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Myoclonus–dystonia: clinical and genetic evaluation of a large cohort

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ABSTRACT

Background: Myoclonus–dystonia (M-D) is an autosomal dominant inherited movement disorder. Various mutations within the *epsilon-sarcoglycan* (*SGCE*) gene have been associated with M-D, but mutations are detected in only about 30% of patients. The lack of stringent clinical inclusion criteria and limitations of mutation screens by direct sequencing might explain this observation.

Methods: Eighty-six M-D index patients from the Dutch national referral centre for M-D underwent neurological examination and were classified according to previously published criteria into definite, probable and possible M-D. Sequence analysis of the *SGCE* gene and screening for copy number variations were performed. In addition, screening was carried out for the 3 bp deletion in exon 5 of the *DYT1* gene.

Results: Based on clinical examination, 24 definite, 23 probable and 39 possible M-D patients were detected. Thirteen of the 86 M-D index patients carried a *SGCE* mutation: seven nonsense mutations, two splice site mutations, three missense mutations (two within one patient) and one multiexonic deletion. In the definite M-D group, 50% carried an *SGCE* mutation and one single patient in the probable group (4%). One possible M-D patient showed a 4 bp deletion in the *DYT1* gene (c.934_937delAGAG).

Conclusions: Mutation carriers were mainly identified in the definite M-D group. However, in half of definite M-D cases, no mutation could be identified. Copy-number variations did not play a major role in the large cohort.

Myoclonus–dystonia (M-D) is a genetically heterogeneous movement disorder with an autosomal dominant inheritance. The disorder is clinically characterised by myoclonic jerks and dystonic movements, which often respond to alcohol.¹ Psychiatric abnormalities can be part of the phenotype. A major gene locus maps to the *epsilon-sarcoglycan* gene (*SGCE*, *DYT11*)² on human chromosome 7q21–22, which encodes a transmembrane protein that is widely expressed in the brain.^{3,4} The function of the protein remains to be elucidated. Various types of *SGCE* mutations have been reported in several familial and sporadic M-D cases, such as missense, nonsense and splice site mutations or deletions.^{2,5,6} A reduced penetrance was observed due to maternal imprinting.^{7,8} Little is known about genotype–phenotype associations, and still for many patients no mutation could be identified. Recent findings of large heterozygous deletions of the complete gene and single or multiple exons indicate the need for *SGCE*

gene dosage analysis in M-D patients, as exon deletions or duplications might have been overlooked by standard procedures.^{9,10} It has been suggested that comprehensive clinical criteria for M-D patients will help to precede genotype–phenotype associations.¹⁰

In this study, we screened a large cohort of M-D patients for *SGCE* mutations, including exonic rearrangements, and grouped them according to recently published criteria.¹⁰ In addition, mutation analysis for the *DYT1* 3 bp deletion was performed, since an association between both proteins has been observed.¹¹

METHODS

Patients

After obtaining informed consent, a detailed history was taken and neurological examination and blood withdrawal were performed on 86 M-D index patients. They have all been tested for *SGCE* mutations in our centre, a national referral centre for M-D, between 2004 and the end of 2007. All index patients were examined and classified into three groups (by MAJT, EMJF, JDS) and three of them were seen by other experienced movement disorder neurologists (BRB, RC, WV). The classification was based on published criteria:¹⁰ definite M-D (early-onset myoclonus and dystonia or isolated myoclonus predominantly in the upper body half and a positive family history for myoclonus and/or dystonia), probable M-D (early-onset myoclonus and dystonia or isolated myoclonus predominantly in the upper body half) and possible M-D (jerky dystonia of neck or isolated jerky movements of variable distribution or signs of dystonia and/or myoclonus in the lower body half or no response to alcohol). The age of onset below 26 years was considered as early onset. Twenty-one additional M-D index patients were excluded, as they have not been seen by named neurologists or because sufficient clinical information was lacking. Previously published data of 31 M-D patients were included in this study (large heterozygous deletions had not been screened for in the previous study).¹² Two patients were diagnosed in early childhood. We considered age at onset as 5 years for calculations. The association between age of onset and gender was analysed using Mann–Whitney U tests.

