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_B 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.,

2002]. Other GGE entities comprise childhood absence epilepsy, juvenile absence epilepsy, and epilepsy with grand mal seizures on awakening. In addition to the rare known monogenic forms, GGE has repeatedly been associated with various copy number variants (CNVs), such as deletions of 15q11.2, 15q13.3, and 16p13.11 [Helbig et al., 2009; de Kovel et al., 2010]. Other CNVs appear to be rare; however, de Kovel et al. [2010], Lal et al. [2015], and Kim et al. [2016] described 8 GGE individuals carrying a microdeletion of 22q11.2. Lal et al. [2015] also recognized that 3/1,366 GGE cases had the deletion but not one of 5,234 controls did (p value = $8.85E^{-3}$).

About 90% of individuals with 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 individuals (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

Patient and publication	VCFS typical craniofacial findings	Heart	Intellectual disability	Behaviour	Hypocalcaemia	GTCs	Myoclonus	Febrie seizures	EEG	MRTI/CT	Diagnosis	Age at onset, years	Method	Size, Mb	Origin
1 this study	+	-	-	shy, psychotic	+	+	+	+	bilateral spikes and polyspike-waves, shortly after awaking, sometimes combined with bilateral myoclonies	cysts inside petrosal bone	JME	16	MLPA	≥2.5	dn
2 this study	+	ASD	moderate	autistic, hyperactive	-	+	+	+	generalized bilateral spike-waves	polymicrogyria parietal, occipital and insular normal	JME	10	FISH	NA	dn
3 this study	+	NA	NA	NA	NA	-	+	NA	brief bursts with generalized spike and wave activity with frontal pronounciation	normal	JME	14	NA	NA	NA
4 this study	NA	NA	NA	NA	NA	+	+	-	polyspikes and polyspike-waves, max. bifrontal	NA	JME	12	FISH	NA	NA
5 this study	NA	NA	NA	NA	NA	+	-	-	generalized polyspike complexes during photostimulation	NA	GGE	10	aCGH	NA	pat
6 this study	NA	NA	NA	NA	NA	+	+	+	questionable multifocal	NA	GGE	2	FISH	NA	NA
7 Lemke et al. 2009	+	VSD	mild, IQ 72	shy, psychotic	-	+	+	-	bilateral frontocentocentral polyspike-waves, photosensitive	normal	JME	14	MLPA	≥2.5	dn
8 de Kovel et al. 2010	NA	NA	mild	NA	NA	+	NA	NA	NA	NA	GGE	9	aCGH	≥2.5	NA
9 de Kovel et al. 2010	+	ASD	-	normal	-	+	-	-	generalized spikes and polyspike-waves	normal	GGE	20	aCGH	≥2.5	dn
10 El Tahir et al. 2004	+	VSD	mild, IQ 76	impulsive, aggressive, schizophrenia	NA	+	+	+	bursts of high-ampl. slow waves with sharp spikes, photosensitive	NA	JME	17	FISH	NA	NA
11 El Tahir et al. 2004	+	-	moderate, IQ 48	shy, agitated schizoaffective psychosis	NA	+	+	+	moderate/high-ampl. activity about 9–12 Hz, bursts of high-ampl. slow waves about 3–4 Hz combined with moderate/high-ampl. activity about 9–12 Hz	normal	GGE	16	FISH	NA	NA
12 Kao et al. 2004	+	-	NA	NA	+	+	+	-	generalized irregular spikes and polyspikes, sometimes combined with myocloni and spikes right central	normal	GGE	15	FISH	NA	NA
13 Kao et al. 2004	+	VSD, DORV	NA	NA	-	+	+	+	multifocal irregular generalized irregular spikes and polyspikes, sometimes combined with bilateral myocloni	normal	GGE	5	FISH	NA	NA
14 Kao et al. 2004	+	VSD, AA-anomaly	NA	NA	+	+	-	+	bursts about 3/s, irregular	normal	GGE	11	FISH	NA	NA
15 Kao et al. 2004	NA	NA	NA	NA	NA	NA	NA	NA	generalized spike und slow waves	NA	GGE	NA	NA	NA	NA
16 Kao et al. 2004	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	GGE	NA	NA	NA	NA
17 Kao et al. 2004	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	GGE	NA	NA	NA	NA
18 Kao et al. 2004	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	GGE	NA	NA	NA	NA
19 Kao et al. 2004	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	GGE	NA	NA	NA	NA
20 Bernhard et al. 2007	+	-	mild	NA	+	-	+	-	sharp and slow wave complexes occipital with tendency to spread to centro-parietal and short generalized frontal accentuated paroxysms	normal	GGE (atyp. absences)	14	NA	NA	dn

