Copy number variants are frequent in genetic generalized epilepsy with intellectual disability

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ABSTRACT

Objective: We examined whether copy number variants (CNVs) were more common in those with a combination of intellectual disability (ID) and genetic generalized epilepsy (GGE) than in those with either phenotype alone via a case-control study.

Methods: CNVs contribute to the genetics of multiple neurodevelopmental disorders with complex inheritance, including GGE and ID. Three hundred fifty-nine probands with GGE and 60 probands with ID-GGE were screened for GGE-associated recurrent microdeletions at 15q13.3, 15q11.2, and 16p13.11 via quantitative PCR or loss of heterozygosity. Deletions were confirmed by comparative genomic hybridization (CGH). ID-GGE probands also had genome-wide CGH.

Results: ID-GGE probands showed a significantly higher rate of CNVs compared with probands with GGE alone, with 17 of 60 (28%) ID-GGE probands having one or more potentially causative CNVs. The patients with ID-GGE had a 3-fold-higher rate of the 3 GGE-associated recurrent microdeletions than probands with GGE alone (10% vs 3%, $p = 0.02$). They also showed a high rate (13/60, 22%) of rare CNVs identified using genome-wide CGH.

Conclusions: This study shows that CNVs are common in those with ID-GGE with recurrent deletions at 15q13.3, 15q11.2, and 16p13.11, particularly enriched compared with individuals with GGE or ID alone. Recurrent CNVs are likely to act as risk factors for multiple phenotypes not just at the population level, but also in any given individual. Testing for CNVs in ID-GGE will have a high diagnostic yield in a clinical setting and will inform genetic counseling. *Neurology*® 2013;81:1507-1514

GLOSSARY

ASD = autism spectrum disorder; **CGH** = comparative genomic hybridization; **CI** = confidence interval; **CNV** = copy number variant; **GGE** = genetic generalized epilepsy; **ID** = intellectual disability; **OR** = odds ratio.

Recurrent deletions and duplications, also referred to as copy number variants (CNVs), are important contributors to neurodevelopmental disorders with complex inheritance, including epilepsy.¹ Three microdeletions are established as risk factors for genetic generalized epilepsy (GGE) (formerly known as idiopathic generalized epilepsy): microdeletion of 15q13.3, 15q11.2, and 16p13.11.²⁻⁶ Each is present in 0.5% to 1% of patients with GGE, but is rare in unaffected controls. Each deletion is also associated with risk of other neurodevelopmental disorders, including autism spectrum disorders (ASDs), intellectual disability (ID), and schizophrenia. It is not unusual for affected individuals to have more than one diagnosis.⁷⁻¹³

The relationship between CNVs and “dual disability,” has not been fully explored, although small case series of patients with epilepsy and ID or ASD have been reported.¹⁴ The presence of ID has historically excluded diagnosing GGE. Despite this, among those with intellectual impairment, a number have epilepsy with the classic electroclinical characteristics of GGE. This includes the seizure types of absence, myoclonic, and generalized tonic-clonic seizures, together with 3-Hz or faster generalized spike-wave on EEG.⁶

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Here, we hypothesized that probands with both ID and epilepsy consistent with GGE, which we term ID-GGE, would show a higher rate of epilepsy-associated CNVs than those with GGE and normal intellect. We compared the frequency of 15q13.3, 15q11.2, and 16p13.11 microdeletions in a cohort of patients with GGE and normal intellect with a cohort of patients with ID-GGE. We also performed whole-genome CNV screening in the ID-GGE cohort to identify novel CNVs that may contribute to the phenotype.

METHODS **Standard protocol approvals, registrations, and patient consents.** Informed consent was obtained from all patients and in the case of minors, their parents or legal guardians. The study was approved by the Human Research Ethics Committee of Austin Health.

