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Is psychopathology part of the phenotypic spectrum of Myoclonus-Dystonia?
A study of a large Dutch M-D family

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Abstract

Background: Myoclonus-Dystonia (M-D) is a movement disorder frequently caused by mutations in the epsilon-sarcoglycan gene (*SGCE*, DYT11). In several M-D families, psychiatric symptoms accompanying the motor symptoms have been reported, but a shared genetic etiology remains unclear.
Objective: To assess neuropsychological functioning and psychopathology in DYT11 mutation carriers (MC) and their family members using standardized neuropsychological and psychiatric measures.

Methods: Cognitive and behavioural characteristics of 27 DYT11 MC (14 symptomatic and 13 asymptomatic) and 42 control subjects within one Dutch M-D family were studied. Neuropsychological tests encompassed memory, language, mental speed, concentration, visuospatial function and executive functions. Psychiatric assessment addressed qualitative (according to DSM-IV criteria) as well as quantitative measures of depression, anxiety, panic attacks and obsessive-compulsive disorder (OCD), using self administered and interview based scales.

Results: No differences were observed on tests of cognitive functioning between DYT11 MC and controls. The frequency of DSM-IV diagnoses was higher in the symptomatic DYT11 MC than in controls. The symptomatic DYT11 MC showed more depressive and anxiety symptoms, including panic attacks but no increase in OCD compared to controls. No differences were found between asymptomatic DYT11 MC and controls on any of the psychopathological tests.

Conclusions: Cognitive dysfunction nor OCD seem to be associated with the DYT11 phenotype in this large Dutch pedigree. Depressive and anxiety symptoms are increased in symptomatic, but not in asymptomatic DYT11 MC. Future research has to determine whether the psychiatric symptoms are part of or secondary to the DYT11 phenotype.

Introduction

Myoclonus-Dystonia (M-D) is a movement disorder characterized by myoclonic jerks and dystonic postures/movements that are often responsive to alcohol. M-D has an autosomal dominant inheritance pattern with reduced penetrance due to maternal imprinting and is frequently caused by mutations in the epsilon-sarcoglycan gene (SGCE) on chromosome 7q21. [1,2] M-D has been classified as DYT11 among the hereditary forms of dystonia and is considered to be a dystonia-plus syndrome. [3] Phenotypic and genotypic has been demonstrated in M-D.[4-7]
Cognitive function in M-D has been previously addressed in only one study showing impaired verbal learning and memory. [8] Psychiatric disorders have been frequently reported in several M-D families. [9-20] However, only three studies have systematically addressed the presence of psychiatric symptoms. [8,21,22]

In the present study, one single Dutch M-D family was studied using rigourous neuropsychological and psychiatric measures to confirm or refute the previously suggested association of psychopathology with the DYT11 genotype. A highly matched control group was used encompassing the DYT11 negative family members, and 4 married-in spouses. The advantage of this control group over a case-control design is that the patients and controls share a similar social-economic and family background, and have genetic similarities.

Methods

Patients

Sixty-nine subjects from one large Dutch M-D family with a two-base pair deletion in exon 5 (c.619_620delAG) which has recently been described [23] consented to participate in the study. Twenty-seven subjects were DYT11 mutation carriers (MC) and 42 subjects served as controls: 38 DYT11 negative family members and 4 married-in spouses. Clinical status was assessed by an independent movement disorder specialist (MT). Patients with clinical symptoms by history and neurological examination were defined as symptomatic MC (SMC) and as asymptomtic MC (AMC) when no clinical complaints of myoclonus or dystonia were reported. The severity of motor symptoms in the DYT 11 MC group was assessed using the Burke-Fahn-Marsden dystonia rating scale (BFMDRS, Burke et al, 1985) and a modified version of the Unified Myoclonus rating scale (UMRS, Frucht et al, 2002). [25,26] The study was approved by the local ethics committee and all participating individuals gave written informed consent.

Neuropsychological assessment

A trained neuropsychologist blinded for the DYT11 carrier status (but not for the movement disorder) and the relationship within the family of the subjects, performed the interviews and neuropsychological testing.

