JAMA Neurology | Original Investigation

Prevalence of Pathogenic Copy Number Variation in Adults With Pediatric-Onset Epilepsy and Intellectual Disability

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IMPORTANCE Copy number variation (CNV) is an important cause of neuropsychiatric disorders. Little is known about the role of CNV in adults with epilepsy and intellectual disability.

OBJECTIVES To evaluate the prevalence of pathogenic CNVs and identify possible candidate CNVs and genes in patients with epilepsy and intellectual disability.

DESIGN, SETTING, AND PARTICIPANTS In this cross-sectional study, genome-wide microarray was used to evaluate a cohort of 143 adults with unexplained childhood-onset epilepsy and intellectual disability who were recruited from the Toronto Western Hospital epilepsy outpatient clinic from January 1, 2012, through December 31, 2014. The inclusion criteria were (1) pediatric seizure onset with ongoing seizure activity in adulthood, (2) intellectual disability of any degree, and (3) no structural brain abnormalities or metabolic conditions that could explain the seizures.

MAIN OUTCOMES AND MEASURES DNA screening was performed using genome-wide microarray platforms. Pathogenicity of CNVs was assessed based on the American College of Medical Genetics guidelines. The Residual Variation Intolerance Score was used to evaluate genes within the identified CNVs that could play a role in each patient's phenotype.

RESULTS Of the 2335 patients, 143 probands were investigated (mean [SD] age, 24.6 [10.8] years; 69 male and 74 female). Twenty-three probands (16.1%) and 4 affected relatives (2.8%) (mean [SD] age, 24.1 [6.1] years; 11 male and 16 female) presented with pathogenic or likely pathogenic CNVs (0.08-18.9 Mb). Five of the 23 probands with positive results (21.7%) had more than 1 CNV reported. Parental testing revealed de novo CNVs in 11 (47.8%), with CNVs inherited from a parent in 4 probands (17.4%). Sixteen of 23 probands (69.6%) presented with previously cataloged human genetic disorders and/or defined CNV hot spots in epilepsy. Eight nonrecurrent rare CNVs that overlapped 1 or more genes associated with intellectual disability, autism, and/or epilepsy were identified: 2p16.1-p15 duplication, 6p25.3-p25.1 duplication, 8p23.3p23.1 deletion, 9p24.3-p23 deletion, 10q11.22-q11.23 duplication, 12p13.33-13.2 duplication, 13q34 deletion, and 16p13.2 duplication. Five genes are of particular interest given their potential pathogenicity in the corresponding phenotypes and least tolerability to variation: *ABAT, KIAA2022*, *COL4A1, CACNA1C,* and *SMARCA2*. *ABAT* duplication was associated with Lennox-Gastaut syndrome and *KIAA2022* deletion with Jeavons syndrome.

CONCLUSIONS AND RELEVANCE The high prevalence of pathogenic CNVs in this study highlights the importance of microarray analysis in adults with unexplained childhood-onset epilepsy and intellectual disability. Additional studies and comparison with similar cases are required to evaluate the effects of deletions and duplications that overlap specific genes.

JAMA Neurol. doi:10.1001/jamaneurol.2017.1775
Published online August 28, 2017.

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Copy number variations (CNVs) are thought to be an important mechanism of genomic diversity and evolutionary changes in humans.[1,2] Often, CNVs are seen in healthy control individuals, and determination of the pathogenicity of newly identified CNVs can be challenging. Since 2004, genome-wide identification of CNVs has become efficient through array comparative genomic hybridization, allowing the detection of causative submicroscopic CNVs that were not previously identified by karyotype,[1,3] especially in neuropsychiatric disorders.[4]

The importance of rare CNVs has been well recognized in patients with epilepsy with partial and generalized seizures,[5,6] epileptic encephalopathies,[7] genetic generalized epilepsy with intellectual disability (ID),[8,9] atypical Rolandic epilepsy,[10] fever-associated syndromes,[11] and absence epilepsy.[12] Rare CNVs have also been identified in individuals with developmental disabilities and/or congenital anomalies.[13,14] Of note, these comorbidities are seen in a high proportion of adult patients who did not outgrow their childhood-onset epilepsies.[15]

In an adult epilepsy clinic, it can be difficult to diagnose specific childhood-onset epilepsy syndromes for several reasons. The clinical features might have evolved since childhood. Key diagnostic features, such as characteristic electroencephalograms (EEGs), or certain seizure types may no longer be present; even if phenotyping were performed during childhood, without those previous notes, the current features may no longer be enough for a clinical diagnosis. In addition, parents often have difficulties remembering the characteristics of certain seizures that have long been replaced by other seizure types. Finally, for some patients, despite phenotyping, the clinical manifestations are not diagnostic of any specific epileptic syndrome. Therefore, genetic testing in adults, interpreted in light of clinical features, may help clarify the etiologic diagnosis.[16,17]

We sought to determine the prevalence of pathogenic and likely pathogenic CNVs in adults with pediatric-onset epilepsy and ID of unknown origin. We also aimed to identify novel genes within these CNVs that may be related to seizures and could then be studied further and compared with similar cases.

Key Points

Question What is the role of copy number variation investigation in adults with unexplained epilepsy and intellectual disability?

Findings In this cross-sectional study, pathogenic and/or likely pathogenic copy number variations were found in 16.1% of the probands investigated using microarray analysis; 8 nonrecurrent rare copy number variations were identified. Lennox-Gastaut syndrome was associated with an *ABAT* duplication and Jeavons syndrome with a *KIAA2022* deletion.