Cohort 1: GGE. A total of 359 patients with GGE and normal intellect were identified from the database of the Epilepsy Research Centre.⁶ All had seizure types consistent with GGE including absence, myoclonic, and generalized tonic-clonic seizures, and generalized spike-wave or polyspike-wave on EEG.⁶ All available medical records were reviewed in addition to a standardized epilepsy phenotyping questionnaire.¹⁵ Those with ID or borderline intellect (see below) were excluded from this cohort as were probands with a clinical diagnosis of ASD or psychosis. Patients were then divided into GGE syndromes including juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, and generalized tonic-clonic seizures alone. Those with absence seizures as their major seizure type and epilepsy onset before age 4 years were coded as early-onset absence epilepsy. Of these probands, 278 of 359 had previously been screened for the 15q13.3 deletion with 4 microdeletions found²; none had been screened for deletions of 15q11.2 or 16p13.11.

Cohort 2: ID-GGE. We identified a second cohort of patients with developmental delay, ID, or borderline intellect combined with GGE. A diagnosis of borderline intellect was defined by an IQ of 70 to 85 in line with clinical practice and was also consistent with the threshold used in the European study of GGE that established the role of these CNVs in epilepsy.^{3,4} Patients were assessed for dysmorphic features in the clinic and were excluded if dysmorphic features were prominent and led to testing with a molecular karyotype. In total, 60 patients with this combination of features, which we termed ID-GGE, were identified. Of this group, 49 of 60 had formal neuropsychological assessment of intellect, mostly with qualitative categorization of intellect reported rather than numerical full-scale IQ. A further 9 individuals had no documented assessment but had been through the Special School system, which is restricted to those with ID on formal testing. The remaining 2 probands had a clear history of developmental delay in one instance and a work and social outcome strongly suggestive of intellectual impairment in the second case. Borderline ID was present in 37 of 60, mild ID in 16 of 60, and moderate ID in 7 of 60. Probands with ID and mild autistic features were included, but those with a clinical diagnosis of ASD were excluded as were patients with a history of psychosis. All probands had seizure types consistent with GGE and generalized spike-wave on EEG. We included patients with onset of epilepsy before 4 years but after 12 months for the ID-GGE cohort and classified these cases as early-onset. Of the ID-GGE probands, 13

of 60 had previously been screened for the 15q13.3 microdeletion with 2 microdeletions found.²

Controls. CNV rates in the general population were taken from published controls.^{4,16,17}

Deletion screening. Probands with GGE and normal intellect were screened for the 3 recurrent deletions at 15q13.3, 15q11.2, and 16p13.11. Quantitative PCR was used to screen for the 15q13.3 microdeletion as previously described.² For deletions of 15q11.2 and 16p13.11, samples were initially analyzed for loss of heterozygosity in the region of the recurrent microdeletions with microsatellite markers (M15HO02, D15S1035, M15HO03, M15HO04, M15HO15 for 15q11.2 and M16HO09, M16HO04, M16HO05, D16S3060 for 16p13.11). Putative deletions identified by microsatellite analysis were confirmed using real-time quantitative PCR. Recurrent deletions and their boundaries were confirmed and characterized using a custom-made oligonucleotide array with high-density coverage (average probe spacing of 1 kb) of 15q11.2, 15q13.3, and 16p13.11.

Genome-wide array comparative genomic hybridization. ID-GGE samples were assessed using 1 of 2 commercially available genome-wide array comparative genomic hybridization (CGH) platforms: either the Human Genome CGH 2 × 400 K platform (Agilent Technologies, Santa Clara, CA) (n = 50) or the Human CGH 3 × 720 K Exon-Focused Array (NimbleGen; Roche Diagnostics, Indianapolis, IN) (n = 10). The 3 × 720 K array data were analyzed as described previously.¹⁸ All Agilent arrays were processed and analyzed according to the manufacturer's instructions. All reported CNVs were filtered to exclude regions 1) that did not encompass an exon (refseq, build Hg19); 2) were smaller than 10 kb; or 3) with a >50% overlap with CNVs detected in 4,159 healthy published controls (excluding the known recurrent CNV regions 15q11.2, 16p13.11, 16p11.2).^{16,19} All rare CNVs adhering to these criteria were validated, and familial segregation analysis was performed, using a targeted custom 8 × 60 K CGH array (Agilent).

