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SGCE and myoclonus dystonia: motor characteristics, diagnostic criteria and clinical predictors of genotype

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Ethical standards This study has been approved by the appropriate ethics committee and therefore has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants in this study gave their informed consent prior to their inclusion in this study.

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Abstract

Myoclonus dystonia syndrome (MDS) is a young-onset movement disorder. A proportion of cases are due to mutations in the maternally imprinted *SGCE* gene. We assembled the largest cohort of MDS patients to date, and determined the frequency and type of *SGCE* mutations. The aim was to establish the motor phenotype in mutation carriers and utility of current diagnostic criteria. Eighty-nine probands with clinical features compatible with MDS were recruited from the UK and Ireland. Patients were phenotypically classified as “definite”, “probable” or “possible” MDS according to previous guidelines. *SGCE* was analyzed using direct sequencing and copy number variant analysis. In those where no mutation was found, *DYT1* (GAG deletion), *GCH1*, *THAP1* and *NKX2.1* genes were also sequenced. Nineteen (21.3 %) probands had an *SGCE* mutation. Three patterns of motor symptoms emerged: (1) early childhood onset upper body myoclonus and dystonia, (2) early childhood onset lower limb dystonia, progressing later to more pronounced myoclonus and upper body involvement, and (3) later childhood onset upper body myoclonus and dystonia with evident cervical involvement. Five probands had large contiguous gene deletions ranging from 0.7 to 2.3 Mb in size with distinctive clinical features, including short stature, joint laxity and microcephaly. Our data confirms that *SGCE* mutations are most commonly identified in MDS patients with (1) age at onset ≤10 years and (2) predominant upper body involvement of a pure myoclonus-dystonia. Cases with whole *SGCE* gene deletions had additional clinical characteristics, which are not always predicted by deletion size or gene involvement.

Keywords

Myoclonus; Dystonia; Genetic and inherited disorders; *SGCE*

Introduction

Myoclonus dystonia syndrome (MDS) is a rare movement disorder with onset in the first two decades of life. The typical clinical pattern is of alcohol responsive truncal and upper limb myoclonus with cervical dystonia and/or writer’s cramp [1]. The disorder affects males and females equally [2] and is clinically consistent across ethnicities [3-5]. Previous work has shown evidence of prominent co-morbid psychiatric disorders, specifically compulsivity, anxiety disorders and excessive alcohol use [6-9].

Mutations in the epsilon-sarcoglycan gene (*SGCE*) are responsible for a proportion of these cases [10, 11]. *SGCE* mutations are inherited in an autosomal dominant manner with variable penetrance due to maternal imprinting [12,13]. *SGCE* encodes the epsilon-sarcoglycan protein, a single pass transmembrane protein forming part of the dystrophin-associated glycoprotein complex [14-16].

SGCE mutation rates have varied amongst previously reported cohorts, some reporting no mutations [17], while others report rates from 21 to 80 % [5, 18-21]. Genetic heterogeneity has been offered as an explanation with linkage in a large Canadian family to a locus on chromosome 18p, [22, 23] although the causative gene within this region is yet to be identified. Copy number variants (CNVs) provide another possible explanation, and more recently, both exonic [24, 25] and whole gene deletions having been identified [26, 27].

This study represents one of the largest cohorts to undergo systematic clinical and genetic evaluation, identifying the largest cohort of contiguous gene deletions involving *SGCE* to date. We also describe motor symptom pattern evolution from onset to examination and compare our results to the current MDS diagnostic criteria.

Methods

Patients with suspected MDS, some with previously confirmed *SGCE* mutations, were referred by adult and paediatric movement disorder specialists throughout the UK and Ireland. The study was approved by the Multi-Centre Research Ethics Committee for Wales (MREC 09/MRE09/56 and 09/MRE09/35). Written informed consent or assent from parents/guardians was obtained for all participants.

