Metabolic changes in *DYT11* myoclonus-dystonia

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ABSTRACT

Objective: To identify brain regions with metabolic changes in *DYT11* myoclonus-dystonia (DYT11-MD) relative to control subjects and to compare metabolic abnormalities in DYT11-MD with those found in other forms of hereditary dystonia and in posthypoxic myoclonus.

Methods: [^{18}F]-fluorodeoxyglucose PET was performed in 6 subjects with DYT11-MD (age 30.5 ± 10.1 years) and in 6 nonmanifesting *DYT11* mutation carriers (NM-DYT11; age 59.1 ± 8.9 years) representing the parental generation of the affected individuals. These data were compared to scan data from age-matched healthy control subjects using voxel-based whole brain searches and group differences were considered significant at $p < 0.05$ (corrected, statistical parametric mapping). As a secondary analysis, overlapping abnormalities were identified by comparisons to hereditary dystonias (*DYT1*, *DYT6*, dopa-responsive dystonia) and to posthypoxic myoclonus.

Results: We found significant *DYT11* genotype-specific metabolic increases in the inferior pons and in the posterior thalamus as well as reductions in the ventromedial prefrontal cortex. Significant phenotype-related increases were present in the parasagittal cerebellum. This latter abnormality was shared with posthypoxic myoclonus, but not with other forms of dystonia. By contrast, all dystonia cohorts exhibited significant metabolic increases in the superior parietal lobule.

Conclusions: The findings are consistent with a subcortical myoclonus generator in DYT11-MD, likely involving the cerebellum. By contrast, subtle increases in the superior parietal cortex relate to the additional presence of dystonic symptoms. Although reduced penetrance in DYT11-MD has been attributed to the maternal imprinting epsilon-sarcoglycan mutations, NM-DYT11 carriers showed significant metabolic abnormalities that are not explained by this genetic model.
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GLOSSARY

BA = Brodmann area; **DG** = dystrophin-glycoprotein; **DRD** = dopa-responsive dystonia; **DYT11-MD** = *DYT11* myoclonus-dystonia; **FDG** = ^{18}F-fluorodeoxyglucose; **FWE** = family-wise error; **MD** = myoclonus-dystonia; **MNI** = Montreal Neurological Institute; **NM-DYT11** = nonmanifesting *DYT11* mutation carriers; **SSRI** = selective serotonin reuptake inhibitor.

Myoclonus-dystonia (MD) is a hyperkinetic movement disorder characterized by variable combinations of mild to moderate dystonia and predominant myoclonus, i.e., brief "lightning-like" jerks without other neurologic dysfunction.[1] The most frequent genetic variant of MD, *DYT11*, has been related to various loss of function mutations in the epsilon-sarcoglycan gene (*SGCE*) located on chromosome 7q21.[2,3]

Inheritance of *DYT11* is autosomal dominant with incomplete penetrance. Nearly all penetrant cases have been found to be paternally transmitted, consistent with maternal imprinting.[2] In this vein, molecular studies have shown maternal imprint of the *SGCE* gene in human blood cells,[4] murine embryogenic fibroblasts,[5] and neonatal as well as embryonic brain tissue.[6] However, in adult rodent brain tissue, the maternal imprint was found to be incomplete (figure 3 in reference 5). Despite the established link between *SGCE* mutations and DYT11-MD, the

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Supplemental Data

From the Center for Neurosciences (M.C., V.D., D.E.), The Feinstein Institute for Medical Research, Manhasset; Mirken Department of Neurology (D.R., R.S.-P., S.B.), Beth Israel Medical Center, New York; and Department of Neurology (L.O., S.F.), Mount Sinai School of Medicine, New York, NY.

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mechanisms by which the mutated protein produces the clinical manifestations of the disorder remain largely unknown.