All statistical comparisons were made using Fisher exact test and calculated with the software package "R" (version 2.10.0, available from rproject.org).

RESULTS **Recurrent microdeletions.** In the cohort of patients with GGE and normal intellect, we found that 3% of probands (11/359) carried a recurrent microdeletion at 15q11.2, 15q13.3, or 16p13.11 (table 1). For each microdeletion, this represents a significant enrichment compared with controls and is consistent with previous studies.^{4,5} In the ID-GGE cohort, 10% of patients (6/60) harbored 1 of the 3 recurrent microdeletions. This rate is significantly higher than controls and also significantly higher than the 3% in those with GGE and normal intellect ($p = 0.02$).

The greatest difference observed between the 2 patient groups was for deletion of 15q13.3 whereby 6% of probands (4/60) with ID-GGE had the deletion. This is significantly higher than the frequency in patients with GGE alone (1.1% vs 6%, $p = 0.04$). The pedigrees and clinical details of the recurrent CNV carriers and the GGE syndromes for available family members are shown in figure 1 and table 2.

Whole-genome CNV discovery in ID-GGE. Given the increased frequency of the 3 epilepsy-associated

Table 1 Recurrent microdeletion rates in GGE and ID-GGE

Microdeletion	Controls	GGE	ID-GGE
16p13.11	0.05% (4/8,008)	0.8% ^a (2/359); OR = 11 (95% CI 1-77)	1.5% ^a (1/60); OR = 34 (95% CI = 1-340)
15q11.2	0.2% (54/18,267)	1.4% ^a (5/359); OR = 5 (95% CI 1.5-12)	1.5% (1/60)
15q13.3	0.02% (4/18,267)	1.1% ^a (4/359); OR = 50 (95% CI 9-270)	6% ^{a,b} (4/60); OR = 325 (95% CI 60-1,800)
All 3	0.3% (22/8,008)	3% ^a (11/359); OR = 11 (95% CI 5-24)	10% ^{a,b} (6/60); OR = 40 (95% CI 13-110)

Abbreviations: CI = confidence interval; GGE = genetic generalized epilepsy; ID = intellectual disability OR = odds ratio. Control rates drawn from refs. 4 and 16. For 15q13.3 and 16p13.11, additional controls were drawn from ref. 17. ORs and CIs are for comparison to control carrier rates.

^a Statistically significant to control carrier rate ($p < 0.05$).

^b Statistically significant to both the control and GGE carrier rate ($p < 0.05$).

recurrent deletions in patients with ID-GGE, we next analyzed the ID-GGE cohort for other, rare CNVs. In addition to the recurrent microdeletions, 22% of ID-GGE probands (13/60) had other, rare CNVs, including 2 individuals with a rare CNV in addition to one of the recurrent CNVs (table 3). We identified 3 patients with a CNV at 16p11.2, including 2 deletions and 1 duplication. We identified a de novo 15q26 deletion in proband 15, spanning 3.5 Mb and encompassing numerous brain-expressed genes. Two additional patients each had a rare CNV (deletion

of 18q21.32 in proband 14; deletion of 2p25.2 in proband 22) that was inherited from an affected parent. The 18q21.32 deletion segregated with GGE in family 14 (figure 2). The remaining CNVs were all inherited from an unaffected parent, so the clinical significance is not clear.

No relationship between the classic GGE syndromes and the likelihood of detecting a CNV was noted. There were, however, more CNVs in the individuals with early-onset GGE (7/19) than in those in whom epilepsy began from 4 years of age (15/400). However,

Figure 1 Pedigrees of newly identified probands with GGE and ID-GGE

Probands carrying 1 of the 3 recurrent microdeletions screened in both cohorts are included. Note proband 10 carries 2 paternally inherited deletions: 15q13.3 recurrent microdeletion and a nonrecurrent duplication at 10p15.1; the father had GGE and normal intellect. CNV = copy number variant; GGE = genetic generalized epilepsy; GTCS = generalized tonic-clonic seizure; ID = intellectual disability.