The Dutch Adult Reading Test was used to test premorbid intelligence. [26] To evaluate global intelligence subtests of the Weschler Adult Intelligence Scale-version 3 (WAIS-III) (similarities and matrix reasoning) [27] and the subtest Spatial Reasoning of the "Differentiële Aanleg Test", a Dutch version of the Differential Aptitude Test (DAT) were administered. [28] The WAIS-III letter-number sequencing [27], the Stroop Test (word and color conditions) [29] and the Trailmaking Test (TMT) part A [30] were used to assess psychomotor speed and attention. Executive functioning was assessed using the short version of the Wisconsin Card Sorting Test (WCST) [31], the Stroop test (color-word condition) [29], the Trailmaking Test (TMT) part B [30]. Language functioning was evaluated with a short version of the Boston Naming Test (BNT), phonemic fluency and category fluency (animals and occupations). [32,33] Memory functions were evaluated using the Weschsler Memory Scale-version 3 (WMS-III), immediate and delayed recognition of faces (visual memory) [27], the Rivermead Behavioural Memory Test (RBMT) [34], immediate and delayed story recall (logical memory) and the Rey Auditory Verbal Learning Test (RAVLT) [35], immediate and delayed recall of 15 words (verbal memory). Reaction speed was assessed using the Vienna Test System (subtests S1 simple reaction speed, and S3, two-choice reaction speed). [36] To evaluate dysexecutive symptoms and cognitive functioning in daily life, the DEX questionnaire of the Behavioural Assessment of the Dysexecutive Syndrome [37] and the Cognitive Failure Questionnaire (CFQ) were administered. [38]

Psychiatric assessment

Two trained neuropsychiatric test-technicians, blinded for the DYT11 carrier status (but not for the movement disorder) and the relationship within the family of the subjects, performed the interviews and testing. All persons were administered the Structured Clinical Interview (SCID-I) on DSM-IV diagnoses. [39] Quantitative ratings of anxiety (general anxiety, panic disorder and social phobia), obsessive compulsive symptoms and depression were taken. To assess general anxiety, the Beck's Anxiety Inventory (21 items self-report, scores per item between 0-4) was used. The Anxiety Scale (AS), (40 items self-report, scores per item between 0-3) was applied to assess panic severity. [40] The Liebowitz Social Anxiety Scale (L-SAS) was performed to evaluate social anxiety symptoms (a 48 item interview containing 24 items to rate social anxiety and 24 items to rate avoidance behaviour, scores per item between 0-4). [41] OC symptoms were assessed using the Yale Brown Obsessive Compulsive Scale-severity (YBOCS-severity) (a 10 items interview, scores per item between 0-4) and the Yale Brown Obsessive Compulsive Scale-symptoms (self-report). To assess depressive symptoms, the Montgomery-Asberg Depression rating scale (MADRS) (a 10 items interview, scores per item between 0-6) [42,43]

and the Beck Depression Inventory (BDI), (21 items self-report, scores per item between 0-3) were applied. [44]

Statistical analysis

Correlation between mutation carriers and controls in the pedigree

Except for the 4 spouses, all 27 DYT11 MC and 38 non-carriers were related to each other. Because family-relationships between the mutation carriers and controls may influence the testresults, correlation structures between these 65 family-members were tested on significance using the score-test developed by Houwing-Duistermaat et al [45].The correlation between two members i and j was assumed to be according to Wright's kinship coefficient: $0.5^{d(ij)}$, where d(ij) was the number of meioses between members i and j.
For all variables assessed, the score test was nonsignificant ($p>0.43$), and almost all correlations were estimated to be zero. Further statistical analysis was done with standard statistical methods while ignoring the family-relationships between mutation carriers and controls.

Neuropsychological data

We compared DYT11 MC with controls using multivariate analysis of covariance for each of the six cognitive domains, co-varying for age, sex, level of education and IQ where necessary. We seperately compared the symptomatic and the asymptomatic DYT11 MC with controls using the same analysis.

Psychiatric data

We compared DYT11 SMC, DYT11 AMC and controls on all measures using the Kruskal-Wallis test to detect differences between groups. Subsequently, we compared DYT11 SMC with controls, DYT11 AMC with controls and DYT11 SMC and DYT11 AMC in a posthoc analysis using the Mann-Whitney U-test. Correlations between the presence of psychiatric symptoms and the severity of motor symptoms in the DYT11 SMC were calculated using the Spearman's rho two-tailed non parametic test.
The data of the SCID were analysed using the Chi-square test. Alpha ≤ 0.05 was considered statistically significant. We did not correct for multiple comparisons by adjusting the level of significance, since in these exploratory analyses we were more concerned about type II error (failing to detect a difference) than about type I error (detect a difference when there is actually not a difference).[46]

Results

Demographic data

The demographic data of DYT 11 MC and controls are summarized in **Table 1**. Of the 27 DYT11 MC, 14 were symptomatic (SMC) and 13 asymptomatic (AMC). The DYT11 AMC group considered themselves not affected, but in 5 of 13 DYT11 AMC subtle signs of axial dystonia were noticed at neurologic examination. These patients were previously described as 'possibly affected'. [24] There were statistically significant differences between the DYT11 MC and control group with respect to sex (p=0.038) and age (p=0.012).

