Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Congenital Mirror Movements in a New Italian Family

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Abstract: Mirror movements (MMs) occur on the contralateral side of a limb being used intentionally. Because few families with congenital MMs and no other neurological signs have been reported, the underlying mechanisms of MMs are still not entirely clear. We report on the clinical, genetic, neurophysiological and neuroimaging findings of 10 of 26 living members of a novel four-generation family with congenital MMs. *DCC* and *RAD51* were sequenced in affected members of the family. Five of the ten subjects with MMs underwent neurophysiological and neuroimaging evaluations. The neurophysiological evaluation consisted of electromyographic (EMG) mirror recordings, investigations of corticospinal excitability, and analysis of interhemispheric inhibition using transcranial magnetic stimulation techniques. The neuroimaging evaluation included functional MRI during finger movements. Eight (all females) of the ten members examined presented MMs of varying degrees at the clinical assessment. Transmission of MMs appears to have occurred according to an autosomal-dominant fashion with variable expression. No mutation in *DCC* or *RAD51* was identified. EMG mirror activity was higher in MM subjects than in healthy controls. Short-latency interhemispheric inhibition was reduced in MM subjects. Ipsilateral motor-evoked potentials were detectable in the most severe case. The neuroimaging evaluation did not disclose any significant abnormalities in MM subjects. The variability of the clinical features of this family, and the lack of known genetic abnormalities, suggests that MMs are heterogeneous disorders. The pathophysiological mechanisms of MMs include abnormalities of transcallosal inhibition and corticospinal decussation.

Mirror movements (MMs) are involuntary movements on one side of the body that accompany and mirror intentional movements on the opposite side, mainly involving the distal upper limbs.[1] MMs are present in patients with a variety of movement disorders, such as dystonia,[2] Parkinson's disease,[3] and essential tremor,[4] as well as in congenital nervous system disorders, including Klippel-Feil,[5] Kallmann syndrome,[6] and congenital hemiplegia.[7]

MMs may also be present in healthy subjects and, on rare occasions, even in several members of the same family with no other neurological signs ("congenital MMs").[8–11] Mutations in the *DCC* gene were found to be the cause of congenital MMs in three unrelated families.[12,13] The likelihood of genetic heterogeneity is supported by the observation that no mutations in the *DCC* gene were found either in sporadic cases with congenital MMs[11] or in a French and German family.[13] More recently, one of these families and another family from Germany were found to carry heterozygous mutations introducing premature termination codons in the *RAD51* gene.[14,15] *RAD51* has been suggested to be involved in the decussation process of the corticospinal pathways[14] as well as in the development of normal interhemispheric inhibition and bilateral cortical activation of primary motor areas during intended unimanual movements.[15]

Neurophysiological studies in subjects with congenital MMs point to a failure in corticospinal crossing and the development

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of abnormal ipsilateral branching of the corticospinal pathways.[1] An impairment in interhemispheric inhibitory connections or a functional alteration in motor planning and execution have also been proposed as additional mechanisms involved in MMs.[15–17]

A neuroimaging evaluation, based on voxel-based morphometry, diffusion tensor imaging, or functional MRI (fMRI) in patients with MMs with different etiologies disclosed various types of abnormalities, including changes in the volume of the corpus callosum (CC), reduced fractional anisotropy of transcallosal motor fibers, and bilateral M1 activation.[17]

In order to provide a better understanding of the complex phenomenology and pathophysiology of congenital MMs, we investigated the clinical features, possible genetic abnormalities, and functional and structural properties of corticospinal and interhemispheric pathways in members belonging to a novel four-generation family with congenital MMs not associated with other neurological abnormalities.

Patients and Methods

Participants

Ten of twenty-six living members of a four-generation family presenting congenital MMs were clinically evaluated and videotaped (Fig. 1; Table 1). Sequencing of *DCC* and *RAD51* was performed in 3 MM subjects, including the index case. Five of the ten subjects evaluated clinically were included in a neurophysiological and neuroimaging assessment and were studied in a single experimental session. Ten age- and gender-matched subjects without a history of medical or neurological disorders served as healthy controls (HCs). All subjects gave their informed consent to the videotape recording and to all the experimental procedures, which were approved by the local ethics committee and conducted in accord with the international safety recommendations. None of the participants reported adverse effects during or after the experiments.