Table 2 Clinical details of recurrent microdeletion carriers

						Onset age of seizure type			
Proband	CNV inheritance	Age at last review, y	Cohort	Intellect	Syndrome	Absence	Myoclonic	GTCS	Seizure outcome
del16p13.11									
1	Unknown	50	GGE	Normal	JME	—	7 y	7 y	Seizure-free
2	Maternal	35	GGE	Normal	JME	—	21 y	21 y	Unknown
3	Maternal	12	ID-GGE	Borderline	Early-onset myoclonic epilepsy	—	5 y	5 y	Unknown
del15q11.2									
4	Paternal	19	GGE	Normal	CAE	12 y	—	—	Seizure-free
5	Maternal	27	GGE	Normal	GTCSA	—	—	16 y	Seizure-free
6	Paternal	13	GGE	Normal	CAE	6 y	—	—	Seizure-free
7	Maternal	21	GGE	Normal	CAE	10 y	—	15 y	Seizure-free
8	De novo	15	GGE	Normal	CAE	4 y	5 y	—	Seizure-free
9	Maternal	6	ID-GGE	Mild ID	EOAE	18 mo	—	—	Unknown
del15q13.3									
10 ^a	Paternal	13	ID-GGE	Borderline	EOAE	3 y	—	—	Refractory
11	Not maternal	19	ID-GGE	Borderline	EOAE	3 y	—	14 y	Refractory
Family 2 ^b	De novo	28	GGE	Normal	JME	—	6 y	17 y	Occasional myoclonus
Family 3 ^b	Unknown	77	GGE	Normal	JME	—	7 y	70 y	Occasional myoclonus
Family 6 ^b	Unknown	58	GGE	Normal	JME	—	11 y	11 y	Seizure-free
Family 7 ^b	Maternal	12	GGE	Normal	CAE	6 y	—	—	Seizure-free
Family 4 ^b	Maternal	17	ID-GGE	Borderline	JAE	11 y	—	—	Seizure-free
Family 5 ^{a,b}	De novo	23	ID-GGE	Borderline	CAE-JME	10 y	21 y	15 y	Seizure-free

Abbreviations: CAE = childhood absence epilepsy; CNV = copy number variant; EOAE = early-onset absence epilepsy; GGE = genetic generalized epilepsy; GTCS = generalized tonic-clonic seizure; GTCSA = GGE with generalized tonic-clonic seizures alone; ID = intellectual disability; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy.

^aFurther CNVs detected on whole-genome scan in addition to recurrent CNV. See table 3.

^bPreviously published.² Additional CNVs were detected by whole-genome comparative genomic hybridization in proband 10 and family 5 (see table 3 for details).

all 19 early-onset patients had ID and were therefore part of the ID-GGE cohort; hence, we do not have a comparison group comprising patients with early-onset GGE and normal intellect. It is likely that the increased rate of CNVs in the early-onset group is attributable to having this “dual disability” rather than the type of epilepsy per se.

DISCUSSION We performed CNV detection in 2 independent cohorts, one with GGE in the setting of normal intellect and the second with ID-GGE, to test the hypothesis that patients with both disorders have a higher burden of CNVs. Indeed, microdeletion screening in 359 probands with GGE and 60 patients with ID-GGE revealed significantly more individuals with the 3 recurrent epilepsy-associated deletions (15q11.2, 15q13.3, and 16p13.11) in the ID-GGE cohort (10%, 6/60) compared with the cohort with GGE alone (3%), supporting our hypothesis. In addition, we detected a rare CNV in a further 18% (11/60) of the ID-GGE cohort at both

known neurodevelopmental-associated CNVs and novel loci. ID-GGE is thus a phenotype with a remarkably high yield of rare CNVs (28%, 18/60). It is likely that a number, if not all, of these CNVs contribute to one or both comorbidities.

