Generalized Epilepsy and Myoclonic Seizures in 22q11.2 Deletion Syndrome

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Key Words
Deletion syndrome 22q11.2 · DiGeorge syndrome · GABA receptors · Juvenile myoclonic epilepsy · Velocardiofacial syndrome

Abstract
Prompted by the observations of juvenile myoclonic epilepsy (JME) in 22q11.2 deletion syndrome (22q11DS) and recurrent copy number variants in genetic generalized epilepsy (GGE), we searched for further evidence supporting a possible correlation of 22q11DS with GGE and with myoclonic seizures. Through routine diagnostics, we identified 3 novel individuals with the seemingly uncommon combination of 22q11DS and JME. We subsequently screened the literature for reports focussing on the epilepsy phenotype in 22q11DS. We additionally screened a database of 173 22q11DS patients and identified a fourth individual with JME as well as 2 additional cases with GGE. We describe 6 novel and 22 published cases with co-occurrence of 22q11DS and GGE. In many patients, GGE was associated with myoclonic seizures allowing for a diagnosis of JME in at least 6 individuals. Seventeen of the 173 22q11DS cases (10\%) had a diagnosis of either focal or generalized epilepsy. In these cases, focal epilepsy could often be attributed to syndrome-associated hypocalcaemia, cerebral bleeds, or structural brain anomalies. However, the cause of GGE remained unclear. In this study, we describe and review 28 individuals with 22q11DS and GGE (especially JME), showing that both disorders frequently co-occur. Compared to the reported prevalence of 15–21\%, in our case series only 10\% of 22q11DS individuals were found to have epilepsy, often GGE. Since 22q11.2 does not contain convincing GGE candidate genes, we discuss the possibility of an aetiological correlation through a possibly disturbed interaction with the GABA\textsubscript{\textalpha} receptor.

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Genetic generalized epilepsy (GGE) is a common epileptic disorder with largely unknown genetic origin. However, mutations in genes encoding certain ion channels, e.g., GABA receptor subunits, have been associated with several forms of GGE [Escayg et al., 2000; Cossette et al., 2002; Haug et al., 2003; Suzuki et al., 2004]. With 4–11\% of all cases, juvenile myoclonic epilepsy (JME) represents a major subgroup within GGE [Bai et al.,...
22q11.2 deletion syndrome (22q11DS; OMIM 192430) share a common deletion of nearly 3 Mb on 22q11.2 [Carlson et al., 1997; Emanuel, 2008]. 22q11DS has previously also been referred to as Velocardiofacial syndrome, DiGeorge syndrome, or CATCH 22. Estimates of prevalence vary from 1:4,000 to 1:6,395 [Devriendt et al., 1998]. The deletion is associated with a broad spectrum of phenotypic features, comprising heart defects, palatal anomalies, psychiatric disorders, distinct dysmorphism, and a cognitive development ranging from close to normal to moderate intellectual disability. Sixty percent of the patients have hypocalcaemia, and 21% are reported to develop epileptic seizures [Ryan et al., 1997]. However, seizures can be attributed to hypocalcaemia in only two-thirds of the cases [Ryan et al., 1997]. Furthermore, fever, recurrent infections and structural brain anomalies, such as polymicrogyria or lesions due to haemorrhage may predispose to 22q11-associated epilepsy, and many yet unknown mechanisms may be involved in epileptogenesis in 22q11DS [Ryan et al., 1997; Kao et al., 2004]. In a recent study on 145 patients with 22q11DS, 22 patients (15.2%) were reported with epileptic seizures. Epilepsy with a structural aetiology was diagnosed in 10 patients (45.5%). In 12 patients, epilepsy was stated to be genetic (54.5%) [Kim et al., 2016]. Isolated case reports focussed on epilepsy phenotypes in 22q11DS and described individuals with Rolandic-like epilepsy [Coppola et al., 2001], atypical absences [Roubertie et al., 2001; Bernhard et al., 2007], generalized epilepsy with myoclonic jerks, or JME [El Tahir et al., 2004; Lemke et al., 2009]. Prompted by these reports and the description of CNVs in a subset of GGE cases, we reviewed published and unpublished 22q11DS cases with respect to their epilepsy phenotype and collected further individuals with 22q11DS and GGE/JME. We focussed on GGE and myoclonic seizures and discuss a possible link to the deletion locus and contribute to a recent discussion on this topic [Helbig et al., 2013a, b; Piccione et al., 2013].