Clinical Assessment

Information on perinatal history, development, medical history, onset, distribution, and functional impact of MMs were obtained in all subjects. MM severity was assessed by means of the Woods & Teuber scale (W&TS)[18] as well as by a modified version more recently proposed by Espay et al.[19] Finally, members who reported cognitive impairment underwent a neuropsychological assessment based on a standard battery. See Supporting Data 1 in the Supporting Information for additional details.

Sequencing

The entire coding sequence, as well as the exon-intron boundaries of *DCC* (NM_005215.3) and *RAD51* (NM_002875), were screened for mutations in the 3 affected individuals (II-1, II-4, and III-10). Primers were designed using Primer3[20] or were taken from a previously published article.[12] Polymerase chain reaction products were sequenced on the ABI 3700 sequencer at the Genome Quebec Center for Innovation, according to the manufacturer's recommended protocol (Applied Biosystems, Foster City, CA). Sequences were aligned and analyzed using SeqMan 4.03 (DNASTAR, Madison, WI).

Neurophysiological Assessment

The neurophysiological assessment consisted of electromyographic (EMG) mirror recordings during finger movements and an evaluation of corticospinal and interhemispheric pathways at rest using transcranial magnetic stimulation (TMS) techniques.

EMG activity was recorded from both first dorsal interosseous (FDI) muscles through pairs of Ag/AgCl electrodes placed in a belly-tendon montage. The motor task consisted in performing abductions with the dominant index finger (task hand), in response (though not as an immediate reaction) to a "go" signal, given randomly at a rate of ~0.2 Hz, and in returning to

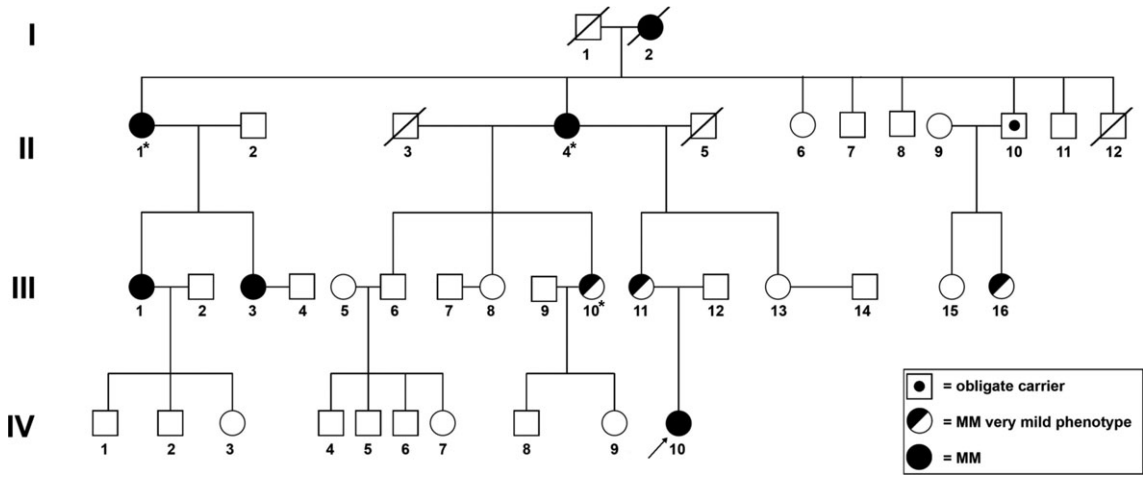

Figure 1 The four-generation family tree of the MM subjects enrolled in the present study (see Table 1 for further details). **DCC* and *RAD51* sequenced in these individuals.

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TABLE 1 Clinical and neurophysiological characteristics of the family members enrolled in the study

Case	Age	Gender	LQ	W&TS		Espay et al. Scale		Affected Region	EMG Mirroring (Left Hand) %	MEP (Left M1)	s-IHI (%)	l-IHI (%)
				R	L	R	L					
II-1*	71	F	70.0	11	11	24	24	Hands Forearms	NA	NA	NA	NA
II-4*	60	F	82.6	9	9	29	29	Hands Forearms Feet	NA	NA	NA	NA
II-10	55	M	65.2	0	0	0	0	None	NA	NA	NA	NA
III-1*	38	F	NA	1	1	2	1	Fingers Right foot	58.7	Contra	121.3	72.3
III-3*	37	F	80.9	1	1	4	3	Hands Right foot	94.9	Contra and ipsi	78.6	130.2
III-6	40	M	71.4	0	0	0	0	None	NA	NA	NA	NA
III-10*	33	F	80.9	0	0	0	0	Hand (only observed during writing)	5.0	Contra	49.6	78.2
III-11*	36	F	52.4	2	2	0	0	Hands	4.8	Contra	109.8	40.0
III-16*	24	F	57.9	1	0	9	3	Right fingers	4.5	Contra	63.4	161.1
IV-10*	5	F	NA	NA	NA	NA	NA	Hands	NA	NA	NA	NA