The results here reinforce the concept that recurrent microdeletions of 15q11.2, 15q13.3, and 16p13.11 are risk alleles contributing to the complex inheritance of GGE. Only a few transmitting parents (3/9) had a phenotype associated with one of the microdeletions. The presence of microdeletions at 16p13.11 and 15q11.2 in control populations also argues against these CNVs acting as the sole cause of the ID or GGE phenotype. For deletions at 15q11.2 (odds ratio [OR] = 5, 95% confidence interval [CI] 1.5–12) and 16p13.11 (OR = 11, 95% CI 1–77), even the upper end of the CI for the OR is not consistent with a high-penetrance monogenic allele. If the OR is used as an estimate of relative risk, the chances of GGE would be increased at most 80-fold in a carrier of this deletion. The

Table 3 Nonrecurrent CNVs in ID-GGE probands

Proband	CNV	Hg18 coordinates (Mb)	Inheritance	Age at last review, y	Intellect	Syndrome	Absence, y	Myoclonic, y	GTCS, y	Seizure outcome	Candidate gene(s)
12	16p11.2 deletion (1.6 Mb)	chr16:28.4-30.1	De novo	12	Mild ID	CAE	6	—	—	Seizure-free	SEZ6L2
13	16p11.2 duplication (678 kb)	chr16:29.5-30.2	Paternal	43	Borderline	JAE	28	28	—	Seizure-free	SEZ6L2
14	18q21.32 deletion (28 kb) ^a	chr18:54.73-54.76	Paternal	20	Borderline	CAE	6	—	—	Ongoing absence	ZNF532
15	15q26 deletion (~3.5 Mb)	chr15:88.8-91.2	De novo	26	Borderline	EOAE	2	4	4	Ongoing absence	SV2B, CHD2
16	1p34.3 duplication (864 kb)	chr1:34.8-35.7	Not maternal	17	Moderate ID	EOAE	1	—	—	Ongoing absence	DLGAP3
17	10q21 deletion (80 kb) ^b ; 2p15 deletion (240 kb)	chr10:63.78-63.86; chr2:62.8-63.1	Unknown	12	Moderate ID	CAE	4	—	—	Seizure-free	ZNF365, EHBP1
18	16p13.12 duplication (213 kb)	chr16:12.5-12.8	Maternal	16	Mild ID	CAE	5	—	5	Sudden unexplained death in epilepsy	CPPED1
19	9p22.1 deletion (1 Mb)	chr9:17.7-18.7	Paternal	—	Mild ID	BMEI	—	2	—	Seizure-free	SH3GL2, ADAMTSL1
20	2p23.3 deletion (244 kb)	chr2:28.0-28.2	Maternal	8	Borderline	CAE	4	—	6	Ongoing absence	BRE
21	7q21.11 deletion (60 kb)	chr7:83.61-83.67	Maternal	20	Borderline	EOAE	3	—	12	Seizure-free	SEMA3E
22	2p25.2 deletion (600 kb)	chr2:45.1-51	Paternal	16	Borderline	CAE-JME	7	14	—	Ongoing absence	LOC727982
10 ^b	15q13.3 deletion; 10p15.1 duplication	chr10:62-63	Both paternal	13	Borderline	EOAE	3	—	—	Refractory	
Family 5 ^{b,c}	15q13.3 deletion; 16p11.2 deletion (13 kb)		De novo/maternal	23	Borderline	CAE-JME	10	21	15	Seizure-free	

Abbreviations: BMEI = benign myoclonic epilepsy in infancy; CAE = childhood absence epilepsy; CNV = copy number variant; EOAE = early-onset absence epilepsy; GGE = genetic generalized epilepsy; GTCS = generalized tonic-clonic seizure; ID = intellectual disability; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy.

^a The chromosomal regions encompassing these CNVs are poorly covered in the control datasets used in this study; however, no larger CNVs encompassing these genes were detected.