Methods

Following the report of JME in an individual with 22q11DS [Lemke et al., 2009], we describe the phenotypic details of 4 additional patients with the co-occurrence of both disorders. All patients were identified through routine clinical genetic diagnostics. Independently, we reviewed clinical data on 173 22q11DS patients diagnosed in the genomic laboratory of the Department of Medical Genetic at UMC Utrecht. We focussed especially on epilepsy phenotypes and describe our findings.

Finally, we searched the literature (www.ncbi.nlm.nih.gov/pubmed) for reports of patients with a microdeletion 22q11.2 and epileptic seizures and/or myoclonic features (using search terms such as ‘22q11’, ‘DiGeorge’, or ‘Velocardiofacial’ combined with either ‘seizures’, ‘epilepsy’, or ‘myoclonic’).

Results

We describe 6 so far unreported 22q11DS patients with GGE. Four of these 6 patients (patients 1–4) met diagnostic criteria for JME (table 1).

Patient 1

Patient 1 was a 19-year-old man, born to healthy non-consanguineous parents of German origin. He was reported to have had febrile seizures in infancy. At the age of 7 years, he developed generalized seizures due to hypocalcaemia and hyperparathyroidism. At the age of 16 years, the patient was diagnosed with JME with generalized seizures, myoclonic jerks of the upper extremities during morning hours, and parieto-occipital polyspike-wave discharges on the EEG. The patient had normal psychomotor and intellectual development. He visited the final year of high school but was hospitalized due to newly developed psychotic disturbances. The clinical suspicion of 22q11DS was confirmed by detection of a de novo microdeletion 22q11.2 of classic size by MLPA.

Patient 2

Patient 2 was a 12-year-old boy, born to healthy non-consanguineous parents of German origin. Developmental delay was noted at the age of 6 months. Aided walking was achieved with 4 years. There was nearly no speech development. The patient had generalized tonic-clonic seizures (GTCS) and myoclonic seizures typical for JME. He had autistic and partly hyperactive behaviour. MRI
### Table 1. Phenotypes of patients with 22q11DS and generalized epilepsy