Table 1. Demographic characteristics of DYT11 MC and controls

	DYT 11 MC		Controls
	SMC	AMC	
Men/women	10/4	3/10	12/30
Age	48.5 (13.3)	42.6 (13.7)	38.0 (12.9)
Levels of education (ISCED)	3.4 (1.3)	4.7 (0.7)	4.6 (1.2)
DART-IQ	75.5 (8.4)	95.0 (11.0)	91.1 (13.0)
Severity of motor symptoms, BFMDRS+UMRS	20.7 (4-53)	5.6 (2-8)	-

Values are means (SD), except for severity of motor symptoms: values are means (range)
DYT11 MC= DYT 11 mutation carriers, S=symptomatic, A=asymptomactic, ISCED=International Standard Classification of Education, DART=Dutch Adult Reading Test, BFMDRS= Burke-Fahn-Marsden Dystonia Rating Scale, UMRS= Unified Myoclonus Rating Scale.

Years of education and Mulder IQ did not differ between the two groups (p=0.09 and p=0.177). There were no significant differences between the DYT11 SMC and DYT11 AMC with respect to age, sex and years of education (data not shown).

Neuropsychological assessment

Two DYT11 SMC were excluded from analysis because of pre-existing learning disorders.

The results of the neuropsychological test scores for the DYT11 MC and controls are displayed in **Table 2**. Mancovas showed no significant differences between the 25 DYT11 MC and 42 controls in any of the cognitive domains when covarying for sex and age. No significant differences could be demonstrated when comparing the 12 DYT11 SMC and the 13 DYT11 AMC (data not shown).

Psychiatric assessment

One of the 13 DYT11 AMC was not willing to participate in the psychopathological part of the study.

Table 2. Results of neuropsychological assessment

	DYT 11 MC N=25 mean (SD)	Controls N=42 mean (SD)	p-value
Intelligence			**.553**
WAIS III-similarities (ss)	7.88 (2.819)	8.74 (2.855)	.982
WAIS-III matrix reasoning (ss)	9.42 (3.215)	9.81 (3.125)	.652
DAT- forms S+T (st)	4.69 (1.644)	5.48 (1.798)	.246
Psychomotor Speed and Attention			**.863**
WAIS-III digit span (ss)	8.15 (3.120)	8.88 (2.643)	.756
WAIS-III letter-number sequencing (ss)	8.68 2.996	9.27 2.259	.657
WAIS-substitution (T)	57.48 (12.684)	54.27 (12.758)	.894
Stroop word (T)	44.31 (14.543)	45.90 (12.681)	.624
Stroop color (T)	46.77 (12.101)	48.14 (9.506)	.788
Trailmaking A (T)	45.31 (10.990)	49.26 (10.750)	.310
Executive Functioning			**.869**
WCST-short version (T)	42.84 (10.111)	42.07 (10.586)	.359
Stroop color-word (T)	49.80 (10.809)	51.32 (10.458)	.924
Trailmaking B (T)	47.96 (13.746)	51.34 (10.051)	.584
Verbal fluency-phonemic (T)	47.65 (14.190)	48.17 (10.581)	.319
Boston Naming-short version	25.308 (4.209)	26.143 (3.621)	.701
animals (st)	4.88 (2.405)	4.69 (1.814)	.174
occupations (st)	3.92 (1.853)	3.86 (1.802)	.254
Memory			**.724**
RBMT immediate recall (T)	46.96 (6.459)	47.33 (7.213)	.509
RBMT delayed recall (T)	48.23 (7.596)	49.43 (6.105)	.889
RAVLT immediate recall (T)	47.12 (12.763)	45.98 (11.942)	.325
RAVLT delayed recall (T)	45.04 (15.434)	44.79 (12.534)	.467
WMS-III faces immediate recall (T)	49.96 (8.632)	47.64 (6.540)	.086
WMS-III faces delayed recall (T)	51.42 (6.081)	50.67 (9.106)	.826
Reaction Speed			**.868**
Vienna Test System-S1 reaction time (T)	52.32 (8.275)	51.24 (7.426)	.157
Vienna Test System-S1 movement time (T)	49.96 (7.525)	51.00 (7.513)	.551
Vienna Test System-S3 reaction time (T)	47.16 (11.971)	44.24 (7.674)	.074
Vienna Test System-S3 movement time (T)	42.36 (7.302)	41.80 (8.004)	.054
Mood and behaviour			**.356**
DEX (raw scores)	18.69 (11.706)	15.02 (8.912)	.150
CFQ (raw scores)	27.77 (12.555)	24.64 (11.331)	.293

