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Beukers, R.J.

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Chapter 3

fMRI motor task data point towards incomplete maternal imprinting in Myoclonus-Dystonia

Richard J. Beukers¹, Elisabeth M.J. Foncke¹, Johan N. van der Meer², Dick J. Veltman³, Marina A.J. Tijssen¹

¹Academic Medical Centre, University of Amsterdam, department of Neurology,

²Academic Medical Centre, University of Amsterdam, department of Clinical Neurophysiology.

³Academic Medical Centre, University of Amsterdam, department of Psychiatry.

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Abstract

Background: Myoclonus-Dystonia (M-D) is an autosomal dominantly inherited movement disorder, clinically characterized by myoclonic jerks and dystonic postures or movements. A previous fMRI study showed altered cortical activation patterns in clinically affected *SGCE* mutation carriers when compared to control subjects consistent with defective sensorimotor integration. Genetically, the disorder is characterized by the maternal imprinting mechanism, i.e. patients inheriting the mutation from their fathers will develop symptoms. However, several clinically manifest M-D cases inheriting the mutation from their mother have been described.

Objective: Cerebral activation patterns of paternally inherited *SGCE* mutation carriers are compared with maternally inherited mutation carriers and a control group.

Design, Setting and Patients: Eight paternally inherited *SGCE* mutation carriers, eight asymptomatic or slightly affected (four out of eight) symptomatic maternally inherited mutation carriers and 11 control subjects were studied in a 3Tesla fMRI scanner using a finger tapping task.

Results: When paternal and maternal gene mutation carriers were compared, hyperresponsiveness was seen in the contralateral secondary somatosensory cortex. When maternal mutation carriers and control subjects were compared, hyperresponsiveness of the ipsilateral cerebellum and supplementary motor area were found. Using a non-parametric analysis to study only the 4 clinically asymptomatic patients, no significant differences were found between groups. Contrast estimates were plotted for the known affected sensorimotor brain areas, showing intermediate activation in maternally inherited mutation carriers, even when this was performed for only the four clinically unaffected mutation carriers.

Conclusions: These results suggest biased gene expression based on parent of origin rather than a strictly dichotomous maternal imprinting mechanism, consistent with clinical observations.

Background

Myoclonus-Dystonia is an autosomal dominantly inherited movement disorder characterized by myoclonic jerks, dystonic posturing of mainly the limbs and psychiatric co-morbidity, i.e. depression, anxiety and/or obsessive compulsive disorder.¹ It is frequently caused by a mutation in the DYT-11 gene encoding epsilon-sarcoglycan (*SGCE*), a membrane protein which function is yet to be elucidated.¹ An interesting feature of the inheritance pattern in this disorder is maternal imprinting, i.e. only patients inheriting the mutated allele from their father develop clinical symptoms, although a few patients with symptoms inheriting the disease from their mother have been described.^{2,3} In a mouse model, the maternal *SGCE* allele is weakly expressed only in the brain but not in other tissues.⁴ This is consistent with a case report of a French patient with the full clinical picture of M-D while inheriting the mutation from her mother and only expressing the paternal allele in peripheral leucocytes.²

An fMRI study by our group showed hyperresponsiveness of the right cerebellum, right premotor cortex and left secondary somatosensory cortex and hyporesponsiveness in the left insula in clinically affected DYT-11 carriers during a finger tapping task⁵, supporting the hypothesis of defective sensorimotor integration in dystonia.⁶ Functional changes in neuroimaging studies in other types of inherited forms of dystonia, i.e. DYT-1, have been reported in both clinically affected and non-affected gene mutation carriers.⁷⁻⁹ The mode of inheritance in these other monogenetic forms of dystonia is autosomally dominant with reduced penetrance, but without the maternal imprinting phenomenon.

In the present fMRI study, we compared eight clinically affected DYT-11 mutation carriers from our previous study who inherited the mutation from their fathers to eight DYT-11 mutation carriers, inheriting the gene from their mothers. Of these eight mutation carriers, none reported symptoms of myoclonus or dystonia. On careful neurological examination however, four of them showed very slight signs of dystonia, inconsistent with a strict mono-allelic expression mechanism of the disease, but rather suggesting incomplete maternal imprinting or a biased gene expression based on a parent of origin effect, also known as preferential expression mechanism. Separate analyses were run without these slightly affected patients, using only data from the four clinically non-affected mutation carriers. Eleven healthy control subjects were also scanned. We focussed on the regions of interest

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detected in our previous study in clinically affected DYT-11 carriers.

We hypothesized that the maternal imprinting mechanism is not complete and that we would detect mild abnormalities in responsiveness in the subjects inheriting the mutation from their mothers comparable to the mild clinical phenotype.