Meaning This study highlights the importance of investigating adults with childhood-onset epilepsy and intellectual disability without an etiologic diagnosis.

Methods

Patients were recruited from the Toronto Western Hospital epilepsy outpatient clinic from January 1, 2012, through December 31, 2014. Inclusion criteria for this cross-sectional study were (1) onset of seizures between birth and adolescence and ongoing seizure activity throughout adulthood, (2) neither obvious causal structural abnormalities in their neuroimaging studies nor evident metabolic conditions that could explain their symptoms, and (3) ID of any degree, diagnosed through a formal neuropsychological evaluation and classified according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*[18] (when IQ test results were available) or *DSM-5*[19] (when patients could not be tested). The exclusion criteria were (1) patients presenting with a classic phenotype of chromosomal abnormalities (eg, Down syndrome) and (2) patients previously diagnosed with well-known single-gene mutations that cause seizure phenotypes (eg, sodium channel, neuronal type I, α subunit [*SCN1A*] [OMIM 182389], and cyclin-dependent kinase-like 5 [*CDKL5*] [OMIM 300203]). Ethical approval for the study was granted by the University Health Network Research Ethics Board, and verbal informed consent was obtained from patients' parents or caregivers.

DNA of all patients was screened for CNVs using clinical genome-wide microarray platforms; labeling and hybridization were performed following standard protocols using platform 4 × 180K Oligonucleotide Array (Agilent Technologies) and CytoSure interpret (Oxford Gene Technologies) analysis software. Some samples were studied with CytoScan HD SNP Array (Affymetrix) genomic platform and ChAS (Affymetrix) analysis software.

Patients who harbored a CNV of interest were offered segregation testing. Available relatives were tested with fluorescence in situ hybridization (FISH) analysis with probes obtained from The Centre for Applied Genomics or with microarray testing using the same technology that was used to identify the CNV in their relatives. For the latter cases, only the region of interest was subject to analysis.

Pathogenicity of CNVs was predicted based on their size and gene content according to the American College of Medical Genetics guidelines for interpretation of CNV results.[20] Whenever known epilepsy genes were within the deleted or duplicated interval and there was a correlation with the patient's phenotype, the CNV was considered to be pathogenic.

For each relevant Online Mendelian Inheritance in Man (OMIM) gene that could play a role in the patient's phenotype, we applied the Residual Variation Intolerance Score (RVIS) and the percentile of most intolerant genes (MIG) to guide the interpretation of potential clinical significance.[21] The RVIS is based on allele frequency as represented in whole-exome sequence data from the National Heart, Lung, and Blood Institute Exome Sequencing Project 6500 data set. A gene with a positive score has more common functional variation, and a gene with a negative score has less variation and is referred to as intolerant. The more intolerant a gene is, the more likely it is associated with disease if mutated or at abnormal levels.

Results

Of the 2335 adult patients, a subset of 143 probands (6.1%) was investigated using clinical microarray (mean [SD] age, 24.6

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[10.8] years; 69 male and 74 female). There were 23 probands (16.1% of the total sample investigated) and 4 affected relatives (2.8%) with 1 or more pathogenic or likely pathogenic CNV (**Table 1**). The investigated patients' age ranged from 17 to 41 years (median, 22 years), and 16 were female.

Among the 27 individuals with pathogenic and likely pathogenic CNVs, deletions were found in 15 patients and duplications in 10. These CNVs varied from 0.08 to 18.9 Mb (median, 4.84 Mb). Five probands had more than 1 CNV detected, including 2 patients with 2 pathogenic CNVs (patients 4 and 12; both had unbalanced translocations confirmed by FISH or G-banding), and 3 patients with a second CNV deemed to be a variant of unknown significance (patients 3, 18, and 21).

Parental testing revealed de novo CNVs in 11 of 23 probands (47.8%) and CNVs inherited from parents in 4 (17.4%), the latter representing unbalanced segregation of parental balanced rearrangements in 3 probands (patients 3, 4, and 6) and maternal X-linked inheritance in a male proband (patient 26). One mother (patient 6) presented with mild dysmorphic features similar to her offspring and borderline intellectual functioning.

Eight adult patients (34.8%) had only 1 or none of the parents available for testing. However, the CNVs in 7 of them (patients 12, 15, 16, 17, 18, 19, and 20) were pathogenic according to the American College of Medical Genetics guidelines.[20] The remaining patient (patient 21) had 1 likely pathogenic CNV and 1 large (>500 kb) variant of unknown significance.

Table 1 contains the seizure phenotype, cognitive profile,[22,23] systemic manifestations, and microarray results for 23 unrelated patients and 4 affected siblings, each of whom shared the respective proband's clinically relevant CNV(s). Sixteen unrelated patients (69.6%) presented with genetic disorders associated with seizures, including OMIM cataloged human genes and genetic disorders and defined hot spots for CNVs in epilepsy.

Among the CNVs previously associated with seizures, we found a phenotype caused by *KIAA2022* (OMIM 300524) deletion (patient 27; de novo Xq13.3 deletion) of particular interest: a 23-year-old woman with Jeavons syndrome (JS) and cognitive difficulties since elementary school. Her seizures were characterized by absence with eyelid myoclonia and rare bilateral convulsive seizures. Her EEGs showed polyspikes and generalized spike waves induced by eye closure, disappearing with eye opening. Her seizures were well controlled with topiramate monotherapy. Results of investigation for glucose transporter 1 deficiency were negative (solute carrier family 2 [facilitated glucose transporter], member 1 [*SLC2A1*] [OMIM 138140] sequencing was normal), as were results for another 476 genes tested in the same epilepsy genetic panel.