Psychiatric evaluation

Psychiatric diagnosis has been assessed for seven of the 13 *SGCE* mutation carriers according to the

Table 1 Characteristics of *epsilon-sarcoglycan* gene mutation positive myoclonus–dystonia (M-D) index patients

Group	No	Mutation	Sex	Age at onset	Age at exam.	Starting symptom	Myoclonus distribution	Dystonia distribution	Alc. sens	Family history	Additional features
Definite (DE) M-D	DE1	c.946delG; p.D316fsX318*	f	1	14	M: C, UL D: C	C, T, UL	C	+	+ (affected relatives from father's side); M, D†	? (aunt, grandfather: suicide attempt; sister of father: alcohol abuse)†
	DE2	c.1037+2T>C diff. splicing	f	1	39	M: T, UL, LL D: C	T, UL, LL	C, UL, LL	+	+ (brother); M‡	Depression, social phobia‡
	DE3	c.T524C, c.A529T p.L175S*, p.S177C*	f	4	41	M: C, T, UL D: C	C, L, T, UL	C	+	+ (great aunt on father's side); D‡	Anxiety‡
	DE4	c.232+1G>A diff. splicing	f	8	45	M: C D: C	C, UL	C	+	+ (niece on father's side); M, D†	Depression†
	DE5	c.256delA p.T86HfsX91*	m	8	25	?	C, T, UL	WC	?	+ (father, probably sister); M†	Mild anxiety†
	DE6	c.619_620delAG p.R207GfsX215	m	8	45	M: UL, LL D: LL	T, UL, LL	LL	+	+ (father's side); ^{1,16} M, D‡	Chronic depression, anxiety, social phobia, mild OCD‡
	DE7	c.808T>C p.W270R	f	10	25	M: C D: C	C, T	Cr, C	+	+ (grandmother on father's side); M†	Depression†
	DE8	c.304C>T p.R102X	m	11	43	M: C D: C	C, T, UL, LL	C	?	+ (sister); M, D‡	Depression, social phobia‡
	DE9	c.974_977del CGGC p.S325X*	m	14	21	M: UL D: C	UL	C	+	+ (sister); M†	Panic attacks, agoraphobic, alcohol abuse†
	DE10	c.exon6–9del*	m	14	28	M: C, F D: C	C, T, UL, LL	C, W	+	+ (father and sister): jerks, tics‡	Facial tics, panic/anxiety attacks, social phobia‡
	DE11	c.856C>T p.Q286X	f	16	44	M: C D: C	C, UL, LL	C, UL	–	+ (father and brother): M†	Depression†
	DE12	c.884dupT p.L295FfsX3	m	17	25	M: C D: C	C, T, UL, LL	C	+	+ (father, grandfather, aunt on father's side); M, D‡	Depression‡
Probable (PR) M-D	PR1	c.179A>C p.H60P	m	7	15	M: C, T, UL D: C	C, T, UL	C	+	–	Depression, social phobia, mild OCD, alcohol abuse, borderline personality‡

*Novel mutation.

†By history.

‡Investigated.

–, negative; ?, unknown; +, positive; Alc. sens. alcohol sensitivity; C, cervical; Cr, cranial; D, dystonia; Diff. splicing, differential splicing; exam., examination; F, facial; f, female; L, laryngeal; LL, lower limbs; m, male; M, myoclonus; OCD, obsessive compulsive disorder; PD, Parkinson disease; T, trunk; UL, upper limbs; W, writer's cramp.

Table 2 Characteristics of *epsilon-sarcoglycan* gene mutation negative myoclonus–dystonia (M-D) index patients

