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1. Blümcke, Ingmar, et al. "Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy." *Epileptic Disorders* 21.2 (2019): 129-140.

ILAE/5/2020/PRINT

FULL-LENGTH ORIGINAL RESEARCH

A survey of seizures and current treatments in 15q duplication syndrome

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Epilepsia, 55(3):396–402, 2014
doi: 10.1111/epi.12530

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Summary

Objective: **Seizures are common in individuals with duplications of chromosome 15q11.2-q13 (Dup15q). The goal of this study was to examine the phenotypes and treatments of seizures in Dup15q in a large population.**

Methods: **A detailed electronic survey was conducted through the Dup15q Alliance containing comprehensive questions regarding seizures and their treatments in Dup15q.**

Results: **There were 95 responses from Dup15q families. For the 83 with idic(15), 63% were reported to have seizures, of which 81% had multiple seizure types and 42% had infantile spasms. Other common seizure types were tonic–clonic, atonic, myoclonic, and focal. Only 3 of 12 individuals with int dup(15) had seizures. Broad spectrum antiepileptic drugs (AEDs) were the most effective medications, but carbamazepine and oxcarbazepine were also effective, although typical benzodiazepines were relatively ineffective. There was a 24% response rate (>90% seizure reduction) to the first AED tried. For those with infantile spasms, adrenocorticotropic hormone (ACTH) was more effective than vigabatrin.**

Significance: **This is the largest study assessing seizures in Duplication 15q syndrome, but because this was a questionnaire-based study with a low return rate, it is susceptible to bias. Seizures are common in idic(15) and typically difficult to control, often presenting with infantile spasms and progressing to a Lennox-Gastaut–type syndrome. Seizures in those with int dup(15) are less common, with a frequency similar to the general autism population. In addition to broad spectrum AED, medications such as carbamazepine and oxcarbazepine are also relatively effective in controlling seizures in this population, suggesting a possible multifocal etiology, which may also explain the high rate of infantile spasms. Our small sample suggests a relative lack of efficacy of vigabatrin and other γ-aminobutyric acid (GABA)ergic medications, such as typical benzodiazepines, which may be attributable to abnormal GABAergic transmission resulting from the duplication of a cluster of GABAβ3 receptor genes in the 15q11.2-13 region.**

KEY WORDS: **Dup15q, Epilepsy, Isodicentric chromosome 15q, Seizures.**

Accepted November 26, 2013; Early View publication Feburary 6, 2014.

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Copy number variants (CNVs) are a common finding in autism. Perhaps the most common CNV in autism are proximal duplications of the long arm of chromosome 15 (15q) due to the presence of low copy repeats, which make this region susceptible to chromosomal rearrangement.[1,2] There are five common breakpoints (BP1–BP5) in the 15q11.2-q13 region, which are at the boundaries of both deletions and duplications of chromosomal regions. Deletions result

in either Angelman syndrome (AS) or Prader-Willi syndrome (PWS), depending on the parent-of-origin of the affected allele containing the PWS/AS critical region (PWACR) located between BP2-BP3. Conversely, the reciprocal duplication of the region between BP2 and BP3 results in interstitial duplications (int dup(15)) that confer an increased risk of autism.[3] In addition, U-type crossover recombinations can result in a supernumerary isodicentric chromosome (idic(15)) most often due to recombination between BP4 and BP5, resulting in two extra copies of the BP2–BP3 region.[4] Maternal duplications of this region are the most commonly identified genetic cause of autism,[5] with prevalence estimates in autism ranging from 0.5% to 3%.[3]

Multiple genes from this region are implicated in the pathogenesis of autism spectrum disorders, epilepsy, and schizophrenia,[2,6–8] and numerous studies implicate *UBE3A* as the causative gene resulting in impaired cognitive function in AS.[9] These results suggest that altered function of *UBE3A* through underexpression (AS) or overexpression (idic(15) or int dup(15)) impairs neurocognitive development.

