RESEARCH ARTICLE OPEN ACCESS

Adult Phenotype of *CHD2*-Associated Disorders

Marlene Rong, MSc, Quratulain Zulfiqar Ali, MD, Angel Aledo-Serrano, MD, Allan Bayat, MD, PhD, Orrin Devinsky, MD, PhD, Farah Qaiser, Ilakkiah Chandran, BSc, Anum Ali, Alfonso Fasano, MD, PhD, Anne S. Bassett, MD, and Danielle M. Andrade, MD

Correspondence
Dr. Andrade
Danielle.Andrade@uhn.ca

Neurol Genet 2024;10:e200194. doi:10.1212/NXG.0000000000200194

Abstract

Background and Objectives

Pathogenic *CHD2* variants are associated with neurodevelopmental disorders and developmental and epileptic encephalopathy. While pediatric *CHD2* phenotypes have been readily explored, adult phenotypes are not well understood. We aimed to investigate the phenotypic spectrum of adult patients with *CHD2* variants.

Methods

Patients 18 years or older with likely pathogenic or pathogenic (LP/P) *CHD2* variants were included. We used standardized tools to evaluate current seizures, medication use, sleep, gastrointestinal symptoms, pain response, gait, social communication disorder, and adaptive behavioral skills of patients.

Results

In this prospective study, 14 unrelated adult patients (age range: 18–45 years, median: 21 years) with LP/P *CHD2* variants were described. Eleven novel variants were identified. No genotype-phenotype correlations were identified. 79% of adults still have ongoing seizures. Photosensitivity was present in 64% of adult patients. Autism spectrum disorder was diagnosed in 71% of patients. Only 29% were able to read and understand material at a sixth-grade level or higher. Behavioral issues were reported in 100% of adult patients, and 71% had internalizing features, such as anxiety. Self-injurious behaviors were present in 50%. Only 43% could ambulate independently. Additional characteristics included reflux (36%), constipation (71%), and abnormal pain responsiveness (43%). 1 patient presented with nonepileptic breath-holding spells leading to cyanosis. No patient could perform all basic activities of daily living independently, all the time. Higher seizure severity was associated with worse nonseizure outcomes ($p = 0.04$).

Discussion

Most adults with *CHD2* continue to have seizures, and seizure severity is associated with worse comorbidities such as maladaptive behaviors, gait, gastrointestinal, sleep, and abnormal pain responsiveness. Longevity has not been systematically studied in this group of patients. Here we describe a group of adult patients (up to 45 years of age) and the natural history of this condition. These data may provide prognostic insights for families of pediatric patients and help identify key points to be addressed in future precision trials for patients with *CHD2* variants.

From the Institute of Medical Science (M.R.), University of Toronto; Adult Genetic Epilepsy (AGE) Program (M.R., Q.Z.A., F.Q., I.C., A.A., D.M.A.), Krembil Neurosciences Institute, Toronto Western Hospital, University Health Network, Canada; Epilepsy Unit (A.A.-S.), Vithas Clinical Neuroscience Institute, Vithas Madrid University Hospitals; Faculty of Experimental Sciences (A.A.-S.), Francisco de Vitoria University, Madrid, Spain; Department of Drug Design and Pharmacology (A.B.), University of Copenhagen; Department for Genetics and Personalized Medicine (A.B.), Danish Epilepsy Centre, Dianalund; Institute for Regional Health Services (A.B.), University of Southern Denmark, Odense; NYU Langone Epilepsy Center (O.D., F.Q., A.A.); Edmond J. Safra Program in Parkinson's Disease (A.F.), Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN; Division of Neurology (A.F., D.M.A.), Department of Medicine, University of Toronto; Krembil Brain Institute (A.F., D.M.A.); Clinical Genetics Research Program (A.S.B.), Centre for Addiction and Mental Health; The Dalglish Family 22q Clinic (A.S.B.), Toronto General Hospital, University Health Network; Department of Psychiatry (A.S.B.), University of Toronto, Ontario; Toronto Congenital Cardiac Centre for Adults (A.S.B.), Division of Cardiology, Department of Medicine, and Department of Psychiatry, University Health Network and Toronto General Hospital Research Institute and Campbell Family Mental Health Research Institute (A.S.B.), Toronto, Ontario, Canada.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

ADLs = activities of daily living; **ASD** = autism spectrum disorder; **DBS** = deep brain stimulation; **DEE** = developmental and epileptic encephalopathy; **EMA** = eyelid myoclonia with absence; **ID** = intellectual disability; **NDD** = neurodevelopmental disorder; **SCQ** = Social Communication Questionnaire; **VABS3** = Vineland Adaptive Behavior Scale 3; **VNS** = vagus nerve stimulation.

Introduction

The *CHD2* gene, located at chromosome 15q26.1, encodes chromodomain helicase DNA-binding protein 2 (CHD2), which is an ATP-dependent chromatin-remodeling enzyme. This gene interacts with gene regulatory sequences and histones necessary for early cortical development and synaptic function.[1]

In humans, pathogenic variants leading to *CHD2* loss of function are mainly associated with developmental and epileptic encephalopathy (DEE) (OMIM#615369) but may also manifest as neurodevelopmental disorders (NDDs) without epilepsy.[2] In 2009, a 30-month-old girl was described with refractory myoclonic epilepsy, intellectual disability (ID), delayed growth, and a distinctive facial appearance.[3] She had a microdeletion of 15q26.1, which encompasses the *CHD2* gene. In 2013, the *CHD2* gene was specifically identified as a cause of DEE.[4]

The true prevalence of *CHD2*-related disorders is not known, in part because of its clinical heterogeneity and limited genetic testing to date, especially in adults. However, de novo *CHD2* pathogenic variants were present in an estimated 1% of individuals included in cohorts with various DEEs.[4,5] In another report of nearly 10,000 pediatric patients with epilepsy referred for genetic testing using a comprehensive epilepsy panel, 1 in 400 individuals were identified with a *CHD2* pathogenic variant.[6]

Of all patients with *CHD2* reported so far, only 27 individuals, reported across 16 publications, are adults older than 18 years[2,4,7–21] Given the paucity of information on adult outcomes of patients with *CHD2* variants, we performed a literature review of all reported cases of adults with *CHD2* variants, both with and without seizures. We then conducted a prospective, cross-sectional study by recruiting and evaluating an international group of adults with DEE and NDDs without seizures. All patients harbored likely pathogenic or pathogenic (LP/P) *CHD2* variants. Seizures, sleep and gastrointestinal disturbances, pain responsiveness, walking abilities, social communication skills, daily living abilities, and maladaptive behaviors were assessed. Findings were compared with those of previously reported adults with *CHD2* and other adults with DEE to better distinguish the phenotype of adults with *CHD2* variants specifically.