Cases were assessed systematically and a videotaped clinical examination performed. In patients for whom this was not possible, clinical information was obtained retrospectively using a systematic pro forma for data extraction from clinical records. We recorded the presence or absence of myoclonus, dystonia, tremor, chorea and tics, age at onset of the movement disorder and family history. Patients were classified as ‘definite’, ‘probable’ or ‘possible’ according to previously published clinical criteria [28]. Psychiatric symptoms were also assessed, the results of which have been published elsewhere [8]. Recruitment methods were also previously reported and are summarized in Supplementary Fig. 1. This cohort represents the same cohort as has been published elsewhere; however, in this article specific emphasis is placed on the demographic, clinical and genetic characteristics of the cohort [8].

Blood samples were collected from all cases and DNA was isolated from peripheral blood lymphocytes using standard protocols. All samples underwent direct sequencing of exons 1-12 (including alternatively spliced exons 1a and 11b) of the *SGCE* gene. In those cases where no *SGCE* mutation was found, MLPA analysis was performed using the commercially available probe set P099B (MRC Holland, Amsterdam, The Netherlands) according to manufacturer’s instructions. Cases with whole gene deletions were analyzed on a custom oligonucleotide CGH array platform (Roche Nimblegen) with 5,900 probes covering chr7:88000000-98000000 (NCBI36/hg18 genome build). Data was analyzed using the segment tool and visualized using SignalMap (Roche Nimblegen).

To exclude other potential genetic diagnoses, all samples negative for *SGCE* mutations were assessed for mutations in *DYT1* (GAG deletion) *GCH1*, *THAP1* and *NXK2.1* genes by direct sequencing. Cases found with mutations in these latter genes were excluded from further analysis.

Statistical analysis was performed using the ‘R’ statistical software package. Fisher’s exact testing, binomial stepwise multiple logistic regression and ANOVA were used as appropriate.

Results

Demographics

Eighty-nine probands were recruited, 50 males and 39 females, with a median age at movement disorder onset of 5 years (range 0–50 years). Nineteen (21.3 %) were found to have an *SGCE* mutation with a slight female predominance (8 M:11F). Median age at onset was 5 years younger in the mutation positive group compared to those without a mutation (3 vs. 8 years, respectively) with 79 % of those with an *SGCE* mutation developing symptoms <10 years (Table 1). With recruitment of additional affected family members the number of *SGCE* positive patients increased to 27 (8 additional patients) and mutation negative cases to 76 (6 additional patients) (Supplementary Fig. 1).

Motor characteristics

SGCE mutation positive cohort

At onset: Myoclonus and dystonia were the only types of movement disorder observed, each being present in 19 cases. No cases were reported to have evidence of tremor, chorea or tics. Myoclonus predominantly involved the upper limbs and neck both overall and in each age-at-onset subgroup (Tables 2, 3). Dystonia was also most frequently reported in the upper limbs; however, the two age subgroups differed with lower limb involvement. Almost half of those with onset of the movement disorder <10 years had either foot or leg involvement while this was not reported in those whose symptoms developed between 10 and 20 years of age.

At examination: Median age at examination was 28 years (range 3–74 years). Myoclonus was observed in all but one case, predominantly involving the upper limbs and neck across both age subgroups. Truncal involvement was greater than had been reported at onset (65 % compared to 26 %), consistent in those with onset above and below 10 years of age. Dystonia was observed in all cases with the upper limbs most frequently affected overall and for those with onset <10 years. Cervical involvement was most common in the older age sub-group and more pronounced in those with onset <10 years than had been reported at onset (67 vs. 24 %). Lower limb dystonia demonstrated the largest difference, present in over half of the younger sub-group but only in a single case of onset between 10 and 20 years.

SGCE mutation negative cohort—Multiple extrapyramidal features were seen, including myoclonus, dystonia, tremor, tics and chorea, with dystonia being most prevalent (41 %). The upper limbs were the most commonly affected body part for all movement disorder subtypes with the exception of tics where a more pronounced cranio-cervical involvement was observed.