Eight nonrecurrent, rare pathogenic or likely pathogenic CNVs that contained 1 or more genes associated with ID, autism, and seizures were identified (**Table 2**)[24-48]: 2p16.1-p15 duplication, 6p25.3-p25.1 duplication, 8p23.3p23.1 deletion, 9p24.3-p23 deletion, 10q11.22-q11.23 duplication, 12p13.33-13.2 duplication, 13q34 deletion, and 16p13.2 duplication. Four genes found in these CNVs may have had a role in patients' neurodevelopment phenotype and had low RVISs as follows: 4-aminobutyrate aminotransferase (*ABAT*) (OMIM 137150), -0.33 (30.7% MIG); collagen, type IV, α-1 (*COL4A1*) (OMIM 120130), -2.82 (0.6% MIG); calcium channel, voltage-dependent, L type, α-1C subunit (*CACNA1C*) (OMIM 114205), -2.09 (1.5% MIG); and SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 2 (*SMARCA2*) (OMIM 600014), -1.97 (1.82% MIG).

ABAT duplication (patient 21; 16p13.2 duplication) was identified in a 23-year-old man with developmental delay and a history of multiple seizure types since the age of 6 months. He died shortly after genetic testing was completed. Over time, his seizure phenotype evolved and became consistent with Lennox-Gastaut syndrome (LGS) with tonic, atonic, and atypical absence seizures and corroborant EEGs. He required partial callosotomy at the age of 4 years, ketogenic diet from the ages of 8 to 9 years, vagus nerve stimulator insertion when he was 10 years of age, and completion of callosotomy at 11 years of age. At the time of testing, he was nonverbal and incontinent and presented with a wide-based gait and bilateral hand dystonic posture. He had no dysmorphic features. The case was reviewed in the context of the CNV finding, and thus, cerebrospinal fluid γ-aminobutyric acid (GABA) testing could have provided support for GABA-transaminase overexpression as a consequence of his *ABAT* duplication. However, this analysis was not performed because his family decided to not pursue an invasive test.

COL4A1 deletion and *CACNA1C* duplication (patient 12; 13q34 deletion and 12p13.33-13.2 duplication) were seen in a 24-year-old woman with severe ID and dysmorphisms characterized by a prominent forehead, low hair implantation, and bilateral auricular appendix. She was born in Ethiopia to nonconsanguineous parents. There was no family history of seizures or ID. Seizure phenotype was characterized by bilateral convulsive seizures starting when the patient was 17 years of age; despite her severe ID, her EEG showed a normal background and spike and slow wave discharges over the left frontal and central regions. Seizures were controlled with levetiracetam and topiramate.

SMARCA2 deletion (patients 4 and 5; 9p24.3-p23 deletion and 6p25.3-p25.1 duplication) was present in a pair of siblings who developed focal-onset seizures in adolescence (15 and 17 years of age); their seizures have been controlled with monotherapy with levetiracetam. In addition to ID and autistic features, mood oscillation and intermittent aggression outbursts not aggravated (or ameliorated) by the antiepileptic therapy have been their main problems. The female sibling was born with cleft palate, and the male has developed sensorineural deafness over time.

Discussion

This study of adults with epilepsy and ID revealed that a high proportion of patients had clinically relevant CNVs. Twenty-three probands (16.1%) had pathogenic or likely pathogenic CNVs, including 8 nonrecurrent rare CNVs. These CNVs encompassed genes that could explain the epilepsy and should be further studied. Of importance, this study underscores the

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Table 1. Clinical Features of Patients With Epilepsy and Intellectual Disability With 1 or More Pathogenic or Likely Pathogenic CNV