<table>
<thead>
<tr>
<th>Patient and publication</th>
<th>VCFS typical craniofacial findings</th>
<th>Intellectual disability</th>
<th>Behaviour</th>
<th>Intellectual disability</th>
<th>Heart</th>
<th>Myoclonus</th>
<th>Focal seizures</th>
<th>EFG</th>
<th>MRT/CT</th>
<th>Diagnosis</th>
<th>Age at onset, years</th>
<th>Method</th>
<th>Size, Mb</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 this study</td>
<td>+</td>
<td>–</td>
<td>shy, psychotic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>bilaterals spikes and polispike-waves, shortly after awaking, sometimes combined with bilateral myoclonies</td>
<td>cysts inside petrosal bone</td>
<td>JME</td>
<td>16</td>
<td>MLPA ≥2.5</td>
<td>dn</td>
<td></td>
</tr>
<tr>
<td>2 this study</td>
<td>+</td>
<td>ASD</td>
<td>moderate autistic, hyperactive</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>generalized bilateral spike-waves</td>
<td>polymicrogyria parietal, occipital and insular</td>
<td>JME</td>
<td>10</td>
<td>HSH</td>
<td>NA</td>
<td>dn</td>
</tr>
<tr>
<td>3 this study</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>+</td>
<td>NA</td>
<td>brief bursts with generalized spike and wave activity with frontal pronunciation</td>
<td>polyspikes and polispike-waves, max. bifrontal</td>
<td>NA</td>
<td>JME</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>4 this study</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>–</td>
<td>generalised polyspike complexes during photostimulation</td>
<td>polyspikes and polispike-waves, photosensitive</td>
<td>NA</td>
<td>GGE</td>
<td>10</td>
<td>aCGH</td>
</tr>
<tr>
<td>5 this study</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>–</td>
<td>questionable multifocal</td>
<td>polyspike-waves, photosensitive</td>
<td>NA</td>
<td>GGE</td>
<td>2</td>
<td>HSH</td>
</tr>
<tr>
<td>6 this study</td>
<td>NA</td>
<td>VSD</td>
<td>mild, IQ 72</td>
<td>shy, psychotic</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>bilateral fronto-occipito-central</td>
<td>polyspike-waves, photosensitive</td>
<td>NA</td>
<td>GGE</td>
<td>14</td>
<td>MLPA ≥2.5</td>
</tr>
<tr>
<td>7 Lemke et al. 2009</td>
<td>+</td>
<td>VSD</td>
<td>mild, IQ 72</td>
<td>shy, psychotic</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>bilateral fronto-occipito-central</td>
<td>polyspike-waves, photosensitive</td>
<td>NA</td>
<td>GGE</td>
<td>14</td>
<td>MLPA ≥2.5</td>
</tr>
<tr>
<td>8 de Kovel et al. 2010</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>generalised spikes and polispike-waves</td>
<td>bursts of high-ampl, slow waves with sharp spikes, photosensitive</td>
<td>NA</td>
<td>JME</td>
<td>14</td>
<td>MLPA ≥2.5</td>
</tr>
<tr>
<td>9 de Kovel et al. 2010</td>
<td>+</td>
<td>ASD</td>
<td>–</td>
<td>normal</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>normal</td>
<td>normal</td>
<td>NA</td>
<td>GGE</td>
<td>20</td>
<td>aCGH</td>
</tr>
<tr>
<td>10 El Tahir et al. 2004</td>
<td>+</td>
<td>VSD</td>
<td>mild, IQ 76</td>
<td>impulsive, aggressive, schizophrenia, shy, agitation</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>normal</td>
<td>normal</td>
<td>NA</td>
<td>GGE</td>
<td>16</td>
<td>HSH</td>
</tr>
<tr>
<td>11 El Tahir et al. 2004</td>
<td>+</td>
<td>VSD</td>
<td>mild, IQ 48</td>
<td>moderate, schizophrenia, shy, agitation, schizoid, affective psychosis</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>normal</td>
<td>normal</td>
<td>NA</td>
<td>GGE</td>
<td>15</td>
<td>HSH</td>
</tr>
<tr>
<td>12 Kao et al. 2004</td>
<td>+</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>multifocal irregular generalized irregular spikes and polyspikes, sometimes combined with bilateral myoclonies</td>
<td>normal</td>
<td>GGE</td>
<td>5</td>
<td>HSH</td>
<td>NA</td>
</tr>
<tr>
<td>13 Kao et al. 2004</td>
<td>+</td>
<td>VSD, DORV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>normal</td>
<td>normal</td>
<td>GGE</td>
<td>11</td>
<td>HSH</td>
</tr>
<tr>
<td>14 Kao et al. 2004</td>
<td>+</td>
<td>VSD, A- anomaly</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>normal</td>
<td>normal</td>
<td>GGE</td>
<td>NA</td>
</tr>
<tr>
<td>15 Kao et al. 2004</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>normal</td>
<td>normal</td>
<td>GGE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>16 Kao et al. 2004</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>normal</td>
<td>normal</td>
<td>GGE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>17 Kao et al. 2004</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>normal</td>
<td>normal</td>
<td>GGE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>18 Kao et al. 2004</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>normal</td>
<td>normal</td>
<td>GGE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>19 Kao et al. 2004</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>normal</td>
<td>normal</td>
<td>GGE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>20 Bernhard et al. 2007</td>
<td>+</td>
<td>–</td>
<td>mild</td>
<td>NA</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>normal</td>
<td>normal</td>
<td>GGE (atyp. absences)</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
revealed parietal, occipital, and insular polymicrogyria. FISH analysis revealed a de novo microdeletion 22q11.2.