Group	No	Sex	Age of onset (years)	M	D	Alc. sens.	Additional features	Family history	Transmission
Definite (DE) M-D	DE13	f	1	+	+	+	—	+ (M, D)	?
	DE14	f	1	+	+	+	—	+ (M, D)	?
	DE15	m	1	+	—	?	—	+ (M)	?
	DE16	f	Childhood	+, T	—	+	A	+ (M, D)	Pat
	DE17	m	5	+	+	?	—	+ (M)	Pat
	DE18	f	10	+, T	+	?	—	+ (D)	Mat
	DE19	f	12	+	+	+	—	+ (M)	?
	DE20	m	12	+	+	—	—	+ (M)	?
	DE21	m	15	+	+	—	OCD	+ (D, T)	Mat
	DE22	m	17	+	+	+	—	+ (M, D)	Mat
	DE23	m	18	+	+	—	—	+ (M)	?
	DE24	f	22	+, T	—	+	—	+ (M, D)	Pat
Mean			10						
Probable (PR) M-D	PR3	f	0	+	+	?	—	—	—
	PR4	m	0	+	—	?	ADHD	—	—
	PR5	f	5	+	+	+	—	—	—
	PR6	f	5	+, T	+	—	areflexia	—	—
	PR7	m	5	+	—	+	—	—	—
	PR8	m	5	+	+	+	DP	—	—
	PR9	m	5	+	+	+	—	—	—
	PR10	m	5	+	—	?	—	—	—
	PR11	f	8	+	+	—	—	—	—
	PR12	f	8	+	+	?	—	?	—
	PR13	f	8	+	+	?	—	—	—
	PR14	f	8	+	—	?	—	—	—
	PR15	m	10	+	+	?	MR, E	—	—
	PR16	f	13	+	+	?	—	—	—
	PR17	m	14	+	+	+	—	—	—
	PR18	f	15	+, T	+	?	—	—	—
	PR19	f	16	+	+	+	DP	+ (T)	?
	PR20	m	16	+	—	?	—	+ (PD, T, AA)	?
	PR21	f	17	+	+	?	—	?	—
	PR22	f	19	+, T	+	?	—	+ (T)	Pat
	PR23	m	20	+	+	?	Mild MR	+ (T, DP)	Pat
	PR24	f	21	+	+	—	—	+ (PD, AA)	Pat
Mean			10						

Continued

DSM-IV axis 1 classification system using the Structural Clinical Interview DSM-IV diagnoses (SCID-I)¹³ or the Mini International Neuropsychiatric Interview (MINI) version 5.0.0.¹⁴ Psychiatric evaluations were performed by trained neuropsychologists.

Mutation analysis

DNA was extracted from white blood cells by standard procedures. All patients were sequenced for mutations in 11 exons (exon 1–12 except for exon 10, a rare splicing variant) and flanking intronic regions of the *SGCE* gene. Patients were also screened for the 3 bp deletion (c.904_906delGAG, NM_000113.2) in exon 5 of the *DYT1* gene by direct sequencing. The sequence reactions were performed with the ABI big dye v3.1 chemistry and sequenced with an ABI 3730 capillary system (Applied Biosystems, Foster City, California).

Multiplex ligation-dependent probe amplification (MLPA) was performed using the commercially available probe set P099B (MRC Holland, Amsterdam, The Netherlands) according to the manufacturer's instructions. All samples were tested in duplicate. Ratios between 0.8 and 1.2 were considered normal.

The double mutation was further characterised by restriction-enzyme digestion using *MscI* (NEB, Westburg, Leusden, The Netherlands). The recognition sequence of *MscI* (TGGCCA) encompasses both mutated nucleotides and only cleaves the wild-type sequence.

Deletion mapping

The detected deletion was narrowed by long-range PCR (Expand Long Template PCR System, Roche Diagnostics, Almere, The Netherlands) and by quantitative real-time PCR (FRET technology, LightCycler 480 instrument, Roche Diagnostics) (conditions are available upon request). The deletion was confirmed by sequencing on cDNA level. RNA was extracted from whole blood using the PAXgene system (Qiagen, Venlo, The Netherlands).

RESULTS

Clinical classification

Eighty-six M-D patients were included in the present study and classified according to their clinical features: 24 patients as definite, 23 as probable and 39 as possible M-D (see tables 1, 2).