Patient No./ Sex/Age, y	Seizure Onset Age, y	Seizure Type[a]	Cognitive and Neuropsychiatric Features[22,23]	Systemic and Dysmorphic Features	CNV	Genomic Coordinates (Genome Build)	Associated Genetic Syndrome	Interpretation
1/M/20	4	FDS	Moderate ID, autistic features	Brachycephaly, hypermetropia, deep-set eyes, flat nasal bridge, asymmetric ears, thickened helices, dilated cardiomyopathy, right sensorioneural hearing loss, and overweight	de novo 1p36.33-p36.31 del (5.64 Mb)	chr1:890 951-6 606 297(NCBI 37/hg 19)	1p36 del syndrome (OMIM 607872)	Pathogenic
2/M/32	2	FDS	Mild ID	Retinitis pigmentosa	de novo 2p16.1-p15 dup (1.7 Mb)	chr2: 60 326 674-62 025 420 (NCBI 37/hg 19)	NA	Likely pathogenic
3/F/20	1	Myoclonic absence, tonic	Moderate ID, OCD, aggressive behaviors, and hallucinations	Bicuspid aortic valve, short stature, small right fourth finger and right fourth toe phalanges, and obesity	Maternally inherited unbalanced translocation 2q37.3 del (5.62 Mb), 8p23.3 dup (2.96 Mb)	chr2: 237 382 286-243 007 607 (NCBI 37/hg 19), chr8: 13 938-2 981 379 (NCBI 37/hg 19)	2q37 del syndrome (brachydactyly-mental retardation syndrome) (OMIM 600430), NA	Pathogenic, VUS
4/F/26[b]	15	FDS->BCS	Mild ID, autistic features	Cleft palate	Maternally inherited unbalanced translocation 6p25.3-p25.1 dup (6.58 Mb), 9p24.3-p23 del (12.0 Mb)	chr6: 152 630-6 736 897 (NCBI 37/hg 19), chr9: 12 934-11 981 505 (NCBI 37/hg 19)	NA	Pathogenic for both
5/M/29[b]	17	FDS->BCS	Moderate ID, autistic features, and aggressive behaviors	Sensorineural deafness	As for sibling (patient 4) (2 CNVs)	As for sibling (patient 4) (2 CNVs)	NA	As for sibling (patient 4) (2 pathogenic CNVs)
6/M/17[c]	1	FS, afebrile BCS	Mild ID	Short stature, left eye astigmatism, and mild dysmorphic features	Maternally inherited 8q21.13q22.2 dup (18.9 Mb)	chr8:80 258 449-99 137 278 (NCBI 37/hg 19)	NA	Likely pathogenic
7/F/20[c]	3	Absence, BCS	Mild ID	High-arched palate, mild dysmorphic facies	As for sibling (patient 6)	As for sibling (patient 6)	NA	As for sibling (patient 6)
8/F/25[c]	0.8 (10 mo)	FS, afebrile BCS, and absence	Mild ID	Short stature, high-arched palate, and mild dysmorphic facies	As for sibling (patient 6)	As for sibling (patient 6)	NA	As for sibling (patient 6)
9/M/22	10	FDS->BCS, CSWS	Severe ID, autistic features	Inguinal hernia, slightly swollen and erythematous extremities	de novo 8p23.3p23.1 del (11.0 Mb)	chr8:229 785-11 245 018 (NCBI 37/hg 19)	NA	Likely pathogenic
10/F/18[d]	2	FS, FDS, and hemiclonic or tonic posture seizures	Severe ID, autistic features	Short stature, microcephaly	de novo (monozygotic twins) 10q11.22 dup (1.73 Mb)	chr10:49 314 418-51 046 099 (NCBI 37/hg 19)	NA	Likely pathogenic
11/F/18[d]	2	FDS, hemiclonic	Moderate ID, autistic features	Short stature, microcephaly	As for monozygotic twin (patient 10)	NA	NA	As for monozygotic twin (patient 10)
12/F/24	17	BCS, atonic	Severe ID	Prominent forehead with low hair implantation, bilateral auricular appendix	Unknown inheritance 12p13.33-13.2 dup (11.0 Mb), unknown inheritance 13q34 del (4.39 Mb)	chr12:204 618-11 221 959 (NCBI 37/hg19), chr13:110 930 206-115 105 655 (NCBI 37/hg 19)	NA	Pathogenic for both
13/F/21	11	Nocturnal tonic evolving to BCS	Moderate ID, aggressive behaviors	Overweight	de novo 15q11.2-13.1 dup (8.56 Mb)	chr15:20 063 340-29 087 002 (NCBI 37/hg 19)	15q11-q13 dup syndrome (OMIM 608636)	Pathogenic
14/M/28	12	FDS	Mild ID, autistic features	Dysmorphic facies	de novo isodicentric 15q11.1-q13.1 dup (9.05 Mb)	chr15: 20 172 533-29 227 358 (NCBI 37/hg 19)	15q11-q13 dup syndrome (OMIM 608636)	Pathogenic
15/F/22	7	FS, BCS	Severe ID, autistic features	Mild brachycephaly	Unknown inheritance 15q11.2-q13.1 del (4.84 Mb)	chr15: 23 676 399-28 525 218 (NCBI 37/hg 19)	Angelman syndrome (OMIM 105830)	Pathogenic

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Table 1. Clinical Features of Patients With Epilepsy and Intellectual Disability With 1 or More Pathogenic or Likely Pathogenic CNV (continued)