W&TS[17]: score, 0 to 12; Espay's scale[18]: score, 0 to 40.
*Subjects with MMs at clinical assessment.
M, male; F, female, NA, not available; LQ, Laterality Score of the Edinburgh inventory–appendix 2[28] (score: 0–100).

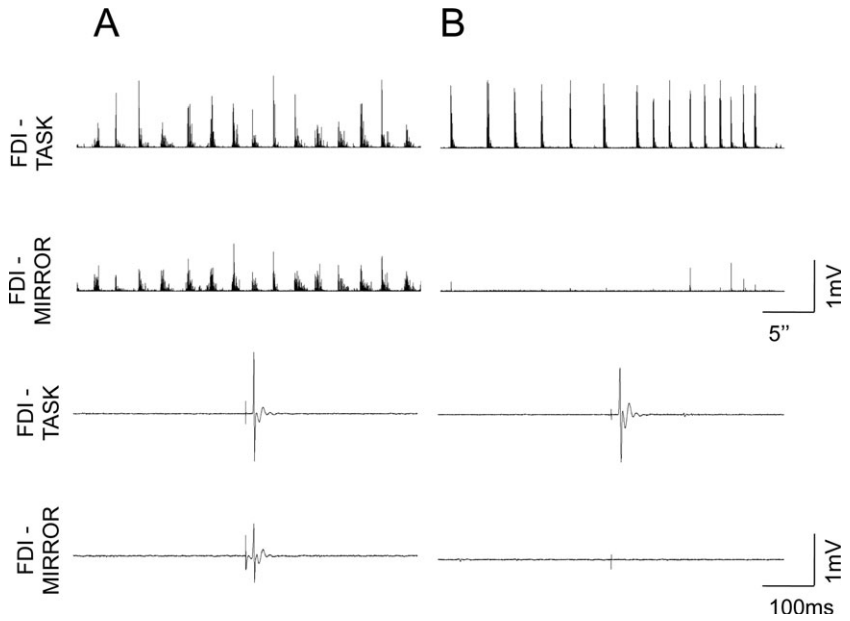

Figure 2 EMG traces from the FDI-TASK and the FDI-MIRROR during the motor task and single-pulse TMS of M1 contralateral to the hand performing the motor task in 2 representative subjects with a marked (A, subject III-3) and a mild phenotype (B, subject III-11). Upper traces show the DC-corrected and rectified EMG from the FDI-TASK and the FDI-MIRROR representing 15 movements. Lower traces show the MEP responses in the FDI-TASK and FDI-MIRROR. Note that an ipsilateral MEP was only detected in the subject exhibiting the highest EMG mirroring activity.

the neutral position. The EMG mirror was expressed as the ratio between the area under the curve of the DC corrected and rectified voluntary EMG burst activity (right hand) and the mirror EMG burst activity of the contralateral hand.[21] Thus, a value of 0% indicates absence of EMG mirroring, whereas a value of 100% indicates that the EMG mirroring is as high as the EMG bursts (Fig. 2).

Cortical excitability in both hemispheres was assessed by single-pulse TMS delivered using a Magstim 200 magnetic stimulator with a monophasic current waveform (The Magstim Company Ltd., Whitland, UK) connected to a figure-of-eight coil. As a measure of corticospinal excitability on the M1-TASK, we used the resting motor threshold (RMT). As a measure of corticospinal excitability on the M1-MIRROR, we adjusted the stimulus

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intensity (percentage of the maximal stimulator output) to evoke motor-evoked potentials (MEPs) of ~1 mV peak-to-peak in amplitude (1 mV-MEP). The measurement of corticospinal excitability was followed by the measurement of interemispheric inhibition (IHI) targeting the M1-MIRROR.[22–24] See Data S1 in the Supporting Information for additional details.