Table 1 (continued)

Patient and publication	VCFS typical craniofacial findings	Heart	Intellectual disability	Behaviour	Hypocalcaemia	GTCS	Myoclonus	Febrile seizures	EEG	MRTI/CT	Diagnosis	Age at onset, years	Method	Size, Mb	Origin
21 Roubertie et al. 2001	+	VSD	severe, IQ 41	NA	+	+	NA	NA	bilateral 3/s spikes and waves, sometimes followed by high-ampl. delta waves right temporal	diffuse mild atrophy	GGE (atypical absences)	6	FISH t(22;X)	NA	dn
22 Lal et al. 2015	NA	NA	moderate	NA	NA	NA	NA	NA	NA	NA	GGE	NA	aCGH	NA	NA
23 Lal et al. 2015	NA	ASD	NA	NA	NA	NA	NA	NA	NA	NA	GGE	NA	aCGH	NA	NA
24 Lal et al. 2015	NA	NA	mild	NA	+	NA	NA	NA	NA	NA	GGE	NA	aCGH	NA	NA
25 Boot et al. 2015	NA	NA	mild	schizophrenia	+	+	+	NA	NA	cortical atrophy, microangiopathic changes	GGE	36	NA	NA	NA
26 Kim et al. 2016	NA	NA	+	-	NA	+	-	NA	focal and generalized epileptiform discharges	normal	GGE	0	NA	NA	NA
27 Kim et al. 2016	NA	NA	-	-	NA	+	-	NA	focal and generalized epileptiform discharges	normal	GGE	0	NA	NA	NA
28 Kim et al. 2016	NA	NA	-	-	NA	+	+	NA	generalized epileptiform discharges	normal	GGE	16	NA	NA	NA

AA = Aortic arch; aCGH = array comparative genomic hybridization; ASD = atrial septal defect; atyp. = atypical; dn = de novo; DORV = double outlet right ventricle; NA = not available; pat = paternally inherited; VSD = ventricular septum defect.

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 pronounciation.

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 a ventral position of the anus, for which she needed surgery, and dysmorphic features were noted. At the age of 10 years, she developed GTCS seizures classified as generalized epilepsy with photosensitivity. EEG showed generalized polyspikes and polyspike waves. Brain MRI was normal. She also had mild developmental delay and was diagnosed with an atypical 1.14-Mb 22q11 deletion at the age of 13 years by array CGH. The deletion was inherited from her father, who was also reported to have had seizures as a child. The patient was successfully treated 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

Table 2. Results of PubMed search

Publications ^a (n = 106)	Topic
28	seizures due to hypocalcaemia
17	seizures due to malformations
26	general aspects of 22q11DS
22	chromosomal abnormalities
12	specific seizure phenotype in 22q11DS
1	myoclonic features in 22q11DS without seizures

^a Duplicates excluded.

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 focussed 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. Only the remaining 12 articles focussed on different seizure 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 unspecific (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.

Fig. 1. Distribution of reported patients with 22q11DS and idiopathic epilepsy (n = 53). IFE = Idiopathic focal epilepsy; MF = myoclonic features.

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 post-synaptic 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 GABA_B receptors due to haploinsufficiency of GABA_B interactors on 22q11.2 may contribute to the complex pathoaetiology of GGE and/or myoclonic seizures in 22q11DS.

