HM events ranged from 1 month to 14 years, and changes in HM severity over time showed increases or decreases of >2 severity levels in 12 of 122 events. Eight individuals had epilepsy, but severity of epilepsy was only weakly correlated with frequency and severity of HM events. While levetiracetam (n = 6) and acetazolamide (n = 5) were the most frequently used medications, they did not show efficacy in HM prevention or severity reduction. However, verapamil (risk differences [RD] 0.10, CI 0.05–0.15) and valproate (RD 0.08, CI 0.04–0.12) were associated with a modest prevention of HM, but not reduction in severity.

Discussion

The longitudinal course of *CACNA1A*-related HM lacks recognizable patterns for timing and severity of HM events or strong correlation with seizure patterns. Our data underscore the unpredictability of *CACNA1A*-related HM, highlighting the need for close surveillance for reoccurring HM events even in individuals with symptom-free periods.

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Glossary

CHOP = Children's Hospital of Philadelphia; **ED** = emergency department; **EMR** = electronic medical record; **FDR** = false discovery rate; **HM** = hemiplegic migraine; **HPO** = human phenotype ontology; **ICU** = intensive care unit; **OR** = odds ratio; **RD** = risk differences; **VNS** = vagal nerve stimulator.

Introduction

Hemiplegic migraine (HM) is a rare neurologic condition associated with pathogenic variants in several identified genes, primarily *CACNA1A* and *ATP1A2*, and less frequently *SCN1A*, *PRRT2*, and *SCN2A*.[1-4] Initially described in 1996 as a rare subtype of migraine with aura, HM is presently defined by the International Classification of Headache Disorders (ICHD-3) as a phenomenon characterized by transient unilateral motor weakness during the aura phase lasting minutes to weeks with additional symptoms including visual, sensory, and speech disturbances; accompanying headache is not necessary for the diagnosis.[5,6] HM caused by pathogenic variants in *CACNA1A* (located on chromosome 19p13.13) have historically been classified as either familial hemiplegic migraine type 1 (FHM1), resulting from inherited variants, or sporadic hemiplegic migraine type 1 (SHM1), resulting from de novo pathogenic variants. The literature has suggested a correlation between severity and underlying genetic etiologies, not only in the manifestations of the hemiplegic events but in the overarching phenotype of the patients, including baseline neurodevelopmental trajectory.[1,2,7-10] However, these classifications prove inadequate in wholly describing the phenotype of individual patients. In particular, these definitions do not address the more severe presentations of HM that can be seen within the pediatric population, which can range from mild episodes of transient weakness to severe episodes of protracted hemiplegia, encephalopathy, seizure, and even life-threatening cerebral edema.[9] Consequently, they underestimate the potential severity and urgency of events in this population.

CACNA1A-related HM is one of several *CACNA1A*-related neurologic conditions, which also include epilepsy, neurodevelopmental disorders, and episodic and progressive ataxia, among other movement disorders.[1,2,7-10] Prior studies, including case reports, have described the clinical features of HM events in individuals with pathogenic *CACNA1A* variants, but these have rarely conducted a longitudinal analysis of event frequency and severity.[4,11-15] In addition, while these case reports have narratively reconstructed patient histories, they have rarely surpassed 2 to 3 individuals per report.[1,2,4,7,8,10,11,13,15-26] By contrast, most studies with relatively large sample sizes have reported on overall lifetime features rather than evolution of features over time or trends in events over the lifetime and have reported features independently of one another (i.e., looking at seizures and HM independently without examining the possible bidirectional relationships between the occurrences of either).[11,15,19,27] Finally, data on treatment efficacy for *CACNA1A*-related HM are largely limited to anecdotal accounts of single cases or small numbers of patients.[4] Taken together, these factors render *CACNA1A*-related HM an elusive phenomenon with an unclear clinical pattern and unexplored trajectories.

While prospective studies pose significant challenges for rare genetic conditions such as *CACNA1A*-related HM, electronic medical record (EMR) data can be used to comprehensively delineate clinical spectra of such genetic neurodevelopmental disorders and epilepsies.[28-30] Human phenotype ontology (HPO), a standardized biomedical ontology, serves as a powerful tool to standardize the wealth of heterogeneous clinical information and allow high-throughput analyses on it.[31-33] By using a systematic computational approach to information contained within the EMR, data can be successfully harmonized and tracked over time, allowing the in-depth characterization of a given condition and relevant clinical subgroups within it.

Here, leveraging the HPO framework and standardized computational approaches to the EMR data, we investigate the complexity of *CACNA1A*-related HM within the pediatric population by delineating the longitudinal time course of HM events and seizure history in 15 unrelated individuals with known pathogenic or likely pathogenic de novo variants in *CACNA1A* and a diagnosis of at least 1 lifetime HM. We describe the incidence and severity of HM events, comorbid epilepsy, neurodevelopmental phenotypes, and medication histories. This longitudinal cohort analysis contributes to a more complete phenotypic characterization of *CACNA1A*-related conditions in a pediatric population.

Methods

Identification of Individuals With *CACNA1A*-Related HM

The cohort for this longitudinal analysis was obtained from individuals enrolled in the Epilepsy Genetics Research Project at the Children's Hospital of Philadelphia (CHOP, Philadelphia, PA) and patients enrolled in a similar study from the Cleveland Clinic (CCF, Cleveland, OH). The international cohort included individuals from both the United States and Australia. Inclusion criteria included documentation of a pathogenic or likely pathogenic variant in the *CACNA1A* gene and at least 1 lifetime HM. A certified genetic counselor reviewed the clinical laboratory reports for all diagnostic genetic tests performed to confirm that each participant had a pathogenic or likely pathogenic variant in *CACNA1A* and to

ensure that no individuals had a second genetic disorder affecting the CNS that could act as a confounder for the effect of the *CACNA1A* variant. Of note, 2 individuals were previously reported as case reports (individual #5[14] and individual #14[34]). Clinical information was obtained via medical records accessed by a clinician or the family.