The 15q11.2-q13 region is subject to genomic imprinting, by which one parental allele is silenced by a methylation dependent process. Parent-of-origin gene dosing appears to influence phenotype in idic(15); maternally inherited or derived interstitial duplications are associated with increased autism risk.[1,10–13] Idic(15) chromosomes that include the BP2–BP3 region are virtually all maternally derived. Large maternally derived partial hexosomy for 15q11.2-q13 in two boys with intractable epilepsy further suggests that increased dosage of maternally expressed genes negatively impacts the idic(15) phenotype.[11]

It is likely that the maternally expressed *UBE3A* gene is a major contributing factor to the autism phenotype in both int dup(15) and idic(15), since paternal duplications of this region, which do not over-express *UBE3A*, often do not result in an autistic spectrum disorder (ASD) phenotype.[3,10] The most likely candidates involved in seizure phenotypes in the 15q syndrome are a cluster of biallelically expressed γ-aminobutyric acid $(GABA)_A$-receptor subunit genes: *GABRB3*, *GABRA5*, and *GABRG3*, which are not subject to imprinting and are located within the same BP2–BP3 critical region. Two single nucleotide polymorphisms in the *GABRG3* gene are associated with autism in large studies,[14] and *GABRB3* is reduced in postmortem brain samples of individuals with ASD.[15,16] *GABRB3* transcript and protein levels, however, were not increased in cortical brain samples from individuals with 15q duplications.[17] *GABRB3* knockout mice have severe neurologic manifestations, including seizures.[18,19] Studies of the PWACR in idic(15) suggest an effect of both dose-dependent gene expression of the $GABA_A$-receptor subunits and the size of the duplication.[6,20–23]

The X-linked gene, *MeCP2*, encodes the methyl CpG binding protein 2 (MeCP2), which binds to sites in the imprinting control region (PWACR) as well as intermittent binding along the 15q11.2-q13 region, perhaps isolating functional domains of imprinted regions for expression.[24] Some studies showed that *MeCP2* deficiency is associated with impaired expression of both *UBE3A* and *GABRB3*,[15,16,25] thus linking Rett, Angelman, and Dup15q syndromes at the molecular level.

Seizures in AS are frequent (>80%) and well characterized,[26,27] but seizure data in individuals with Dup15q are limited,[28–30] with lifetime prevalence estimates of 26.5–50%.[6,8,31,32] Infantile spasms are associated with maternally inherited duplications of 15q11-q13, suggesting a role for GABAergic synapses and postsynaptic density in the etiology of Dup15q seizure semiology.[33]

Idic(15) is characterized by developmental delay, severe epilepsy, moderate-to-severe intellectual disability, early central hypotonia, autistic behavior, absent or poor language (e.g., marked echolalia), and minor dysmorphic features (e.g., down-slanting palpebral fissures, epicanthal folds, low-set ears, "coarse" facial features, and hypopigmented areas of the skin).[29,30] Metabolic workup and intracranial magnetic resonance imaging (MRI) are typically normal and characterization of seizures is limited in prior studies, which describe early onset of treatment-refractory epilepsy evolving into a Lennox-Gastaut syndrome (LGS) phenotype.[23,29] Among 10 individuals with idic15, 7 presented with epilepsy and the most severely affected had the smallest duplication marker in the PWACR. Seizures were characterized by infantile spasms, with four evolving into epilepsy with multiple seizure types and one remaining seizure-free following spasms responsive to steroid treatment.[21]

Int dup(15) typically has a much milder phenotype than idic(15). ASD occurs in int dup(15),[34,35] and the largest study of 20 children reported developmental delay but no subjects with clinical seizures.[34] Recently, Urraca et al.[13] found that maternal duplication resulted in an autism phenotype in 10 of 14 int dup(15) individuals. None of these individuals had clinical seizures, but excessive beta activity on electroencephalography (EEG) was found in 10 of 14 individuals with int dup(15) regardless of the parental origin of the duplicated chromosome.

This 15q duplication syndrome cohort provides a rare opportunity to study epilepsy in a population of individuals who share a common duplication. To gain a better understanding of the character and effective treatments for epilepsies associated with Dup15q beyond prior case-based reports, we performed a detailed electronic survey assessing seizures and their treatments for 95 family members of Dup15q individuals. To our knowledge, this is the largest study to date assessing seizures and response to antiepileptic treatments in an international population of individuals with 15q duplication syndromes.