References

- Bai D, Alonso ME, Medina MT, Bailey JN, Morita R, et al: Juvenile myoclonic epilepsy: linkage to chromosome 6p12 in Mexico families. *Am J Med Genet* 113:268–274 (2002).
- Baralle D, Trump D, Ffrench-Constant C, Dick DJ: Myoclonic movement disorder associated with microdeletion of chromosome 22q11. *J Neurol Neurosurg Psychiatry* 73:600–601 (2002).
- Bernhard MK, Kantzer AK, Kujat A, Merken-schlager A: 22q11.2-Mikrodeletion mit atypischen Absencen, Dysmorphie und Skoliose. *Monatsschr Kinderheilkd* 155:62–64 (2007).
- Boot E, Butcher NJ, van Amelsvoort TA, Lang AE, Marras C, et al: Movement disorders and other motor abnormalities in adults with 22q11.2 deletion syndrome. *Am J Med Genet A* 167A:639–645 (2015).
- Carlson C, Sirotkin H, Pandita R, Goldberg R, McKie J, et al: Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. *Am J Hum Genet* 61:620–629 (1997).
- Coppola G, Sciscio N, Russo F, Caliendo G, Pascotto A: Benign idiopathic partial seizures in the velocardiofacial syndrome: report of two cases. *Am J Med Genet* 103:172–175 (2001).
- Cossette P, Liu L, Brisebois K, Dong H, Lortie A, et al: Mutation of *GABRA1* in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat Genet* 31:184–189 (2002).
- Cossette P, Lachance-Touchette P, Rouleau GA: Mutated GABA_A receptor subunits in idiopathic generalized epilepsy; in Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV (eds): *Source Jasper's Basic Mechanisms of the Epilepsies* [Internet], ed 4 (National Center for Biotechnology Information, Bethesda 2012).
- de Kovel CG, Trucks H, Helbig I, Mefford HC, Baker C, et al: Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies. *Brain* 133:23–32 (2010).
- Devriendt K, Fryns JP, Mortier G, van Thienen MN, Keymolen K: The annual incidence of DiGeorge/velocardiofacial syndrome. *J Med Genet* 35:789–790 (1998).
- El Tahir MO, Kerr M, Jones RG: Two cases of generalized seizures and the Velocardiofacial syndrome – a clinically significant association? *J Intellect Disabil Res* 48:695–698 (2004).
- Emanuel BS: Molecular mechanisms and diagnosis of chromosome 22q11.2 rearrangements. *Dev Disabil Res Rev* 14:11–18 (2008).
- Escayg A, De Waard M, Lee DD, Bichet D, Wolf P, et al: Coding and noncoding variation of the human calcium-channel beta4-subunit gene *CACNB4* in patients with idiopathic generalized epilepsy and episodic ataxia. *Am J Hum Genet* 66:1531–1539 (2000).
- Haug K, Warnstedt M, Alekov AK, Sander T, Ramírez A, et al: Mutations in *CLCN2* encoding a voltage-gated chloride channel are associated with idiopathic generalized epilepsies. *Nat Genet* 33:527–532 (2003).
- Helbig I, Mefford HC, Sharp AJ, Guipponi M, Fichera M, et al: 15q13.3 microdeletions increase risk of idiopathic generalized epilepsy. *Nat Genet* 41:160–162 (2009).
- Helbig I, Hartmann C, Mefford HC: Clarifying the role of the 22q11.2 microdeletion in juvenile myoclonic epilepsy. *Epilepsy Behav* 29:589–590 (2013a).
- Helbig I, Hartmann C, Mefford HC: The unexpected role of copy number variations in juvenile myoclonic epilepsy. *Epilepsy Behav* 28 Suppl 1:S66–68 (2013b).
- Kao A, Mariani J, McDonald-McGinn DM, Maisenbacher MK, Brooks-Kayal AR, et al: Increased prevalence of unprovoked seizures in patients with a 22q11.2 deletion. *Am J Med Genet A* 129A:29–34 (2004).
- Kim EH, Yum MS, Lee BH, Kim HW, Lee HJ, et al: Epilepsy and other neuropsychiatric manifestations in children and adolescents with 22q11.2 deletion syndrome. *J Clin Neurol* 12:85–92 (2016).
- Lal D, Ruppert AK, Trucks H, Schulz H, de Kovel CG, et al: Burden analysis of rare microdeletions suggests a strong impact of neurodevelopmental genes in genetic generalised epilepsies. *PLoS Genet* 11:e1005226 (2015).
- Lemke JR, Beck-Wödl S, Zankl A, Riegel M, Krämer G, Dorn T: Juvenile myoclonic epilepsy with photosensitivity in a female with Velocardiofacial syndrome (del(22)(q11.2)) – causal relationship or coincidence? *Seizure* 18:660–663 (2009).
- Lemke JR, Syrbe S, Dorn T: Idiopathische generalisierte Epilepsien bei Patienten mit velokardiofazialem Syndrom (Mikrodeletion 22q11.2). *Epileptologie* 27:189–197 (2010).
- O'Hanlon JF, Ritchie RC, Smith EA, Patel R: Replacement of antipsychotic and antiepileptic medication by L-alpha-methyldopa in a woman with velocardiofacial syndrome. *Int Clin Psychopharmacol* 18:117–119 (2003).
- Pal DK, Evgrafov OV, Tabares P, Zhang F, Durner M, Greenberg DA: BRD2 (RING3) is a probable major susceptibility gene for common juvenile myoclonic epilepsy. *Am J Hum Genet* 73:261–270 (2003).
- Parrini E, Ferrari AR, Dorn T, Walsh CA, Guerrini R: Bilateral frontoparietal polymicrogyria, Lennox-Gastaut syndrome, and *GPR56* gene mutations. *Epilepsia* 50:1344–1353 (2009).