Methods

Search Strategy

A systematic online literature search of the PubMed and MEDLINE databases from inception through June 2024 was conducted using the search term "*CHD2*" (Figure 1). The references cited in the identified publications were searched for additional studies. Inclusion criteria included studies with clinical outcomes of humans. Studies were excluded if they (1) did not involve humans, (2) did not present new or unique data, (3) were non-English studies, (4) were unrelated, and (5) did not provide information on clinical phenotypes. Information that was not reported by the authors was left blank. "N/A" was used when authors explicitly stated that information was not available.

Study Population and Data Collection

Between July 2021 and February 2023, patients aged 18 years or older with *CHD2* LP/P variants were enrolled in this prospective study. Recruitment was conducted using the author's practices and with the assistance of Coalition to Cure *CHD2*. Study materials were translated and made available in English and Spanish. Clinical data collection involved the completion of 3 validated assessment tools, described further.

Standard Protocol Approvals, Registrations, and Patient Consents

Institutional approval for the study was granted by the Research Ethics Board at the University Health Network (protocol number 21-5009) based in Toronto, Canada. Informed and written consent was obtained from the substitute decision makers for all patients.

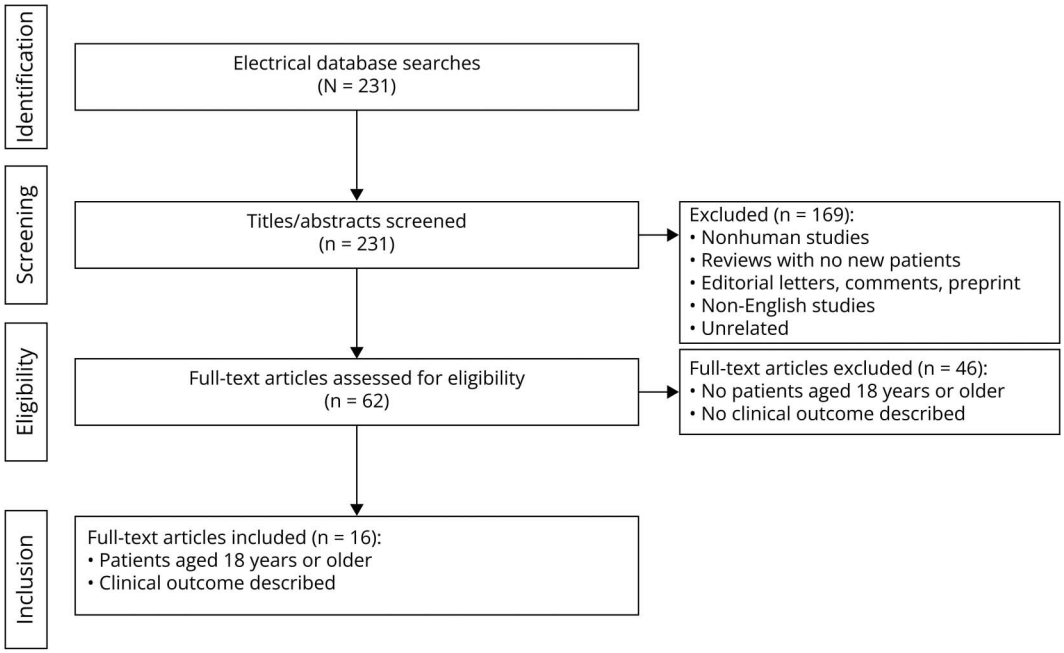
Severity of Clinical Outcomes

Disease severity was assessed using the modified version of the Severity Assessment[22] tool that provided a composite score. 51 items consisting of a Likert scale rating were used to investigate seizures, treatments, gait, pain responsiveness, toileting, reflux, and sleep abnormalities. Ratings of each patient's overall condition and therapy effectiveness were also assessed. Clinical phenotype was considered most severe with a maximum score of 129/129. Seizures were classified using the 2017 International League Against Epilepsy guidelines.[23]

Social Communication Skills

The presence of communication deficits was screened using the Social Communication Questionnaire (SCQ) (Lifetime

Figure 1 Study Identification Flow Diagram



Of 231 searches for "*CHD2*," 16 full-text articles featuring patients aged 18 years or older were identified.

Version).[24] Total scores were yielded and interpreted in reference to the cutoff score of 15. If patients scored more than the cutoff, it is likely that they are on the autism spectrum, suggesting that a more extensive evaluation should be conducted to confirm the screening findings.

Adaptive Behavioral Skills

Adaptive behavioral abilities were assessed using the Vineland Adaptive Behavior Scale 3 (VABS3).[25] The VABS3 assessed abilities in the following domains: communication (receptive, expressive, and written), daily living skills (personal, domestic, and community), socialization (interpersonal relationships, play/leisure, and coping skills), motor ability (fine and gross motor), and maladaptive behaviors. An overall rating was given based on the patient's results compared with those of a norm sample, which is a representative group of patients the same age from across the United States. From each domain, raw scores were extracted and selected because of floor effects found in age-wise comparisons.

Statistical Analyses

Patient characteristics and clinical features were summarized using descriptive statistics. A comparison of assessment scores with variant types (missense, nonsense, deletion, splice acceptor, and frameshift where applicable) and affected functional domains was conducted using the Kruskal-Wallis test. Analyses were conducted using R, and statistical significance was set to <0.05. Statistical values were not reported for nonstatistically significant findings. Figures were created using GraphPad Prism.

Variant Interpretation

The pathogenicity of *CHD2* variants was interpreted as per the American College of Medical Genetics and Genomics guidelines.[26] The GRCh38 or hg38 build was used. The ClinVar database and GnomAD browser were used to query each of the *CHD2* variants.[27,28]

Data Availability

Deidentified data may be provided on reasonable request.

Results

Cohort Description

Fourteen adult patients (7 women) participated in the study, with a median age of 21 years (range: 18–45 years) (Table 1). Patients were recruited from the following countries: Canada, the United States, and Spain. All patients came from nonconsanguineous families. One patient had a family history of epilepsy. This study presents the oldest patient with a *CHD2* variant, who is a 45-year-old woman.

Patients had a spectrum of genetic variants: 2 patients had nonsense, 5 had missense, and 6 had frameshift leading to protein truncation. In addition, 1 patient had a pathogenic 223.362 kb deletion in chromosome 15q26.1, which partially overlaps with the *CHD2* gene. Of our cohort, 13 (93%) of 14 variants arose de novo. One patient did not have both parents available for testing, so inheritance is unknown.