Methods

Eight paternally inherited DYT-11 mutation carriers (median age 50, range 22-64, 6 males), eight maternally inherited DYT-11 mutation carriers (median age 52, range 35-65, 3 males), and 11 healthy control subjects (median age 45, range 23-71, 6 males) underwent an fMRI scanning session in which a finger tapping task was performed, using the methodology described previously.⁵ Data were analyzed in SPM2 (Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>). For the analyses regarding only the 4 clinically non-affected mutation carriers, fMRI data were analyzed using a non-parametric approach (SnPM version 3b, Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>) in MatLab 2006b (The MathWorks, Natick, MA, USA). In addition, although the number of clinically non-affected subjects was too small to perform reliable parametric analyses, we explored the BOLD response of this group of patients compared to controls and symptomatic M-D patients in regions of interest identified in our previous study, i.e. right cerebellum, right premotor cortex and contralateral secondary somatosensory cortex and left insula (see **Figure**). All DYT-11 mutation carriers were clinically scored using the Burke-Fahn-Marsden dystonia rating scale (BFMDRS)¹⁰ and the Unified Myoclonus rating scale (UMRS).¹¹ Clinical characteristics are summarized in **Table 1**. Informed consent was obtained in all subjects and the study was approved by the local medical ethics committee.

Results

When subjects with the paternally inherited mutations (PIM) were compared to subjects with maternally inherited mutations (MIM), hyperresponsiveness was seen in the contralateral secondary somatosensory cortex. When MIM subjects were compared to control subjects, hyperresponsiveness was found in the supplementary motor area and ipsilateral cerebellum (**Table 2**).

Table 1 Subject characteristics of DYT-11 mutation carriers

Subject	Age (yrs)	Gender	BFMDRS/ UMRS	Psychiatric Symptoms	Medication	Type of inheritance
1	22	F	2 / 28	Depr	Paroxetin	Fa
2	64	M	3 / 8	-	-	Fa
3	52	M	0 / 4	Anx	-	Fa
4	40	F	22 / 80	Depr, Anx	Citalopram	Fa
5	55	M	2 / 4	Anx	-	Fa
6	48	M	14 / 12	Depr, Anx, OCD	Clomipramin	Fa
7	55	M	10 / 43	OCD	-	Fa
8	34	M	2 / 42	-	-	Fa
9	60	F	6 / 0	-	-	Mo
10	53	F	8 / 0	Anx	Venlafaxin	Mo
11	65	M	6 / 0	-	-	Mo
12	50	F	6 / 0	Depr, Anx	Clomipramin	Mo
13	35	M	0 / 0	-	-	Mo
14	48	F	0 / 0	-	-	Mo
15	62	F	0 / 0	-	-	Mo
16	51	M	0 / 0	-	-	Mo

Table legend: M: male, F: female, UMRS: Unified Myoclonus Rating Scale, BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale, Fa: Father, Mo: mother, Depr: depression, Anx: anxiety disorder, OCD: obsessive compulsive disorder.

Table 2: Motor task: MNI coordinates and Z values for areas with significant differences in activation

Groups compared	Activated brain areas	Brodmann area	MNI	Z score
paternal>maternal	Secondary somatosensory cortex	40	-36 -57 48	3.83
maternal>control	Ipsilateral cerebellum	-	36 -51 -48	3.33
	Supplementary motor area	6	24 -3 63	3.39
control>maternal	-	-	-	-
maternal>paternal	-	-	-	-

Table legend: MNI: Montreal Neurological Institute

Non-parametric analysis between clinically non-affected MIM (n=4) and control subjects and subsequently between clinically non-affected MIM and PIM subjects revealed no significant differences.

Contrast-estimates were plotted in SPM2 for the right cerebellum, right premotor cortex, left secondary somatosensory cortex and left insula (**Figure**). BOLD responses of the maternally inherited DYT-11 mutation carriers fell between the paternally mutation carriers and control subjects in all four areas (see middle panels of **Figure**). When contrast estimates were plotted for the same areas omitting the 4 maternally inherited mutation carriers showing slight dystonia, similar results were obtained (see right panels of **Figure**). The paternally inherited mutation carriers and control subjects are the same in both middle and right panels.

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Figure: Contrast estimates for the affected brain areas