Patient No./ Sex/Age, y	Seizure Onset Age, y	Seizure Type[a]	Cognitive and Neuropsychiatric Features[22,23]	Systemic and Dysmorphic Features	CNV	Genomic Coordinates (Genome Build)	Associated Genetic Syndrome	Interpretation
16/M/19	1.5	FS, afebrile BCS	Severe ID, autistic features	Aortic stenosis, severe scoliosis	Unknown inheritance (mother and dizygotic twin negative) 15q11.2 del (0.32 Mb)	chr15:22 762 571-23 090 364 (NCBI 37, hg 19)	15q11.2 del syndrome (OMIM 615656)	Pathogenic
17/F/35	18	Atonic, myoclonic, and FDS->BCS	Severe ID	None	Unknown inheritance 15q11.2q13.1 dup (5.87 Mb)	chr15: 22 770 421-28 644 578 (NCBI 37/hg 19)	15q11-q13 dup syndrome (OMIM 608636)	Likely pathogenic
18/F/23	2	FDS, BCS	Severe ID, autistic features	Overweight	Unknown inheritance (mother negative) 15q11.2-q13.1 del (4.84 Mb), maternally inherited 2p21 dup (0.57 Mb)	chr15: 23 676 399-28 577 846 (NCBI 37/hg 19), chr2: 45 394 739-45 961 741 (NCBI 37/hg 19)	Angelman syndrome (OMIM 105830), NA	Pathogenic VUS
19/M/19	9	Absence, single provoked BCS	Moderate ID, autistic features	Two extra wisdom teeth	Unknown inheritance 15q13.1-q13.3 del (3.49 Mb)	chr15: 29 209 620-32 706 883 (NCBI 37/hg 19)	15q13.3 del syndrome (OMIM 612001)	Pathogenic
20/F/41	4	Absence, myoclonic, and BCS	Mild ID	Hypothyroidism, slight dysarthria	Unknown inheritance 15q13.2-13.3 del (1.65 Mb)	chr15:30 888 800-32 539 670 (NCBI 37/hg 19)	15q13.3 del syndrome (OMIM 612001)	Pathogenic
21/M/22 (deceased)	0.5	Tonic, atonic, BCS, and atypical absence (LGS)	Severe ID, autistic features	None	Unknown inheritance 16p12.1 dup (0.66 Mb), unknown inheritance 16p13.2 dup (0.08 Mb)	chr16:26 576 269-27 245 599 (NCBI 37, hg 19), chr16:8 714 859-8 802 589 (NCBI 37/hg 19)	NA	VUS, likely pathogenic
22/F/19	3	Absence, BCS	Mild ID, ADHD	Hearing loss (bilateral Mondini deformity), overweight	de novo 16p13.11 del (1.28 Mb)	chr16: 15 051 527-16 309 165 (NCBI 37/hg 19)	Encompasses recurrent 16p13.11 microdeletion region[5,8,9]	Pathogenic
23/M/24	2	FS, FDS->BCS	Moderate ID, psychosis not otherwise specified	Tetralogy of Fallot, hypothyroidism, hypocalcemia, and relative hypoparathyroidism	de novo 22q11.21 del (2.55 Mb)	chr22: 18 894 902-21 440 515 (NCBI 37/hg 19)	22q11.2 del syndrome (OMIM 192430 /188400)	Pathogenic
24/F/21	3	FS, BCS	Moderate to severe ID, autistic features, and schizophrenia	Hypothyroidism, hypocalcemia, and relative hypoparathyroidism	de novo 22q11.21 del (2.73 Mb)	chr22: 18 713 432-21 440 515 (NCBI 37/hg 19)	22q11.2 del syndrome (OMIM 192430/ 188400)	Pathogenic
25/F/26	1.2 (14 mo)	FDS->BCS	Mild ID, mood disorder	None	de novo Xq21.31-q22.1 del (8.05 Mb)	chrX: 91 558 811-99 611 401 (NCBI 37/hg 19)	Epilepsy, female-limited epilepsy syndrome (*PCDH19*) (OMIM 300088)	Pathogenic
26/M/37	12	Atonic, BCS	Severe ID, autistic features	Dysmorphic facies	Maternally inherited Xq28 dup (0.64 Mb)	chrX:152 964 386-153 605 466 (NCBI 37/hg 19)	*MECP2* dup syndrome (OMIM 300260)	Pathogenic
27/F/23	1.3 (16 mo)	Absence with eyelid myoclonia, BCS (Jeavons syndrome)	Mild ID, anxiety	None	de novo Xq13.3 del (0.08 Mb)	chrX:73 930 523-74 007 913 (NCBI 37/hg 19)	Mental retardation-98 (OMIM 300919) XLR encompasses *KIAA2022* gene	Pathogenic

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BCS, bilateral convulsive seizures; chr, chromosome; CNV, copy number variation; CSWS, continuous spike and slow wave during slow wave sleep; del, deletion; dup, duplication; FDS, focal dyscognitive seizures; FDS->BCS, focal dyscognitive seizures evolving to bilateral convulsive seizures; FS, febrile seizures; ID, intellectual disability; LGS, Lennox-Gastaut syndrome; NA, not applicable; NCBI, National Center for Biotechnology Information; OCD, obsessive-compulsive disorder; VUS, variant of unknown significance; XLR, X-linked recessive.

[a] Seizure types based on electrocardiographic data and seizure semiologic findings.

[b] Siblings with similar phenotype.

[c] Three siblings with similar phenotype.

[d] Monozygotic twins.

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Table 2. Nonrecurrent Rare Pathogenic or Likely Pathogenic CNVs and Candidate Gene Information for Epilepsy With ID