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.

- Piccione M, Vecchio D, Cavani S, Malacarne M, Pierluigi M, Corsello G: The first case of myoclonic epilepsy in a child with a de novo 22q11.2 microduplication. *Am J Med Genet A* 155A:3054–3059 (2011).
- Piccione M, Vecchio D, Salzano E, Corsello G: Delineating a new critical region for juvenile myoclonic epilepsy at the 22q11.2 chromosome. *Epilepsy Behav* 29:587–588 (2013).
- Roubertie A, Semprino M, Chaze AM, Rivier F, Humbertclaude V, et al: Neurological presentation of three patients with 22q11 deletion (CATCH 22 syndrome). *Brain Dev* 23:810–814 (2001).
- Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, et al: Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet* 34:798–804 (1997).
- Sachdev P: Schizophrenia-like illness in velo-cardio-facial syndrome: a genetic subsyndrome of schizophrenia? *J Psychosom Res* 53:721–727 (2002).
- Sander T, Bockenkamp B, Hildmann T, Blasczyk R, Kretz R, et al: Refined mapping of the epilepsy susceptibility locus EJM1 on chromosome 6. *Neurology* 49:842–847 (1997).
- Sander T, Peters C, Kämmer G, Samochowiec J, Zirra M, et al: Association analysis of exonic variants of the gene encoding the GABA_B receptor and idiopathic generalized epilepsy. *Am J Med Genet* 88:305–310 (1999).
- Schuler V, Lüscher C, Blanchet C, Klix N, Sansig G, et al: Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic GABA_B responses in mice lacking GABA_B(1). *Neuron* 31:47–58 (2001).
- Suzuki T, Delgado-Escueta AV, Aguan K, Alonso ME, Shi J, et al: Mutations in *EFHC1* cause juvenile myoclonic epilepsy. *Nat Genet* 36:842–849 (2004).
- Zunner D, Deschermeier C, Kornau HC: GABA_B receptor subunit 1 binds to proteins affected in 22q11 deletion syndrome. *Biochem Biophys Res Commun* 393:185–189 (2010).