^b Also carry recurrent CNV and also listed in table 2.

^c Previously published.²

population risk of GGE is approximately 0.5% so that even with such an increase in risk, only about a third of carriers would be expected to develop epilepsy.²⁰ As we have previously reported, the OR for a deletion of 15q13.3 is also consistent with complex inheritance (OR = 50, 95% CI 9–270).²

All 3 recurrent microdeletions associated with GGE are associated with other neuropsychiatric disorders including ID, schizophrenia, and ASD. The cohort with ID-GGE has a 3-fold increase in the rate of recurrent microdeletions over GGE alone, while in turn, GGE shows a higher rate of these recurrent CNVs than these other disorders.^{8,10,21,22} This suggests that the microdeletions contribute to both intellectual impairment and GGE, rather than acting as a risk factor for only one of the phenotypes in any given individual.

ID is usually regarded as an exclusion criterion for the diagnosis of GGE. Despite this, patients with comorbid ID can present with the typical electroclinical

patterns and pharmacoresponsiveness of GGE. Moreover, these patients have already been described among the CNV carriers in cohorts with GGE tested for microdeletions.^{3–5}

The genome-wide CNV screen in ID-GGE detected 13 additional rare CNVs that may contribute to the phenotype in these probands. Interestingly, we identified 3 CNVs at 16p11.2 (table 3); rearrangements in this region are associated with both schizophrenia and ID.^{23–25} CNVs at 16p11.2 have not clearly been shown to be associated with GGE to date.^{4,5} Seizures have been reported in patients with both deletions and duplications, although the epilepsy phenotypes are not well characterized.^{26,27} One of the 16p11.2 deletions (table 2, family 5) involves only the candidate gene *SEZ6L*, supporting the case that this is a critical gene in this region. Our results provide further evidence for the role of 16p11.2 rearrangements in epilepsy.

Figure 2 Inheritance of CNV identified by genome-wide screen in probands with ID-GGE

CNV = copy number variant; GGE = genetic generalized epilepsy; GTCS = generalized tonic-clonic seizure; ID = intellectual disability.

We detected a large de novo deletion at 15q26 (approximately 3.5 Mb) in proband 15. While not identical, CNVs overlapping this locus have been reported in probands with multiple developmental anomalies including ID and epilepsy.²⁸ Interestingly, only a single gene, *CHD2*, is frequently deleted in all

patients. We have recently demonstrated that mutations in this gene are associated with epileptic encephalopathy.²⁹

The remaining CNVs did not overlap with known neurodevelopmental loci, and were inherited. Two CNVs were inherited from an affected parent, suggesting

that they may have a role in epilepsy pathogenesis (figure 2). The deletion in proband 14 involves a single gene, *ZNF532*, that is highly expressed in the brain. Interestingly, this paternally inherited deletion segregates with GGE in several affected family members, supporting its pathogenic role. We detected a total of 3 ID-GGE probands (5%) with more than one rare CNV, including two 15q13.3 deletion carriers.

Because of relatively small numbers when the cohort is divided into groups with borderline intellect vs ID, the influence of the severity of the developmental disability in the ID-GGE cohort on the risk of having a CNV is unclear. Although the 3 GGE-associated CNVs are more common in those of borderline intellect compared with those who have ID (14% vs 4%) and vice versa for other CNVs (19% vs 22%), neither comparison reaches statistical significance ($p > 0.3$).

Testing for CNVs in individuals with ID-GGE in the clinical setting will have a high diagnostic yield. Recurrent CNVs at 4 loci (15q13.3, 15q11.2, 16p13.11, 16p11.2) account for 13% of cases in this study, and an additional 15% carry a nonrecurrent rare CNV. The genetic risk associated with each recurrent CNV is better understood than that of a unique CNV, enabling more precise genetic counseling regarding diagnosis, prognosis, and recurrence risk. Genetic counseling is complicated, as each recurrent CNV carries a risk of several different neurocognitive disorders. This study also reinforces that recurrent CNVs can lead to different neurocognitive phenotypes in different individuals, as well as multiple phenotypes in a single carrier. The diagnosis of a 15q13.3 deletion in a proband with ID also carries the risk of developing GGE and schizophrenia as the microdeletion may act as a susceptibility factor contributing to each of these disorders. Therefore, in addition to genetic counseling, early diagnosis will enable monitoring and early treatment, ultimately resulting in improved care.