CNV	Similar Deletions or Duplications Previously Described and Associated Clinical Features	Genes in Region	Known or Candidate Epilepsy Gene(s)	Associated Disease(s) and Mode of Inheritance	RVIS (% of MIG)	Gene Expression Studies	Added Information From This Case
2p16.1-p15 duplicate (1.70 Mb)	2p15-16.1 deletion syndrome (OMIM 612513) and 2p16.1 deletion: delayed psychomotor development, ID, microcephaly, brain malformations, autistic features, attention deficit, and dysmorphic features[24]	*PEX13*, *MIR4432*, *BCL11A*, *PAPOLG*, *FLJ16341*, *REL*, *PUS10*, *KIAA1841*, *LOC339803*, *C2orf74*, *AHSA2*, *USP34*, *SNORA70B*, and *XPO1*	*BCL11A*	Chromosome 2p16.1-p15 deletion syndrome (OMIM 612513) (ICs), intellectual developmental disorder with persistence of fetal hemoglobin (OMIM 617101) (AD)	-1.16 (6.1)	Expressed in neural tissues[25]	2p16.1-p15 duplications were not previously reported in association with seizures; *BCL11A* is required for neuronal cell polarity switch and migration of the upper layer projection neurons[26]
6p25.3-p25.1 duplicate (6.58 Mb)	6p25 duplication: developmental ocular abnormalities, ID, craniofacial anomalies, and renal complications[27-29]	45 RefSeq genes, including *IRF4*, *FOXC1*, *SERPINB6*, *TUBB2A*, *FARS2*, and *F13A1*	*TUBB2A*	Complex cortical dysplasia with other brain malformations) (OMIM 615763) (AD)	-0.12 (44.5)	High expression in neural tissues[30,31]	6p25.3-25.1 duplication has not been associated with seizures; *TUBB2A* heterozygous mutations have been associated with complex structural brain malformations not seen in our patients 4 and 5; these patients also have a 9p24.3-p23 deletion
8p23.3p23.1 deletion (11.0 Mb)	8p23 deletions: mild dysmorphic features, developmental delay[32]	92 RefSeq genes, including *CLN8*, *ARHGEF10*, *MCPH1*, and *RP1L1*	*MCPH1*, *CLN8*	Microcephaly, primary (OMIM 607117) (AR); ceroid lipofuscinosis, neuronal (OMIM 600143) (AR)	1.39 (94.6), -0.14 (43.7)	Expressed in fetal brain, particularly forebrain and walls of lateral ventricles[33]; expressed throughout development and in mature brain[34]	Although seizures may be present in patients with *MCPH1* and *CLN8* mutations, these genes are associated with AR disorders; at present, it is not possible to determine how this CNV contributes to patient 9's seizure phenotype
9p24.3-p23 deletion (12.0 Mb)	Overlaps with described distal 9p deletions: ID, dysmorphic features[35]	47 RefSeq genes, including *DOCK8*, *KANK1*, *SMARCA2*, *VLDLR*, *KCNV2*, *GLIS3*, *SLC1A1*, *JAK2*, and *GLDC*	*KANK1*, *SMARCA2*	Cerebral palsy, spastic quadriplegic (OMIM 612900); inheritance pattern to be determined, Nicolaides-Baraitser syndrome (OMIM 601358) (AD)	-0.92 (9.78), -1.97 (1.82)	Expression in most tissues, including neural tissue[36]; high expression in the cerebral cortex[31]	*KANK1* deletion was described in 9 children with congenital neurodegenerative disease evolving to spastic quadriplegia, transient nystagmus, and ID[37]; Nicolaides-Baraitser syndrome, caused by heterozygous mutations of *SMARCA2*, is characterized by severe ID, dysmorphic features, sparse hair, behavioral problems, and seizures[38]; patients 4 and 5 presented with behavioral problems and adolescence onset of seizures but no myoclonic-astatic seizures or dysmorphisms, resembling Nicolaides Baraitser syndrome
10q11.22-q11.23 duplicate (1.73 Mb)	Rare 10q11.22-q11.23 duplications described: phenotypic features not described[39]	22 RefSeq genes, including *GPRIN2*, *ERCC6*, and *CHAT*	*GPRIN2*	Likely modifier of Rett syndrome,[40] likely corroborant of autism and ID,[41] and inheritance pattern to be determined	1.09 (91.9)	Medium expression in neural tissues,[31] highly expressed in the cerebellum[40]	Genes within this interval have not been previously associated with seizures

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Table 2. Nonrecurrent Rare Pathogenic or Likely Pathogenic CNVs and Candidate Gene Information for Epilepsy With ID (continued)

CNV	Similar Deletions or Duplications Previously Described and Associated Clinical Features	Genes in Region	Known or Candidate Epilepsy Gene(s)	Associated Disease(s) and Mode of Inheritance	RVIS (% of MIG)	Gene Expression Studies	Added Information From This Case
12p13.33-13.2 duplicate (11.0 Mb)	Nil of this size	190 RefSeq genes, including *WNK1, CACNA2D4, CACNA1C, FGF23, KCNA1, KCNA5, VWF, TNFRSF1A, SCNN1A, CD4, GNB3,TPI1, ATN1, EMG1, C1S, PEX5, GDF3, AICDA, A2M, CLEC7A*, and *OLR1*	*KCNA1, CACNA1C*	Episodic ataxia, myokymia, and seizures (OMIM 176260) (AD); Timothy syndrome, affects multiple systems, and includes autism and ID (OMIM 601005) (AD)	-0.56 (19.5), -2.09 (1.5)	Predominantly neural tissues,[31] ubiquitous expression[31]	Patient 12 presented with an unbalanced translocation, resulting in a partial trisomy of chromosome region 12p13.2 to 12p ter and partial monosomy of region 13q34 to 13q ter; at present, it is not possible to determine the effects of *KCNA1* and *CACNA1C* duplications in patient 12; seizures have been reported in only 1 patient with a 12p13.33 duplication and 15q11.2 deletion or uncertain inheritance, overlapping the *CACNA1C* gene[42]
13q34 deletion (4.39 Mb)	4 Patients with 13q33-34 deletions, all presenting microcephaly and ID[43]	39 RefSeq genes, including *COL4A1, ING1, F7, F10,* and *GRK1*	*COL4A1*	Porencephaly-1 (OMIM 175780) (AD), HANAC syndrome (OMIM 611773) (AD), brain small vessel disease with or without ocular anomalies (OMIM 607595) (AD), and susceptibility to intracerebral hemorrhage (OMIM 614519) (AD)	-2.82 (0.6)	Low expression in neural tissues[31]	*COL4A1* mutations are usually associated with brain structural abnormalities not found in patient 12
16p13.2 duplicate (0.08 Mb)	None encompassing the same gene content	*ABAT, METTL22*	*ABAT*	GABA-transaminase deficiency (OMIM 613163) (AR)	-0.33 (30.7)	High expression in neural tissues[31]	Homozygous or compound heterozygous *ABAT* mutations underlie a severe neurologic condition characterized by psychomotor retardation and refractory seizures attributable to GABA-transaminase deficiency[44-48]; because our patient presents with duplication, we hypothesize whether he has an overexpression of *ABAT* leading to a hypo-GABAergic state

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CNV, copy number variation; GABA, γ-aminobutyric acid; HANAC, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; ICs, isolated cases; ID, intellectual disability; MIG, most intolerant genes; RefSeq, reference sequence; RVIS, Residual Variation Intolerance Score.

