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

**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.

**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.

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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. All had seizure types consistent with GGE including absence, myoclonic, and generalized tonic-clonic seizures, and generalized spike-wave or polyspike-wave on EEG. All available medical records were reviewed in addition to a standardized epilepsy phenotyping questionnaire. 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 as previously described. 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 (M15HO04, D15S5035, 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. 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, 16p13.12). 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. 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
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,

<table>
<thead>
<tr>
<th>Microdeletion</th>
<th>Controls</th>
<th>GGE</th>
<th>ID-GGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>16p13.11</td>
<td>0.05% (4/8,008)</td>
<td>0.8%* (2/359); OR = 11 (95% CI 1–77)</td>
<td>1.5%* (1/60); OR = 34 (95% CI 1–340)</td>
</tr>
<tr>
<td>15q11.2</td>
<td>0.2% (54/18,267)</td>
<td>1.4%* (5/359); OR = 5 (95% CI 1.5–12)</td>
<td>1.5% (1/60)</td>
</tr>
<tr>
<td>15q13.3</td>
<td>0.02% (4/18,267)</td>
<td>1.1%* (4/359); OR = 50 (95% CI 9–270)</td>
<td>6%** (4/60); OR = 325 (95% CI 60–1,800)</td>
</tr>
<tr>
<td>All 3</td>
<td>0.3% (22/8,008)</td>
<td>3%* (11/359); OR = 11 (95% CI 5–24)</td>
<td>10%** (6/60); OR = 40 (95% CI 13–110)</td>
</tr>
</tbody>
</table>

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.

*Statistically significant to control carrier rate (p < 0.05).

**Statistically significant to both the control and GGE carrier rate (p < 0.05).
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 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 2** Clinical details of recurrent microdeletion carriers

<table>
<thead>
<tr>
<th>Proband</th>
<th>CNV inheritance</th>
<th>Age at last review, y</th>
<th>Cohort</th>
<th>Intellect</th>
<th>Syndrome</th>
<th>Onset age of seizure type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Seizure type</td>
<td>Absence</td>
</tr>
<tr>
<td>del16p13.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Unknown</td>
<td>50</td>
<td>GGE</td>
<td>Normal</td>
<td>JME</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Maternal</td>
<td>35</td>
<td>GGE</td>
<td>Normal</td>
<td>JME</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Maternal</td>
<td>12</td>
<td>ID-GGE</td>
<td>Borderline</td>
<td>Early-onset myoclonic epilepsy</td>
<td>—</td>
</tr>
<tr>
<td>del15q11.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Paternal</td>
<td>19</td>
<td>GGE</td>
<td>Normal</td>
<td>CAE</td>
<td>12 y</td>
</tr>
<tr>
<td>5</td>
<td>Maternal</td>
<td>27</td>
<td>GGE</td>
<td>Normal</td>
<td>GTCSA</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Paternal</td>
<td>13</td>
<td>GGE</td>
<td>Normal</td>
<td>CAE</td>
<td>6 y</td>
</tr>
<tr>
<td>7</td>
<td>Maternal</td>
<td>21</td>
<td>GGE</td>
<td>Normal</td>
<td>CAE</td>
<td>10 y</td>
</tr>
<tr>
<td>8</td>
<td>De novo</td>
<td>15</td>
<td>GGE</td>
<td>Normal</td>
<td>CAE</td>
<td>4 y</td>
</tr>
<tr>
<td>9</td>
<td>Maternal</td>
<td>6</td>
<td>ID-GGE</td>
<td>Mild ID</td>
<td>EOAE</td>
<td>18 mo</td>
</tr>
<tr>
<td>del15q13.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10a</td>
<td>Paternal</td>
<td>13</td>
<td>ID-GGE</td>
<td>Borderline</td>
<td>EOAE</td>
<td>3 y</td>
</tr>
<tr>
<td>11</td>
<td>Not maternal</td>
<td>19</td>
<td>ID-GGE</td>
<td>Borderline</td>
<td>EOAE</td>
<td>3 y</td>
</tr>
<tr>
<td>Family 2a</td>
<td>De novo</td>
<td>28</td>
<td>GGE</td>
<td>Normal</td>
<td>JME</td>
<td>—</td>
</tr>
<tr>
<td>Family 3a</td>
<td>Unknown</td>
<td>77</td>
<td>GGE</td>
<td>Normal</td>
<td>JME</td>
<td>—</td>
</tr>
<tr>
<td>Family 6a</td>
<td>Unknown</td>
<td>58</td>
<td>GGE</td>
<td>Normal</td>
<td>JME</td>
<td>—</td>
</tr>
<tr>
<td>Family 7a</td>
<td>Maternal</td>
<td>12</td>
<td>GGE</td>
<td>Normal</td>
<td>CAE</td>
<td>6 y</td>
</tr>
<tr>
<td>Family 4b</td>
<td>Maternal</td>
<td>17</td>
<td>ID-GGE</td>
<td>Borderline</td>
<td>JAE</td>
<td>11 y</td>
</tr>
<tr>
<td>Family 5ab</td>
<td>De novo</td>
<td>23</td>
<td>ID-GGE</td>
<td>Borderline</td>
<td>CAE-JME</td>
<td>10 y</td>
</tr>
</tbody>
</table>

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.