To date, electrophysiologic and imaging studies in MD[1,e1–e7] have suggested a subcortical origin for myoclonus. In this study, we used [^{18}F]-fluorodeoxyglucose (FDG)-PET to assess genotypic and phenotypic metabolic changes in patients with DYT11-MD and in nonmanifesting carriers of this mutation (NM-DYT11). We hypothesized that significant subcortical abnormalities are present in DYT11-MD affecteds. However, because of maternal imprinting of the *SGCE* mutation, we hypothesized that corresponding changes are not evident in nonmanifesting carriers of this gene. We also performed several secondary analyses to determine which of the metabolic features of DYT11-MD are shared with the primary hereditary dystonias (*DYT1*, *DYT6*),[e8] dopa-responsive dystonia (DRD),[e9] and posthypoxic myoclonus.[e10]

METHODS **Subjects.** We studied 6 subjects with DYT11-MD (age 30.5 ± 10.1 years; 3 male/3 female) and 6 NM-DYT11 carriers (age 59.1 ± 8.9 years; 6 male/0 female) from 5 families. The *DYT11* families were recruited through the Mirken Department of Neurology at Beth Israel Medical Center in New York. Three of the DYT11-MD patients and 2 of the NM-DYT11 carriers were on chronic antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs). Informed consent was obtained from all participants under protocols approved by the institutional review boards of the participating institutions.

These families carried different mutations of the *SGCE* gene (table 1). Two of these families have been reported previously with a c.1151_1152delT mutation (family 2)[7] and a deletion of exons 2–5 (patient 1).[8] The third family had a previously reported c.304C>T mutation.[9] The remaining 2 families had novel mutations: c.1037+5G>C and c.198_199insGAGAATA. Review of the pedigrees confirmed that all affected subjects had inherited the mutation from their fathers. Of note, the NM-DYT11 carriers constituted the paternal generation of the DYT11-MD affecteds. Thus, an age difference was inherent across the 2 gene-positive groups ($p < 0.01$). Maternal inheritance of the *SGCE* mutation in the NM-DYT11 subjects was confirmed in 4 of the 6 gene carriers (2 had clinically affected mothers and 2 had nonmanifesting mothers in whom the mutation was molecularly confirmed). Scans from 24 healthy volunteer subjects were used as controls for group comparison. Scans from the 12 older members of this group (C_{old}: age 56.5 ± 12.5 years; 5 female/7 male) were compared to those from the NM-DYT11 carriers (age $p = 0.6$; gender $p = 0.12$). Likewise, scans from the 12 younger healthy volunteers (C_{young}: age 28.2 ± 4.8 years; 3 female/9 male) were compared to those from the DYT11-MD affecteds (age $p = 0.6$; gender $p = 0.3$). Because of the low frequency of *SGCE* mutations,[e11] inadvertent inclusion of *SGCE* mutation carriers among the control subjects was considered unlikely.

In secondary analyses, we determined the topographic overlap between the regional metabolic abnormalities observed in the DYT11-MD subjects and those previously described in patients with primary hereditary dystonia (*DYT1:* n = 18; age 40.3 ± 14.2 years; 7 female, 11 male; *DYT6:* n = 13; age 33.6 ± 15.0 years; 8 female, 5 male; see references 10 and e8), with dopa-responsive dystonia (DRD; n = 9; age 49.8 ± 15.0 years; 8 female, 1 male; see reference e9), and posthypoxic myoclonus (n = 7; age 47.7 ± 10.1 years; 3 female, 4 male; see table 1 in reference e10). FDG-PET data from these comparison groups have been published previously.[10,e8–e10]

Clinical characteristics of the manifesting subjects are presented in table 1. Exclusion criteria for all subjects were 1) past history of neurologic illnesses other than the movement disorder leading to study inclusion (i.e., MD, dystonia, or posthypoxic dystonia); 2) prior or current exposure to neuroleptic agents or drug use; 3) past medical history of severe hypertension, cardiovascular disease, or diabetes mellitus; and 4) abnormal MRI. For controls and nonmanifesting subjects, the following additional exclusion criteria were applied: current use of psychotropic medication, abnormal neurologic examination, and past history of dystonic symptoms.

PET. All subjects fasted overnight before PET imaging. Medications (see table 1) were withheld in the affected subjects for at least 12 hours before scanning. FDG-PET studies were performed in 3-dimensional mode using the GE Advance tomograph (General Electric; Milwaukee, WI) at North Shore University Hospital, Manhasset, New York. Subjects were scanned during the resting state in a relaxed and comfortable position. The details of the scanning procedure have been presented elsewhere.[11]

Image analysis. Image data processing and preprocessing were applied using Statistical Parametric Mapping 5 software (SPM5; Institute of Neurology, London, UK; ucl.ac.uk/spm/