Assigning Human Phenotype Ontology Terms to Phenotypic Manifestations

We manually extracted the phenotypic manifestations from the EMRs and chart notes and assigned HPO terms.[35] In addition, in collaboration with clinical experts, we created an ontology for features observed during HM episodes compatible with the HPO framework to harmonize all phenotypes present in *CACNA1A*-related disorders. Automatic reasoning was performed to assign higher-level HPO terms by identifying an initial "base" term and a "propagated" term to overcome the heterogeneity of the depth of the HPO terms, as has been previously described.[28,30,36]

Reconstruction of Hemiplegic Migraine Event History in Monthly Intervals

To recreate the HM history of each study participant, we reviewed the medical records for the occurrence of HM. We recorded the frequency and severity of events in monthly increments, using an analogous strategy to the reconstruction of seizure histories our group has performed in the past.[28] We defined an HM event as per the ICHD-3 for consistency.[5] We recorded each patient's neurologic history, including the age of the first diagnosed HM; any preceding episodes of concern, where relevant; and the age of the last assessment. Once identified, the severity for each event was graded on an increasing ordinal scale from grade 1 to 5 (based on time to recovery to baseline and duration of hospitalization) along with associated clinical features of the event, where features such as cerebral edema, encephalopathy, reduced consciousness, status epilepticus, and abnormal MRI/EEG were associated with a higher score (see Table 1). Grade 1 was transient and required no visit to the emergency department (ED). Grade 2 could involve an ED visit but did not require a transfer to the intensive care unit (ICU). Grade 3 had a longer duration, 1–3 days, and could involve admission to the ICU. Grade 4 involved more than 3 days of hospitalization before return to baseline but less than 1 week. Grade 5 events required more than 7 days of hospitalization and recovery time. Severe features were isolated to grade 4 and grade 5 events which correlated reasonably well with time to recovery. The age of the first documented abnormal brain imaging on either MRI and/or CT was also recorded.

Reconstruction of Seizure History in Monthly Increments

In individuals with seizures, we also recorded the frequency and severity of seizures in monthly increments. We used HPO terms to label the seizure types. We used a previously reported protocol[28] to assign seizure severity and plotted the frequency over time for the life of each individual. To summarize, seizure severity was defined on an increasing scale from 0 to 5 and correlated with the number of seizures in a given month (0 = none, 1 = monthly, 2 = weekly, 3 = daily, 4 = 2–5 per day, 5 = >5 per day).

Delineation of Preventative Therapeutics for Hemiplegic Migraine

We reviewed medical records to document the use of preventive therapies for HM and/or epilepsy over time for each study participant. Similar to how our group assessed the effectiveness of anti-seizure medications in the past, we retrospectively assessed the comparative effectiveness of various medications in preventing HM by examining the frequency and severity of HM episodes, using a similar method to those previously reported.[28,37] We reviewed the statistical significance of medications used by at least 3 individuals by comparing HM frequency and severity in individuals on the given medication with those in individuals on any other medication. Median HM frequency and severity grades for six-month periods while on one of these medications was compared with median HM frequency and severity grades for all other medications during these six-month periods, respectively. Owing to small sample sizes, we defined reduction of HM severity as either a reduction in median HM severity during the period or when there was no HM recorded during that period.

Statistical Analysis

All computations were performed using the R Statistical framework.[38-40] Statistical testing for associations is reported with correction for multiple comparisons using a false discovery rate (FDR) of 5%. Statistical significance of the medication comparative effectiveness was calculated with the use of Fisher exact test. Because of our small sample sizes, there were some instances where no individuals fit a given category, resulting in division by zero and reported ORs of infinity. In these instances, we supplemented odds ratios (OR) with risk differences (RD). In cases where statistical significance was not reached after correction for multiple comparisons, findings remain descriptive and are presented as odds ratios with 95% confidence intervals. Correlations between seizure and HM occurrence were calculated using a mixed-effects logistic model with partially crossed random effects of participant and time.

Standard Protocol Approvals, Registrations, and Patient Consents

Informed consent was obtained from a legal guardian of all participants in agreement with the Declaration of Helsinki, and the study was performed following local protocols approved by the institutional review boards at CHOP or CCF.

Data Availability

Primary deidentified data for this analysis are available in the supplementary material. Anonymized data not published within this article or the supplementary material will be made available by request from any qualified investigator. Computer code for all analysis is also available on request from the corresponding author.

Table 1 Clinical Features Associated With Hemiplegic Migraine Severity Grades

HM feature	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Time to recovery (including resolution of hemiparesis/paresis)	<1 h	<8 h	1–3 d	4–7 d	>7 d
Cerebral edema	None noted	None noted	Yes/No	Yes	Yes
Encephalopathy	No	Yes/No	Yes/No	Yes	Yes
Reduced consciousness	Yes/No	Yes/No	Yes	Yes	Yes
Seizure	No	No	Yes/No	Yes/No	Yes/No
Status epilepticus	No	No	Yes/No	Yes/No	Yes/No
Abnormal MRI (if performed)	No	No	Yes	Yes	Yes

Each grade was based on time to recovery (return to baseline) and the features seen with each grade, including cerebral edema, encephalopathy, reduced consciousness, seizure, status epilepticus, and abnormal MRI. Cerebral edema was never documented in hemiplegic migraine (HM) events that lasted less than 8 hours and was documented in all HM episodes lasting greater than 3 days.

Results

Demographic and Genetic Information

The 15 individuals with confirmed *CACNA1A*-related HM included 8 male patients (53%) and 7 female patients (47%), ranging in age at time of data collection from 3 years old to late twenties. Age at diagnosis ranged from 1 year to 10 years. Phenotypic features and variant details are listed in Table 2. Twelve of the *CACNA1A* variants were de novo, 1 was inherited from a partially affected parent, 1 was inherited from an unaffected parent with low level mosaicism, and 1 had unknown inheritance. All *CACNA1A* variants were identified through prior diagnostic testing performed at a clinical laboratory, which included whole-exome sequencing (n = 8), epilepsy panel (n = 3), single-gene testing (n = 2), HM panel (n = 1), or autism panel (n = 1). For all participants, the *CACNA1A* variants were deemed clinically explanatory by a genetic counselor. All other variants identified on genetic testing were considered unrelated to the primary neurologic phenotype. Fourteen individuals had missense variants in either the S4 voltage sensor or the S5 and S6 pore transmembrane regions of the protein (eFigure 1). One individual had a missense variant located in the intracellular loop between S5 and S6 (eFigure 1, individual #2). Variants were distributed across all 4 protein domains.

Phenotypic Spectrum in *CACNA1A*-Related HM Demonstrates Broad Variability

Seventy-seven clinical concepts in 7 categories (coded in HPO terminology) were assigned to the cohort (eTable 1). These terms accounted for clinical presentations during both the overall disease trajectory and HM events specifically. Phenotypic features outside of HM episodes included neurodevelopmental features (Figure 1A), seizures, and other features that appear either chronically or episodically.