Myoclonus ($p < 0.0001$) and dystonia ($p < 0.0001$) were strongly associated with the occurrence of an *SGCE* mutation. Tics ($p = 0.0007$) and tremor ($p = 0.002$) were more common in the *SGCE* negative group. Stepwise multiple logistic regression found significant associations of myoclonus ($p < 0.001$) and dystonia ($p = 0.006$) with *SGCE* mutations.

Genetics

SGCE mutation positive—Seventy-nine percent (15/19) had a positive family history of MDS with mutations paternally inherited in 74 % of cases (14/19). Thirteen different mutations were identified, the most prevalent of which was the nonsense mutation c.289C>T (p.97X) in exon 3, occurring in four apparently unrelated families. There were four nonsense, one missense and three splice-site mutations. The missense mutation was present in a three-generation family, co-segregating with the motor disorder and demonstrating the typical autosomal dominant pattern of inheritance with reduced penetrance due to maternal imprinting (affected proband, unaffected father and his affected mother).

A number of deletions were also identified, including three intra-exonic deletions, one single exon deletion (of exon 5 only) and five whole gene deletions (WGD) (Fig. 1). In these patients with WGD (five cases identified in three families), the deleted region ranged in size from 0.7 to 2.3 Mb. Contiguous genes involved, in addition to *SGCE*, included: *PEG10*, *PPP1R9A*, *CASD1*, *COL1A2*, *BET1*, *GNG11*, *GNG1*, *TFP12*, *CALCR*, *HCTR-6*, *KIAA 1861*, *CCDC132*, *HEPACAM2*, *SAMD9L*, *CDK6*. Additional phenotypic features included microcephaly, intrauterine growth retardation, short stature, joint laxity, language delay, cognitive impairment and psychosis (Table 4; Fig. 2).

SGCE mutation negative—70/89 (79 %) unrelated patients did not have an identified *SGCE* mutation with a male predominance (42 M: 28F). No mutations were detected in *DYT1* (*GAG* deletion), *GCH1* or *THAP1*. Two cases were found to have putative *NKX2.1* mutations and were excluded from further analysis.

Diagnostic criteria for MDS

According to previously published MDS diagnostic criteria [28], there were 15 clinically ‘definite’, 4 clinically ‘probable’ and 0 ‘possible’ cases in the *SGCE* mutation positive group. In the mutation-negative group there were 2 ‘definite’, 4 ‘probable’ and 64 ‘possible’ cases (Supplementary Fig. 1). Eighty-eight percent of clinically ‘definite’ and 50 % of clinically ‘probable’ patients carried an *SGCE* mutation. When applied to this cohort, the ‘definite’ diagnostic criteria had 79 % sensitivity, 97 % specificity and 88 % positive predictive value (PPV) in anticipating an *SGCE* mutation. Applying the recently modified criteria [29], we used our previously published data of psychiatric features [8] and further refined ‘young age at onset’ to ≤10 years. Here, we found a reduced sensitivity (66.7 %), preserved specificity (97 %) and improved PPV (90 %).

Discussion

We report a large extensive cohort of MDS patients who we systematically assessed (both clinically and by molecular genetic investigation) and this is one of the few studies to include direct sequencing and CNV analysis. We have identified the largest subgroup of patients with contiguous gene deletions involving *SGCE* as well as allowing the assessment of motor symptom progression.

The frequency of *SGCE* mutations within this cohort (21.3 %) is in keeping with previously reported studies [19, 21, 30]. Significant differences in age at onset of the movement

disorder were observed between those with and without *SGCE* mutations with the latter group manifesting a broader age range (birth–50 years). As has been observed previously [1, 2, 5, 19, 20], 95 % of those with a mutation had an age at onset of 10 years or younger and there were no cases presenting over the age of 20. This suggests that age at onset is a strong predictor of an *SGCE* mutation. A family history of MDS was also an important factor in determining whether cases were ‘definite’ or ‘probable’ resulting in 4 *SGCE* positive probands being labeled as ‘probable’. This was likely due to maternal imprinting causing ‘silencing’ of the mutated gene with several generations of maternal inheritance, however, we were unable to complete parental testing to exclude *de novo* mutations.