Methods

Approximately 400 families were contacted through the Dup15q Alliance and asked to complete a questionnaire survey online regarding the presence and presentation of epilepsy in their family member with a chromosome 15q duplication. It is acknowledged here that, in a questionnaire-based study, it is difficult to determine who is reporting the seizure event. For the purposes of brevity, rather than stating "the family/caregiver/individual reported" the word "had" will be used throughout the text to indicate generically who reported this information. The survey included questions regarding treatments used for their seizures, including open-ended responses for several questions. This was essentially the same questionnaire used in a previous study assessing seizures and their treatment in AS.[26] Family members of individuals with Dup15q, with and without epilepsy, were encouraged to participate and were required to provide a genetic report prior to participation so that the molecular subtype could be accurately classified. These genetic reports were interpreted at Elwyn and the seizure data were analyzed at Massachusetts General Hospital. The seizure severities were classified using the Early Childhood Epilepsy Severity Scale (EChess)[36] and statistical analyses were performed using Microsoft Excel 2007. The survey was available online for 15 months from July 2009 through October 2010. This study was approved by the institutional review board at both Massachusetts General Hospital and Elwyn prior to recruitment of subjects.

Results

Seizures

There were responses from 95 family members of individuals with chromosome 15q duplications, representing a response rate of ~25% of the entire Dup15q Alliance in 2009. There were 12 individuals (5 male, 7 female) with int dup(15)—one with a duplication/triplication mosaic, and the remaining 83 had some variation of a marker idic(15) chromosome. Of the 83 with idic(15), 72 (46 male, 26 female) had four extra copies of the 15q region, with one also having an additional X chromosome (idic (15) + XXY), 8 (5 male, 3 female) had idic(15) mosaicism with one ring idic(15) mosaic, and 3 (all male) had larger idic(15) duplications representing 6X copies of 15q.

Three of the 12 (25%) with int dup(15) had seizures. One subject had both absence and generalized tonic–clonic seizures and one had had infantile spasms that had resolved. The family/caregivers of one child reported a single absence seizure, although whether this was an absence seizure or a focal seizure is difficult to determine from the information available.

For those with idic(15), 52 (63%) of 83 had seizures, 81% of those with seizures having multiple seizure types. In addition, all three (100%) of those with 6X copies had seizures, whereas 4 (50%) of 8 of those with mosaic genotypes had seizures. The most common seizure type was generalized tonic–clonic (60% of those that had seizures), with high rates of other seizure types typically present in Lennox-Gastaut syndrome including atonic (40%), myoclonic (40%), focal onset (40%), tonic (38%), and absence (31%; Table 1).

Of note, 42% of those who had seizures in idic(15) reported a history of infantile spasms. Infantile spasms were the first seizure type for all 22 individuals who had them with 20 (91%) of 22 developing subsequent seizure types. The most common subsequent seizure types were tonic (58%), atonic (46%), myoclonic (42%), and atypical absence (42%).

EChess seizure severity scores were calculated for each molecular subtype, with those with idic(15) having mean scores more than double (11.4, range 4–18) those with int dup(15) (5.3, range 1–8). Those with mosaic idic(15) (11.7, range 9–13) and those with 6X copies (10.7, range 8–15) had similar scores to those with classic idic(15) (Table 2).

Current epilepsy rates (as defined by those with seizures in the past year) for those with idic(15) were calculated by age and showed that seizures were more prevalent in older subjects with the highest rates found in those 15–17 years (64%) and 18+ years (67%; see Fig. 1 for current epilepsy rates among all age groups). There were 17 subjects with idic(15) who were age 15 or older, with 11 (65%) of 17 experiencing a worsening of seizures with puberty, 3 (18%) of 17 experiencing improvement and another 3 (18%) of 17 experiencing no significant changes.

At least one episode of status epilepticus was reported in 17 (33%) of 52 subjects with idic(15) and seizures, with 10 providing information on the frequency of their events. Eight (80%) of 10 reported >10 events of status epilepticus, with the remaining two reporting only single events. In addition, 35 (67%) of 52 had been hospitalized at least once due to seizure activity. Developmental regressions were reported in 33 (63%) of 52, with 20 respondents attributing

Table 1. Seizure types and age of onset in idic(15) (n = 52)

Seizure type	Tonic–clonic	Spasms	Atonic	Myoclonic	Focal	Tonic	Absence
Percentage with seizures (%)	60	42	40	40	40	38	31
Average age of onset (years)	6.9	0.6	9.2	6.9	5.1	5.9	6.7