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role of reinvestigating adults with epilepsy and ID who may have been investigated as children, when the current technology was not available to clarify their diagnosis.

CNVs in Adults With Epilepsy

The role of CNV has been well studied in children with seizures.[6,7,9] The largest study,[6] which analyzed 805 pediatric patients with epilepsy, reported a CNV as an explanation for the patient's phenotype in 5% of patients. In addition, in a systematic assessment[7] of epileptic encephalopathies, rare CNVs were found in 7.9% of 315 patients. In 4.1%, the CNVs were pathogenic.[7] Only 1 study[49] has examined the presence of CNVs in adults with epilepsy and ID, and rare CNVs were present in 9.3% of 279 patients; however, only 29% of the patients studied had ID, and patients with severe ID, major neuropsychiatric issues, and epileptic encephalopathy were not included. In our cohort, all patients had some degree of ID, 47.8% of probands had autistic features, and 30.4% presented with other neuropsychiatric symptoms.

The current study indicates a higher prevalence of CNVs (16.1%) most likely because of our broader inclusion criteria, including patients with pharmacosensitive and pharmacoresistant seizure disorders associated with ID of variable severity. Another explanation for higher yield in our sample compared with the pediatric cohorts could be that studies in children may include patients in whom the phenotype was not entirely developed (eg, ID is not yet apparent or later onset of seizures). Although one could argue that the CNVs found in our study might be the cause of ID and not seizures, all CNVs (except 8p23.3p23.1 duplication and 10q11.22-q1.23 duplication) contain at least 1 gene in which heterozygous mutations have already been associated with epilepsy or that has a mechanism of action that could explain the occurrence of seizures (Table 1 and Table 2).

Of interest, for 69.5% of our cohort, the CNVs or genes present in those CNVs identified had been previously associated with well-known conditions, such as Angelman syndrome and 22q11.2 deletion syndrome. Although these genetic syndromes could have been diagnosed in childhood, (1) genetic tests were not available and/or easily performed when some of these adults were children, and karyotype was not capable of detecting the smaller CNVs currently detected by microarray; (2) mild or atypical phenotypes associated with classic genetic syndromes are sometimes difficult to recognize[50,51]; and (3) some of these conditions are relatively newly described compared with the median age of our cohort (eg, protocadherin 19 [*PCDH19*] [OMIM 300460] causing epilepsy restricted to females with intellectual disability or methyl-CpG-binding protein 2 [*MECP2*] [OMIM 300005] duplication syndrome in males).

New Genetic Findings

The function of most genes identified in the 8 rare nonrecurrent CNVs in the present cohort was previously known, but the effect of hemizygous deletions or duplications was not always clear. As indicated in Table 2, selected genes are expressed in the brain and, overall, present a lower threshold to variation according to their RVISs. Five notable candidate genes were found: *ABAT* in a patient with LGS; *KIAA2022* in a patient with JS; and *COL4A1, CACNA1C,* and *SMARCA2* in 2 patients with seizures and ID not characteristic of any known epileptic syndrome.

Four γ-aminobutyrate aminotransferase gene *(ABAT)* recessive mutations have been described; however, no duplication of this gene has been previously identified to our knowledge. Homozygous or compound heterozygous mutations lead to GABA-transaminase deficiency, causing a hyper-GABAergic state. Such a hyper-GABAergic state underlies severe neurologic conditions characterized by psychomotor retardation and refractory seizures.[44-48] The EEGs in some of these patients have demonstrated hypsarrhythmia,[46] a condition that may evolve into LGS (which patient 21 with *ABAT* duplication also developed). It is not clear whether the patient's duplication led to higher amounts of GABA-transaminase and therefore a hypo-GABAergic state. Of interest, hypo-GABAergic states can also lead to epilepsy with a wide spectrum of seizure severity but not yet including LGS.[52] The definitive diagnosis usually requires measuring levels of GABA in the cerebrospinal fluid or its activity in liver or lymphocytes, but GABA-transaminase activity analysis was not available. However, one could hypothesize that *ABAT* duplication could be causative of the LGS phenotype in patient 21.

Patient 27 is a female with JS and an Xq13.3 de novo deletion overlapping the *KIAA2022* gene. Male patients with *KIAA2022* mutations have been described as having mild to severe ID and several types of seizures, including bilateral convulsive seizures, epileptic spasms, and LGS.[53,54] Female patients with heterozygous *KIAA2022* mutations may present with a milder phenotype compared with males, likely because of random X chromosome inactivation. A female patient with 100% inactivation of the normal X chromosome had a severe phenotype similar to that of males.[55] de Lange and colleagues[56] recently described 14 female patients with heterozygous de novo mutations of the *KIAA2022* gene. Thirteen mutations resulted in a frameshift or premature stop codon that could elicit nonsense-mediated decay, predicting a complete loss of the protein function. Most of these female patients presented with intractable epilepsy with predominant myoclonic seizures and/or absences, with onset in infancy or early childhood, behavioral problems, and mild to severe ID.[56] Likewise, the phenotype in patient 27 is fairly similar to that in previously described patients except that eye closure–induced absence seizures (typical of JS) were not previously described. Thus, it appears that the deletion that contained the *KIAA2022* gene identified in patient 27 may be associated with JS.