Statistical analysis of two comparable MDS cohorts in a recent study found a disease onset in childhood and the presence of psychiatric symptoms to be the strongest factors in discriminating between those with and without *SGCE* mutations. When we applied these to our cohort PPV was improved (90 %), specificity preserved (97 %) but sensitivity reduced (66 %) compared to pre-existing diagnostic criteria. However, Carecchio et al. did not specify an age limit in their ‘young-onset’ definition. In keeping with the findings of this study, we imposed a ≤10 years restriction, which may in part account for the reduced sensitivity. We therefore postulate that to further aid targeted genetic testing, diagnostic guidelines could be altered to reduce the age on onset from <25 to <18 years [31].

Pure myoclonus and dystonia were identified in those with an *SGCE* mutation, their distribution being consistent with pre-existing definitions (predominantly upper body pattern of involvement). [1, 31] Three main patterns of motor involvement emerged with a consistent clinical phenotype: (1) the most common presentation of a young-onset predominantly upper body myoclonus and dystonia, with more pronounced truncal involvement developing during later childhood and adolescence, (2) a group presenting <10 years with isolated or prominent lower limb dystonia, later developing a larger myoclonic component with greater upper body involvement. This pattern has been reported previously in ~20 % *SGCE* patients with isolated dystonia, similar to the 33 % observed in this cohort [2, 30, 32, 33]. (3) A subgroup with onset >10 years with later truncal myoclonus and much more pronounced cervical dystonia. This suggests that even in the absence of myoclonus at examination, *SGCE* testing should still be considered in young children with focal lower limb dystonia. These patterns of clinical presentation and progression became apparent during collection and analysis of the clinical data and should be replicated in a larger cohort of *SGCE* mutation positive cases.

With the exception of a few cases in whom symptom progression is described [34, 35], MDS symptoms usually plateau in adulthood and are associated with a normal life span [36, 37], possibly reflecting maturation of the basal ganglia pathways [38]. There are also reports of spontaneous improvement of dystonia symptoms [39], similar to that seen with primary focal dystonia. Despite some reports of subjective improvement, no spontaneous resolution of dystonia was reported in this cohort, a feature consistent with the findings of a recent report on the impact of dystonia in children [40]. A single case had no evidence of myoclonus on examination despite this being a prominent childhood feature, which again has also been reported in other cohorts [5, 41].

Six cases had *SGCE* deletions detected by MLPA analysis and consistent with previous literature, no duplications were identified [26, 27, 42, 43]. One involved a single exon deletion (exon 5) with a typical MDS clinical phenotype and no additional clinical characteristics, again consistent with previous cases. [24, 28, 44] In the remaining five cases (including two sets of sibling pairs) CGH array analysis showed large contiguous gene deletions involving PEG10, PPP1R9A, CASD1, COL1A2, BET1, GNG11, GNG1, TFP12, CALCR, HCTR-*6, KIAA 1861, CCDC132, HEPACAM2, SAMD9L, CDK6* genes, ranging between 0.7 and 2.3 Mb in size. All five cases had features of both myoclonus and dystonia. The size of the deletion did not dictate age of symptom onset or disease severity. For the two sibling pairs, there was evidence of intra-familial variation in motor symptom severity, the elder sibling manifesting more pronounced and disabling symptoms. This may represent a pattern of motor symptom evolution; however, it is conceivable that as with *SGCE* point mutations, intra-familial phenotypic variation also exists with contiguous gene deletions. There has been previous speculation that the size of the deletion may determine the presence and severity of further clinical characteristics [27].