Table 1 Clinical characteristics of *DYT11* myoclonus-dystonia subjects

		Age at onset, y		Affected sites			
Subject	Age, y	Dystonia	Myoclonus	Dystonia	Myoclonus	Mutation DNA	Centrally active medication
1	26	4	4	Arms, neck, larynx	Arms, neck, trunk, legs	c.304C>T	SSRI, clonazepam, levetriacetam
2	19.5	2.5	3	Currently none	Arms, neck, trunk, legs, lower face	c.1037+5G>C	None
3	44.5	—	12	Currently none	L arm	c.198_199insGAGAATA	None
4	41.5	26	10	Arms, neck, legs	Arms, trunk	c.198_199insGAGAATA	SSRI
5	26.6	8	10	Arms	L arm, trunk	c.1151_1152delT	None
6	24.6	6	4	Arms, R leg	L arm	c.1151_1152delT	SSRI

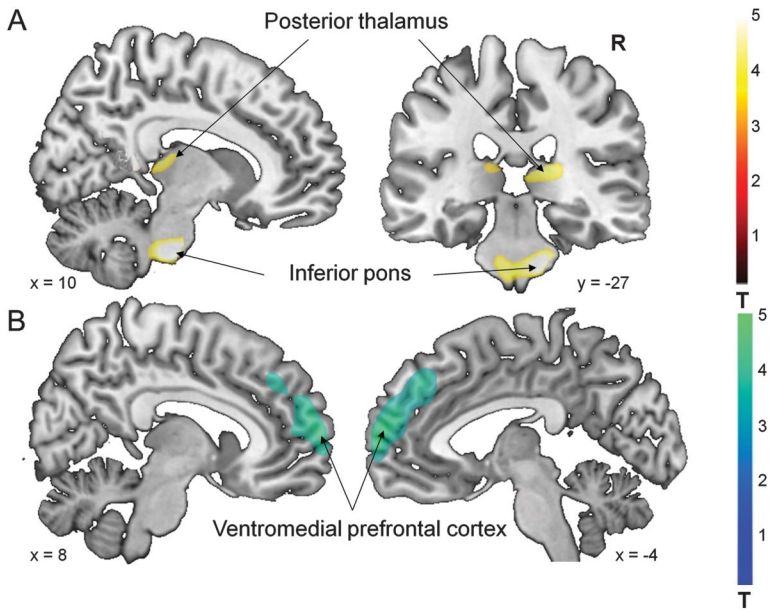
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

software/spm5/) following established standards (realignment, spatial normalizing, smoothing with 10 _ 10 _ 10 mm).

Voxel-wise comparisons were performed using the full factorial model implemented in SPM5. To control for potential confounds resulting from the variability in age and gender, these factors were entered as covariates of no interest. To reduce intersubject variability, regional metabolic measurements were normalized by global hemispheric values. SPM{t} maps were generated to assess the effects of *DYT11* mutation status (conjunction analysis of DYT11-MD vs C_{young} and NM-DYT11 vs C_{old}), as well as the effects of penetrance in carriers of this genotype (DYT11-MD vs NM-DYT11). These comparisons were conducted using the full factorial model with the *DYT11* carriers and the control scans. In the secondary analyses, the model was expanded to include data from groups of patients with *DYT1* or *DYT6* dystonia, DRD, or posthypoxic myoclonus. In this model, shared metabolic abnormalities were identified using conjunction analysis of the respective group contrasts with control images.

For all voxel-based analyses, results were considered significant at $p < 0.05$ corrected for multiple comparisons at the cluster level, for contiguous clusters of $[k_e] > 50$ voxels. The results of the conjunction analyses were considered significant at $p < 0.05$, family-wise error rate (FWE)–corrected without spatial constraint.[12] Given the rarity of the *DYT11* mutation and the small number of mutation carriers available for study, we also reported the results of group contrasts thresholded at $p < 0.001$, voxel-level uncorrected. While considered exploratory, the resulting clusters were constrained by a spatial extent threshold of $[k_e] > 80$ voxels to reduce Type I error. Post hoc analyses on adjusted rCMRGlu values from significant prefrontal and cerebellar clusters were used to test for the effect of SSRIs on group differences. Coordinates were reported in the standard anatomical space developed at the Montreal Neurological Institute (MNI).