Neuroimaging

Brain MRI was performed on a 3.0T GE SignaHDxt 3T (GE Healthcare, Waukesha, WI) using standard echo-planar imaging and a standard radiofrequency, head-coil phased array for the signal received.

fMRI of cerebral blood-oxygen-level–dependent signal changes was performed during active finger tapping of the right hand and passive finger tapping of the left hand. A simple block design with a 15-second rest alternating with 15 seconds of two active conditions (active and passive finger tapping for each hand) was performed.

Statistical Analysis

Given the small sample of subjects involved in the study, data were analyzed using nonparametric tests. Group differences between MM subjects and HCs were evaluated using Mann-Whitney's U test. As for fMRI data, a statistical analysis using the general linear model (GLM) was performed to obtain functional activation maps during the pre- and post-tests separately. Subsequently, the GLM was used to compare active condition versus rest condition for each subject. After a first-level analysis (single subject), in order to see the surviving fMRI activations for each condition (active and passive finger tapping for each hand) between each group (MMs and HCs), we also performed a whole-brain group analysis (second-level analysis) by means of a sample *t* test comparing each contrast from the single-subject fMRI analysis for each condition for each group and then by means of a one-way analysis of variance test, comparing differences in fMRI activations between the two groups (MM>HC, HC>MM) for each condition, using age as a regression factor.

Correlation analyses between clinical, neurophysiological, and neuroimaging data were performed using Spearman's rank-correlation coefficient. The level of significance in all the tests was set at $P < 0.05$. Bonferroni's correction was applied to multiple comparisons. Statistica 7.0 (StatSoft, Tulsa, OK) software was used for all the statistical analyses. Unless otherwise stated, data were presented as mean ± 1 standard error of the mean (SEM).

Results

Clinical Assessment

The index case's mother first sought neurological assistance for episodes of MMs that had affected her 5-year-old daughter since the age of 18 months (IV-10). The clinical interview led to a positive family history of MMs being declared. Transmission of MMs was consistent with an autosomal-dominant fashion with incomplete penetrance. Eight of the ten familial members examined presented MMs at the clinical assessment. Perinatal and developmental histories did not differ between affected and unaffected individuals. No known history of consanguinity emerged. In most subjects, MMs were noted at birth or infancy and persisted unchanged throughout life. The neurological examinations were otherwise normal in all but the 2 oldest affected members, who displayed mild cognitive impairment (cases II-1 and II-4; see Supporting Table 1).

There was a remarkable variability in MM expression among the affected members (Table 1; see Video). All presented MMs in the hands, fingers, and forearms. Three individuals presented MMs in the toes and feet (II-4, III-1, and III-3). A slight degree of asymmetry was also apparent in 3 cases (III-1, III-3, and III-16). Patients were unaware of their MMs, with the exception of subjects II-1 and II-4, who reported clumsiness of the hands and a slight impact on quality of life and motor functioning.

Genetic Test

Sequencing of *DCC* and *RAD51* did not reveal any mutations in the tested affected individuals. The tested individuals harbored heterozygous common polymorphisms in *DCC* (see Supporting Table 2), suggesting that the affected individuals did not harbor a large deletion encompassing all the gene. No polymorphism was detected in *RAD51* in the tested individuals.

Neurophysiological Assessment

In the 5 subjects tested, the mean EMG mirroring was 32.4 ± 19.0% (range, 4.5–94.9) in MM subjects and 1.07 ± 0.21% (range, 0.48–1.5) in HCs ($P < 0.05$; Fig. 2).

Measurements of RMT 50 μV (in the M1-TASK) and of 1 mV-MEP (in the M1-MIRROR) did not differ between MMs and HCs (Supporting Table 3). Ipsilateral MEP responses to single-pulse TMS of the M1-TASK were only detectable in the familial member exhibiting the highest EMG mirroring activity (Fig. 2).

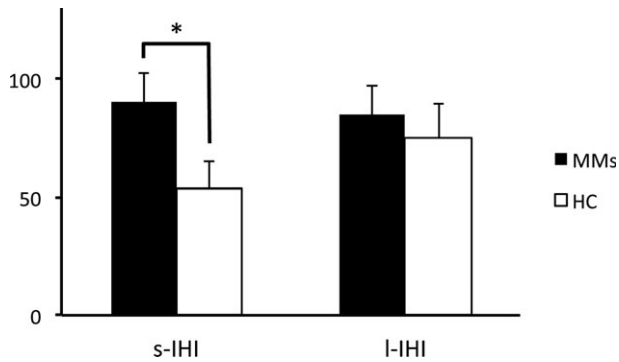

Figure 3 Measurements of s-IHI were higher in the familial member group than in the healthy controls (*$P = 0.022$), whereas l-IHI did not differ between the two groups.