Table 1 Demographics of 14 Adult Patients With *CHD2* Variants and Their Genetic Profiles (n = 14)

Patient #	Age range (y)	Family history	Exon #	cDNA	Protein consequence	Variant type	Inheritance	ACMG interpretation	Variant previously reported?
1	18–25	No	N/A	93306085_ 93529447del	223.362 kbp	Deletion	De novo	Pathogenic	No
2	18–25	No	21	c.2674delC	p.Gln892fs*19	Frameshift	De novo	Pathogenic	No
3	26–30	No	19	c.2397_ 2398delTG	p.Leu800Aspfs*25	Frameshift	De novo	Pathogenic	No
4	18–25	No	19	c.2423_ 2424insAT	p.Asn808Lysfs*11	Frameshift	De novo	Likely pathogenic	No
5	18–25	No	17	c.2087delT	p.Phe696Serfs*38	Frameshift	Parents not tested	Likely pathogenic	No
6	30+	No	19	c.2416_ 2417dupAG	p.Asn808Glyfs*11	Frameshift	De novo	Pathogenic	No
7	18–25	Yes	38	c.4968dup	p.Trp1657Metfs*10	Frameshift	De novo	Pathogenic	Suls et al. (2013)
8	18–25	No	32	c.4133T > G	p.Val1378Gly	Missense	De novo	Likely pathogenic	No
9	18–25	No	21	c.2636C > T	p.Ala879Val	Missense	De novo	Pathogenic	No
10	18–25	No	26	c.3298G > A	p.Ala1100Thr	Missense	De novo	Likely pathogenic	No
11	26–30	No	36	c.4602G > T	p.Trp1534Cys	Missense	De novo	Likely pathogenic	No
12	30+	No	17	c.2095C > T	p.Arg699Trp	Missense	De novo	Pathogenic	De Maria et al. (2022)
13	18–25	No	38	c.4909C > T	p.Arg1637*	Nonsense	De novo	Pathogenic	Suls et al. (2013); Carvill et al. (2013); Galizia et al. (2015)
14	18–25	No	8	c.789dupT	p.Glu264*	Nonsense	De novo	Likely pathogenic	No

Abbreviations: ASD = autism spectrum disorder; F = female; M = male.
Sex, age, ASD diagnosis, family history of epilepsy, and ethnicity are listed when provided. The zygosity of all variants was heterozygous.

11 LP/P variants in our cohort were novel and have not been previously reported (Table 1).

Phenotypic Spectrum

Seizures

Of 14 patients, 7 patients (50%) reported at least 1 nonconvulsive seizure in the past 12 months, 1 (7%) had them monthly, 3 (21%) had them weekly, and 3 (21%) had them daily. 6 (43%) of the 14 patients had at least 1 convulsive seizure in the past 12 months. Specifically, of 14 patients, 3 (21%) had monthly convulsive seizures, 1 (7%) had them weekly, and 2 (14%) had them daily. Disruptive isolated epileptic spasms in the past 12 months were noted in 6 (43%) of the 14 patients, where 3 (21%) had them monthly, 2 (14%) had them weekly, and 1 (7%) had them daily. 1 patient (7%) had prolonged seizures lasting longer than 5 minutes in the previous 12 months. These prolonged seizures happened approximately once a week (Table 2).

Photosensitive epilepsy was reported in 9 (64%) of 14 patients. One patient had strobe light–induced seizures. Avoidance of sunlight was noted in 2 (14%) of 14 adults. Four patients (29%) showed sensitivity to flashing lights. Three (21%) of 14 patients demonstrated photoparoxysmal responses on EEG. Of these 3 patients with PPR, 2 also had clinical photosensitivity (Table 2).

Caregivers reported a median of at least 5 lifetime antiseizure medications (ASMs) (range: 0–5+ ASMs) and a median current usage of 2 ASMs (range: 0–5+ ASMs). Only 2 (14%) of 14 patients have tried the ketogenic diet. Trial of vagus nerve stimulation (VNS) was reported in 2 (14%) of 14 patients, and deep brain stimulation (DBS) was reported in 2 (14%) of 14 patients. Currently, patients #7 and #14 have implanted VNS and patient #9 has an active DBS device.

Walking Abilities and Scoliosis

All patients were able to walk at least 15–50 feet outside the home (Figure 2), but only 6 (43%) of 14 patients could walk independently with no assistance, including the abilities to run, climb on level and uneven terrain, and climb stairs without difficulty or assistance. Of the 8 patients (57%) who

Table 2 Summary of Seizure and Photosensitivity Findings for 14 Adult Patients With *CHD2* Variants in the Past 12 Months

Seizure types	% of patients (n = 14)	Frequency in the past 12 mo			
		At least once	Monthly	Weekly	Daily
Nonconvulsive seizures, n (%)	7/14 (50)	7/14 (50)	1/14 (7)	3/14 (21)	3/14 (21)
Convulsive seizures, n (%)	6/14 (43)	6/14 (43)	3/14 (21)	1/14 (7)	2/14 (14)
Disruptive isolated spasms, n (%)	6/14 (43)	6/14 (43)	3/14 (21)	2/14 (14)	1/14 (7)
Prolonged seizures (>5 mins), n (%)	1/14 (7)	—	—	1/14 (7)	—
Photosensitive epilepsy, n (%)	9/14 (64)	—	—	—	—
PPR response on EEG, n (%)	3/14 (21)	—	—	—	—

One patient (1/14, 7%) did not have any seizures ever.

could not ambulate independently, 5 walked with assistance and 3 used wheelchairs most of the time.

Eight (57%) of 14 patients did not have scoliosis, and 6 (43%) of 14 patients dealt with mild scoliosis not requiring treatment. Leg deformities were reported in 2 patients, as well as gigantism in 1 man.

Social Communication Disorders and Autism Spectrum Disorders

In our cohort, 11 (79%) of 14 patients scored above the threshold on the SCQ. Ten of these 11 patients had a previous formal diagnosis of ASD given by a physician or health care provider. Specific ASD-like features were consistent across patients, including ritual-like behaviors (14/14, 100%), special interests with unusual intensity (10/14, 71%), and odd phrases or echolalia (9/14, 64%).

Adaptive Behaviors

All patients in this cohort had lower scores compared with normative data. All patients (100%) were able to feed themselves with a fork and spoon. Twelve patients (86%) were cooperative in personal activities such as undressing, dressing, and washing of the hands and face. Thirteen (93%) of the 14 patients could dress themselves, such as putting on clothes from the front and pulling up pants with elastic waistbands. 8 patients (57%) could bathe themselves. Twelve patients (86%) were able to sometimes sit unsupported for at least 10 minutes, and all patients were able to stand unsupported for at least 1 minute.

Regarding language abilities, all patients could understand at least 50 words. Thirteen (93%) of 14 patients could say one-word requests and could speak at least 50 words. All patients could recognize their own written name. Thirteen (93%) of 14 could recognize at least 10 alphabet letters while 11 (79%) of 14 could read at least 10 words. Four (29%) of 14 patients were able to read and understand material at a sixth-grade level or higher.

Maladaptive Behaviors

All patients exhibited maladaptive behavioral concerns. Various internalizing behaviors were reported, such as being overly needy/dependent (10/14, 71%), anxiety (10/14, 71%), and irritability (10/14, 71%). Avoidant behavior (8/14, 57%) and fearfulness of common objects or situations (10/14, 71%) were also present. Externalizing features included stubbornness (10/14, 71%), temper tantrums (7/14, 50%), and physical aggression (7/14, 50%). Compulsive behaviors (8/14, 57%) and overfixation on certain topics (10/14, 71%) were also observed. Delusional beliefs were present in 2 (14%) of 14 patients, and self-injurious behaviors were reported in 50%.