Figure 1 **Metabolic abnormalities in *DYT11* mutation carriers regardless of symptoms**



Statistical parametric maps (SPM) comparing [^{18}F]-fluorodeoxyglucose PET scans from *DYT11* mutation carriers to control subjects (table 2). (A) Increased regional metabolism was found in the inferior pons and posterior thalamus (table 2Aiii). (B) Decreased regional metabolism was found in the ventromedial prefrontal cortex (table 2Biii). (SPM{t} maps were superimposed on a single-subject MRI T1 template. Coordinates indicate the position of the slice in Montreal Neurological Institute standard space. The color scales represent *t* scores thresholded at $t = 3.5$, SPM corrected $p < 0.05$.)

Standard protocol approvals, registrations, and patient consents. This study was approved by the institutional review boards of the participating institutions. Written consent was obtained from each subject following detailed explanation of the procedures.

RESULTS

Metabolic abnormalities related to the *DYT11* genotype. We found genotype-related metabolic increases in the ventral inferior pons and in the right posterior thalamus (table 2Aiii, figure 1A). These changes were present in both DYT11-MD patients (table 2Ai) and NM-DYT11 carriers (table 2Aii) when separately compared to age-matched control subjects. Genotype-related metabolic reductions were present bilaterally in the ventromedial prefrontal cortex (table 2B, figure 1B). No effect of SSRIs was evident in this area: the metabolic reduction remained significant even after excluding the 5 *DYT11* subjects on SSRIs (*DYT11:* rCMRGlu (adjusted): 15.8 ± 0.28 mg/dL; Controls: rCMRGlu (adjusted): 17.1 ± 0.17; $p > 0.001$).

Metabolic abnormalities related to phenotype. Group comparison of DYT11-MD compared to NM-DYT11 and healthy control subjects revealed metabolic increases in the left parasagittal cerebellum (lobule V) (table 3, figure 2A). No significant effect of SSRIs was present in this region. In a model that included age and SSRI treatment as covariates, we found an effect of group (DYT11-MD vs NM-DYT11 $p = 0.0004$), but no contribution from SSRI ($p = 0.12$).

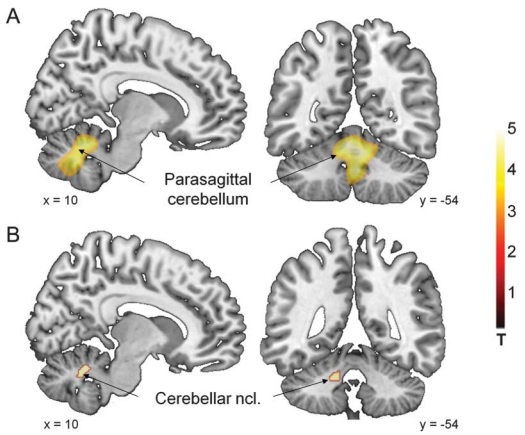
No metabolic reductions were present in this comparison.

Shared abnormalities: Myoclonus-dystonia and other forms of dystonia. Dystonia patients of all subtypes exhibited abnormal metabolic increases in the superior parietal lobule (Brodmann area [BA] 7/40; MNI coordinates −30, −70, 44; Z_{max} 3.05; SPM $p = 0.001$ uncorrected for 80 contiguous voxels). Abnormally reduced metabolic activity was evident in the ventromedial prefrontal cortex of both DYT11-MD and *DYT1* dystonia patients (BA 10; MNI coordinates 6, 62, 2; Z_{max} 4.76; SPM $p = 0.05$, FWE-corrected). Conjunction analysis of metabolic abnormalities in DYT11-MD and posthypoxic myoclonus disclosed the presence of shared increases in the parasagittal cerebellar nuclei bilaterally (figure 2B; right: MNI coordinates 6, −54, −24; Z_{max} 5.18; left: MNI coordinates −14, −44, −32; Z_{max} 4.98; SPM $p = 0.05$, FWE-corrected). Both groups, similar to the overlap with *DYT1* dystonia (see above), also exhibited shared metabolic reductions in the ventromedial prefrontal cortex bilaterally (BA 10; right: MNI coordinates 6, 62, 2; Z_{max} 4.76; left: MNI coordinates −2, −58, 12; Z_{max} 4.70; SPM $p = 0.05$, FWE-corrected).