Within this cohort, while all five cases were of short stature the number, type and nature of the additional features appeared unrelated to deletion size, or genes involved. There was also evidence of intra-familial variation despite having the same or similar size deletion, as exemplified by cases 3 and 4 (Table 4). As shown in Fig. 2 all detected deletions span a large area of chromosome 7 and involve a number of genes. *COL1A2* is one of the best understood, mutations of which are associated with autosomal dominant osteogenesis imperfecta. Hence patients with CNVs involving this gene might be anticipated to develop bone fractures, hypodontia and joint laxity. Despite all five cases in this study harbouring deletions encompassing *COL1A2*, only a single patient (case 2) was observed to have joint laxity without a history of fractures or problems with dentition. These cases provide further evidence that patients with large contiguous gene deletions may be phenotypically distinct from those with *SGCE* point mutations and demonstrate significant clinical variation not predicted by deletion size or gene involved. Investigation of larger cohorts of patients with *SGCE* deletions are required to further delineate the clinical spectrum and elucidate the roles of other genes in the region.

Although data collection and analysis in this study was systematic and used standardized methods, a few limitations are recognized. Motor data collection combined both face-to-face interview and retrospective data collection from the clinical notes. In addition, assessment of age at onset was in most cases retrospective and dependent on patient recall. While