Table 2. Seizure frequencies and severities by molecular subtype

Genetic subtype	Male	Female	Total	Percentage with seizures (%)	Percentage with multiple seizure types (%)	Seizure severity (EChess) (range)
Idic(15)	46	26	72	64	81	11.4 (4–18)
Interstitial duplications	5	7	12	25	33	5.3 (1–8)
Idic(15) mosaic	5	3	8	50	100	11.7 (9–13)
Complex idic(15)	3	0	3	100	100	10.7 (8–15)

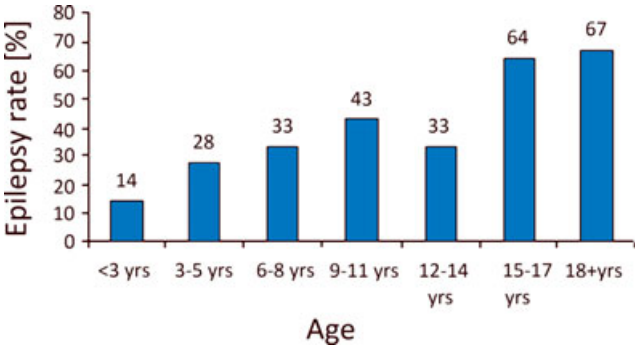

Figure 1.
Rates of epilepsy by age group in subjects with idic(15) and seizures.
Epilepsia © ILAE

these episodes of regression to frequent seizures or nonconvulsive status epilepticus. An additional three respondents attributed this to seizures and/or medications, and the remaining 10 were unsure as to the etiology. Four (8%) of 52 of those with idic(15) and seizures had died, with one family reporting death due to refractory status epilepticus and the other three due to sudden unexpected death in epilepsy (SUDEP).

Seizure treatments

For the 22 children with infantile spasms, the most common first and second medications used were adrenocorticotropic hormone (ACTH)/prednisone (5, first; 7, second) and vigabatrin (VGB; 5, first; 2, second), with the only other medications used by more than one respondent being valproic acid (VPA, 2) and topiramate (TPM, 2). ACTH/prednisone was more effective than VGB in controlling seizures (75% vs. 29% with >90% seizure reduction for those that tried each medication; Table 3) with similar rates of seizure exacerbation.

For all other seizure types, there was an overall 24% response rate (defined as >90% seizure reduction sustained for at least 1 year) to the first medication prescribed, with an additional 21% showing 50–90% seizure improvement (N = 33). For the second medication prescribed (N = 25), there was a 36% response rate. The most commonly prescribed medications were VPA (60%), levetiracetam (LEV, 44%), TPM (40%), lamotrigine (LTG, 37%), carbamazepine (CBZ, 35%), zonisamide (ZNS, 23%), and clonazepam (CLZ, 23%). Family members believed that the most effective medications for controlling seizures were the following: rufinamide (RUF; 67%, N = 6), CBZ (44%, N = 18), LTG (37%, N = 19), oxcarbazepine (OXC; 33%, N = 6), and VPA (32%, N = 31). Overall, only 1 (<5%) of 22 of those who tried a benzodiazepine indicated that it was the most effective medication. The percentage of those still taking each medication at the time of the study was highest in broad-spectrum AED such as RUF (100%, N = 6), LTG (53%, N = 19), VPA (45%, N = 31), and ZNS (42%, N = 12). Intolerable adverse effects were reported most frequently in those taking LEV (52%, most common behavioral), ZNS (50%, sedation), clobazam (CLB; 50%, sedation), OXC (50%, sedation), and TPM (48%, sedation). The full listing of the efficacy of each medication, most common adverse effects for each medication and

Table 3. Rates of efficacy and seizure exacerbation in subjects who have used ACTH/prednisone and/or vigabatrin to treat spasms

Medication	Total tried	>90%[a] Spasm reduction	50–90% Spasm reduction	Spasm exacerbation, %
ACTH/prednisone	N = 12 (ACTH = 11, prednisone = 1) 1st Med = 5 2nd Med = 7	75 (9/12)	17 (2/12)	8 (1/12)
Vigabatrin (VGB)	N = 7 1st Med = 5 2nd Med = 2	29 (2/7)	14 (1/7)	14 (1/7)

[a]Sustained over a period of at least 1 year.

percentage that had seizure exacerbations is listed in Table 4.