Hemiplegic Migraine Episodes

In total, there were 122 episodes across 15 individuals. During HM events, 13 of 15 (87%) individuals had at least 1 episode associated with encephalopathy, 12 of 15 (80%) with reduced consciousness, 12 of 15 (80%) with seizures, 11 of 15 (73%) with documented cerebral edema, 10 of 15 (68%) with status epilepticus, 9 of 15 (60%) with fever, and 9 of 15 (60%) with vomiting (Figure 1B). Less common features included coma (7/15, 47%), dysautonomia (5/15, 33%), and apnea (3/15, 20%). The duration of HM episodes ranged from less than 30 minutes (grade 1, n = 32/122 total episodes, 26%) to greater than 7 days (grade 5, n = 26/122 total episodes, 21%). The most common duration was greater than 30 minutes but less than 8 hours (grade 2, n = 42/122 total episodes, 34%). Durations of 1–3 days (grade 3, n = 18/122 total episodes, 15%) and 4–7 (grade 4, n = 4/122 total episodes, 3%) were less common (Figure 1C). Overall, 11 of 15 (73%) individuals experienced at least 1 HM that would be considered severe (involving cerebral edema or lasting more than 3 days, corresponding to grades 4 or 5. In total, approximately 25% of the HM events were severe, while the majority of HM episodes were of mild severity (lasting 3 days or less, corresponding to grades 1–3). Although grade 3 HM events could involve edema, it was usually mild, unlike the edema seen in grades 4 and 5, correlating with the shorter time to return to baseline. Grade 4 (resolving within 4–7 days) was the least common, representing less than 5% of all HM episodes, suggesting that once an HM episode surpasses 4 days, it is likely to last for a minimum of a week and involve significant cerebral edema (Figure 1C). Of note, 12 of 122 HM events involved a change of greater than 2 severity grades from the prior event (e.g., grade 3 HM followed by grade 5 HM). Six individuals reported minor head trauma as a trigger in at least 1 event and 4 patients cited infections as possible triggers.

Neurodevelopmental Features

Outside of episodic events, we gathered data on neurodevelopmental features, coded into HPO terminology (eTable 1). In our cohort, 12 of 15 (80%) individuals had neurodevelopmental abnormality, including global developmental delay or intellectual disability. At the time of data collection, 3 of 15 (20%) individuals were nonambulatory and

Table 2 Genotypes and Corresponding Phenotypes in This Cohort

Location	ID	Age at study[a]	Feature prompting testing[b]	Age of first HM[a]	cDNA change[c]	Amino acid change[c]	Severity of HM	Epilepsy	Neurodev. traits		Brain atrophy[d]	
									GDD/LD	ASD	Cerebellar	Cerebral
DI S4	1	14–18	HM	10–13	c.569A>G	p.D190G	Severe	None	Nt		None	None
DI S4 loop S5	2	10–13	HM	2–5	c.653C>T	p.S218L	Severe	None	LD		5 Y	5 Y
DI S5	3	2–5	Seizure	0–1	c.678_679delinsCT	p.L226F	Mild	None	GDD		None	None
DI S6	4	2–5	At, GDD	2–5	c.1072G>A	p.V358M	Severe	Controlled	GDD		3 Y	None
DII S6	5	10–13	GDD	2–5	c.2102G>A	p.G701E	Severe	None	GDD	ASD	None	7 Y
DII S6	6	14–18	Seizure	2–5	c.2136C>G	p.V712M	Mild	Controlled	GDD	ASD	None	None
DIII S4	7	6–9	Seizure	2–5	c.4034T>C	p.L1345P	Severe	Refractory	GDD		None	5 Y
DIII S4	8	2–5	HM	2–5	c.4037G>A	p.R1346Q	Severe	None	GDD		None	None
DIII S4	9	6–9	HM	0–1	**c.4046G>A**	**p.R1349Q**	Severe	Refractory	GDD	ASD	5 Y	5 Y
DIII S4	10	14–18	At, GDD	6–9	**c.4046G>A**	**p.R1349Q**	Severe	Refractory	GDD	ASD	None	None
DIII S4	11	>18	Seizure	0–1	c.4055G>A	p.R1352Q	Severe	Controlled	GDD		None	None
DIII S5	12	6–9	Seizure	2–5	**c.4177G>A**	**p.V1393M**	Severe	Controlled	GDD	ASD	None	None
DIII S5	13	6–9	Seizure	2–5	**c.4177G>A**	**p.V1393M**	Mild	Refractory	GDD	ASD	None	5 Y
DIV S5	14	14–18	HM	10–13	c.5126T>C	p.I1709T	Severe	None	GDD	ASD	None	None
DIV S6	15	6–9	HM	2–5	c.5428A>G	p.I1810V	Mild	None		ASD	None	None

Abbreviations: ASD = autism spectrum disorder; At = ataxia; GDD = global developmental delay; HM = hemiplegic migraine; LD = learning disability; Nt = neurotypical; Y = years.
Bolded indicates recurrent variant.
[a] Age range in years.
[b] Most prominent and severe feature presenting before genetic testing; not an exhaustive list of features. See eTable 1 for a more complete list of features.
[c] RefSeq transcript NM_001127221.2.
[d] Age of documented atrophy by available MRI or CT imaging, in years.

4 of 15 (27%) were nonverbal with an additional 4 of 15 (27%) having communication challenges, including speech apraxia and dysarthria. Three (20%) individuals were diagnosed with epileptic encephalopathy, and 8 (5%) individuals had hypotonia. Over half of the cohort had abnormal movements including ataxia (8/15, 53%), tremor (5/15, 33%), paroxysmal tonic upgaze (PTU; 3/15, 20%), and nystagmus (6/15, 40%). Neuropsychiatric disorders were present and included autism (8/15, 53%), attention deficit hyperactivity disorder (3/15, 20%), anxiety (2/15, 13%), paranoia and suicidal ideation (1/15, 7%), and self-injurious behavior (1/15, 7%) (Figure 1a).

Seizures and Epilepsy

Comorbid epilepsy was diagnosed in 8 of 15 (53%) individuals. The mean age of seizure onset was 22 months, and median age at onset was 12 months (range 3 months–6 years). Focal seizures were the most common seizure type present in 6 of 8 individuals with epilepsy (75%). Status epilepticus outside of HM episodes occurred repeatedly in a single individual. In addition, 4 of 8 individuals with epilepsy had seizures refractory to anti-seizure medications (50%). The most common abnormal interictal EEG findings were focal epileptic discharges (4/8 individuals with epilepsy, 50%) and abnormal slow frequencies (3/8 individuals with epilepsy, 37.5%). In the 3 individuals diagnosed with epileptic encephalopathy, seizure onset was at 3 months, 24 months, and 72 months, respectively.