only myoclonus and dystonia were observed in the *SGCE* positive group, chorea, tremor and tics were also observed in the mutation negative group. Although early clinical descriptions frequently reflected difficulty in accurately describing and classifying these movement disorders [45], improved diagnostic criteria [28, 31] suggest that presence of these additional movement disorders likely indicate that a proportion of the mutation negative group do not meet diagnostic criteria for MDS.

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Conclusion

We describe a large cohort of MDS patients systematically and fully assessed *SGCE* mutations, with detailed delineation of motor features and additional clinical characteristics. We conclude that mutations are associated with three distinct motor patterns of presentation based on age of onset, movement phenotype and body distribution. This study also demonstrates that adherence to strict diagnostic criteria; age at onset <18 years, the presence of only myoclonus and/or dystonia as movement disorder subtypes and a positive family history of a similar movement disorder greatly increases the yield of *SGCE* mutations with genetic testing. Neurophysiological testing may also be used to aid diagnostic accuracy prior to genetic testing. Our cohort also reports the largest single series of whole gene deletions involving *SGCE* highlighting importance of microarray studies and MLPA as important diagnostic investigation for complex movement disorders [46].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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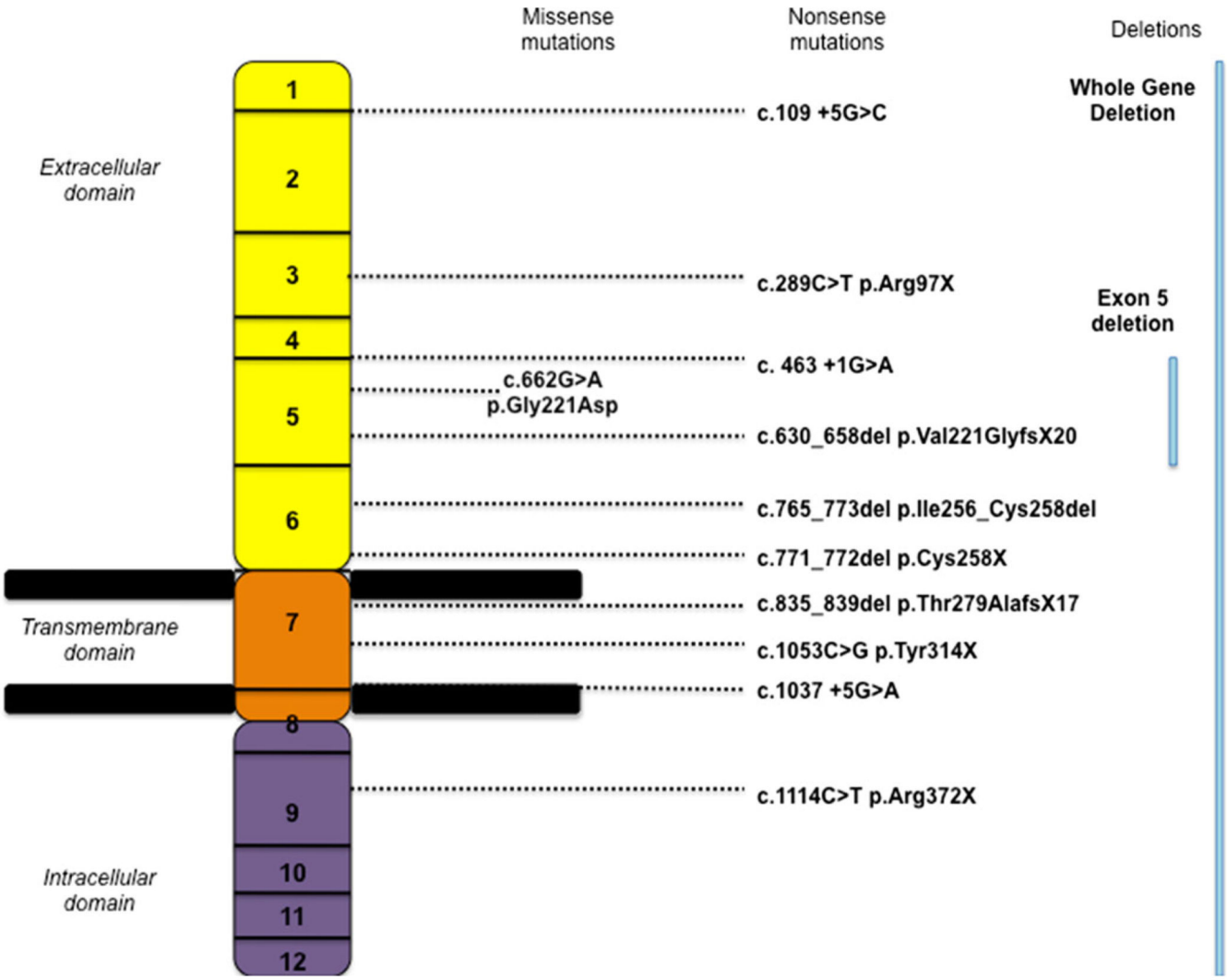