Comorbidities

Summary graphs of gastrointestinal clinical features in *CHD2* adults are shown in Figure 3. In the 12 months before enrolling, swallowing was normal in 13 (93%) of 14 patients, but 1 patient required more than 30 minutes to eat a meal. Reflux was uncontrolled in 2 (14%) of 14 patients but was controlled in 3 (21%) and absent in 9 (64%) of 14 patients. Ten (71%) of 14 patients dealt with constipation issues while 3 of these patients had uncontrolled constipation. One woman was diagnosed with celiac disease at 19 years.

Breathing was normal in 12 (86%) of 14 patients, but 1 patient had occasional breath-holding or hyperventilating spells. Episodes of cyanosis due to abnormal breathing not associated with seizures were reported in 1 patient.

Of 14 patients, 11 (79%) had normal toileting in the past 12 months, 2 (14%) required timed toileting, and 1 patient wore diapers only. Eight (57%) of 14 patients exhibited normal reactions to pain, 2 (14%) of 14 patients showed delayed reactions to minor pain, and 4 (29%) of 14 patients exhibited delayed pain responsiveness to major pain.

Summary graphs of other clinical features in *CHD2* adults are shown in Figure 4. Sleep in the past 12 months was normal for

Figure 2 Walking Abilities of Adults With *CHD2*

Percentage prevalence of a range of walking abilities is provided (n = 14).

10 (71%) of 14 patients. Of the remaining patients, 3 aroused once per week and 1 patient aroused more than once per week. Disruptive daytime sleepiness varied in severity across 12 (86%) of 14 patients. Only 2 (14%) of 14 patients had no issues. While it was rare in 5 (36%) of 14 patients, 7 (50%) of 14 patients had disruptive daytime sleepiness ranging from 2 to 6 days per week. Two of these patients struggled with disruptive, constant daytime sleepiness throughout day, every day.

When comparing the severity scores of nonseizure outcomes with seizure severity scores, we found a statistically significant linear correlation (p = 0.04) (Figure 5). Increasing seizure severity was associated with worse nonseizure outcomes, as presented in Figures 2 and 3.

Longevity

This study features the oldest *CHD2* patient currently presented in detail in the literature. The patient is a 45-year-old woman carrying a de novo pathogenic missense variant (p.Arg669Trp) in exon 15 of unknown inheritance. The patient does not have epilepsy and has never had any known seizures. She does not have photosensitivity. She was diagnosed with "pervasive development disorder with autistic overtones" at 28 years. The patient walks independently without assistance and does not have scoliosis. She lives in a care home with 2 other intellectually disabled women. She works with the support of a job coach, performing assorted tasks for the care home she lives in and earning minimum wage.

However, the patient demonstrates aggressive behaviors, exhibiting aggression toward peers and family members, and has also harmed pets. As such, she cannot be left alone with her peers. ASD-like traits are also readily seen in the patient, including ritualistic behaviors, special interests, and fixations. She exhibits behaviors such as hoarding and overeating. In addition, the patient has delusions surrounding fictional characters, which she claims are "real and live in another realm."

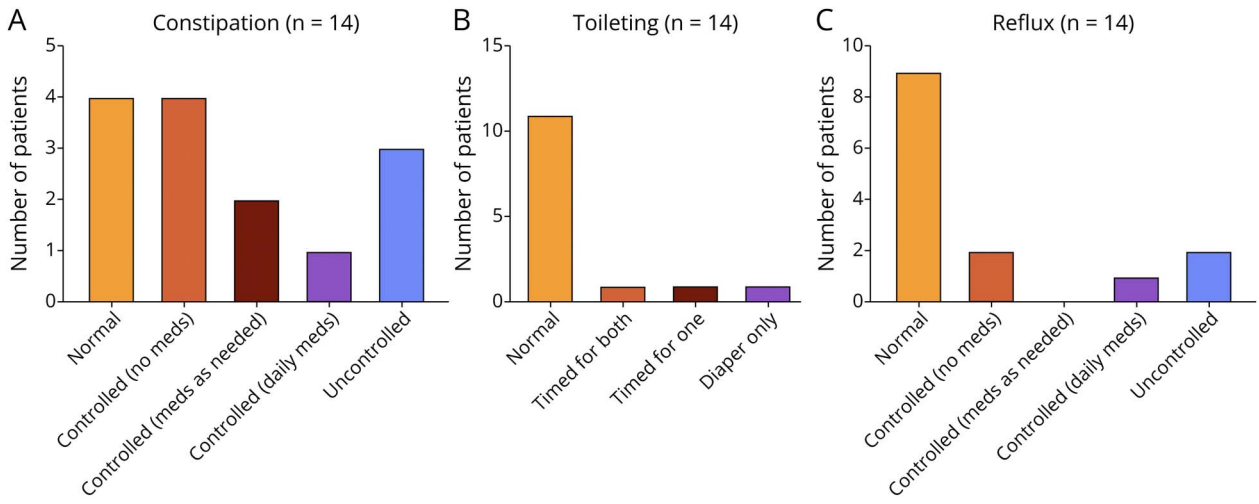
Discussion

This study features the molecular and clinical information of 14 adults with *CHD2*-related NDD. This is the largest study looking at the adult phenotype of this condition, which so far, has been mainly described in children. Our cohort's median age was 21 years (n = 14, range: 18–45 years). Drug-resistant seizures were seen in 79% of patients, adaptive behaviors were low in 100% compared with individuals of their age, and 57% of patients required some form of assistance ambulating. Aggression was observed in half of the adults, and 71% of them had ASD. However, this is possibly an underestimation because 1 patient who scored above the threshold on the SCQ has not yet been formally tested to rule out ASD. No patient was completely independent for activities of daily living (ADLs). In addition, several patients had different degrees of difficulties in other areas such as abnormal sleep, daytime sleepiness, abnormal pain responsivity, reflux, constipation, and toileting issues.

Previously, only 24 adults (median: 26 years, range: 18–65 years) with *CHD2* variants have been reported across 16 different studies that focused mainly on children. The oldest patient (65-year-old) previously described had a concurrent paracentric inversion of chromosome 16 (inv(16)(q22.3q24.1)).[21] We reviewed all those previously published adult cases here (eTable 1) and compared them with our patients.