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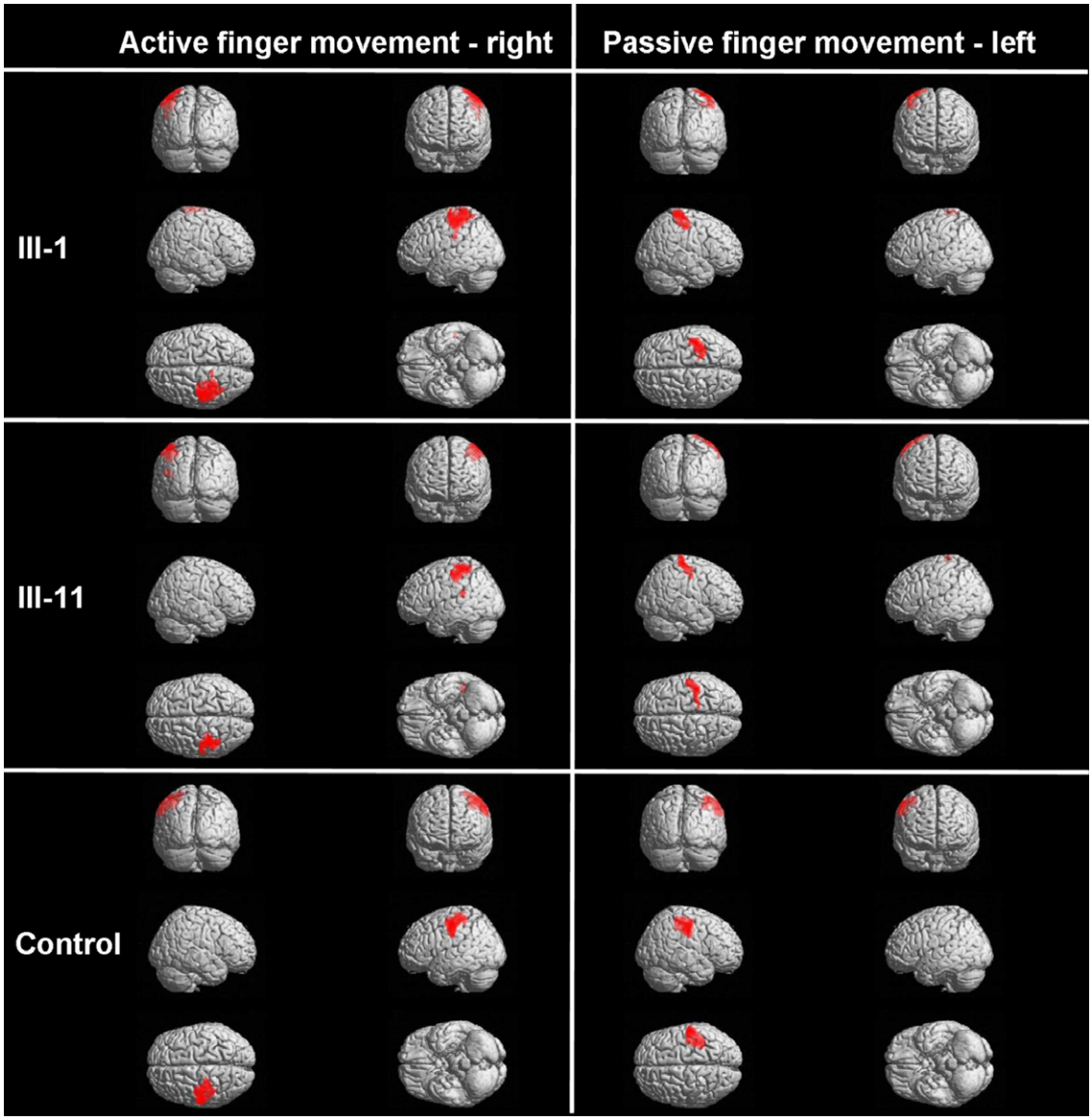

Figure 4 fMRI assessment during active finger tapping of the dominant hand consistently revealed an activation of contralateral frontal and parietal areas with no differences with respect to occurrence and severity of MMs.