Only a few respondents had family members who tried nonpharmacologic treatments including the ketogenic diet (N = 1), vagus nerve stimulation (N = 7), gluten-free diet (N = 1), and surgical resection (N = 1). Not enough data were available to allow an adequate analysis of efficacy or tolerability of these treatments.

Discussion

To our knowledge, this is the largest study assessing seizures and their treatments in duplication 15q syndrome. The main goal was to assess seizure phenotypes and effective treatments in a large population of individuals with duplications of 15q. This was an important objective as there is minimal data in the literature, especially regarding newer AED treatments. A questionnaire-based study was used to recruit as many subjects as possible. This design, however, has inherent flaws in that the results depend on responses from family members and not medical records. Given the complexity of molecular diagnoses in this region, family members were required to send us a genetic report prior to completing the survey, which helped ensure accurate classification of molecular subtypes for data analysis.

For those with int dup(15), only 3 (25%) of 12 had seizures with one of the three reporting only a single seizure. This seizure rate is similar to that reported in the autistic spectrum population in general,[37] and much lower than seizure rates reported in those with idic(15).[6,8,31,32] This, however, may be artificially inflated by response bias, since parents of children with seizures may be more likely to respond to a seizure survey than parents of children with no seizures. It is also possible that families of children with more severe epilepsy might have been more likely to respond. This milder clinical phenotype in int dup(15) has been reported in previous studies.[13,35] Those with idic(15) had more severe epilepsy phenotypes, with mean EChess scores more than twice as high as those with int dup(15) (11.3 vs. 5.3). The rate of seizures in those with idic(15) (63%) was higher than reported previously in smaller cohorts,[5,8,30,31] but this may reflect response bias for families of individuals with seizures.

A striking finding was the high prevalence of infantile spasms in children with idic(15) who had seizures (42%). This high prevalence is similar to other genetic disorders such as tuberous sclerosis complex.[38] The prevalence of spasms may be underestimated as epileptic spasms beyond infancy are often misdiagnosed as atonic or myoclonic seizures. One of the most common causes of epileptic spasms is cortical dysplasia, and children with idic(15) have a significantly higher burden of microdysgenesis than those with idiopathic ASD.[39] The other most common seizure types in idic(15) were generalized tonic–clonic (60%), followed by atonic, myoclonic, focal-onset, and tonic (38–40%). This is consistent with prior studies reporting an LGS phenotype,[23,31] and LGS is associated with focal lesions such as cerebral dysgenesis.

Active seizures (nonspasms), as defined by those with seizures in the past year, increased in nearly every age group

Table 4. Percentage of subjects who tried each medication with response rates (>90%[a], 50–90%, and 0–50%), seizure exacerbation rates and intolerable adverse effects

Medication	% Tried	>90%[a]	50–90%	0–50%	Seizure exacerbation (%)	Adverse effects (%)	Most common side effects
Broad spectrum							
Valproic acid (VPA)	60 (N = 31)	41 (N = 22)	32	18	9 (2/22)	29	Sedation (8), liver toxicity (3), anorexia/irritable (2)
Levetiracetam (LEV)	44 (N = 23)	15 (N = 13)	15	23	46 (6/13)	52	Behavior (4), sedation (2)
Topiramate (TPM)	40 (N = 21)	15 (N = 13)	15	46	23 (3/13)	48	Sedation (5), behavior (2), anorexia/swallowing (2)
Lamotrigine (LTG)	37 (N = 19)	18 (N = 11)	27	36	18 (2/11)	21	Rash (2)
Zonisamide (ZNS)	23 (N = 12)	14 (N = 7)	57	14	14 (1/7)	50	Sedation (3), drooling (2)
Rufinamide (RUF)	12 (N = 6)	75 (N = 4)	25	0	0 (0/4)	0	
Non–broad spectrum							
Carbamazepine (CBZ)	35 (N = 18)	29 (N = 14)	36	29	7 (1/14)	17	Rash (3), sedation (3)
Oxcarbazepine (OXC)	12 (N = 6)	25 (N = 4)	0	50	25 (1/4)	50	Rash (1), hyponatremia (1), sedation (1)
Phenytoin (PHT)	10 (N = 5)	0 (N = 1)	0	100	0 (0/1)	40	Gum problems (1), cognitive slowing (1)
Phenobarbital (PB)	6 (N = 3)	0 (N = 1)	100	0	0 (0/1)	0	
Gabapentin (GBP)	10 (N = 5)	0 (N = 1)	100	0	0 (0/1)	0	
Benzodiazepines							
Clonazepam (CZP)	23 (N = 12)	0 (N = 6)	0	50	50 (3/6)	17	Fever (1), vomiting (1), loss of coordination (2)
Lorazepam (LZP)	12 (N = 6)	0 (N = 1)	0	0	100 (1/1)	0	
Clobazam (CLB)	8 (N = 4)	50 (N = 2)	0	50	0 (0/2)	50	Sedation (1)