No phenotype-genotype correlations could be extrapolated in this study, and 11 of 14 patients had novel P/LP variants in *CHD2*. Both the pathogenic p.Trp1657Metfs*10 PTV and p.Arg699Trp variants have been reported once.[2,9] The p.Arg1637* pathogenic variant has been reported in 2 other patients.[4,29] The p.Trp1657Metfs*10 variant has been seen in a 24-year-old woman with normal development before seizure onset at 2 years of age.[2] Seizure types included eyelid myoclonia with absences (EMAs), myoclonic seizures, and GTCS. Seizures were pharmacoresistant and often cluster. She has a lifetime medication usage of 8 ASMs and continues to have drug-

Figure 3 Summary Graphs of Gastrointestinal Clinical Features in Adults With *CHD2*



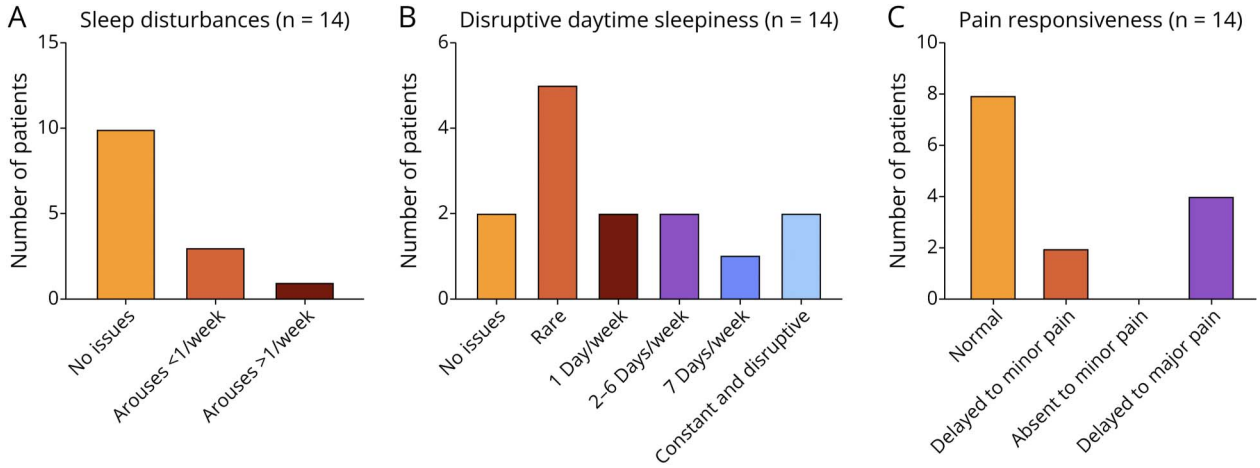
Information on (A) constipation, (B) toileting, and (C) reflux are provided (n = 14). No statistically significant differences between variant types or functional domains were found.

resistant seizures. Our patient with the same p.Trp1657Metfs*10 variant is an 18-year-old man with the most severe phenotype across our cohort. He has daily convulsive and weekly nonconvulsive seizures. Prolonged seizures lasting longer than 5 minutes requiring rescue medications occurred more than 5 times in the previous 12 months. In addition, the patient has weekly isolated epileptic spasms and myoclonic jerks that tend to cluster. Like the patient previously reported,[2] our patient has pharmacoresistant epilepsy despite being on 4 ASMs and having an implanted VNS.

The p.Arg1637* variant has been reported in 2 patients.[27,28,30] Detailed seizure description of one of these cases showed evolution from early-onset absence epilepsy to idiopathic photosensitive occipital epilepsy.[28] In our study, a 19-year-old woman carrying an p. Arg1637* variant has epilepsy, ID, and ASD diagnoses. She has daily nonconvulsive seizures and monthly convulsive seizures. She has isolated epileptic spasms that cluster and occur weekly. She required rescue medications twice in the past 12 months and 2 emergency department visits in the past 12 months because of her seizures.

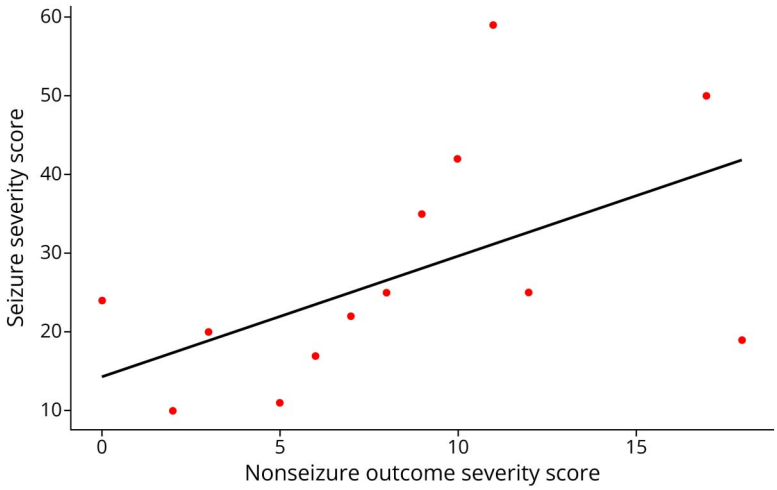
The 45-year-old patient in this study shares a variant (p.Arg699Trp) previously reported in 2 patients with epilepsy.[9] One 21-year-old man exhibited a more severe phenotype featuring DEE and severe ID. This patient was nonverbal, had scoliosis, and demonstrated aggressive behavior. The other patient with the same variant was a 2-year-

Figure 4 Summary Graphs of Other Clinical Features in Adults With *CHD2*



Information on (A) sleep disturbances, (B) disruptive daytime sleepiness, and (C) pain responsiveness are provided (n = 14). No statistically significant differences between variant types or functional domains were found.

Figure 5 Seizure Severity Scores vs Nonseizure Outcome Severity Score



s (p = 0.04) Increasing seizure severity was associated with increasing severity of nonseizure outcomes reported in Figures 2 and 3.

old girl with a milder clinical presentation with pharmacoresponsive epilepsy, language delay, and attention deficits. Her development was normal with no scoliosis. The exact cause of such variation in the phenotype cannot be confirmed. They are likely multifactorial, including gene-environment interactions and polygenic burden of autism, ID, and epilepsy.[30-32] Furthermore, it is unclear how the 2-year-old patient will evolve and whether she will eventually develop pharmacoresistant epilepsy.

Previous investigations of *CHD2* patients have noted that seizure onset typically occurs between 6 months and 4 years; however, disease onset may occur as early as 3 months[27-29,33] Although 23 (85%) of 27 patients previously described had seizures starting mainly in the first few years of life, it is unclear how many of them still had seizures in adulthood. As such, our findings of drug-resistant seizures in 79% of all adults in this cohort are a significant alert that this symptom needs life-long management.