Table 2 Continued

Group	No	Sex	Age of onset (years)	M	D	Alc. sens.	Additional features	Family history	Transmission
Possible (PO)	P01 (<i>DYT1</i>) *	f	50	+	+	—	Mild PD, DP	—	—
M-D	P02	f	Childhood	Jerks	+	+	ADHD	+ (T)	Pat
	P03	f	12	T	+	—	—	+ (M, D)	Pat
	P04	f	18	T	+	?	—	+ (PD)	?
	P05	f	20	T	+	—	—	—	—
	P06	f	21	Jerks	+	+	DP	+ (PD)	?
	P07	f	22	Jerky T	+	—	—	+ (T)	Mat
	P08	m	24	T	+	?	A, DP	—	—
	P09	f	27	T	+	+	SA	—	—
	P010	m	27	Jerks	+	—	—	—	—
	P011	m	28	Jerks	+	?	—	—	—
	P012	m	29	+	—	?	C, A, DP	+ (DP, A)	Mat
	P013	m	30	+	+	?	—	+ (D)	Pat
	P014	f	30	Jerks	+	?	—	—	—
	P015	f	30	T	+	+	DP	—	—
	P016	f	31	Jerks	+	—	—	+ (T)	Mat
	P017	f	33	Jerks	+	—	DP	—	—
	P018	f	33	Jerks	+	?	—	+ (jerks)	?
	P019	f	34	+	+	?	—	?	—
	P020	f	34	+	+	+	DP	—	—
	P021	f	34	Jerks	+	?	DP	—	—
	P022	f	35	T	+	+	—	—	—
	P023	f	36	T	+	+	—	+ (T)	?
	P024	f	37	+, T	+	+	—	+ (T)	Mat
	P025	f	37	Jerks	+	+	—	+ (D)	Mat
	P026	m	38	T	+	?	—	—	—
	P027	m	39	+	—	+	OT, OCD, A, DP	+ (OCD, OT)	Pat
	P028	f	39	T	+	—	—	+ (D)	?
	P029	f	42	T	+	—	—	—	—
	P030	f	44	Jerks	+	?	—	+ (T)	Pat
	P031	f	48	+	+	?	—	—	—
	P032	f	52	+	+	—	—	—	—
	P033	m	52	+	+	?	PA	+ (M, D, T)	?
	P034	f	53	+	+	+	DP	—	—
	P035	m	53	—	+	?	S	—	—
	P036	f	57	—	+	?	—	—	—
	P037	f	60	T	+	+	—	?	—
	P038	f	62	T	+	?	—	—	—
	P039	f	65	+	+	?	A	+ (M, T)	?
Mean			36						

**DYT1* mutation carrier: c.934_937delAGAG (p.R312FfsX325).

—, negative; ?, unknown; +, positive; A, anxiety; AA, alcohol abuse; ADHD, attention-deficit/hyperactivity disorder; Alc. sens., alcohol sensitivity; C, chorea; D, dystonia; DP, depression; E, epilepsy; f, female; m, male; M, myoclonus; Mat, maternal; MR, mental retardation; OCD, obsessive compulsive disorder; OT, orthostatic tremor; PA, panic attacks; Pat, paternal; PD, Parkinson disease; S, spasticity; SA, suicide attempt; T, tremor.

Mutation screening

In 13 of the 86 M-D index cases, heterozygous *SGCE* mutations were identified. Seven cases have been reported previously (patients DE2, DE6, DE7, DE8, DE11, DE12, PR1).¹² In addition, a splice site mutation in intron 2 (known mutation),¹⁵ four novel point mutations or small deletions, and one multiexonic deletion were detected (see table 1). We describe for the first time a patient with the M-D phenotype who carries two heterozygous mutations separated by only four bases in the *SGCE* gene (DE3, fig 1A). None of the tested relatives (son, five siblings, mother and two siblings of the father) carried the mutation, suggesting that both mutations are located on the same allele. This observation was confirmed by restriction-enzyme analysis; digestion of genomic DNA of a healthy subject with *MscI* resulted in two bands, and DNA of the index patient resulted in three bands deriving from the cut wild-type allele

and the uncut mutated allele (fig 1A). In one patient, a heterozygous deletion of four exons was detected (c.exon6–9del, DE10). None of the patients carried the known 3 bp deletion in *DYT1* gene. However, we identified a 4 bp deletion in exon 5 of the *DYT1* gene (c.934_937delAGAG, NM_000113.2) leading to a frameshift and resulting in a premature stop codon at position 325 (p.R312FfsX325, PO1, fig 1C).