Patient 3

This patient was a 17-year-old boy, born to a mother with JME. Additionally, 2 maternal cousins are known to have JME. The boy was diagnosed with a cleft palate. 22q11DS was diagnosed by detection of a classic microdeletion 22q11.2 at the age of 5 years. Parental DNA was not available for confirmation of a de novo origin of the deletion. The patient developed myoclonic jerks at the age of 14 years. There is no history of GTCS or absences. MRI revealed no evidence of epileptogenic lesions or vascular malformations. EEG showed brief bursts with generalized spike and wave activity with frontal pronunciation.

Patient 4

Patient 4 is a female patient born after an uncomplicated pregnancy at AD 37 + 2 weeks. She was diagnosed with 22q11DS by FISH. At the age of 12 years, she was diagnosed with JME. Her EEG records mentioned a normal background activity, polyspikes and polyspike-waves with a maximum in bifrontal regions.

Patient 5

This female patient was born after an uncomplicated pregnancy at AD 38 weeks. Postnatally, she was diagnosed with and treated for pyloric hypertrophy. She had a mild speech delay and velopharyngeal insufficiency. At the age of 2 years, she developed GTCS and later also partial seizures. EEG showed normal background activity, generalized spikes and polyspike waves as well as multifocal activity. Brain MRI was normal. His epilepsy was classified as generalized epilepsy. Seizures persisted despite treatment with levetiracetam.

Patient 6

This male patient was born after an uncomplicated pregnancy. Postnatally, he was diagnosed with and treated for pyloric hypertrophy. He had a mild speech delay and velopharyngeal insufficiency. At the age of 2 years, he developed GTCS and later also partial seizures. EEG showed normal background activity, generalized spikes and polyspike waves as well as multifocal activity. Brain MRI was normal. His epilepsy was classified as generalized epilepsy. Seizures persisted despite treatment with
valproate and levetiracetam. At the age of 3 years, he was diagnosed with a severe delay in speech development and subsequently 22q11DS by FISH.

**Cohort of 173 22q11DS Patients**

The screening of a cohort of 173 22q11DS patients revealed 17 patients (10%) suffering from epileptic seizures. As expected, in several of the 17 epilepsy cases, seizures were attributed to objective hypocalcaemia (n = 4 cases), cerebral bleeds (n = 3 cases), or structural brain anomalies (n = 1 case with polymicrogyria). However, 3 patients had generalized epilepsy, one of whom was diagnosed with JME (table 1). In the remaining 6 cases, there was insufficient clinical data on the epilepsy phenotype and its putative causes. MRI had been performed on 8 of the 17 cases.

A PubMed search on 22q11DS individuals with epilepsy and/or myoclonic features yielded 106 publications (table 2). Of these 106 articles, 28 described individuals with seizures due to hypocalcaemia. In further 17 articles, seizures were attributed to malformations of the central nervous system (mainly polymicrogyria). Twenty-six articles focused on general aspects or other features of 22q11DS and did not address epilepsy phenotypes in more detail. Twenty-two reports described patients with chromosomal abnormalities beyond the classic microdeletion 22q11.2 and did not address epilepsy phenotypes. One out of these 12 reports described 2 individuals with 22q11DS and Rolandic-like epilepsy [Coppola et al., 2001]. Another report described atypical absence epilepsy in an individual with 22q11DS [Roubertie et al., 2001]. This observation is supported by a second, not PubMed-listed report on a similar single case [Bernhard et al., 2007]. Seven out of 12 reports revealed 22 22q11DS patients with GGE [El Tahir et al., 2004; Kao et al., 2004; Lemke et al., 2009; de Kovel et al., 2010; Kim et al., 2016]. Among these, 6 individuals were described with generalized epilepsy and myoclonic seizures [El Tahir et al., 2004; Kao et al., 2004], and 2 further individuals were diagnosed with JME [El Tahir et al., 2004; Lemke et al., 2009; Kim et al., 2016]. The remaining 11 patients had generalized epilepsy not described in further detail. Finally, 4 out of 12 reports describe the occurrence of myoclonic jerks in association with undefined epilepsy [Sachdev, 2002; O’Hanlon et al., 2003; Kim et al., 2016] or without epilepsy [Baralle et al., 2002].