Clinical photosensitivity is a common feature of *CHD2*-related conditions, especially EMA, and such seizures can even be self-induced.[7,9,29,30,33,34] A review of patients with *CHD2* has found that photosensitivity (either clinical or electrographic) has an overall prevalence of 46%.[9] Of interest, photosensitivity was slightly more prevalent in our adult population (64%). Despite the strong association between photosensitivity and *CHD2* variants, the specific cause is unknown. Knockdown of *chd2* in zebrafish results in larvae with stunted growth, seizure-like behavior, and photosensitivity, which align with findings in humans.[2,29]

In our adult cohort, gait abnormalities requiring walking assistance were seen in over half of the patients (57%). This is a very high proportion of gait abnormalities in a group of mainly "young adults." Of the 27 adults with *CHD2* previously described in 16 different studies, "gait problems" were seen in 26%. The methodology in the different studies may account for the difference in the proportion of adults with gait abnormalities, as in this study we used the Severity Assessment Tool[20] in all patients. Gait abnormalities have also been documented in adults with other DEEs. For example, only 21% of patients with *STXBP1*-DEE[35] could walk independently on all surfaces, and no adults with *SYNGAP1*-DEE[36] were able to walk independently (Table 3).

Unfortunately, lower mobility has been associated with a decreased ability to complete activities of daily living in older adult patients with ID.[37] Finally, scoliosis was observed in 43% of adults in this cohort, which is increased compared with 15% of current adults with *CHD2* in the literature.[8,14,15]

Social communication deficits were an important finding in our adult cohort, recapitulating *CHD2* as a high-risk gene associated with ASD, with or without seizures.[38] In a literature review of 102 patients with *CHD2*, ASD and autistic features had a prevalence of 56%.[9] Of interest, among the 27 adults identified in our literature review, only 8 (30%) of them had ASD.[7-10,17-19] We found a much higher proportion of diagnosed ASD in our adult population (71%). This significantly higher prevalence could be attributed to potential underdiagnoses, as seen with one of our patients who scored above the SCQ threshold but has never been formally tested for ASD.

A review of patients with *CHD2* (across pediatric and adult cases) found that behavioral issues were noted in 42% of patients in the literature.[9] However, no systematic evaluation of maladaptive behaviors has been previously published in patients with *CHD2*. Of interest, using the VABS3, 100% of our adults with *CHD2* showed maladaptive behavioral issues. The discrepancy may be attributed to differences in methodology or

Table 3 Comparison of *CHD2* Adults With Those of Other Studies Systematically Evaluating Nonseizure Outcomes and Adaptive Behaviors in Adults With Other DEEs (*SYNGAP1*-DEE and *STXBP1*-DEE)

	***CHD2* (this study)**	***SYNGAP1* (Rong et al., 2023)**	***STXBP1* (Stamberger et al., 2021)**
No. of patients	14	14	Varied (26–28)
Demographic	Adults (18+ y)	Adults (18+ y)	Adults (18+ y)
Nonseizure outcomes, %			
Abnormal swallowing	7	36	
Constipation	71	71	
Abnormal toileting	21	71	71
Abnormal pain responsiveness	43	100	
Sleep disturbances	29	86	
Disruptive daytime sleepiness	86	79	
Walking abilities, %			
Independent, all surfaces	43	0	21
Independent, level surfaces	0	14	29
With assistance (crutches, walkers)	36	50	11
Usually wheelchair/no regular walking	21	29	7
Nonambulatory	0	7	32
Verbal abilities, %			
Single words or more	100	100	29
Nonverbal	0	0	71
Independence for daily living skills, %			
Washing independence	57	14	0
Dressing independence	93	64	0
Toileting independence	64	21	7
Feeding independence	100	64	4

Abbreviation: DEE = developmental and epileptic encephalopathy.
Features not evaluated were left blank.

the fact that maladaptive behaviors are more common (or more easily diagnosed) in adults. Specific internalizing maladaptive behaviors such as anxiety and being overly needy have not been systematically evaluated in patients with *CHD2*. We found that those symptoms were present in 71% of our adults studied. When compared with descriptions in 3 (11%) of 27 adults with *CHD2* (with or without seizures) in the literature,[2,4,7-16] this finding offers new insights into the adult *CHD2* phenotype. Finally, aggression and oppositional behavior have been reported in 14 (52%) of 27 adults even in nonepileptic phenotypes,[9,17] which falls in line with the 50% prevalence in our cohort.

Verbal ability has been reported in 11 (41%) of 27 adults in the literature, and 100% demonstrated language and speech deficits.[7-10,13,14,17,22] While the exact definitions of verbal ability were not specified in previous works, all adults in this study demonstrated language abilities of at least 50 words. None of our *CHD2* adults was nonverbal, although most had a very limited vocabulary of 50 words or less. Verbal skills in adults with *CHD2* were similar to those seen in adults with *SYNGAP1* and much better than those seen in adults with *STXBP1* where 71% of adults were nonverbal (Table 3).[35,36]

Delusions were observed in 2 adults in this study. Psychotic episodes and delusions not associated with seizures have been noted in 4 (15%) of 27 patients in the literature, where all patients were adults.[7,10,14]

Basic activities of daily living refer to the ability of a person to manage his/her own physical needs, including eating, transferring, or ambulating; personal hygiene; dressing;

and toileting. ADLs have not been systematically evaluated in adults nor pediatric populations with P/LP *CHD2*. In this study, we evaluated adult independency to complete ADLs. No adult patients with *CHD2* were completely independent for all their ADLs. However, they overall did better than adults with *SYNGAP1* and *STXBP1*-DEEs (Table 3).

Various clinical features such as sleep dysfunction, toileting accidents, and abnormal pain processing are also seen in our *CHD2* adults.[39] These abnormalities are also seen in other patients with DEEs and are compared in Table 3.

This study details the oldest patient with *CHD2* reported so far. This is a 45-year-old patient, who has never had seizures but has problematic aggressive behaviors. She has a de novo c.2095C > T *CHD2* missense variant. The lifespan of patients with *CHD2*-associated conditions is currently unknown. The previously oldest patient in the literature was a 35-year-old woman reported in 2015. That patient had a de novo 2.4 Mb deletion involving *CHD2* and had a mild phenotype, described only as "disadvantaged." She also had epilepsy and exhibited ASD-like traits and aggression.[7]

Limitations of this study include its cross-sectional design. Furthermore, despite being large for such rare conditions, the sample size is still small. This might be in part due to the somewhat recency of *CHD2* being linked to NDDs and DEEs and the fact that adult neurologists generally do not update genetic testing previously performed in childhood.[40,41]

This study presented the spectrum of clinical outcomes of adults specifically with *CHD2*-associated disorders and the oldest patient (45-year-old woman) currently described in the literature. Specifically, 79% of adults still have pharmacoresistant seizures. Both externalizing and internalizing behavioral issues were identified as prominent in adults with *CHD2*. While 57% of patients required some form of assistance walking, all adults with *CHD2* were ambulatory. Overall, adult patients with *CHD2* are not independent for ADLs and dependent on their caregivers. These data will be relevant when evaluating the results of precision drug trials on seizures and nonseizure comorbidities. Further longitudinal studies using standardized scales will help build a more comprehensive landscape of adult *CHD2* phenotypes.

Acknowledgment

The authors thank all patients and their families and the Coalition to Cure CHD2 for participating in this study.