Fig. 1.
Diagrammatic representation of identified *SGCE* mutations

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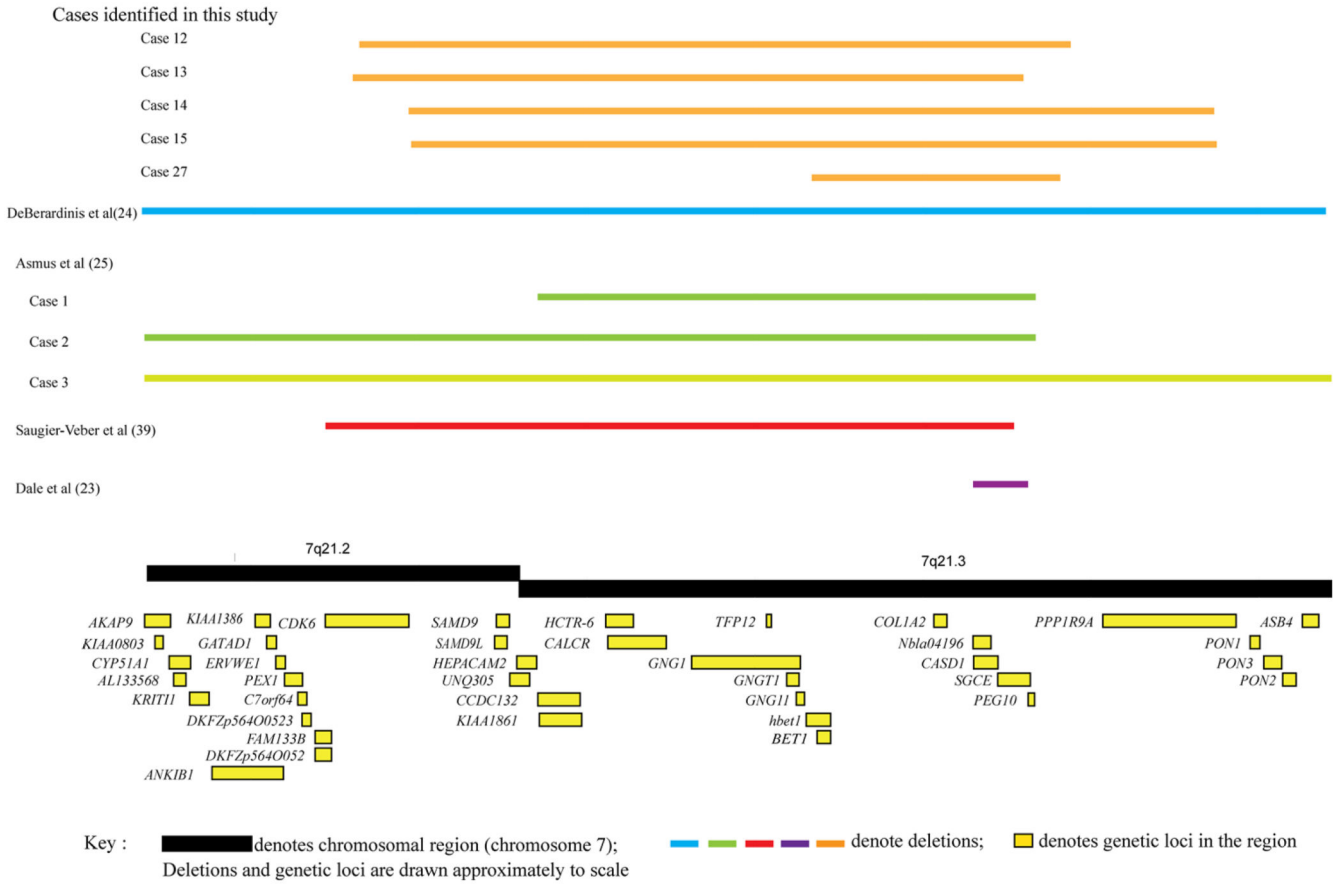

Fig. 2.

Diagrammatic representation of contiguous gene deletions involving *SGCE* identified in this cohort

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Table 1

Demographic and clinic features

	Proband only cohort			All *SGCE* mutation positive cases
	Overall	***SGCE* mutation positive**	***SGCE* mutation negative**	
n	89	19	70	27
Male:female	50:39	8:11	45:33	10:27
Median age at onset (range)	5 (0–50)	3 (1–18)	8 (0–50)	3 (1.5–18)
Age at onset				
<10 years	56	15 (79 %)	41 (59 %)	21 (78 %)
10–20 years	20	4 (21 %)	16 (23 %)	6 (22 %)
>20 years	4	0	4 (6 %)	0
Clinical likelihood of MDS				
Definite	17	15 (79 %)	2 (3 %)	25 (93 %)
Probable	8	4 (21 %)	4 (6 %)	2 (7 %)
Possible	64	0	64 (91 %)	0