In summary, we found 53 published patients with 22q11DS and epilepsy of unknown cause. Twenty-five of these patients (47%) were diagnosed with focal epilepsy [Coppola et al., 2001; Roubertie et al., 2001; El Tahir et al., 2004; Kao et al., 2004; Bernhard et al., 2007; Lemke et al., 2009; de Kovel et al., 2010; Boot et al., 2015; Lal et al., 2015; Kim et al., 2016]. Twenty-two patients (41%) had the diagnosis of GGE. Eight of the 22 patients with GGE (15%) had additional myoclonic features. In 6 of them these were unspecified (11%), whereas in at least 2 cases (4%), the phenotype supported a diagnosis of JME [Roubertie et al., 2001; El Tahir et al., 2004; Kao et al., 2004; Bernhard et al., 2007; Lemke et al., 2009; de Kovel et al., 2010; Lal et al., 2015; Kim et al., 2016]. Additional 3 patients (6%) had myoclonic jerks and unspecified epilepsy, and 3 patients (6%) had unspecified epilepsy without myoclonic features (fig. 1) [Sachdev, 2002; O’Hanlon et al., 2003; Kim et al., 2016]. However, these numbers may underlie a selection bias, and their exact proportion within patients with 22q11DS still remains to be investigated prospectively.

All published 22q11DS individuals, where the data are available exhibited the classic microdeletion 22q11.2 nearly 3 Mb in size.

**Discussion**

Our observations confirm that in the majority of published 22q11DS cases, seizures can be attributed to syndrome-associated features, such as hypocalcaemia and structural or vascular brain lesions. However, the remainder appears to have a significant susceptibility to GGE.

The incidence of epileptic seizures in 17 out of 173 (10%) 22q11DS cases in our series appears to be lower than the previously reported 15–21% [Ryan et al., 1997; Kim et al., 2016]. This lower yield is most likely influenced by incomplete clinical data on many individuals in our cohort.

### Table 2. Results of PubMed search

<table>
<thead>
<tr>
<th>Publications&lt;sup&gt;a&lt;/sup&gt; (n = 106)</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>seizures due to hypocalcaemia</td>
</tr>
<tr>
<td>17</td>
<td>seizures due to malformations</td>
</tr>
<tr>
<td>26</td>
<td>general aspects of 22q11DS</td>
</tr>
<tr>
<td>22</td>
<td>chromosomal abnormalities</td>
</tr>
<tr>
<td>12</td>
<td>specific seizure phenotype in 22q11DS</td>
</tr>
<tr>
<td>1</td>
<td>myoclonic phenotype in 22q11DS without seizures</td>
</tr>
</tbody>
</table>

<sup>a</sup> Duplicates excluded.

GGE in 22q11.2DS

Mol Syndromol 2016;7:239–246

DOI: 10.1159/000448445
We reviewed 22 published cases with co-occurrence of 22q11DS and GGE including at least 2 individuals with JME (table 1). In addition to these reports, we described 6 further individuals with the co-occurrence of 22q11DS and GGE, 4 of them displaying JME. Patient 2 had a structural brain malformation that did not reveal evidence for epileptic foci and therefore does not fully explain the patient’s epilepsy. However, it may still elicit GGE [Parrini et al., 2009]. Patient 3 had maternal family members with a diagnosis of JME (but not 22q11DS), suggesting a familial GGE disorder independent of 22q11DS.