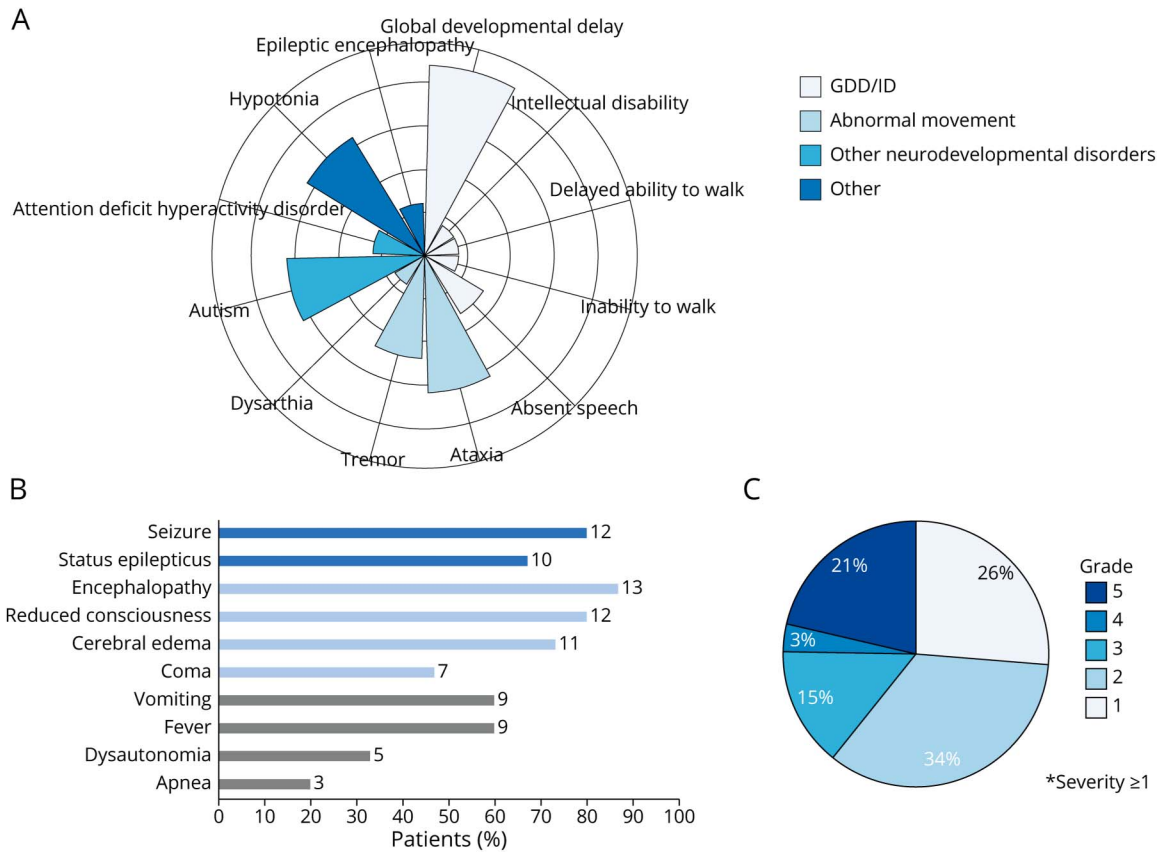
Neuroimaging Features

Cerebral atrophy was identified on imaging in 5 of 15 individuals (33%), and cerebellar atrophy was identified in 3 of 15 individuals (20%), both at a median age of 5 years. Two of the 3 individuals with cerebellar atrophy also had cerebral atrophy. Of those with documented atrophy, volume loss in the cerebellum was not apparent on imaging before the age of 3 or in the cerebrum before the age of 5 (Table 2).

Longitudinal Analysis Highlights the Range of Severity and Unpredictability of HM Events

Frequency and severity of each HM were recorded monthly for each individual from birth through the age at data capture,

Figure 1 Phenotypic Features of the Cohort



(A) Atypical neurodevelopmental traits, categorized by color: white—global developmental delay (GDD)/intellectual disability (ID) and related terms; light blue—abnormal movements; blue—other neurodevelopmental disorders; dark blue—other. Numbers next to bars indicate the number of individuals (of 15 total). (B) Manifestations observed during hemiplegic migraine episodes. Features grouped by color: dark blue—seizure-related features; light blue—other severe features; dark gray—other nonsevere features. (C) Distribution of hemiplegic migraine severity scores for all hemiplegic migraine events reported in the cohort. The most frequent hemiplegic migraine severity was grade 2 at 34%, followed by grade 1 at 26%. Severe episodes (grades 4 and 5) accounted for 25% of all episodes.