Characterisation of the exon 6–9 deletion

The heterozygous deletion of exon 6 to 9 in the *SGCE* gene was detected by MLPA and confirmed by quantitative real-time PCR. The deletion comprises at least 7.83 kb (data not shown). The deletion of exon 6 to 9 does not alter the open reading frame. Analysis of *SGCE* mRNA by RT-PCR confirmed the predicted exon 5–11 fusion product (fig 1B).

Figure 1 Sequences and additional information of the double mutation and the multiexonic deletion in the *epsilon-sarcoglycan* (*SGCE*) gene, and the 4 bp deletion in the *DYT1* gene. (A) Sequence of part of exon 5 (*SGCE*) of patient DE3. Heterozygous sequence alterations are indicated by arrows (NM_003919.1). Both mutations lead to an amino acid change. Pedigree: round circles represent female and squares male family members. Black symbols indicate affected M-D patients. Asterisks (*) denote investigated individuals. Index patients are marked with an arrow. Pedigree numbers are shown below the symbols. Two daughters of the index patient are under age with a normal phenotype and have not been tested. Restriction enzyme analysis: agarose-gel electrophoresis of MscI-digested PCR-products (*SGCE* exon 5). (1 kb ladder; D, digested; ND, not digested; III:1/II:1/1:2, pedigree numbers of tested individuals; c, control/non-family member) The restriction enzyme only cleaves the wild-type sequence. (B) cDNA sequence of patient DE10 visualising the deletion of exon 6 to 9 in the *SGCE* gene. The alternative spliced exon 10 is not expressed. Pedigree: see annotations above. Symbols with a question mark indicate possibly affected members. (C) Sequence of part of exon 5 (*DYT1*) of patient P01 displaying the 4 bp deletion (NM_000113.2).

Clinical characteristics of the M-D mutation carriers

Twelve of the 24 definite (50%), one of the 23 probable (4%) and none of the 39 possible M-D cases carried a mutation in the *SGCE* gene. In addition, one possible M-D patient showed a mutation in the *DYT1* gene.

All 13 *SGCE* mutation carriers reported an early age of onset (mean age 9 (SD 5) years, range 1–16 years) with no significant difference between male and female mutation carriers ($p = 0.15$). Twelve of them had a positive family history (92%) with paternal transmission in 75% (9/12). No parental blood was available for the other three patients DE2, DE8 and DE9. The single patient with a negative family history (probable M-D) showed a de novo mutation (PR1). Initial dystonic symptoms were restricted to cervical dystonia and remained focal in most cases. In three patients upper and lower limbs were involved. Initial myoclonic symptoms presented mainly in the upper part of the body and at a later stage in the trunk, neck and upper as well as lower limbs. Alcohol alleviated the symptoms in 10 of 11 M-D patients. In two patients this information was not available. Evidence for psychiatric comorbidity was observed in all 13 *SGCE* mutation carriers by history with depression as the main feature (eight cases). Psychiatric assessment was performed for seven cases confirming our observations. Clinical details of *SGCE* mutation negative cases are summarised in table 2.

DISCUSSION

In the present study, we screened 86 M-D index patients for mutations in the *SGCE* gene, including a screen for genomic rearrangements, and for the 3 bp deletion in the *DYT1* gene. All patients were classified according to previously published criteria.¹⁰

We identified mutations in the *SGCE* gene in 50% of the definite (12/24), 4% of the probable (1/23) and none in the possible M-D group. All mutation carriers exhibit myoclonic and dystonic features. Myoclonus was responsive to alcohol in most of the cases as reported in several studies.^{2 15 17 18} Psychiatric abnormalities were found in all mutation carriers by history and confirmed with formal testing in seven. Paternal transmission was observed in 75% of mutation carriers, in the remaining carriers no parental blood was available, and there was one de novo mutation. Our findings are in line with a previously published study observing mutation carriers in 60% (6/10) of definite, 20% (3/15) of probable and no mutation in possible M-D cases.¹⁰ We report many different types of mutations, including nonsense, missense, splice site, frameshift to stop mutations, and one large in-frame deletion. The majority of mutations (seven cases with nonsense or frameshift to stop mutations) may result in a null allele due to nonsense mediated decay.¹⁹ There is evidence that missense mutations in the *SGCE* gene lead to protein degradation and thus also to loss of function.¹¹ Recently, an association between gender and age at onset has been reported in mutation carriers with girls having an earlier age of onset.²⁰ We could not confirm these findings in our small number of gene positive cases. Further studies are required to study the influence of gender and age at onset.