Short-latency IHI (s-IHI) was reduced in MM subjects than in healthy controls ($P = 0.022$), whereas long-latency IHI (l-IHI) did not differ between the two groups (Fig. 3). No significant correlation emerged between TMS measurements (corticospinal excitability and IHI), MM clinical scores, and EMG mirroring.

Neuroimaging

The fMRI assessment during active finger tapping of the dominant hand consistently disclosed an activation of contralateral frontal and parietal areas, with a variable expression in *z*-scores and with no significant differences between groups (MMs and HCs; data not shown). Notably, no significant activation was detected in the ipsilateral hemisphere (Fig. 4).

Discussion

This study has investigated the clinical, genetic, neurophysiological, and neuroimaging features of a four-generation family with congenital MMs. The clinical evaluation disclosed a marked heterogeneity of the MM phenotype, which affected 8 of the 10 members examined. Transmission of MMs appears to have occurred according to an autosomal-dominant fashion, but no mutation of the *DCC* and *RAD51* genes were found. The neurophysiological assessment confirmed an enhanced EMG mirror activity in the familial members with clinically evident MMs. A reduced s-IHI was present in MM subjects. An ipsilateral MEP was only detectable in the most severe case. Also, fMRI during active and passive finger movements disclosed a normal contralateral activation of cortical motor areas in MM subjects. No

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correlations between clinical, neurophysiological, and neuroimaging data emerged.

Although the family described in this study shares some similarities with previously reported families, including onset in infancy or early childhood, predominance in the upper limbs with a distal-to-proximal severity gradient and little, or no, motor disability, its phenotype is somewhat different from those reported in families with *DCC* or *RAD51* gene mutations. The first difference found in the present study is the high variability in the clinical expression of MMs, a feature not clearly recognized in other previously described families with congenital MMs.[9,10,13] Second, MMs in our family varied from slight MMs of the fingers, of which the subjects were unaware, to gross MMs of the fingers, hand, and forearm that affected motor skills. This is in contrast to the majority of the MMs in the subjects reported thus far, who were graded 3 on the W&TS. The reason for the variability in MM expression observed in our family is unknown; it is, however, likely to reflect the effect of modifying genetic and environmental factors, including age and gender. Although we did not find a correlation between age and MM severity, progression over time is difficult to ascertain (also resulting from the poor awareness of MMs). Consistently, it is worth noting that the oldest subjects examined (II-1 and II-4) presented the most severe phenotype. It is possible that superimposed factors related to aging might influence expression of MMs. The course of congenital MMs has been described as stable in the majority of previously reported cases[9,10,13] and has even been anecdotally reported to improve with aging.[13] In the present study, subjects II-1 and II-4 also presented cognitive decline, mainly characterized by visuospatial impairment, associated with severe MMs (Supporting Table 1). The pathophysiological relevance of a possible association between MMs and cognitive decline has not, however, yet been established because no study has specifically addressed this issue. Finally, the MMs in our family were detected exclusively in females, in contrast to the male preponderance previously described in two large families[9,10] subsequently found to carry a mutation in the *DCC* gene.[12]

In the present family, transmission of MMs appears to have occurred according to an autosomal-dominant fashion. Thus far, multigeneration involvement has been described in a limited number of families.[9,10,13,14] Private mutations in the *DCC* gene have been detected in a large four-generation French-Canadian family,[10,12] a previously described Iranian family,[9,12] and an Italian family.[13] Heterozygous mutations in the *RAD51* gene have been described more recently in a large four-generation French family and a German family, neither of which had previously been found to carry *DCC* gene mutations.[13,14] In our family, we did not find any mutations in either the *DCC* or *RAD51* genes, though small intragenic microrearrangements could not be ruled out. This is in keeping with the genetic heterogeneity of congenital MMs. Worthy of note is another family from the UK (Family C in a previous study[14]) that was also found to be negative for both the *DCC* and *RAD51* genes mutations. This further supports the existence of other genetic defects underpinning the presence of congenital MMs in humans.