Despite these constraints, 22q11DS appears to display a predisposition to syndrome-associated GGE with or without myoclonic features, which is unlikely to be simply the result of a coincidental co-occurrence. For all individuals of whom clinical data are published or available, the respective phenotype was in line with the clinical diagnosis of 22q11DS. At least 1 of the two 22q11DS individuals of a large GGE study [de Kovel et al., 2010] also had typical syndrome-associated features (cleft palate and atrial septum defect) [Lemke et al., 2010]. In reference to previous discussions [Helbig et al., 2013a, b; Piccione et al., 2013], we consider 22q11.2 microdeletions to be unlikely predisposing to isolated JME or GGE, which is additionally supported by the lack of significant LOD scores on 22q11.2 in GGE linkage studies.

Mutations in several GABA_A receptor subunits and other ion channels contribute to numerous forms of GGE [Cossette et al., 2012]. No such genes occur within the chromosomal region 22q11.2 [Kao et al., 2004; de Kovel et al., 2010]. However, the 2 genes DGCR6 und DGCR6L (DiGeorge syndrome critical region 6 and 6-like) in 22q11.2 have been identified as interaction partners of the GABA_B1 receptor subunit. It was proposed that haploinsufficiency of DGCR6 in 22q11DS patients could affect GABA_B1 expression levels and/or intracellular localization potentially comprising GABA_B receptor function [Zunner et al., 2010].

GABA_B1-deficient mice show a loss of pre- and postsynaptic GABA_B response causing abnormal behaviour and spontaneous epileptiform activity with frequent clonic and occasional tonic-clonic as well as absence-type seizures and phases of 3- to 5-Hz spike and wave discharges [Schuler et al., 2001]. The EEGs of these mice were indicative for ‘atypical’ rather than ‘typical’ absence seizures paralleling previous reports [Roubertie et al., 2001; Bernhard et al., 2007].

GABBR1, the gene encoding the GABA_B1 receptor subunit is localized in 6p21.3, which is one of currently 4 known susceptibility loci for JME [Sander et al., 1997]. However, patient 5 has JME and an atypical microdeletion sparing the potential GABA_B1 receptor interactors DGCR6 und DGCR6L. Furthermore, Sander et al. [1999] found no association of GABBR1 with common GGE subtypes and the neighbouring gene BRD2 is reported to possibly predispose to GGE instead [Pal et al., 2003].

Independent from our observation of GGE in 22q11DS, we additionally found evidence for an increased prevalence of myoclonic seizures. At least 12 of the described 28 patients had myoclonic jerks, 6 of which had JME. Myoclonic seizures were not necessarily associated with GGE, but can occur independent of epilepsy [Baralle et
al., 2002] and have been observed also in the context of 22q11.2 duplication [Piccione et al., 2011], suggesting a different aetiology than GGE, maybe mediated by different genes within the same locus.

In summary, we show that GGE and myoclonic seizures (in particular JME) have a high prevalence in 22q11DS. Patients usually have phenotypic features suggestive of 22q11DS, which is why the deletion of the locus cannot simply be considered as a predisposition factor for isolated, nonsyndromic forms of GGE. It remains to be further investigated whether a disturbance of GABAB receptors due to haploinsufficiency of GABAB interactors on 22q11.2 may contribute to the complex pathoetiology of GGE and/or myoclonic seizures in 22q11DS.

**Statement of Ethics**

Written informed consent was obtained from patients or their legal guardians prior to genetic testing and in accordance with the national ethics guidelines and with approval from the local ethics committees at the participating study centers (e.g. by the Ethics Commission of the Medical Faculty of the University of Leipzig: 224/16-ek).

**Disclosure Statement**

The authors have no disclosures to declare.

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**References**