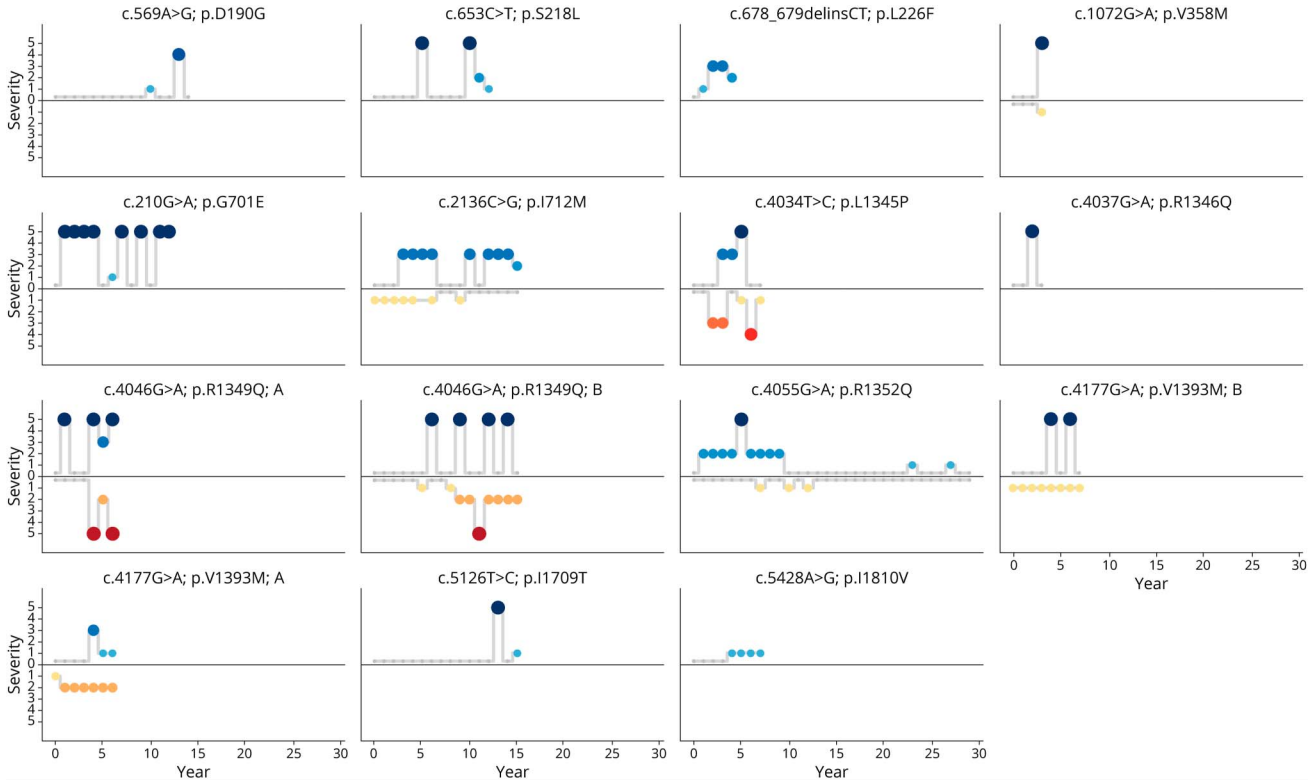
totaling 1,956 patient-months (163 patient-years, Figure 2). First-documented HM episode ranged from 14 months to 13 years, with a mean age at onset of approximately 4 years and a median age of 3 years. No events with hemiplegia or hemiparesis occurred before 1 year of age. The frequency and intensity of confirmed HM episodes varied for each individual, with no distinct pattern emerging. Four individuals (27%) never experienced severe episodes (individuals #3, 6, 13, 15), while others (2/15, 13%) had the most severe type of event (grade 5) nearly annually (individuals #5 and 9). Two individuals (13%) had a later onset of HM episodes, experiencing their first HM event at age 10 and 13, respectively (individuals #1 and 14). Others experienced more frequent attacks that began at a much younger age (5/15, 33% experienced >3 HM events under 5 years of age, individuals #3, 5, 6, 11, and 13).

For 4 of the 15 (27%) individuals in the cohort, episodes suspicious for encephalitis without hemiplegia occurred before the first-confirmed HM. These events involved altered consciousness, fever, and often status epilepticus. Individual #13 experienced the earliest of such episodes at 3 months and then again at 5 and 6 months with status epilepticus occurring each time. Individual #6 experienced 6 events after mild head trauma beginning at age 8 months and included status epilepticus, altered consciousness with and without fever. Individual #12 experienced an event at 9 months with global weakness that lasted approximately 2 hours. Finally, individual #5 was the oldest to experience these types of events, which occurred at 22 months with status epilepticus and 25 months with global weakness that resolved in less than an hour. The duration of these episodes ranged from a few hours to greater than 3 days. Given that the diagnostic workup in these episodes was negative, it may be reasoned that these episodes represent early HM events.

Seizures Have Variable Severity Over Time and Weakly Associate With HM Events

As with HM presentation, the seizure severity varied within and between individuals in the cohort. Seizure frequencies ranged from monthly (severity score 1) to multiple times per day (severity score 5). The severity of epileptic activity and simultaneous HM event intensity were weakly associated with

Figure 2 Longitudinal Analysis of Hemiplegic Migraine and Seizure Events per Year for Each Individual in the Cohort



All events are plotted left to right, with graphs starting at age 0. (Note: Multiple events within a year were collapsed into 1 event.) Intensity is ranked from 1 (mildest—smallest dot and lightest color) to 5 (most severe—largest dot and darkest color). Above the x-axis: hemiplegic migraine (HM) events (shades of blue). Below the x-axis: seizures (shades of yellow to red). Each individual demonstrated their own unique pattern. A noteworthy finding was that no HM events occurred before the age of 1.

a marginal R^2 value of 0.37. eFigure 2 is a visual depiction of the association but not a reflection of the correlation analysis.

Preventative Medication Data Suggest Drug Efficacy in Reducing HM Frequency or Recovery Time to Baseline, but Not Both

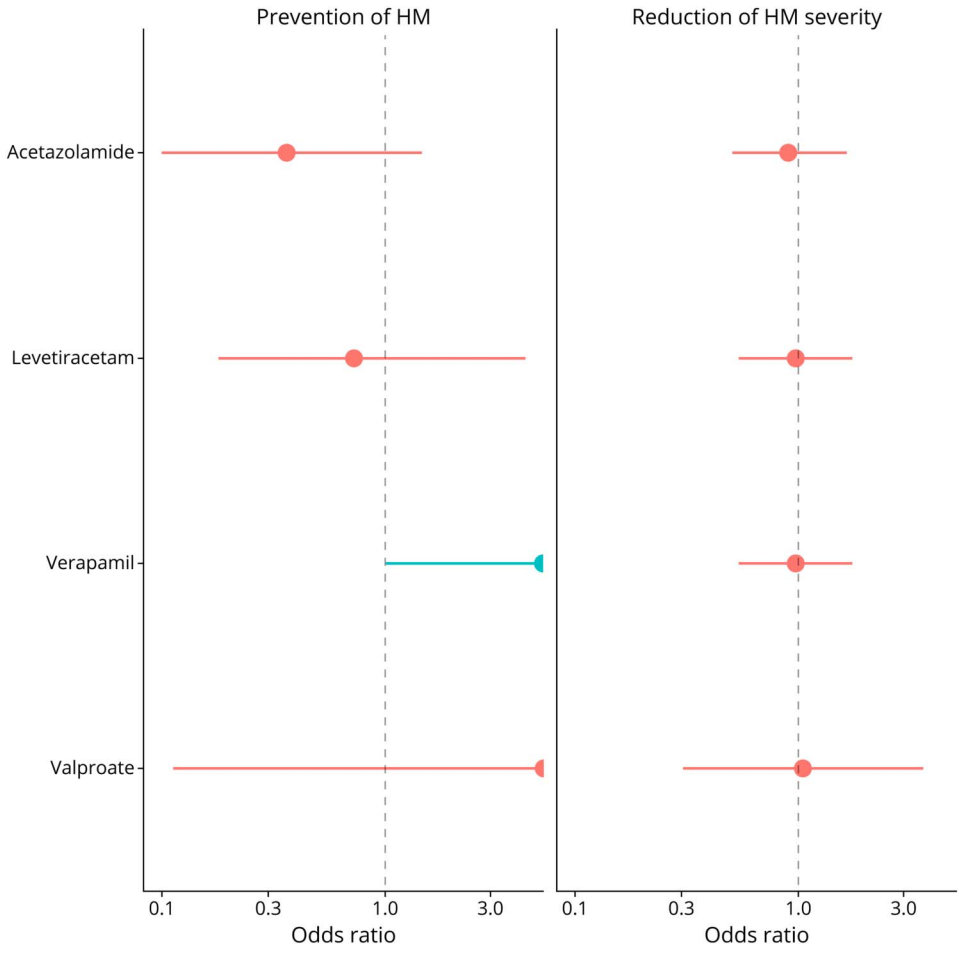
Medications primarily used to prevent future HM events were used in 10 of 15 (67%) individuals within the cohort and included verapamil, acetazolamide, and topiramate (Figure 3). In addition, 14 of 15 (93%) were managed with antiseizure medications, including valproate, lacosamide, oxcarbazepine, and clobazam. Of these, 8 of 14 (53%) were diagnosed with epilepsy, and as noted earlier, 4 of 8 (50%) individuals with epilepsy were refractory to 2 or more medications. Outside of medications, epilepsy treatments included a partial left temporal lobectomy in 1 individual who ultimately became seizure free (individual #6). Two individuals had vagal nerve stimulator (VNS) placement, and 2 individuals were on the ketogenic diet at some point during the disease trajectory. Neither VNS placement nor the ketogenic diet had clear effects on reducing HM frequency or severity. Abortive medications for HM events applied in our cohort included steroids and acetazolamide. The ability to analyze the benefit of abortive treatments was limited because of a small number of events when such strategies were applied.