Additional findings of the present study emerge from the neurophysiological assessment of the subjects with congenital MMs. EMG mirroring recordings revealed highly variable results between individuals, thereby confirming the clinical observations. Because we observed similar corticospinal excitability values (resting motor thresholds) between MM subjects and HCs, it is unlikely that MMs were related to the excitability of both M1s. Our MM subjects had reduced s-IHI values, but normal l-IHI values, targeting the mirror M1, if compared to HCs. Because we did not detect any correlation between the severity of MMs (or degree of EMG mirroring) and s-IHI measurements, we believe that reduced s-IHI is only one of the possible underlying mechanisms involved in the generation of MMs in the present family. The reduced s-IHI we observed in our MM subjects is in keeping with experimental studies on healthy subjects showing that individuals with lower s-IHI at rest have a reduced potential for controlling contralateral spread of motor overflow during unilateral intentional movement.[1,25–27] In addition, the reduced s-IHI values we observed in our MM subjects also agrees with previous findings suggesting that defective transcallosal inhibition plays a major role in generating MMs in congenital[17] and other pathological conditions, including movement disorders.[28] The observation that subjects with MMs examined in the present study show reduced s-IHI implies that this neurophysiological parameter could be developed as a possible diagnostic tool for congenital MMs, especially in those cases with very mild or clinically undetectable MMs. This issue might be particularly relevant considering that genetic testing might be inconclusive, because to date not all congenital MMs genes are known. An ipsilateral MEP was detectable in the case with the most severe MMs. The latencies of the bilateral MEPs were similar, thus excluding a possible spread of excitation across the CC and pointing to the existence of a misdirected ipsilateral corticospinal connection. Because the intensity of TMS pulses was ~50% of the maximum stimulator output, it cannot be excluded that ipsilateral MEP could be obtained also in patients with mild MMs, if stronger TMS pulses had been used. This finding is consistent with results yielded by neurophysiological studies showing that stimulation of the motor cortex in patients with congenital MMs evokes, in contrast to normal subjects, a bilateral response,[12,17] which indicates a misdirected ipsilateral corticospinal connection.

Because of the functional alteration in motor planning and motor execution, bilateral M1 activation is another mechanism that may be involved in the pathogenesis of congenital MMs. Subjects with congenital MMs exhibit bilateral M1 activation during unimanual tasks, as shown by functional neuroimaging studies (for a review, see a previous work[17]). In our study, we did not detect any differences between MM subjects and HCs in the pattern of cortical area activation during the fMRI evaluation. We therefore exclude the possibility that abnormal motor programming resulting in the spread of functional connections originating from premotor areas is involved in the generation of MMs in this newly described family.

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In conclusion, differently from previous reports in congenital MMs, we observe highly variable clinical features among members of this newly described family. We did not detect any mutation in the gene sequencing, which indicates that congenital MMs are genetically heterogeneous. Neurophysiological and -imaging investigations suggests that the occurrence and severity of MMs depend on multifactorial mechanisms likely related to an abnormal reduction in the transcallosal inhibitory pathways and an abnormal anatomy of the corticospinal tract. The role of abnormal uncrossed corticospinal fibers as an important substrate of congenital MMs in the present family is supported not only by the evidence of the ispilateral MEP in the most severe case, but also by the lack of activation of hemisphere ipsilateral to the task hand at fMRI and lack of correlation between the degree of MMs and s-IHI reduction in the other MM subjects. This study suggests that congenital MMs are heterogeneous disorders.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique

A.F.: 1A, 1B, 1C, 3A, 3B
M.B.: 2A, 2B, 3A, 3B
E.I.: 1B, 1C
L.P.: 1B, 1C, 2A, 2B, 3A
M.S.: 1C, 3A, 3B
F.D.B.: 1A, 1B, 1C
G.G.: 1B, 1C, 2C
G.A.R.: 1C, 3A, 3B
A.L.: 1C, 3A, 3B
F.S.: 2C, 3C
C.C.: 3B
A.B.: 1A, 1B, 1C, 3B

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Supporting Information

A video accompanying this article is available in the supporting information here.

Video. The severity and distribution of MMs varies greatly across family members. The video shows 4 representative subjects: the oldest members with the most severe phenotype (II-1 and II-4); 2 subjects with a very subtle phenotype (III-1 and the obligate carrier III-11); and the 5-year-old index case (IV-10).

Supporting Data 1. Additional methods (clinical assessment, neurophysiological assessment, and neuroimaging).

Supporting Table 1. Neuropsychological assessment of the 2 MM family members presenting cognitive impairment.

Supporting Table 2. Variants identified through sequencing of *DCC* and *RAD51*.

Supporting Table 3. Corticospinal excitability values in MM subjects and HCs. Data indicate the maximal stimulator output (%) ± 1 SEM.

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