DISCUSSION

This study showed that *SGCE* mutations are associated with abnormal metabolic increases

Figure 2 **Metabolic abnormalities in symptomatic *DYT11* mutation carriers**



(A) Metabolic increases in *DYT11* myoclonus-dystonia (MD) relative to nonmanifesting *DYT11* mutation carriers and to age-matched controls were present in the parasagittal cerebellum bilaterally (see table 3). (B) Metabolic increases of parasagittal cerebellar nuclei were a shared characteristic of DYT11-MD and posthypoxic myoclonus. (Statistical parametric maps [SPM{t}] were superimposed as in figure 1 [with identical slice positions of figure 2, A and B]. The color scales represent *t* scores thresholded at $t = 3.0$, SPM corrected $p < 0.001$.)

in the pontine nuclei and in the posterior thalamus, in conjunction with metabolic decreases in the ventromedial prefrontal cortex. Importantly, these changes were present irrespective of clinical penetrance. That said, additional changes were present in the parasagittal cerebellum, where DYT11-MD affecteds exhibited higher metabolic activity than their nonmanifesting counterparts as well as healthy control subjects.

These findings are difficult to reconcile with the notion of maternal imprinting of the *SGCE* gene in that the pontocerebellar and ventromedial prefrontal metabolic changes seen in the affecteds were also present in nonmanifesting parental gene carriers. Indeed, abnormal motor activation responses have recently been reported in NM-DYT11 carriers, consistent with the presence of an underlying functional change in these subjects. It is likely, however, that maternal imprinting is not a binary, all-or-nothing regulator of gene penetrance. The molecular evidence for maternal imprinting stems from data from human blood cells and rodent neurons[4–6]; evidence demonstrating methylation of the promotor region of *SGCE* in human neurons is currently lacking. In fact, imprinting varies by species, tissue, and developmental stage.[13–16] Of note, imprinted genes have been shown to play an important role during embryogenesis. This notion has been expanded to include their important functional role in neurodevelopment.[15] While imprinted genes are labeled in all tissues and during all stages of development, their expression is not invariably maintained, and can change considerably during development, differentiation, and disease.[13,17] In particular, it has been noted that imprinted expression can be lost during cellular differentiation in a tissue-specific manner. This applies particularly to *SGCE*, for which weak maternal expression, in addition to the paternal expression, has been shown in adult rodent neuronal cells,[5] even though the maternal imprint was maintained in neonatal[6] and embryonic brain tissue.[5] Thus, it is possible that a biallelic expression of *SGCE* is needed during certain periods of neurodevelopment, during which a loss-of-function mutation in the maternal allele (as is posited for DYT11-MD) gives rise to the consistent regional metabolic changes that were observed.

The metabolic increases found in our cohort of DYT11-MD are highly concordant with earlier imaging studies in single cases of DYT11-MD.[e5,e6] These reports described abnormalities in parasagittal cerebellar and posterior thalamic activation responses[18,e5] and in resting-state glucose metabolism.[e6] While *SGCE* expression has been demonstrated in both of these brain regions, particularly high expression has been described in cerebellar Purkinje cells.[19] *SGCE* was identified as a homolog of α-sarcoglycan, but unlike this muscle-specific protein, *SGCE* is highly expressed in the brain, as well as in other tissues.[20] In general, sarcoglycans form one element of a large multiprotein complex, the transmembrane dystrophin-glycoprotein (DG) complex.[21] The participation of *SGCE* in the formation of DG-like complexes in central nervous tissue, however, remains hypothetical. There is evidence for a function of DG-like complexes at central neuronal synapses, in particular at GABAergic synapses of the cerebellum. Moreover, the DG-like complex has been associated with neurodevelopment.[21] *SGCE* has been found in neuronal cells of rodents in the cerebral cortex, striatum, thalamus, pons, midbrain, and cerebellum,[2,19,22,23] with particularly high expression in monoaminergic midbrain neurons and in cerebellar Purkinje cells.[19] A recent study of the human brain showed highest expression of a brain-specific isoform of *SGCE* in Purkinje cells and neurons in the dentate nucleus with moderate to low expression in the caudate, putamen, and substantia nigra.[24]

These neurochemical findings accord with our observation relating the myoclonic component of MD to increased metabolic activity in the parasagittal cerebellum, which was evident in comparisons of DYT11-MD patients with either unaffected NM-DYT1 carriers or healthy control subjects.