Study Funding

M. Rong received unrestricted educational funding from Biocodex. A. Bayat is funded by a BRIDGE—Translational Excellence Programme grant funded by the Novo Nordisk Foundation, grant agreement number: NNF20SA0064340. A.S. Bassett holds the Dalglish Chair in 22q11.2 Deletion Syndrome at the University Health Network and University of Toronto.

Disclosure

M. Rong received an unrestricted education grant from Biocodex. Q. Zulfiqar Ali reports no disclosures relevant to the manuscript. A. Aledo-Serrano received educational, scientific and consulting fees from UCB, Biocodex, Eisai, Angelini, Jazz pharma. A. Bayat reports no disclosures relevant to the manuscript. O. Devinsky receives grant support from NINDS, NIMH, MURI, CDC and NSF. He has equity and/or compensation from the following companies: Ajna Biosciences, Tilray, Receptor Life Sciences, Hitch Biosciences, Tevard Biosciences, Regel Biosciences, Script Biosciences, Actio Biosciences, Empatica, SilverSpike, and California Cannabis Enterprises. He has received consulting fees from Zogenix, Ultragenyx, BridgeBio, GeneMedicine and Marinus. He holds patents for the use of cannabidiol in treating neurologic disorders which are owned by GW Pharmaceuticals for which he waived financial interests. He holds other patents in molecular biology. He is the managing partner of the PhiFund Ventures. F. Qaiser, I. Chandran, A. Ali, A. Fasano, and A.S. Bassett report no disclosures relevant to the manuscript. D.M. Andrade receives grant support from Ontario Brain Institute, McLaughlin Foundation, UHN Foundation, Dravet Syndrome Foundation, SYNGAP1 Research Fund. She also received consulting fees from UCB, Biocodex, Paladin, Jazz, Stoke, and Eisai. Finally, she receives royalties from UpToDate. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* April 10, 2024. Accepted in final form August 26, 2024. Submitted and externally peer reviewed. The handling editor was Deputy Editor Massimo Pandolfo, MD, FAAN.

Appendix Authors

Name	Location	Contribution
Marlene Rong, MSc	Institute of Medical Science, University of Toronto, Adult Genetic Epilepsy (AGE) Program, Krembil Neurosciences Institute, Toronto Western Hospital, University Health Network, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Quratulain Zulfiqar Ali, MD	Adult Genetic Epilepsy (AGE) Program, Krembil Neurosciences Institute, Toronto Western Hospital, University Health Network, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Angel Aledo-Serrano, MD	Epilepsy Unit, Vithas Clinical Neuroscience Institute, Vithas Madrid University Hospitals, Faculty of Experimental Sciences, Francisco de Vitoria University, Madrid, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Allan Bayat, MD, PhD	Department of Drug Design and Pharmacology, University of Copenhagen, Department for Genetics and Personalized Medicine, Danish Epilepsy Centre, Dianalund, Institute for Regional Health Services, University of Southern Denmark, Odense	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Orrin Devinsky, MD, PhD	NYU Langone Epilepsy Center	Drafting/revision of the manuscript for content, including medical writing for content
Farah Qaiser	Adult Genetic Epilepsy (AGE) Program, Krembil Neurosciences Institute, Toronto Western Hospital, University Health Network, Canada	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Ilakkiah Chandran, BSc	Adult Genetic Epilepsy (AGE) Program, Krembil Neurosciences Institute, Toronto Western Hospital, University Health Network, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Anum Ali	Adult Genetic Epilepsy (AGE) Program, Krembil Neurosciences Institute, Toronto Western Hospital, University Health Network, Canada	Analysis or interpretation of data
Alfonso Fasano, MD, PhD	Division of Neurology, Department of Medicine, University of Toronto, Krembil Brain Institute, Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, ON, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Anne S. Bassett, MD	Clinical Genetics Research Program, Centre for Addiction and Mental Health, The Dalglish Family 22q Clinic, Toronto General Hospital, University Health Network, Department of Psychiatry, University of Toronto, Toronto Congenital Cardiac Centre for Adults, Division of Cardiology, Department of Medicine, and Department of Psychiatry, University Health Network, Toronto General Hospital Research Institute and Campbell Family Mental Health Research Institute, ON, Canada	Study concept or design
Danielle M. Andrade, MD	Division of Neurology, Department of Medicine, University of Toronto, Krembil Brain Institute, ON, Adult Genetic Epilepsy (AGE) Program, Krembil Neurosciences Institute, Toronto Western Hospital, University Health Network, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Liu JC, Ferreira CG, Yusufzai T. Human CHD2 is a chromatin assembly ATPase regulated by its chromo- and DNA-binding domains. *J Biol Chem*. 2015;290(1):25-34. doi:10.1074/jbc.M114.609156
2. Suls A, Jaehn JA, Kecskés A, et al. De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome. *Am J Hum Genet*. 2013;93(5):967-975. doi:10.1016/j.ajhg.2013.09.017
3. Veredice C, Bianco F, Contaldo I, et al. Early onset myoclonic epilepsy and 15q26 microdeletion: observation of the first case. *Epilepsia*. 2009;50(7):1810-1815. doi:10.1111/j.1528-1167.2009.02078.x
4. Carvill GL, Heavin SB, Yendle SC, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. *Nat Genet*. 2013;45(7):825-830. doi:10.1038/ng.2646
5. Epi4K Consortium, Epilepsy Phenome/Genome Project, Allen AS, et al. De novo mutations in epileptic encephalopathies. *Nature*. 2013;501(7466):217-221. doi:10.1038/nature12439
6. Truty R, Patil N, Sankar R, et al. Possible precision medicine implications from genetic testing using combined detection of sequence and intragenic copy number variants in a large cohort with childhood epilepsy. *Epilepsia Open*. 2019;4(3):397-408. doi:10.1002/epi4.12348
7. Thomas RH, Zhang LM, Carvill GL, et al. CHD2 myoclonic encephalopathy is frequently associated with self-induced seizures. *Neurology*. 2015;84(9):951-958. doi:10.1212/WNL.0000000000001305
8. Lebrun N, Parent P, Gendras J, Billuart P, Poirier K, Bienvenu T. Autism spectrum disorder recurrence, resulting of germline mosaicism for a *CHD2* gene missense variant. *Clin Genet*. 2017;92(6):669-670. doi:10.1111/cge.13073
9. De Maria B, Balestrini S, Mei D, et al. Expanding the genetic and phenotypic spectrum of CHD2-related disease: from early neurodevelopmental disorders to adult-onset epilepsy. *Am J Med Genet A*. 2022;188(2):522-533. doi:10.1002/ajmg.a.62548
10. Bernardo P, Galletta D, Iasevoli F, et al. CHD2 mutations: only epilepsy? Description of cognitive and behavioral profile in a case with a new mutation. *Seizure*. 2017;51:186-189. doi:10.1016/j.seizure.2017.09.001
11. Chen J, Zhang J, Liu A, et al. CHD2 -related epilepsy: novel mutations and new phenotypes. *Dev Med Child Neurol*. 2020;62(5):647-653. doi:10.1111/dmcn.14367
12. Zhou P, He N, Zhang J-W, et al. Novel mutations and phenotypes of epilepsy-associated genes in epileptic encephalopathies. *Genes Brain Behav*. 2018;17(8):e12456. doi:10.1111/gbb.12456
13. Petersen AK, Streff H, Tokita M, Bostwick BL. The first reported case of an inherited pathogenic CHD2 variant in a clinically affected mother and daughter. *Am J Med Genet A*. 2018;176(7):1667-1669. doi:10.1002/ajmg.a.38835
14. Courage C, Houge G, Gallati S, Schjelderup J, Rieubland C. 15q26.1 microdeletion encompassing only CHD2 and RGMA in two adults with moderate intellectual disability, epilepsy and truncal obesity. *Eur J Med Genet*. 2014;57(9):520-523. doi:10.1016/j.ejmg.2014.06.003
15. Borlot F, de Almeida BI, Combe SL, Andrade DM, Filloux FM, Myers KA. Clinical utility of multigene panel testing in adults with epilepsy and intellectual disability. *Epilepsia*. 2019;60(8):1661-1669. doi:10.1111/epi.16273
16. Mullen SA, Carvill GL, Bellows S, et al. Copy number variants are frequent in genetic generalized epilepsy with intellectual disability. *Neurology*. 2013;81(17):1507-1514. doi:10.1212/WNL.0b013e3182a95829
17. Blackburn PR, Sullivan AE, Gerassimou AG, et al. Functional analysis of the SIM1 variant p.G715V in 2 patients with obesity. *J Clin Endocrinol Metab*. 2020;105(1):355-361. doi:10.1210/clinem/dgz192
18. Lund C, Brodtkorb E, Røsby O, Rødningen OK, Selmer KK. Copy number variants in adult patients with Lennox-Gastaut syndrome features. *Epilepsy Res*. 2013;105(1–2):110-117. doi:10.1016/j.eplepsyres.2013.01.009
19. Lund C, Brodtkorb E, Øye AM, Røsby O, Selmer KK. CHD2 mutations in Lennox-Gastaut syndrome. *Epilepsy Behav*. 2014;33:18-21. doi:10.1016/j.yebeh.2014.02.005
20. Saldaris J, Weisenberg J, Pestana-Knight E, et al. Content validation of clinician-reported items for a severity measure for CDKL5 deficiency disorder. *J Child Neurol*. 2021;36(11):998-1006. doi:10.1177/08830738211019576
21. Angelopoulou E, Theodosiou A, Papaevripidou I, et al. CHD2 pathogenic nonsense variant in a three-generation family with variable phenotype and a paracentric inversion 16: case report. *Heliyon*. 2023;9(12):e22987. doi:10.1016/j.heliyon.2023.e22987
22. Cogliati F, Straniero L, Rimoldi V, et al. Low-grade parental gonosomal mosaicism in CHD2 siblings with Smith-Magenis-like syndrome. *Am J Med Genet B Neuropsychiatr Genet*. 2024;195(6):e32976. doi:10.1002/ajmg.b.32976
23. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the international League against epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia*. 2017;58(4):522-530. doi:10.1111/epi.13670
24. Rutter M, Bailey A, Lord C, et al. *Social Communication Questionnaire, 2003*: Western Psychoical Services; 2003.
25. Sparrow SS, Cicchetti DV, Saulnier CA. *Vineland Adaptive Behavior Scales, Third Edition (Vineland-3)*. NCS Pearson; 2016.
26. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. doi:10.1038/gim.2015.30
27. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res*. 2018;46(D1):D1062-D1067. doi:10.1093/nar/gkx1153

28. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*. 2020;581(7809):434-443. doi:10.1038/s41586-020-2308-7
29. Galizia EC, Myers CT, Leu C, et al. CHD2 variants are a risk factor for photosensitivity in epilepsy. *Brain*. 2015;138(pt 5):1198-1207. doi:10.1093/brain/awv052
30. Cardoso AR, Lopes-Marques M, Silva RM, et al. Essential genetic findings in neurodevelopmental disorders. *Hum Genomics*. 2019;13(1):31. doi:10.1186/s40246-019-0216-4
31. Trost B, Thiruvahindrapuram B, Chan AJS, et al. Genomic architecture of autism from comprehensive whole-genome sequence annotation. *Cell*. 2022;185(23):4409-4427.e18. doi:10.1016/j.cell.2022.10.009
32. International Schizophrenia Consortium, Purcell SM, Wray NR, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460(7256):748-752. doi:10.1038/nature08185
33. Trivisano M, Striano P, Sartorelli J, et al. CHD2 mutations are a rare cause of generalized epilepsy with myoclonic-atonic seizures. *Epilepsy Behav*. 2015;51:53-56. doi:10.1016/j.yebeh.2015.06.029
34. Smith KM, Wirrell EC, Andrade DM, et al. Clinical presentation and evaluation of epilepsy with eyelid myoclonia: results of an international expert consensus panel. *Epilepsia*. 2023;64(9):2330-2341. doi:10.1111/epi.17683
35. Stamberger H, Crosiers D, Balagura G, et al. Natural history study of STXBP1-developmental and epileptic encephalopathy into adulthood. *Neurology*. 2022;99(3):e221-e233. doi:10.1212/WNL.0000000000200715
36. Rong M, Benke T, Zulfiqar Ali Q, et al. Adult phenotype of SYNGAP1 -DEE. *Neurol Genet*. 2023;9(6):e200105. doi:10.1212/NXG.0000000000200105
37. Hilgenkamp TIM, van Wijck R, Evenhuis HM. (Instrumental) activities of daily living in older adults with intellectual disabilities. *Res Dev Disabil*. 2011;32(5):1977-1987. doi:10.1016/j.ridd.2011.04.003
38. O'Roak BJ, Stessman HA, Boyle EA, et al. Recurrent de novo mutations implicate novel genes underlying simplex autism risk. *Nat Commun*. 2014;5(1):5595. doi:10.1038/ncomms6595
39. Scheffer IE, Liao J. Deciphering the concepts behind "Epileptic encephalopathy" and "Developmental and epileptic encephalopathy". *Eur J Paediatr Neurol*. 2020;24:11-14. doi:10.1016/j.ejpn.2019.12.023
40. Andrade DM, Bassett AS, Bercovici E, et al. Epilepsy: transition from pediatric to adult care. Recommendations of the Ontario epilepsy implementation task force. *Epilepsia*. 2017;58(9):1502-1517. doi:10.1111/epi.13832
41. Aledo-Serrano A, García-Morales I, Toledano R, et al. Diagnostic gap in genetic epilepsies: a matter of age. *Epilepsy Behav*. 2020;111:107266. doi:10.1016/j.yebeh.2020.107266