T = age corrected T-scores, i.e. population mean = 50, sd = 10, ss = age-corrected scaled score, i.e. population mean = 10, sd = 3, st = age-corrected stanine score, i.e. population mean = 5, sd = 2, p-value in bold= multivariate p, p-value=mancovas, DYT11 MC= DYT 11 mutation carriers, WAIS-III= Weschler Adult Intelligence Scale-version 3, DAT= Differential Aptitude Test, WCST= Wisconsin Card Sorting Test, RBMT= Rivermead Behavioural Memory Test, RAVLT= Rey Auditory Verbal Learning Test, WMS-III= Weschsler Memory Scale-version 3, DEX= Questionnaire of the Behavioural Assessment of the Dysexecutive Syndrome, CFQ= Cognitive Failure Questionnaire.

Table 3. DSM-IV diagnoses in the DYT11 MC and control group obtained by the SCID

	DYT11 MC (N=26)		Controls (N=42)
	SMC (N=14)	AMC (N=12)	
None	4	11	36
OCD	2	1	1
Depression	2	0	2
Panic Disorder	1	0	0
Social Phobia	5	0	3
Specific Phobia	3	0	2
Alcohol dependence	3	0	0
GAD	2	0	0

DYT11 MC= DYT 11 mutation carriers, S=symptomatic, A=asymptomactic, OCD= Obsessive Compulsive Disorder, GAD= Generalized Anxiety Disorder.

Table 4. Results of neuropsychiatric assessment

Quantitative rating lists	DYT11 SMC (N=14)	DYT11 AMC (N=12)	Controls (N=42)	DYT11 SMC vs. controls	DYT11 AMC vs. controls
YBOCS- severity (.96)*	0 (0-15)**	0 (0-14)	0 (0-11)	.422***	.895
BAI (.90)	25 (21-45)	21 (21-35)	21.5 (21-46)	.015	.646
L-SAS (.96)	58 (48-127)	48 (48-68)	53 (48-125)	.105	.083
AS (.97)	4 (0-82)	0 (0-13)	1 (0-14)	.025	.278
BDI (.87)	4.5 (0-30)	1 (0-21)	2 (0-18)	.009	.717
MADRS (.93)	0 (0-22)	0 (0-20)	0 (0-23)	.059	.745

*=Cronbach's alpha, **=values are median (range), ***=p-values * , DYT11 MC= DYT 11 mutation carriers, S=symptomatic, A=asymptomactic, YBOCS= Yale Brown Obsessive Compulsive Scale, BAI= Beck's Anxiety Inventory, L-SAS= Liebowitz Social Anxiety Scale, AS= Anxiety Scale, BDI= Beck's Depression Inventory, MADRS= Montgomery-Asberg Depression Rating Scale.

DYT11 MC showed significantly more DSM-IV diagnoses than controls: 11 out of 26 DYT11 MC versus 6 out of 42 controls (SCID, χ^2 =14.61 and p<0.001) **(Table 3)**. In the DYT11 AMC group, one out of 12 had a DSM-IV diagnosis, i.e. OCD. None of the 'possibly affected' AMC had a DSM-IV diagnosis. In the DYT11 SMC group, ten out of 14 sMC had a DSM-IV diagnosis. Two out of these ten SMC had two and two had four DSM-IV diagnoses. Six SMC persons had one DSM-IV diagnosis.

The results of the psychiatric interviews and the self-report questionnaires (including Cronbach's alpha's (internal consistency) of the scores) are summarized in **Table 4**.

When correlating the presence of psychopathological symptoms with the severity of motor symptoms in DYT11 sMC, significant correlation was detected between the severity of myoclonus and dystonia (BFMDRS+UMRS) and the L-SAS anxiety score (Spearman's rho= .606, p=.022), and the BDI depression score (Spearman's rho=.745, p=.002). No

significant correlation between the BAI anxiety score (Spearman's rho= .430, p=.125), the MADRS depression score (Spearman's rho= .383, p=.177), the AS panic score (Spearman's rho= .530, p=.051) and the severity of myoclonus and dystonia could be detected.