With respect to the other genes less tolerant to variation found in our cohort, *COL4A1*, *CACNA1C*, and *SMARCA2* had the most negative scores. *COL4A1* was found in the 13q34 deletion and *CACNA1C* in the 12p13.33-13.2 duplication, both in patient 12. This patient did not have clinical and neuroimaging abnormalities previously associated with *COL4A1* mutations,[57,58] such as porencephaly, which is usually accompanied by perinatal intraventricular hemorrhage; brain small vessel disease with or without ocular anomalies; or hereditary angiopathy with nephropathy, aneurysms, and muscle cramps. Of importance, this

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patient also presented with *CACNA1C* duplication. Heterozygous mutation in the *CACNA1C* gene causes Timothy syndrome, characterized by autosomal dominant inheritance, long QT syndrome with syndactyly, dysmorphic features, and neuropsychiatric involvement. This L-type calcium channel gene has not been associated with an epilepsy syndrome, but a patient who harbored 2 variants of unknown significance (12p13.33 duplication and 15q11.2 deletion) that overlapped the *CACNA1C* gene has been described.[42] The seizure phenotype was described as unspecified seizure disorder, with the EEG showing focal epileptiform activity and magnetic resonance imaging showing gray matter heterotopia.[42] At present, it is not possible to determine the effects of *CACNA1C* duplication in our patient, even though some of her craniofacial and neuropsychiatric findings are similar to Timothy syndrome despite absence of cardiac involvement.

Finally, heterozygous mutations in the *SMARCA2* gene cause Nicolaides-Baraitser syndrome, characterized by severe ID, short stature, microcephaly, sparse hair, brachydactyly, prominent interphalangeal joints, behavioral problems, and seizures.[38] Seizures have been reported in two-thirds of patients; however, the seizure phenotypes of such patients have not been detailed except by a single case report of a patient with myoclonic-astatic epilepsy.[59] In that report, Tang and colleagues[59] described an electrographic correlation of negative axial myoclonus, normal magnetic resonance imaging results, and good response to sodium valproate therapy in a patient with *SMARCA2* missense mutation (c.3721C>G; p.Gln1241Glu). The patients in our study (patients 4 and 5) who had deletions, including *SMARCA2*, had some nonspecific features of Nicolaides-Baraitser syndrome, such as ID and behavioral problems. However, their seizures began in adolescence and had a focal onset. They never developed myoclonic-astatic seizures and did not have the typical dysmorphic features described in Nicolaides-Baraitser syndrome.

Diagnosis in Adults

Identification of the origin of epilepsy and ID in adult patients finally ends their prolonged diagnostic process and the associated emotional[60] and financial costs. In addition, diagnosis can help in making treatment decisions; for instance, adults with 22q11.2 deletion (patients 23 and 24) can develop Parkinson disease, and 50% of these patients have psychiatric problems.[61] Clozapine is a commonly used antipsychotic because of its lower propensity to induce extrapyramidal adverse effects; however, patients with 22q11.2 deletion syndrome have a high chance of developing clozapine-induced seizures.[22,23] Therefore, the diagnosis in these cases is directly linked to treatment recommendations. Another example of clinical management based on genetic results was seen in patient 26: at the time of diagnosis of *MECP2* duplication (maternally inherited) in the patient, the patient's sister was 6 months pregnant and did not want to know the child's sex. However, after learning that she could also be a carrier of this duplication and, if carrying a boy, there would be a 50% chance of passing on the *MECP2* duplication, she agreed to be tested for her carrier status. She was not a carrier of this duplication, and she gave birth to a healthy child.

Finally, after genetic diagnosis, patients' families often appreciated being part of support groups, such as the PCDH19 Alliance (http://pcdh19info.org) (patient 25), the Dup 15q Alliance (http://www.dup15q.org (patients 13 and17), and the Rare Disease Foundation.

Limitations

Although our study has several aforementioned strengths, there were also some limitations. Given that our study was a clinical investigation, no gene function analysis was performed. The candidate CNVs and genes identified in our study need to have further functional evaluation and comparison with similar cases. Of note, 16 of the 23 probands underwent further genetic testing through gene panels and whole exome and whole genome sequencing, and no additional pathogenic variants were identified.

Conclusions

This study highlights the importance of reinvestigating adults with childhood-onset epilepsy and ID without a clear etiologic diagnosis. Although most of these patients were thoroughly investigated when their symptoms first appeared, the current genetic technology to allow such diagnosis was not available at that time. In this study, 8 nonrecurrent, rare pathogenic and likely pathogenic CNVs were identified. Two epilepsy syndromes, LGS and JS, were associated with an *ABAT* duplication and a *KIAA2022* deletion, respectively. Further studies and comparison with similar cases are needed to evaluate the functional effects of the CNVs on specific genes. However, interpretation of genetic findings might be complex at times; therefore, phenotyping and continuous collaboration between neurologists and geneticists are important. Alternatively, epilepsy genetics programs in which neurologists seeing adult patients have genetic training could help with etiologic diagnosis and treatment decisions based on genetic findings.

ARTICLE INFORMATION

Accepted for Publication: May 30, 2017.

Published Online: August 28, 2017. doi:10.1001/jamaneurol.2017.1775

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Conflict of Interest Disclosures: Dr Bassett reported holding the Dalglish Chair in 22q11.2 Deletion Syndrome at the Toronto General Hospital. No other disclosures were reported.

Funding/Support: Dr Andrade received research support from EpLink–The Epilepsy Research Program of the Ontario Brain Institute. The Ontario Brain Institute is an independent nonprofit corporation, funded partially by the Ontario government.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Additional Contributions: Cory Tam, MSc, and Kelly Mo, BSc, helped with data collection. Both were compensated for their work. We are grateful to the families who participated in our research.

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