[a]Sustained over a period of at least 1 year.

from <3 years (14%) to 18 years (68%). Active seizures were most prevalent in those 15–17 years old (67%) and 18+ years (68%), but there were relatively few respondents for those 15+ years; therefore, these rates may have been affected by response bias. Spasms typically resolved before 3 years of age, as the average age of onset was 6–7 months with an average duration of nearly 1 year.

Parental reporting indicates that epilepsy in idic(15) is refractory to medication, as only 24% had a >90% seizure reduction from the first medication, sustained over a period of at least 1 year. This rate of response is higher than reported in AS (15%),[26] but much lower than reported in the general adult population (47%).[40] The epilepsy phenotype in idic(15) often begins as infantile spasms, evolving into an LGS-type picture with multiple generalized seizures types (tonic–clonic, tonic, myoclonic, atonic, and absence) along with focal-onset seizures. This type of epilepsy typically responds well to broad spectrum AED and can be exacerbated by medications used to treat focal seizures such as CBZ and OXC. Seizures in those with idic(15) responded well, as expected, to broad-spectrum AED such as RUF, VPA, ZNS, and LTG. They also, however, responded well to CBZ (44% reported that it worked best) and OXC (33% reported that it worked best), with only 7% (1/14) of those on CBZ reporting seizure exacerbation. Because these medications typically worsen generalized epilepsy, this may suggest that epilepsy in idic(15) is more of a multifocal epilepsy with secondary generalization than a true generalized epilepsy, even though the prevalence of focal seizures (40%) is similar to that reported in other LGS-type epilepsies, including AS, in which seizures are exacerbated by CBZ and OXC.[26]

Generalized epilepsies typically respond very well to benzodiazepines, but those with idic(15) did not respond well to benzodiazepines, with only 1 (4.5%) of 22 who tried CLB, CLZ, or lorazepam (LZP) reporting that it was the medication that worked best. For those taking CLZ or LZP who provided enough information (N = 7), none had >50% seizure reduction and 4(57%) of 7 had seizure exacerbation. CLB, an atypical benzodiazepine, was better tolerated with none reporting seizure exacerbation and two (50%) of four reporting >90% seizure reduction, although the other two (50%) of four reported sedation as an intolerable adverse effect. For those with idic(15) and spasms, ACTH/prednisone was superior to VGB, with 9 (75%) of 12 of those using ACTH/prednisone reporting a >90% reduction in spasms as opposed to 2 (29%) of 7 of those using VGB. Because VGB is also a GABAergic medication, it appears that AEDs that are GABA agonists are relatively ineffective and, in some cases, may exacerbate seizures in this population. This may be because GABA receptor subunits are duplicated in 15q duplication syndrome in contrast to AS in which these genes are deleted and benzodiazepines have been shown to be very effective.[26]

Conclusions

Epilepsy is common in idic(15) with a high prevalence of infantile spasms and is typically refractory to medication. Although the epilepsy phenotype in idic(15) appears to be most consistent with an LGS-type of epilepsy and responds well to broad spectrum AEDs, the seizures also respond well to CBZ, which typically exacerbates LGS, suggesting that these epilepsies may be more multifocal than generalized. These seizures did not respond well to typical benzodiazepines, with lower response rates and relatively higher rates of seizure exacerbation, although CLB, an atypical benzodiazepine, was relatively effective and had no reported seizure exacerbations.