Discussion

In the present M-D study, normal cognitive but impaired emotional functioning was found in DYT 11 SMC compared to DYT11 AMC as well as their unaffected family members, using a standardized battery of tests on both qualitative and quantitative measures of cognition and psychopathology. Depressive symptoms, anxiety and panic attacks were more prevalent in DYT11 SMC. Contrary to previous reports, OC symptoms were not increased in DYT11 SMC compared to controls.

To date, little is known about the cognitive and emotional functioning of M-D patients and other types of myoclonus or dystonia. DYT11 MC in the present study performed similarly as controls on an extensive neuropsychological test battery. This is in contrast to a previous cognitive study showing impaired verbal learning in 11 out of 13 manifesting DYT11 MC from three M-D families. [8] However, in that study no definite conclusions could be drawn due to the small number of patients studied. Two other small reports have been published on cognitive dysfunction in M-D. [15,47] In one family with a severe M-D syndrome due to a novel truncating *SGCE* mutation, impaired cognitive function was described in eight family members but did not cosegregate with the DYT11 mutation. Therefore, cognitive dysfunction could not be considered as part of the DYT11 phenotype. [15] The other M-D report described a 32-month-old child with myoclonus, slight dysmorphic features and language delay. [47] Mutation analysis showed an interstitial deletion of chromosome 7q21 completely removing the SGCE and surrounding genes. It was hypothesized that the non-motor symptoms could be due to the absence of the neighbouring genes.
Neuropsychological studies in patients with other types of subcortical myoclonus are not available. In other types of dystonia, no or only subtle changes in cognitive performance have been reported. [48-53] Balas and co-workers found larger retro-active interference in verbal memory in a homogeneous group of 28 DYT1 MC. [48] In a heterogeneous group of 14 patients with primary dystonia, attention-shift deficits were demonstrated. [53] It should be noted that these cognitive deficits were subtle and other cognitive functions were normal. Based on the large current study in M-D and the aforementioned studies, one may conclude that in general cognitive function in dystonic patients is preserved.

Detailed neuropsychiatric evaluation revealed that depression, anxiety, and panic attacks were more prevalent in DYT11 SMC compared to controls in the Dutch pedigree, whereas the DYT11 AMC did not differ from controls on any of the measurements taken.

Table 5. Review of reports on Myoclonus-Dystonia and psychiatric symptoms

	Patients		DYT11 genotype	DYT11 phenotype	
	Familial	**Sporadic**		**SMC**	**AMC**
Hess et al. 2007(21)	30 (5)		+	20	10
Misbahuddin et al. 2006(16)	2 (1)		+	2	
Tézenas et al., 2006(19)	38 (14)		+	32	6
Asmus et al., 2005(10)	12 (2)		+	8	
Riordan et al., 2004(17)	3 (1)		+	3	
Hedrich et al., 2004(13)	19 (4)		+	6	13
Schüle et al., 2004(5)	6 (2)		+	5	1
Valente et al., 2003(20)	6 (6)	10	-	10	
Marechal et al., 2003(15)	6 (1)		+	6	
Foncke et al., 2003(12)	5 (1)		+	4	1
Asmus et al., 2002(9)	24 (9)		+	24	
Saunders-Pullman et al, 2002(22)	55 (3)		+	16	11
Doheny et al., 2002(8)	24 (3)		+	13	6
Doheny et al., 2002(11)	6 (1)		+	5	1
Scheidtmann et al., 2000(18)	1 (1)		+	1	
Klein et al., 1999 (14)	10 (1)		+	8	2

*=familial patients, n (# families),**= sporadic, DYT11 MC= DYT11 mutation carriers, S=symptomatic, A=asymptomactic, nm= not mentioned, OCD= Obsessive Compulsive Disorder, A= alcoholdependence, D= depression, P= panic attacks, An= anxiety, GAD= generalized anxiety disorder, SA= substance abuse, Pe= personality disorder, CIDI= Composite International Diagnostic Interview, DIGS= Diagnostic Interview for Genetic Studies, YBOCS= Yale Brown Obsessive Compulsive Scale.

Psychiatric symptoms have been reported in other M-D families. [9-20] However, in the majority of the reports on M-D, psychopathology has either not been assessed or in a non-standardized manner **(Table 5)**.