Using a previously established method to assess relative efficacy of treatments on reconstructed longitudinal data,[28] we assessed the effect on HM frequency and severity for treatments used in at least 3 individuals: levetiracetam, acetazolamide, verapamil, and valproate (Figure 4, ORs only). In our analyses, verapamil (n = 3, $p < 0.001$, OR inf, RD 0.10, CI 0.05–0.15) and valproate (n = 3, $p < 0.001$, OR inf, RD 0.08, CI 0.04–0.12) were significantly associated with a modest prevention of HM. Acetazolamide (n = 5, $p = 0.138$, OR 0.36, CI 0.10–1.47) and levetiracetam (n = 6, $p = 0.709$, OR 0.73, CI 0.18–4.33) did not significantly affect prevention of HM. None of the medications had significant associations with the reduction of HM severity: verapamil (n = 3, $p = 0.802$, OR 1.08, CI 0.64–1.82), acetazolamide (n = 5, $p = 0.781$, OR 0.92, CI 0.51–1.64), levetiracetam (n = 6, $p = 1$, OR 0.99, CI 0.54–1.79), and valproate (n = 3, $p = 1$, OR 1.06, CI 0.31–3.63).

Discussion

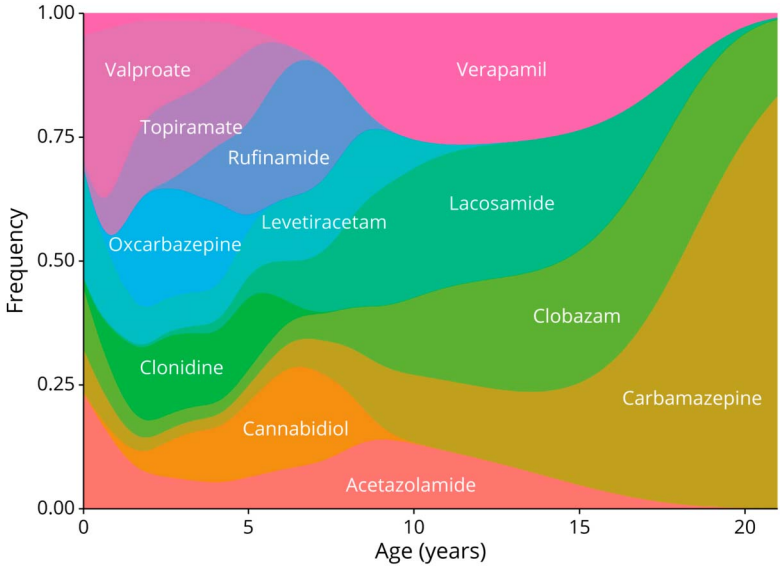
In this article, we examine the longitudinal trajectory of HM in children with *CACNA1A*-related disorders. Our study highlights the unpredictability and heterogeneity of *CACNA1A*-related disorders, which include HM episodes of varying severity, epilepsy, and a range of neurodevelopmental

Figure 3 Distribution of Prescriptions for Preventative Treatments for Hemiplegic Migraine, Including Anti-Seizure Medications



The frequency of medicine corresponds to the percentage of individuals on the specific medication at the age listed on the x-axis. Of note, this does not include rescue medications.

Figure 4 Comparative Usefulness of Preventative Therapeutics for Hemiplegic Migraine



Left to right: Prevention of hemiplegic migraine (HM) events; reduction of HM severity. Blue indicates nominally statistical significance. For each individual, the frequency of events was compared with the month prior to determine whether there was a decrease in frequency of HM events (left graph) or decrease in severity of HM events (right graph). OR = 1 means no change. OR > 1 (on left graph) indicates less frequency of HM events. OR > 1 (on right graph) indicates HM events with less severity. Only medications used in 3 or more individuals were included. Note that only the ORs are shown here for consistency—RDs are reported in text but not displayed in the figure.

features. Neuroimaging findings including brain atrophy were a common finding in our cohort.

We identified several notable findings about the trajectory and severity of HM events. First, events found in our cohort reflect the severe end of the spectrum reported in the literature: 25% of all HM events were severe, lasting greater than 3 days or involving cerebral edema, and the majority of the cohort (73%) had at least 1 severe HM in their lifetime. No clear patterns emerged regarding the severity or frequency of HM events either in individual study participants or in the cohort as a whole. These findings suggest that although the majority of HM episodes will not be life-threatening, most individuals will have at least 1 potentially life-threatening event in their lifetime. Given the unpredictability of HM episodes, a lack of prior severe HM events does not exclude the possibility of a future severe event. Finally, with first severe HM episodes observed as late as age 13, there does not appear to be a clear age at which an individual outgrows their risk for severe HM. Given that the full severity of an HM event may not be recognized immediately, all HM events in individuals with *CACNA1A*-related disorders should be treated as potentially life-threatening.