Although this is the largest study to date assessing epilepsy in this population, larger studies—ideally prospective studies—would be necessary to make more definitive determinations regarding the treatment of seizures in this population. This would overcome the major limitation of the current study which, with a questionnaire response rate of only about 25%, could have been subject to considerable responder bias.

Acknowledgments

This study was performed with assistance from the Dup15q Alliance. We greatly appreciate the cooperation of the families who completed in the surveys.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Dennis NR, Veltman MW, Thompson R, et al. Clinical findings in 33 subjects with large supernumerary marker(15) chromosomes and 3 subjects with triplication of 15q11-q13. *Am J Med Genet A* 2006;140:434–441.
2. Mulley JC, Mefford HC. Epilepsy and the new cytogenetics. *Epilepsia* 2011;52:423–432.
3. Hogart A, Wu D, LaSalle J, et al. The comorbidity of autism with the genomic disorders of chromosome 15q11.2-q13. *Neurobiol Dis* 2010;38:181–191.
4. Roberts SE, Maggouta F, Thomas NS, et al. Molecular and fluorescence in situ hybridization characterization of the breakpoints in 46 large supernumerary marker 15 chromosomes reveals an unexpected level of complexity. *Am J Hum Genet* 2003;73:1061–1072.
5. Schroer RJ, Phelan MC, Michaelis RC, et al. Autism and maternally derived aberrations of chromosome 15q. *Am J Med Genet* 1998;76:327–336.
6. Torrisi L, Sangiorgi E, Russo L. Rearrangements of chromosome 15 in epilepsy. *Am J Med Genet* 2001;106:125–128.
7. Hogart A, Leung KN, Wang NJ, et al. Chromosome 15q11-13 duplication syndrome brain reveals epigenetic alterations in gene expression not predicted by copy number. *J Med Genet* 2009;46:86–93.
8. Kleefstra T, de Leeuw N, Wolf R, et al. Phenotypic spectrum of 20 novel patients with molecularly defined supernumerary marker