In a recently published study by Hess and coworkers, alcohol dependence was hypothesized to result from self-treatment of the M-D motor symptoms and not due to the gene defect, but OCD was considered to be a manifestation of the gene. [21] However, in the present Dutch M-D family OCD nor alcohol dependence were associated with the DYT11 carrier status. Hess and coworkers used the Composite International Diagnostic Interview (CIDI) to assess DSM-IV diagnoses. It is well-established that the CIDI, being an epidemiological instrument, has a lower threshold for psychopathology than the SCID, possibly leading to overdiagnoses in clinical samples. This might explain the differences in DSM-IV diagnoses of alcohol dependence between our study and the study by Hess et al. With respect to their finding of OC symptoms, we used the YBOCS to assess OC

DYT11 MC with psychiatric symptoms		
n	**Symptoms**	**Assessment**
	OCD, A	CIDI
	D, one with suicide	History
0		History
2 sMC	A	CIDI
3 sMC	A	History
3 sMC	D	History
0		History
2	mild D	History
3 sMC	OCD, D with suicide	DSM-IV
2 sMC	D	DIGS, YBOCS
5 sMC	D, P,agoraphobia	History
	OCD in 4 sMC and 1 aMC, GAD in 6 sMC and 2 aMC, MAD in 5 sMC and 2 aMC, A in 7 sMC	CIDI
12 sMC, 5 aMC	SA, An, P, Pe, OCD	DIGS, YBOCS
3 sMC	D, An, P,A	DIGS, YBOCS
	P	DSM-IV
5 sMC, 1aMC	OCD, D,P,An	History

symptoms, which is very sensitive to pick up OC symptomatology in addition to the DSM-IV diagnosis of OCD. YBOCS symptoms and severity scores were extremely low in the present M-D family. Our findings are in line with the negative findings by Tezenas et al. [19] Reports on the frequency of psychiatric symptoms in patients with other types of subcortical myoclonus are not available. Psychopathology has been described in different forms of primary dystonia [54-58,59,60] The question in all these studies, including the present study, remains whether psychopathology is primary or secondary to the motor symptoms.

Recently, a study of patients with primary torsion dystonia (DYT1 MC) revealed a higher rate of depression but no OCD in both DYT1 SMC and DYT1 AMC. [77,78] The authors suggested that psychopathology is part of the phenotype of DYT1 dystonia patients, because of the lack of correlation with the severity of dystonia in the manifesting DYT1 MC and the higher rate of depression in the non manifesting DYT1 MC. Studies in cervical dystonia patients revealed a higher rate of depression, social phobia and panic attacks compared to patients with other chronic diseases. [55-57] The prevalence of psychiatric symptoms did not correlate with the severity of motor symptoms and sometimes

preceded the onset of motor symptoms, suggesting that psychopathology was not due to the burden of chronic debilitating motor symptoms. [50,55]

However, in the current study, the correlation between depression/ anxiety and the severity of motor symptoms of the SMC points towards psychopathology being secondary to the motor symptoms. Moreover, no psychopathology could be detected in the DYT11 AMC, although an escape from maternal imprinting has been reported in several studies, including the presence of five "possibly affected" DYT11 MC in the present Dutch M-D family. [21,23] Therefore, when assuming that psychopathology is part of the DYT11 phenotype, one would have expected to find psychiatric symptoms in at least more than one of the AMC. Saunders-Pullman and co-workers described two out of ten DYT11 AMC with a major affective disorder and five out of ten with substance abuse. [21,22] In the 3 M-D families studied by Doheny and coworkers, two out of the six DYT11 AMC were diagnosed with depression and 3 out of 6 suffered from substance abuse. [8]

Earlier age of onset of psychiatric symptoms than the M-D motor symptoms would suggest that psychiatric symptoms are an expression of the DYT11 genotype. In the present study, 10 of 14 SMC developped motor symptoms in childhood which makes it unlikely that psychiatric symptoms preceeded the motor symptoms. However, this has not been formal assessed.

A possible limitation of the present study is the assessment of psychiatric symptoms in sMC with the same two-base pair deletion in exon 5 of the SGCE gene and the lack of a sex-and age matched control group. To date, it is unclear whether the presence of psychiatric symptoms may be due to specific sites of mutations in the epsilon-sarcoglycan gene. This could explain the different results in the studied M-D series up to date.

Because of the limited number of available psychopathological data in DYT11 sMC and especially DYT11 AMC and the lack of insight into the mechanism of escape from imprinting, it remains unclear whether psychopathology is cosegregating with the DYT11 gene.

The conflicting results regarding the type of psychopathology (OCD, depression, anxiety) and the low prevalence of DYT11 MC stresses the importance of formal and uniform psychiatric assessment in additional M-D families.

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