AUTHOR CONTRIBUTIONS

Saul A. Mullen: draft/revise manuscript, study design, data analysis, acquisition of data, statistical analysis. Gemma L. Carvill: draft/revise manuscript, study design, data analysis, acquisition of data. Susannah Bellows: draft/revise manuscript, data analysis, acquisition of data. Marta A. Bayly: data analysis, acquisition of data. Samuel F. Berkovic: draft/revise manuscript, study design, obtain funding. Leanne M. Dibbens: draft/revise manuscript, study design, data analysis, acquisition of data, study coordination, obtain funding. Ingrid E. Scheffer and Heather C. Mefford: draft/revise manuscript, study design, data analysis, study coordination, obtain funding.

STUDY FUNDING

Supported by the NIH (National Institute of Neurological Disorders and Stroke 1R01NS069605 to H.C.M.); Career Award for Medical Scientists from the Burroughs Wellcome Fund (1007607.01 to H.C.M.); the National Health and Medical Research Council of Australia (400121

to S.F.B. and I.E.S.); RACP GlaxoSmithKline fellowship (S.A.M.); and the Operational Infrastructure Support Program of the State Government of Victoria, Australia.

DISCLOSURE

S. Mullen has received research support from The Royal Australian College of Physicians and from the Viertel Foundation. G. Carvill, S. Bellows, and M. Bayly report no disclosures. S. Berkovic has received a grant(s) from the National Health and Medical Research Council; has received honoraria from UCB; has a patent for *PCDH19* testing planned; has received payment for development of educational presentations from UCB Pharma, Novartis Pharmaceuticals, Sanofi-Aventis, and Janssen-Cilag; has a patent for *SCN1A* testing held by Bionomics Inc. and licensed to various diagnostic companies, with no financial return; and was a consultant to Bionomics and Athena diagnostics more than 3 years ago. L. Dibbens may accrue future revenue on a pending patent re: Therapeutic compound that relates to discovery of *PCDH19* gene as the cause of familial epilepsy with mental retardation limited to females; and receives/has received research support from the National Health and 382 Neurology 77 July 26, 2011 Medical Research Council of Australia, the Thyne Reid Charitable Trusts, and the MS McLeod Trustees. I. Scheffer has served on scientific advisory boards for UCB and Janssen-Cilag EMEA; serves on the editorial boards of the *Annals of Neurology* and *Epileptic Disorders*; may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has received speaker honoraria from GlaxoSmithKline, Athena Diagnostics, UCB, Biocodex, and Janssen-Cilag EMEA; has received funding for travel from Athena Diagnostics, UCB, Biocodex, GlaxoSmithKline, and Janssen-Cilag EMEA; and receives/has received research support from the National Health and Medical Research Council of Australia, NIH, Australian Research Council, Health Research Council of New Zealand, CURE, American Epilepsy Society, US Department of Defense Autism Spectrum Disorder Research Program, the Jack Brockhoff Foundation, the Shepherd Foundation, Perpetual Charitable Trustees, and The University of Melbourne. H. Mefford has received a grant from the NIH/National Institute of Neurological Disorders and Stroke (1R01NS069605); received support for travel to meetings for the study or other purposes from Sanger Center (invited speaker, Genomic Disorders 2011—The Genomics of Rare Diseases) and NIH/National Institute of Neurological Disorders and Stroke (invited participant, Genetics of Epilepsy Workshop); and was a consultant for the Simons Foundation (SFARI Gene Advisory Board). Go to Neurology.org for full disclosures.

Received February 14, 2013. Accepted in final form July 18, 2013.

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