We also found that the majority of our study population had significant comorbid features, including brain atrophy, neurodevelopmental traits, and epilepsy. Brain atrophy was prevalent in the cohort at 40% with an average age at onset of 5 years, including both cerebral and cerebellar atrophy. Although various degrees of cerebellar atrophy are a known feature of *CACNA1A*-related disorders, the early onset and involvement of supratentorial structures is out of proportion to what is known about *CACNA1A*-related disorders. This finding emphasizes the overall severity of *CACNA1A*-related disorders with HM in children. Global developmental delay (88%), autism spectrum disorder (53%), and communication deficits (53%) were common in our cohort, and only a single individual was neurotypical. In addition, more than 50% of the cohort had epilepsy with half those individuals having refractory seizures. This wide spectrum of comorbid features and severities highlights the complexity of *CACNA1A*-related disorders even outside of HM events and has significant implications for clinical management.

A surprising finding in our study was the presence of suspected episodes of encephalitis in 27% of individuals prior to their first hemiplegic migraine event. In retrospect, these early events, which included encephalopathy with status epilepticus, may reflect the same pathophysiology as HM events and may be precursors of HM. It is therefore important to consider *CACNA1A*-related HM in individuals with unusual infantile presentations of suspected encephalitis that do not meet diagnostic criteria for infection or inflammation, especially in children with comorbid developmental differences or epilepsy.

In addition, we identified mild head trauma for at least 1 episode in 27% of individuals, although this trigger was only present in a minority of overall events. Mild head trauma is a well-known trigger for HM,[4,10,25] and our finding emphasizes while most individuals have at least a single event provoked by mild head trauma, most events did not have an identifiable trigger. We found limited evidence for the benefit of preventative medications, particularly regarding reducing the severity of HM events. This highlights the clinical complexity of *CACNA1A*-related HM.

As with most rare disorders, the small sample size limited our statistical power and may have introduced ascertainment bias. All participants sought evaluation at pediatric tertiary care hospitals and chose to pursue genetic testing and research enrollment. As such, our participants were mostly prepubertal and may represent the more severe end of HM in *CACNA1A*-related disorders. Despite this, the participants in our study still showed a wide range of severity and patterns of lifetime HM, suggesting that these findings may still be generalizable to many individuals with *CACNA1A*-related HM. Further studies are needed to ascertain the effect of hormonal changes on HM and seizure frequency and intensity, as well as the natural history of the disorder into adulthood. Analysis of the effectiveness of preventative agents was similarly, limited by a small sample size, as well as the paroxysmal nature of events and the lack of defined triggers.

In summary, our study examines the longitudinal trajectory of *CACNA1A*-related HM in children, an understudied episodic neurologic event with significant morbidity in affected individuals. Our study emphasizes the unpredictable nature of HM with risk of future events in affected individuals that may present as severe, resulting in life-threatening consequences that require immediate intervention. Triggers are largely unknown, with mild head trauma as an inconsistent trigger. Accordingly, in our clinical practice, we recommend that individuals with a *CACNA1A* variant that has potential to cause HM should be provided an action plan for HM and guidance to treat all HM events as if they could be severe. Furthermore, neurodevelopmental features and epilepsy are very common comorbid features that add complexity to management and ultimate prognosis. Our study also provides insights into the natural history of *CACNA1A*-related HM that can serve as groundwork for further studies of genotype-phenotype relationships, treatment efficacy, triggers, and delineation of the natural history through puberty into adulthood.