In only one patient we identified exonic rearrangements, an in-frame deletion of exon 6 to 9. This patient was diagnosed as definite M-D, with facial tics as an additional symptom. It remains elusive whether the deletion will lead to protein degradation or whether there is an association between the tics and the mutated protein. One previous study reported the phenotypic association of M-D and Tourette syndrome in a family, but they excluded *SGCE* mutations including exonic

Research paper

rearrangements.²¹ Eleven heterozygous exonic or whole gene deletions of the *SGCE* gene have been previously detected in M-D patients.^{6 9 10 22 23} Most of the reported single or multiple exon deletions lead to a frameshift and premature termination. Only one large in-frame deletion has been reported so far (c.exon2-del), but it is unknown whether this patient has additional symptoms.¹⁰ In all cases with a deletion of the whole *SGCE* gene, the deletion included neighbouring genes. This is concordant with additional non-motor symptoms of these patients like joint problems or osteoporosis.

In order to exclude that *SGCE* mutation negative cases carry the *DYT1* deletion (c.904_906delGAG), we screened all patients for this mutation. We did not identify the 3 bp deletion in our patients. However, a 4 bp deletion in exon 5 of the *DYT1* gene (c.934_937delAGAG) was detected in a possible M-D patient displaying myoclonic and dystonic features, a negative family history, late onset and showing mild signs of Parkinson's disease (PD). This mutation has been previously described in a control case.²⁴ This putative healthy control showed no symptoms during a routine examination by a general practitioner at the age of 39 years and refused further examination. There is no evidence for involvement of *DYT1* mutations in PD.^{24 25} Recently, an association between both proteins, DYT1 and SGCE, has been reported, suggesting a role for DYT1 in the recognition and processing of misfolded SGCE.¹¹ It remains unclear whether this deletion plays a role in the development of the parkinsonian or M-D symptoms.

In summary, *SGCE* mutations are predominantly identified in the definite M-D group. This is in line with previous findings. However, patients with a typical M-D phenotype and a young-onset with a negative family history as well as patients with a typical M-D phenotype, late onset but a positive family history should also be considered for genetic testing, as mutation carriers with a late age of onset have been reported in a Dutch M-D pedigree.¹⁶ Possible M-D cases do not need to be tested for *SGCE* mutations. Screening for exon rearrangements did not increase the number of mutation carriers significantly. For 50% definite M-D cases, no mutation could be identified, suggesting the involvement of other genes, still not identified pathogenic mutations in the *SGCE* promoter or non-coding regions, or epigenetic defects. The 3 bp deletion in the *DYT1* gene is not involved in the pathogenesis of M-D. It remains unclear whether the detected in-frame deletion of four exons plays a role in the development of tics in our definite M-D patient.