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

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

### Table 3 Nonrecurrent CNVs in ID-GGE probands

<table>
<thead>
<tr>
<th>Proband</th>
<th>CNV</th>
<th>Hg18 coordinates (Mb)</th>
<th>Inheritance</th>
<th>Age at last review, y</th>
<th>Intellect</th>
<th>Syndrome</th>
<th>Absence, y</th>
<th>Myoclonic, y</th>
<th>GTCS, y</th>
<th>Seizure outcome</th>
<th>Candidate gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>16p11.2 deletion (1.6 Mb)</td>
<td>chr16:28.4–30.1</td>
<td>De novo</td>
<td>12</td>
<td>Mild ID</td>
<td>CAE</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>Seizure-free</td>
<td>SEZ6L</td>
</tr>
<tr>
<td>13</td>
<td>16p11.2 duplication (678 kb)</td>
<td>chr16:29.5–30.2</td>
<td>Paternal</td>
<td>43</td>
<td>Borderline</td>
<td>JAE</td>
<td>28</td>
<td>28</td>
<td></td>
<td>Seizure-free</td>
<td>SEZ6L</td>
</tr>
<tr>
<td>14</td>
<td>18q21.32 deletion (28 kb)*</td>
<td>chr18:54.73–54.76</td>
<td>Paternal</td>
<td>20</td>
<td>Borderline</td>
<td>CAE</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>Ongoing absence</td>
<td>ZNF532</td>
</tr>
<tr>
<td>15</td>
<td>15q26 deletion (~3.5 Mb)</td>
<td>chr15:88.8–91.2</td>
<td>De novo</td>
<td>26</td>
<td>Borderline</td>
<td>EOAIE</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>Ongoing absence</td>
<td>SV2B, CHD2</td>
</tr>
<tr>
<td>16</td>
<td>1p34.3 duplication (864 kb)</td>
<td>chr1:34.8–35.7</td>
<td>Not maternal</td>
<td>17</td>
<td>Moderate</td>
<td>ID</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>Ongoing absence</td>
<td>DLGAP3</td>
</tr>
<tr>
<td>17</td>
<td>10q21 deletion (80 kb)*; 2p15 deletion (240 kb)</td>
<td>chr10:63.78–63.86; chr2:62.8–63.1</td>
<td>Unknown</td>
<td>12</td>
<td>Moderate</td>
<td>ID</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>Seizure-free</td>
<td>ZNF365, EHBPI</td>
</tr>
<tr>
<td>18</td>
<td>16p13.12 duplication (213 kb)</td>
<td>chr16:12.5–12.8</td>
<td>Maternal</td>
<td>16</td>
<td>Mild ID</td>
<td>CAE</td>
<td>5</td>
<td>—</td>
<td>5</td>
<td>Sudden unexplained death in epilepsy</td>
<td>CPPED1</td>
</tr>
<tr>
<td>19</td>
<td>9p22.1 deletion (1 Mb)</td>
<td>chr9:17.7–18.7</td>
<td>Paternal</td>
<td>8</td>
<td>Mild ID</td>
<td>BMEI</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>Seizure-free</td>
<td>SH3GL2, ADAMT5L1</td>
</tr>
<tr>
<td>20</td>
<td>2p23.3 deletion (244 kb)</td>
<td>chr2:28.0–28.2</td>
<td>Maternal</td>
<td>8</td>
<td>Borderline</td>
<td>CAE</td>
<td>4</td>
<td>—</td>
<td>6</td>
<td>Ongoing absence</td>
<td>BRE</td>
</tr>
<tr>
<td>21</td>
<td>7q21.11 deletion (80 kb)</td>
<td>chr7:83.61–83.67</td>
<td>Maternal</td>
<td>20</td>
<td>Borderline</td>
<td>EOAIE</td>
<td>3</td>
<td>—</td>
<td>12</td>
<td>Seizure-free</td>
<td>SEMA3E</td>
</tr>
<tr>
<td>22</td>
<td>2p25.2 deletion (600 kb)</td>
<td>chr2:45.1–51</td>
<td>Paternal</td>
<td>16</td>
<td>Borderline</td>
<td>CAE-JME</td>
<td>7</td>
<td>14</td>
<td>—</td>
<td>Ongoing absence</td>
<td>LOC727982</td>
</tr>
<tr>
<td>10b</td>
<td>15q13.3 deletion; 16p15.1 duplication</td>
<td>chr10:62–63</td>
<td>Both paternal</td>
<td>13</td>
<td>Borderline</td>
<td>EOAIE</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>Refractory</td>
<td></td>
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<tr>
<td>Family Bbc</td>
<td>15q13.3 deletion; 16p11.2 deletion (13 kb)</td>
<td>De novo/maternal</td>
<td>23</td>
<td>Borderline</td>
<td>CAE-JME</td>
<td>10</td>
<td>21</td>
<td>15</td>
<td>Seizure-free</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

*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.

**Also carry recurrent CNV and also listed in table 2.

### Table 3 Nonrecurrent CNVs in ID-GGE probands
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, \textit{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 may 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

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

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