We note that hypermetabolism of the fastigial nuclei was a shared feature of DYT11-MD and posthypoxic myoclonus. While the cerebellum is implicated in primary dystonia,[25,e8] this structure has also been associated with various myoclonus syndromes.[26,e12] Hypermetabolism of the parasagittal cerebellum distinguished manifesting from nonmanifesting *DYT11* carriers, and was also found to link the metabolic landscape of

Table 2 Genotype-related metabolic changes in *DYT11* mutation carriers[a]

Brain region	MNI coordinates x	y	z	Z_{max}
A) Metabolic increases in *DYT11* mutation carriers				
i. C_{young} < DYT11-MD				
R pontine nuclei; inferior pons[b]	14	−26	−38	3.71
Bilateral parasagittal cerebellar cortex (lobule V)[b]	0	−56	−16	3.27
L superior occipital cortex (BA 19)[b]	36	−19	30	4.11
R inferior parietal lobule, postcentral gyrus (BA 1, 2, 3, 40)[b]	64	−30	44	4.13
ii. C_{old} < NM-DYT11				
R pontine nuclei; inferior pons[b]	10	−20	−38	4.43
R posterior thalamus, lateral posterior nuclei, anterior pulvinar[b]	15	−28	9	4.84
iii. C_{old} < NM-DYT11 ∩ C_{young} < DYT11-MD				
R pontine nuclei; inferior pons[c]	14	−26	−38	5.54
R posterior thalamus, lateral posterior nuclei, anterior pulvinar[c]	24	−34	8	4.84
B) Metabolic decreases in DYT11-MD				
i. C_{young} > DYT11-MD				
Bilateral ventromedial prefrontal cortex (BA 10)[b]	0	66	10	4.12
ii. C_{old} > NM-DYT11				
L ventromedial prefrontal cortex (BA 10)[b]	−18	54	20	4.10
L medial prefrontal cortex (BA 9, 10)[d]	−4	38	40	4.02
R ventral prefrontal cortex (BA 11)[b]	26	48	−20	3.78
L premotor cortex (BA 6)[b]	−22	6	56	3.72
L precentral and postcentral gyrus (BA 3, 4)[b]	−14	−38	72	4.04
iii. C_{old} > NM-DYT11 ∩ C_{young} > DYT11-MD				
L ventromedial prefrontal cortex (BA 10)[c]	−4	64	14	5.21
L ventromedial prefrontal cortex (BA 10)[c]	−18	56	16	4.90
R inferior frontal gyrus (BA 45)[c]	58	38	4	5.62

Abbreviations: BA = Brodmann area; MD = myoclonus-dystonia; MNI = Montreal Neurological Institute; SPM = statistical parametric mapping.
[a] Ai: DYT11-MD vs age-matched controls (C_{young}); Aii: nonmanifesting *DYT11* carriers (NM-DYT11) vs age-matched controls (C_{old}); Aiii: shared metabolic increases in all *DYT11* mutation carriers relative to controls. Bi: DYT11-MD vs C_{young}; Bii: NM-DYT11 vs C_{old}; Biii: Shared metabolic decreases in all *DYT11* mutation carriers relative to controls.
[b] SPM $p < 0.001$, uncorrected for 80 contiguous voxels.
[c] SPM $p < 0.05$, family-wise error–corrected.
[d] SPM $p < 0.05$, corrected for multiple comparisons.

posthypoxic myoclonus with that of MD. It is therefore likely that the parasagittal cerebellar changes point to a role of the cerebellum in DYT11-MD, as suggested in a recent neurophysiologic study.[27] Several case reports have also linked pathology in the parasagittal cerebellum,[e12,e13] the dentate nucleus,[e14] or Purkinje cells[e15,e16] to myoclonus and phenomenologic similarities have been noted between MD and spinocerebellar ataxia type 14.[e17] Indeed, experimental animal models of posthypoxic myoclonus have been shown to exhibit Purkinje cell loss.[e18]