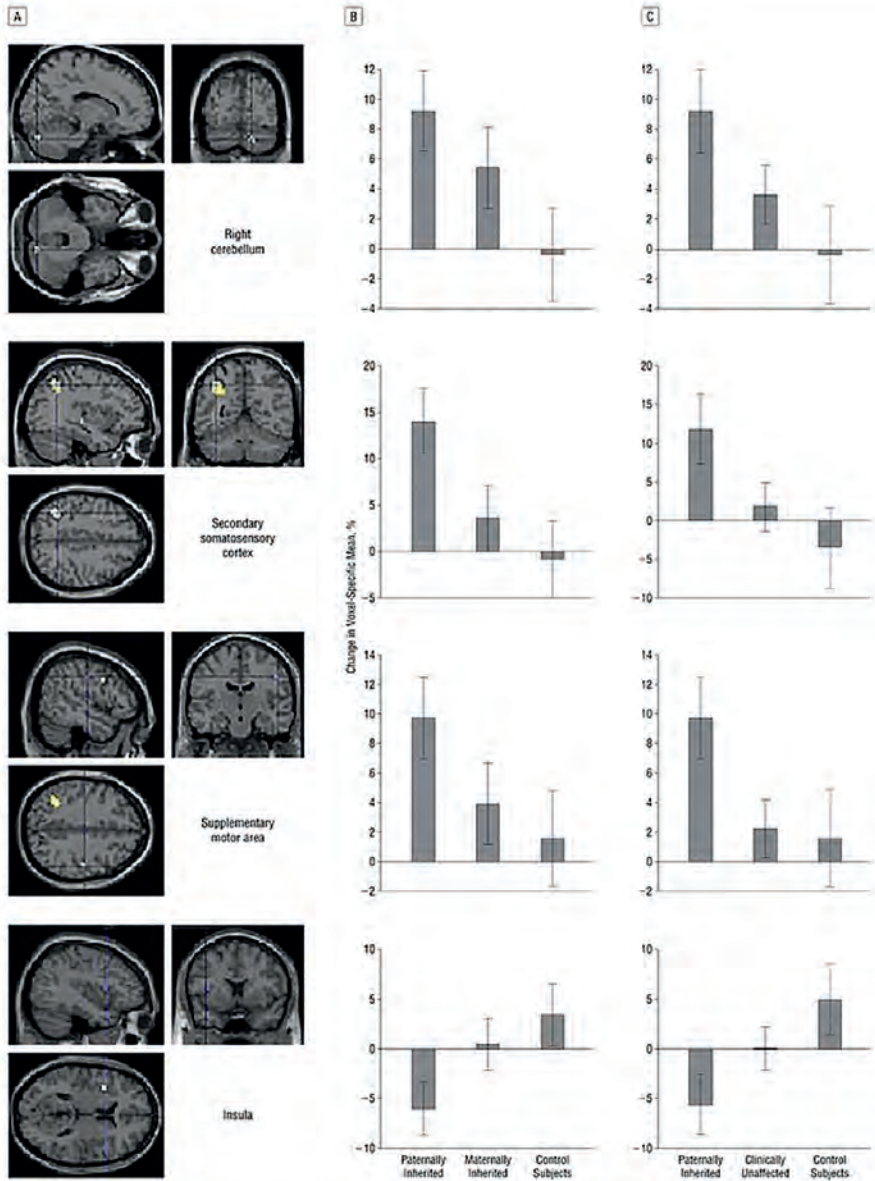


Figure Legend: Contrast estimates for the known affected brain regions (left panel): ipsilateral cerebellum, contralateral secondary somatosensory cortex, ipsilateral supplementary motor area, contralateral insula. Middle panel: contrast estimates for paternally inherited mutation carriers, all maternally inherited mutation carriers and control subjects. Right panel: Contrast estimates for paternally inherited mutation carriers, clinically asymptomatic maternally inherited mutation carriers and control subjects. The paternally inherited mutation carriers and control subjects are the same in both the middle and the right panel.

Comment

In our previous study involving the clinically affected DYT-11 carriers, clear differences in activation patterns were found between patients and control subjects. In the current study, we found that the maternally inherited mutation carriers showed activation patterns which were intermediate between paternally inherited mutation carriers and control subjects. When only clinically non-affected maternally inherited mutation carriers were compared to the same paternally inherited mutation carriers and control subjects the results were similar in all four regions of interest. Although these differences failed to reach statistical significance in the non-parametric analyses regarding only the clinically asymptomatic mutation carriers, probably due to the limited number of patients, our results nevertheless suggest mild functional brain abnormalities in clinically asymptomatic maternally inherited DYT-11 mutation carriers. These results therefore, suggest biased gene expression based on parent of origin, rather than a strictly dichotomous maternal imprinting mechanism. This conclusion is compatible with clinical observations, as several patients have been described with a mild M-D phenotype, while inheriting the gene from their mother.² We also detected these mild phenotypes in our M-D pedigrees.³ In one study of a clinically affected woman inheriting the mutation from her mother, only wild type paternal allele was detectable in cDNA in peripheral leucocytes.² A possible explanation for this result as well as ours would be the existence of brain-specific isoforms of *SGCE*, not detectable by standard amplification in peripheral leucocytes. This would be consistent with the previously described mouse model, weakly expressing the maternal *SGCE* allele in the brain.⁴

We realize that the major drawback of this study is the small number of patients studied, but as all the regions of interest showed a similar pattern, we consider our results reliable. However, larger groups of non-manifesting carriers inheriting the gene from their mother should be studied before definite conclusions can be drawn.

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