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References

1. Carreno O, Corominas R, Serra SA, et al. Screening of CACNA1A and ATP1A2 genes in hemiplegic migraine: clinical, genetic, and functional studies. *Mol Genet Genomic Med*. 2013;1(4):206-222. doi:10.1002/mgg3.24
2. García Segarra N, Gautschi I, Mittaz-Crettol L, et al. Congenital ataxia and hemiplegic migraine with cerebral edema associated with a novel gain of function mutation in the calcium channel CACNA1A. *J Neurol Sci*. 2014;342(1-2):69-78. doi:10.1016/j.jns.2014.04.027
3. Riant F, Thompson CH, DeKeyser JM, et al. Pathogenic SCN2A variants are associated with familial and sporadic hemiplegic migraine. *Review*. 2023. doi:10.21203/rs.3.rs-3215189/v1
4. Zhang L, Wen Y, Zhang Q, et al. CACNA1A gene variants in eight Chinese patients with a wide range of phenotypes. *Front Pediatr* 2020;8:577544. doi:10.3389/fped.2020.577544
5. Gobel H. *The International Classification of Headache Disorders*. ICHD-3; 2018. Accessed November 9, 2022. ichd-3.org/
6. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. *Cell*. 1996;87(3):543-552. doi:10.1016/S0092-8674(00)81373-2
7. Blumkin L, Leshinsky-Silver E, Michelson M, et al. Paroxysmal tonic upward gaze as a presentation of de-novo mutations in CACNA1A. *Eur J Paediatric Neurol*. 2015;19(3):292-297. doi:10.1016/j.ejpn.2014.12.018
8. Curtain RP, Smith RL, Ovcaric M, Griffiths LR. Minor head trauma-induced sporadic hemiplegic migraine coma. *Pediatr Neurol*. 2006;34(4):329-332. doi:10.1016/j.pediatrneurol.2005.08.033
9. Russell MB, Ducros A. Sporadic and familial hemiplegic migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management. *Lancet Neurol*. 2011;10(5):457-470. doi:10.1016/S1474-4422(11)70048-5
10. Tantsis EM, Gill D, Griffiths L, et al. Eye movement disorders are an early manifestation of CACNA1A mutations in children. *Dev Med Child Neurol*. 2016;58(6):639-644. doi:10.1111/dmcn.13033
11. Le Roux M, Barth M, Gueden S, et al. CACNA1A-associated epilepsy: electroclinical findings and treatment response on seizures in 18 patients. *Eur J Paediatric Neurol*. 2021;33:75-85. doi:10.1016/j.ejpn.2021.05.010
12. Prontera P, Sarchielli P, Caproni S, et al. Epilepsy in hemiplegic migraine: genetic mutations and clinical implications. *Cephalalgia*. 2018;38(2):361-373. doi:10.1177/0333102416686347
13. Riant F, Lescoat C, Vahedi K, et al. Identification of CACNA1A large deletions in four patients with episodic ataxia. *Neurogenetics*. 2010;11(1):101-106. doi:10.1007/s10048-009-0208-y
14. Schaare D, Sarasua SM, Lusk L, et al. Concomitant calcium channelopathies involving CACNA1A and CACNA1F: a case report and review of the literature. *Genes*. 2023;14(2):400. doi:10.3390/genes14020400
15. Travaglini L, Nardella M, Bellacchio E, et al. Missense mutations of CACNA1A are a frequent cause of autosomal dominant nonprogressive congenital ataxia. *Eur J Paediatric Neurol*. 2017;21(3):450-456. doi:10.1016/j.ejpn.2016.11.005
16. Camia F, Pisciotta L, Morana G, et al. Combined early treatment in hemiplegic attacks related to CACNA1A encephalopathy with brain oedema: blocking the cascade? *Cephalalgia* 2017;37(12):1202-1206. doi:10.1177/0333102416668655
17. de Vries B, Stam AH, Beker F, et al. CACNA1A mutation linking hemiplegic migraine and alternating hemiplegia of childhood. *Cephalalgia*. 2008;28(8):887-891. doi:10.1111/j.1468-2982.2008.01596.x
18. Gray IN, Cristancho AG, Licht DJ, Liu GT. Ocular dipping in a patient with hemiplegic migraine. *J Pediatr Ophthalmol Strabismus*. 2018;55:e4-e6. doi:10.3928/01913913-20171129-01
19. Humbertclaude V, Krams B, Nogue E, et al. Benign paroxysmal torticollis, benign paroxysmal vertigo, and benign tonic upward gaze are not benign disorders. *Dev Med Child Neurol*. 2018;60(12):1256-1263. doi:10.1111/dmcn.13935
20. Humbertclaude V, Riant F, Krams B, et al. Cognitive impairment in children with CACNA1A mutations. *Dev Med Child Neurol*. 2020;62(3):330-337. doi:10.1111/dmcn.14261
21. Ohmura K, Suzuki Y, Saito Y, Wada T, Goto M, Seto S. Sporadic hemiplegic migraine presenting as acute encephalopathy. *Brain Dev*. 2012;34(8):691-695. doi:10.1016/j.braindev.2011.11.002
22. Stam A, Vanmolkot K, Kremer H, et al. CACNA1A R1347Q: a frequent recurrent mutation in hemiplegic migraine. *Clin Genet*. 2008;74(5):481-485. doi:10.1111/j.1399-0004.2008.00996.x
23. Stubberud A, O'Connor E, Tronvik E, Houlden H, Matharu M. R1352Q CACNA1A variant in a patient with sporadic hemiplegic migraine, ataxia, seizures and cerebral oedema: a case report. *Case Rep Neurol*. 2021;13(1):123-130. doi:10.1159/000512275
24. Topakian R, Pischinger B, Stieglbauer K, Pichler R. Rare clinical findings in a patient with sporadic hemiplegic migraine: FDG-PET provides diminished brain metabolism at 10-year follow-up. *Cephalalgia*. 2014;34(5):392-396. doi:10.1177/0333102413513182
25. Vahedi K, Denier C, Ducros A, et al. CACNA1A gene de novo mutation causing hemiplegic migraine, coma, and cerebellar atrophy. *Neurology*. 2000;55(7):1040-1042. doi:10.1212/wnl.55.7.1040
26. Zangaladze A, Asadi-Pooya AA, Ashkenazi A, Sperling MR. Sporadic hemiplegic migraine and epilepsy associated with CACNA1A gene mutation. *Epilepsy Behav*. 2010;17(2):293-295. doi:10.1016/j.yebeh.2009.12.017
27. Lipman AR, Fan X, Shen Y, Chung WK. Clinical and genetic characterization of CACNA1A-related disease. *Clin Genet*. 2022;102(4):288-295. doi:10.1111/cge.14180
28. Xian J, Parthasarathy S, Ruggiero SM, et al. Assessing the landscape of STXBP1-related disorders in 534 individuals. *Brain*. 2022;145(5):1668-1683. doi:10.1093/brain/awab327
29. Crawford K, Xian J, Helbig KL, et al. Computational analysis of 10,860 phenotypic annotations in individuals with SCN2A-related disorders. *Genet Med*. 2021;23(7):1263-1272. doi:10.1038/s41436-021-01120-1
30. Helbig I, Lopez-Hernandez T, Shor O, et al. A recurrent missense variant in AP2M1 impairs clathrin-mediated endocytosis and causes developmental and epileptic encephalopathy. *Am J Hum Genet*. 2019;104(6):1060-1072. doi:10.1016/j.ajhg.2019.04.001
31. Daniali M, Galer PD, Lewis-Smith D, et al. Enriching representation learning using 53 million patient notes through human phenotype ontology embedding. *Artif Intell Med*. 2023;139:102523. doi:10.1016/j.artmed.2023.102523
32. Lewis-Smith D, Parthasarathy S, Xian J, et al. Computational analysis of neurodevelopmental phenotypes—harmonization empowers clinical discovery. *Hum Mutat*. 2022;43(11):1642-1658. doi:10.1002/humu.24389
33. Ganesan S, Galer PD, Helbig KL, et al. A longitudinal footprint of genetic epilepsies using automated electronic medical record interpretation. *Genet Med*. 2020;22(12):2060-2070. doi:10.1038/s41436-020-0923-1
34. Vithayathil J, Freeman C, Jacobwitz M, Schwartz ES, Agarwal S. Prolonged neurologic deficits with brain MRI changes following ECT in an adolescent with a CACNA1a-related disorder; a case report. *BMC Neurol*. 2022;22(1):466. doi:10.1186/s12883-022-02994-7
35. Human Phenotype Ontology. Accessed October 4, 2022. hpo.jax.org/app/
36. Galer PD, Ganesan S, Lewis-Smith D, et al. Semantic similarity analysis reveals robust gene-disease relationships in developmental and epileptic encephalopathies. *Am J Hum Genet*. 2020;107(4):683-697. doi:10.1016/j.ajhg.2020.08.003
37. Thalwitzer KM, Xian J, de Campo D, et al. Early life seizures and epileptic spasms in STXBP1-related disorders. *Epilepsia*. 2024;65(3):805-816. doi:10.1111/epi.17886
38. R: The R Project for Statistical Computing. Accessed May 14, 2024. r-project.org/
39. Schweinberger M. *Fixed- and Mixed-Effects Regression Models in R*. The University of Queensland, School of Languages and Cultures; 2022. Accessed November 3, 2023. slcladal.github.io/regression.html
40. Mixed Effects Logistic Regression | R Data Analysis Examples. Accessed June 7, 2024. stats.oarc.ucla.edu/r/dae/mixed-effects-logistic-regression/