chromosomes 15 and a review of the literature. *Am J Med Genet A* 2010;152A:2221–2229.
9. Greer PL, Hanayama R, Bloodgood BL, et al. The Angelman Syndrome protein Ube3A regulates synapse development by ubiquitinating arc. *Cell* 2010;140:704–716.
10. Cook EH Jr, Lindgren V, Leventhal BL, et al. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am J Hum Genet* 1997;60:928–934.
11. Mann SM, Wang NJ, Liu DH, et al. Supernumerary tricentric derivative chromosome 15 in two boys with intractable epilepsy: another mechanism for partial hexasomy. *Hum Genet* 2004;115:104–111.
12. Schanen NC. Epigenetics of autism spectrum disorders. *Hum Mol Genet* 2006;15 Spec No 2:R138–R150.
13. Urraca N, Cleary J, Brewer V, et al. The interstitial duplication 15q11.2-q13 syndrome includes autism, mild facial anomalies and a characteristic EEG signature. *Autism Res* 2013;6:268–279.
14. Menold MM, Shao Y, Wolpert CM, et al. Association analysis of chromosome 15 $GABA_A$ receptor subunit genes in autistic disorder. *J Neurogenet* 2001;15:245–259.
15. Hogart A, Nagarajan RP, Patzel KA, et al. 15q11-13 $GABA_A$ receptor genes are normally biallelically expressed in brain yet are subject to epigenetic dysregulation in autism-spectrum disorders. *Hum Mol Genet* 2007;16:691–703.
16. Samaco RC, Hogart A, LaSalle JM. Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. *Hum Mol Genet* 2005;14:483–492.
17. Scoles HA, Urraca N, Chadwick SW, et al. Increased copy number for methylated maternal 15q duplications leads to changes in gene and protein expression in human cortical samples. *Mol Autism* 2011;2:19.
18. DeLorey TM, Handforth A, Anagnostaras SG, et al. Mice lacking the beta3 subunit of the GABAA receptor have the epilepsy phenotype and many of the behavioral characteristics of Angelman syndrome. *J Neurosci* 1998;18:8505–8514.
19. DeLorey TM, Sahbaie P, Hashemi E, et al. Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: a potential model of autism spectrum disorder. *Behav Brain Res* 2008;187:207–220.
20. Robinson WP, Dutly F, Nicholls RD, et al. The mechanisms involved in formation of deletions and duplications of 15q11-13. *J Med Genet* 1998;35:130–136.
21. Webb T, Hardy CA, King M, et al. A clinical, cytogenetic and molecular study of ten probands with supernumerary inv dup (15) marker chromosomes. *Clin Genet* 1998;53:34–43.
22. Chifari R, Guerrini R, Pierluigi M, et al. Mild generalized epilepsy and developmental disorder associated with large inv dup(15). *Epilepsia* 2002;43:1096–2100.
23. Valente KD, Freitas A, Fridman C, et al. Inv dup (15): is the electroclinical phenotype helpful for this challenging clinical diagnosis? *Clin Neurophysiol* 2006;117:803–809.
24. Yasui DH, Peddada S, Bieda MC, et al. Integrated epigenomic analyses of neuronal MeCP2 reveal a role for long-range interaction with active genes. *Proc Natl Acad Sci U S A* 2007;104:19416–19421.
25. Makedonski K, Abuhatzira L, Kaufman Y, et al. MeCP2 deficiency in Rett syndrome causes epigenetic aberrations at the PWS/AS imprinting center that affects UBE3A expression. *Hum Mol Genet* 2005;14:1049–1058.
26. Thibert RL, Conant KD, Braun EK, et al. Epilepsy in Angelman syndrome: a questionnaire-based assessment of the natural history and current treatment options. *Epilepsia* 2009;50:2369–2376.
27. Williams CA, Beaudet AL, Clayton-Smith J, et al. Angelman syndrome 2005: updated consensus for diagnostic criteria. *Am J Med Genet A* 2006;140:413–418.
28. Takeda Y, Baba A, Nakamura F, et al. Symptomatic generalized epilepsy associated with an inverted duplication of chromosome 15. *Seizure* 2000;9:145–150.
29. Battaglia A, Gurrieri F, Bertini E, et al. The inv dup(15) syndrome: a clinically recognizable syndrome with altered behavior, mental retardation, and epilepsy. *Neurology* 1997;48:1081–1086.
30. Battaglia A, Parrini B, Tancredi R. The behavioral phenotype of the Idic(15) syndrome. *Am J Med Genet C Semin Med Genet* 2010;154C:448–455.
31. Buoni S, Sorrentino L, Farnetani MA, et al. The syndrome of inv dup (15): clinical, electroencephalographic, and imaging findings. *J Child Neurol* 2000;15:380–385.
32. Martinsson T, Johannesson T, Vujic M, et al. Maternal origin of inv dup(15) chromosomes in infantile autism. *Eur Child Adolesc Psychiatry* 1996;5:185–192.
33. Paciorkowski AR, Thio LL, Rosenfeld JA, et al. Copy number variants and infantile spasms: evidence for abnormalities in ventral forebrain development and pathways of synaptic function. *Eur J Hum Genet* 2011;19:1238–1245.
34. Bolton PF, Dennis NR, Browne CE, et al. The phenotypic manifestations of interstitial duplications of proximal 15q with special reference to the autistic spectrum disorders. *Am J Med Genet* 2001;105:675–685.
35. Browne CE, Dennis NR, Maher E, et al. Inherited interstitial duplications of proximal 15q: genotype-phenotype correlations. *Am J Hum Genet* 1997;61:1342–1352.
36. Humphrey A, Ploubidis GB, Yates JRW, et al. The Early Childhood Epilepsy Severity Scale (E-Chess). *Epilepsy Res* 2008;79:139–145.
37. Tuchman R, Cuccaro M, Alessandri M. Autism and epilepsy: historical perspective. *Brain Dev* 2010;32:709–718.
38. Chu-Shore CJ, Major P, Camposano S, et al. The natural history of epilepsy in tuberous sclerosis complex. *Epilepsia* 2010;51:1236–1241.
39. Wegiel J, Schanen NC, Cook EH, et al. Differences between the pattern of developmental abnormalities in autism associated with duplications 15q11.2-q13 and idiopathic autism. *J Neuropathol Exp Neurol* 2012;71:382–397.
40. Kwan P, Brodie M. Effectiveness of first antiepileptic drug. *Epilepsia* 2001;42:1255–1260.