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REFERENCES

1. Klein C. Myoclonus and myoclonus-dystonias. In Pulst SM, ed. *Genetics of movement disorders*. San Diego: Academic Press, 2003:451–71.
2. Zimprich A, Grabowski M, Asmus F, et al. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. *Nat Genet* 2001;**29**:66–9.
3. Ettinger AJ, Feng G, Sanes JR. epsilon-Sarcoglycan, a broadly expressed homologue of the gene mutated in limb-girdle muscular dystrophy 2D. *J Biol Chem* 1997;**272**:32534–8.
4. McNally EM, Ly CT, Kunkel LM. Human epsilon-sarcoglycan is highly related to alpha-sarcoglycan (adhalin), the limb girdle muscular dystrophy 2D gene. *FEBS Letters* 1998;**422**:27–32.
5. Klein C, Liu L, Doherty D, et al. Epsilon-sarcoglycan mutations found in combination with other dystonia gene mutations. *Ann Neurol* 2002;**52**:675–9.
6. Asmus F, Salih F, Hjerimind LE, et al. Myoclonus-dystonia due to genomic deletions in the epsilon-sarcoglycan gene. *Ann Neurol* 2005;**58**:792–7.
7. Muller B, Hedrich K, Kock N, et al. Evidence that paternal expression of the epsilon-Sarcoglycan gene accounts for reduced penetrance in myoclonus-dystonia. *American Journal of Human Genetics* 2002;**71**:1303–11.
8. Grabowski M, Zimprich A, Lorenz-Depiereux B, et al. The epsilon-sarcoglycan gene (SGCE), mutated in myoclonus-dystonia syndrome, is maternally imprinted. *Eur J Hum Genet* 2003;**11**:138–44.
9. Han F, Racacho L, Yang H, et al. Large deletions account for an increasing number of mutations in SGCE. *Mov Disord* 2007;**23**:456–60.
10. Grunewald A, Djarmati A, Lohmann-Hedrich K, et al. Myoclonus-dystonia: significance of large SGCE deletions. *Hum Mutat* 2008;**29**:331–2.
11. Esapa CT, Waite A, Locke M, et al. SGCE missense mutations that cause myoclonus-dystonia syndrome impair epsilon-sarcoglycan trafficking to the plasma membrane: modulation by ubiquitination and torsinA. *Hum Mol Genet* 2007;**16**:327–42.
12. Gerrits MC, Foncke EM, de Haan R, et al. Phenotype-genotype correlation in Dutch patients with myoclonus-dystonia. *Neurology* 2006;**66**:759–61.
13. First MB, Spitzer RL, Gibbon M, et al. *Structural clinical interview for DSM-IV Axis I disorders, Clinician Version (SCID-CV)*. Washington: American Psychiatric Press, 1996.
14. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;**59**(20 Suppl):22–33S.
15. Tezenas du MS, Clot F, Vidailhet M, et al. Epsilon sarcoglycan mutations and phenotype in French patients with myoclonic syndromes. *J Med Genet* 2006;**43**:394–400.
16. Foncke EM, Gerrits MC, van Ruissen F, et al. Distal myoclonus and late onset in a large Dutch family with myoclonus-dystonia. *Neurology* 2006;**67**:1677–80.
17. Klein C, Schilling K, Saunders-Pullman RJ, et al. A major locus for myoclonus-dystonia maps to chromosome 7q in eight families. *Am J Hum Genet* 2000;**67**:1314–19.
18. Asmus F, Zimprich A, Tezenas du MS, et al. Myoclonus-dystonia syndrome: epsilon-sarcoglycan mutations and phenotype. *Ann Neurol* 2002;**52**:489–92.
19. Maquat LE. Nonsense-mediated mRNA decay: splicing, translation and mRNP dynamics. *Nat Rev Mol Cell Biol* 2004;**5**:89–99.
20. Raymond D, Saunders-Pullman R, de Carvalho AP, et al. Phenotypic spectrum and sex effects in eleven myoclonus-dystonia families with epsilon-sarcoglycan mutations. *Mov Disord* 2008;**23**:588–92.
21. Orth M, Djarmati A, Baumer T, et al. Autosomal dominant myoclonus-dystonia and Tourette syndrome in a family without linkage to the SGCE gene. *Mov Disord* 2007;**22**:2090–6.
22. Asmus F, Hjerimind LE, Dupont E, et al. Genomic deletion size at the epsilon-sarcoglycan locus determines the clinical phenotype. *Brain* 2007;**130**:2736–45.
23. DeBerardinis RJ, Conforto D, Russell K, et al. Myoclonus in a patient with a deletion of the epsilon-sarcoglycan locus on chromosome 7q21. *Am J Med Genet A* 2003;**121**:31–6.
24. Kabacki K, Hedrich K, Leung JC, et al. Mutations in DYT1: extension of the phenotypic and mutational spectrum. *Neurology* 2004;**62**:395–400.
25. Leung JC, Klein C, Friedman J, et al. Novel mutation in the TOR1A (DYT1) gene in atypical early onset dystonia and polymorphisms in dystonia and early onset parkinsonism. *Neurogenetics* 2001;**3**:133–43.