The localization of the genotype-specific changes in pons and thalamus is consistent with the expression of *SGCE* in these areas.[22] While the *DYT11* carriers included in this study did not share a common genotype, each of the mutations interferes with *SGCE* synthesis by the insertion of stop codons that result in a truncated protein coding sequence. We note that metabolic changes in the inferior pons have been found in essential blepharospasm[28] and may point to a shared mechanism for the alteration in brainstem reflexes that has been found in both MD and this disorder.[29,30] Indeed, a study of DYT11-MD found increased responsivity of the blink reflex.[e3] Thalamic lesions have been associated with secondary MD,[31] and thalamic deep brain stimulation is used to treat MD.[32,33] However, lesions and interventions target mainly the ventral tier thalamic nuclei, whereas the current study localized the metabolic changes in this region to the posterior thalamus, particularly the lateralis posterior and anterior pulvinar nuclei. Although these regions are not considered part of the motor thalamus, a recent retrograde tracer study in the monkey suggested a role for the posterior thalamus in mediating complex motor behavior.[34] Complex motor acts, in particular species-typical motor behaviors (such as reaching, grasping, or defensive acts), can be elicited from distinct functional zones of the posterior parietal cortex in primates.[35,36] Interestingly, Gharbawie et al.[34] showed functionally organized projections from the posterior thalamus to these functional zones. Alternatively, it is also possible that the posterior thalamic changes in our study reflect altered metabolism of the reticular thalamic nucleus. Combined lesions of brainstem and reticular thalamic nucleus were present in an animal model of posthypoxic myoclonus, suggesting these regions as possible myoclonus generators.[37] Due to its shell-like form, a clear separation of the reticular nucleus from adjacent posterior thalamic nuclei is not possible.

The current study confirms our earlier finding of parietal hypermetabolism in manifesting dystonia patients, irrespective of etiology.[10] By contrast, medial prefrontal hypometabolism in DYT11-MD had more restricted overlap with the other disorders in that this feature was present only in manifesting *DYT1* and in posthypoxic myoclonus. Functional changes in this region have been implicated consistently in mood disorders,[38] to which *DYT1* and *DYT11* mutation carriers may be particularly susceptible.[39] The psychiatric comorbidity of posthypoxic myoclonus has not been formally reported. Nonetheless, increased rates of anxiety and depression have been reported in survivors of resuscitation, which include individuals with posthypoxic myoclonus.[40]

Our study has several limitations. Due to the rarity of DYT11-MD and the invasive nature and high costs of the PET procedures, we were able to only include a small number of subjects. Indeed these subjects were derived from only 5 families and the results

Table 3 Phenotype-related metabolic increases in *DYT11* myoclonus-dystonia[a]

Brain region	MNI coordinates x	y	z	Z_{max}
A) NM-DYT11 < DYT11-MD				
L parasagittal cerebellum (lobule V)[b]	−8	−54	−16	3.21
B) [C_{young} + NM-DYT11] < DYT11-MD				
Bilateral parasagittal cerebellum[c]	2	−58	−34	3.97

Abbreviations: MD = myoclonus-dystonia; MNI = Montreal Neurological Institute; SPM = statistical parametric mapping.
[a] A) Metabolic increases in DYT11-MD patients relative to nonmanifesting *DYT11* mutation carriers (NM-DYT11; see figure 2A). B) Metabolic increases in DYT11-MD patients relative to age-matched controls (C_{young}) and NM-DYT11 (see figure 2B).
[b] SPM $p < 0.001$, uncorrected for 80 contiguous voxels.
[c] SPM corrected for multiple comparisons $p = 0.001$.

therefore may not be generalizable to other *DYT11* mutations. Moreover, the control subjects should ideally have been recruited as noncarrier relatives of the manifesting *DYT11* mutation carriers. It is also noteworthy that the MD phenotype was not identical in all subjects. Even though all 6 manifesting carriers had myoclonus at the time of PET, only 4 additionally exhibited dystonia. This may have contributed to the lack of significant overlap of MD with other dystonias. Furthermore, for ethical reasons we refrained from full medication washout from medications with a longer half-life than 12 hours in all cohorts used in this and earlier studies (which were used for comparative reasons here). Systematic effects of medications have been excluded through post hoc analyses in each of the studies.

Our data support the idea of a role of the cerebellum in conjunction with thalamus and pons in DYT11-MD, particularly for myoclonic symptoms. Given the presence of significant metabolic changes in NM-DYT11 carriers localized to brain regions with high *SGCE* expression during adulthood, it is likely that maternal imprinting during adulthood is not the sole regulator of penetrance in this disorder.

AUTHOR CONTRIBUTIONS

S.B. and D.E. directed the study. S.B. received funding for the study. M.C., D.R., L.O., S.B., and D.E. participated in the study design. D.R., R.S.-P., and S.F. participated in subject recruitment. L.O. contributed to sample collection, preparation, and genotyping. V.D. collected imaging data. R.S.-P., S.F., and S.B. performed subject assessments. M.C. performed analysis of imaging data. M.C. wrote the manuscript, which was reviewed and approved by all authors.

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DISCLOSURE

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