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Table 2

SGCE mutation positive cohort—motor characteristics at onset and examination

	Motor characteristics at onset			Motor characteristics at examination		
	Overall	**<10 years**	**10–20 years**	**Overall**	**Onset <10 years**	**Onset 10–20 years**
n	27	21	6	27	21	6
Median age (range)	3 (1.5–18)	2.5 (1.5–8.5)	10.5 (10–18)	28 (3–74)	22 (3–74)	47.50 (19–63)
Myoclonus						
n	19	14	5	26	20	6
Neck	9 (47 %)	6 (43 %)	3 (60 %)	19 (73 %)	15 (75 %)	4 (67 %)
Upper limbs	17 (89 %)	13 (93 %)	4 (80 %)	25 (96 %)	20 (100 %)	5 (83 %)
Trunk	5 (26 %)	5 (36 %)	0	17 (65 %)	14 (70 %)	3 (50 %)
Lower limbs	1 (5 %)	1 (7 %)	0	5 (19 %)	4 (20 %)	1 (17 %)
Dystonia						
n	19	17	2	27	21	6
Neck	5 (26 %)	4 (24 %)	1 (50 %)	20 (74 %)	14 (67 %)	6 (100 %)
Voice	1 (5 %)	1 (6 %)	0	5 (19 %)	4 (19 %)	1 (17 %)
Upper limbs	13 (68 %)	9 (53 %)	2 (100 %)	22 (81 %)	19 (90 %)	3 (50 %)
Trunk	1 (5 %)	1 (6 %)	0	3 (11 %)	2 (10 %)	1 (17 %)
Lower limbs	8 (42 %)	8 (47 %)	0	12 (44 %)	11 (52 %)	1 (17 %)

Table 3

Motor characteristics of *SGCE* mutation negative cohort

	n **(%)**
Myoclonus	
n	16 (23)
Median age at onset (range)	4.75 (0–15)
Neck	8 (50)
Upper limbs	12 (75)
Trunk	8 (50)
Lower limbs	5 (31)
Dystonia	
n	29 (41)
Median age at onset (range)	4.5 (0–48)
Neck	9 (31)
Voice	4 (14)
Upper limbs	15 (52)
Trunk	0
Lower limbs	12 (41)
Tremor	
n	16 (23)
Median age at onset (range)	10 (0.25–48)
Neck	4 (25)
Upper limbs	13 (81)
Trunk	0
Lower limbs	1 (6)
Tics	
n	16 (23)
Median age at onset (range)	7 (0.5–14)
Neck	13 (81)
Voice	8 (50)
Upper limbs	11 (69)
Trunk	1 (6)
Lower limbs	2 (13)
Chorea	
n	7 (10)
Median age at onset (range)	4.5 (0–21)
Neck	3 (43)
Upper limbs	6 (86)
Trunk	0
Lower limbs	3 (43)

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Table 4

Clinical characteristics of cases with contiguous gene deletions involving *SGCE*

Cases	Deletion size (Mb)	Genes involved	Clinical characteristics
This study			
Case 1	2.3	*PPP1R9A, PEG10, SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L*	Short stature, language delay
Case 2	2.3	*PPP1R9A, PEG10, SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L*	Short stature
Case 3	2	*PEG10, SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6*	Intrauterine growth retardation, microcephaly, short stature, joint laxity
Case 4	1.9	*SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6*	Microcephaly, short stature, cognitive impairment
Case 5	0.7	*PEG10, SGCE, CASD1, COL1A2*	Short stature, psychosis
DeBerardinis et al.			
Case 1	9–16.5	*SGCE* (and contiguous genes, not further defined)	Intrauterine growth retardation, microcephaly, short stature, dysmorphic facies, language delay
Asmus et al.			
Case 1	1.63	*PEG10, SGCE, COL1A2*	Short stature, joint laxity, dental caries, joint laxity, blue sclerae, cerebral cavernous malformations
Case 2	4.99	*PEG10, SGCE, COL1A2, PEX1, KRITI*	
Case 3	8.78	*PEG10, SGCE, COL1A2, PEX1, KRITI, DLX5*	Dysmorphic facies, dental caries, cognitive impairment, split-hand split-foot syndrome
Saugier-Veber et al.			
Case 1	1.88	*SGCE, CASD1, COL1A2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA 1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6*	Intrauterine growth retardation, microcephaly, short stature, joint laxity, cognitive impairment
Dale et al.			
Case 1	0.17	*SGCE, CASD1*	Language delay, cognitive impairment
Case 2	0.17	*SGCE, CASD1*	Nil
Case 3	0.17	*SGCE, CASD1*	Psychosis