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# Assessment of the corticospinal fiber integrity in mirror movement disorder

Bilgehan Solmaz [a], Mustafa Görkem Özyurt [b], Demir Berk Ata [c], Fulya Akçimen [d], Mohammed Shabsog [b], Kemal Sıtkı Türker [b], Hakkı Dalçik [e], Oktay Algin [f], Ayşe Nazlı Başak [d], Merve Özgür [g], Safiye Çavdar [g,*]

[a] Department of Neurosurgery, Istanbul Education and Research Hospital, Istanbul, Turkey
[b] Department of Physiology, School of Medicine, Koç University, Istanbul, Turkey
[c] Department of Molecular Biology and Genetics, School of Medicine, Koç University, Istanbul, Turkey
[d] Neurodegeneration Research Laboratory, Suna and İnan Kıraç Foundation, Boğaziçi University, İstanbul, Turkey
[e] Department of Preclinical Science, Anatomy Unit, Faculty of Medicine, The University of the West Indies, St. Augustine, Trinidad and Tobago
[f] Department of Radiology, Bilkent University, Ankara, Turkey
[g] Department of Anatomy, School of Medicine, Koç University, Istanbul, Turkey

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ABSTRACT

Mirror movements are unintended movements occurring on one side of the body that mirror the contralateral voluntary ones. It has been proposed that mirror movements occur due to abnormal decussation of the corticospinal pathways. Using detailed multidisciplinary approach, we aimed to enlighten the detailed mechanism underlying the mirror movements in a case subject who is diagnosed with mirror movements of the hands and we compared the findings with the unaffected control subjects. To evaluate the characteristics of mirror movements, we used several techniques including whole exome sequencing, computed tomography, diffusion tensor imaging and transcranial magnetic stimulation. Computed tomography showed the absence of a spinous process of C5, fusion of the body of C5-C6 vertebrae, hypoplastic dens and platybasia of the posterior cranial fossa. A syrinx cavity was present between levels C3-C4 of the spinal cord. Diffusion tensor imaging of the corticospinal fibers showed disorganization and minimal decussations at the lower medulla oblongata. Transcranial magnetic stimulation showed that motor commands were distributed to the motor neuron pools on the left and right sides of the spinal cord via fast-conducting corticospinal tract fibers. Moreover, a heterozygous missense variation in the deleted in colorectal carcinoma gene has been observed. Developmental absence of the axonal guidance molecules or their receptors may result in abnormalities in the leading of the corticospinal fibers. Clinical evaluations and basic neuroscience techniques, in this case, provide information for this rare disease and contribute to our understanding of the normal physiology of bimanual coordination.



## 1. Introduction

Mirror movements (MM) are involuntary movements of the one side of the body that mimic the voluntary movements on the other side. Two types of MM have been described: the first type is physiological and regarded as normal during the infancy of healthy children. This type of MM usually disappears in the first decade of life. The second type of MM is observed in the adult population and is congenital, often inherited autosomal dominantly and may also occur sporadically [1,2].

MM are observed in the distal parts of the extremities mostly in the hand and rarely in the forearm and toes [2,3], its occurrence is more common in males and in left-handed individuals [4]. Patients with MM usually have difficulties in bimanual coordination, causing difficulty in tasks that require each limb to act independently [3,4].

MM have been shown to be related to the abnormal crossing of the corticospinal tract in the medulla or upper cervical level or due to unintended excitations of the contralateral motor cortex through the corpus callosum [5,6]. Data collected from clinical cases showed considerable variations of the corticospinal tract size, myelination, decussation and the presence of aberrant fibers [7,8]. It has been shown that the decussation of this tract is asymmetrical. The fibers from the left hemisphere cross more extensively and more rostrally than those from the right hemisphere [7,8].

* Corresponding author at: Department of Anatomy, School of Medicine, Koç University, Rumelifeneri Yolu, 34450 Sarıyer, Istanbul, Turkey.
*E-mail address:* scavdar@ku.edu.tr (S. Çavdar).

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Adult-type MM may accompany congenital disorders such as Klippel-Feil syndrome [9,10], X-linked Kallman's syndrome [11], or hemiplegic cerebral palsy [12,13]. They may also be acquired later in life as a result of either a neurodegenerative disease, such as amyotrophic lateral sclerosis [14], or an acute lesion after a hemiplegic stroke [15]. The presence of MM in Parkinson's disease has been studied in detail, and unlike congenital disorders, MM in Parkinson's disease were typically unilateral [16,17].

In the present case, we describe a patient with MM and aim to contribute detailed knowledge for the understanding of the MM using transcranial magnetic stimulation (TMS), Hoffmann reflex (H-reflex), computed tomography (CT), magnetic resonance imaging (MRI), diffusion tensor images (DTI) and the genetic background of the present case.

## 2. Methods

The Human Ethics Committee of Koç University approved the experimental procedure in accordance with the Declaration of Helsinki. Both control group and MM patient were asked to fill the informed consent form. The index patient is a 20-year-old right-handed male. He is a university student studying fine arts. The parents noticed the abnormal movements of the hands in the last six years. He has no relevant family history. He had no pre- and post-natal history. However, he had a febrile convulsion at the age of 2. His major complaint was the movement of one hand which was accompanied by the same movement of the unintended hand. No other movement disorder was present. He also had complications in bimanual activities such as; writing a message on his mobile telephone using both hands, tying up his shoe-laces, cutting vegetables, two-handed typing and buttoning up his shirts. He also complained of not being able to recognize an object in his pocket without looking (astereognosia). The general examination showed a deep dimple of the skin at the C2 level. The patient has no other gross abnormalities. Control subjects who had no known neurological disorders were recruited from Koç University. Further radiological, physiological, genetic assessments were made to clarify the case.

### 2.1. Radiology

Three-tesla MRI and DTI sequences were performed on all subjects (including the patient and controls) at Bilkent University. The examinations were performed by using a 3T unit (Trio with Tim; Siemens Healthcare AG, Erlangen, Germany) with 32-channel birdcage head coil. Multiplanar and curved reformatted images were obtained with Leonardo software (Neuro 3D, Siemens Healthcare AG, Germany). An experienced neuroradiologist evaluated the MRI data during acquisition. Details of the routine anatomical imaging sequences (except DTI sequence) are given in Table 1. The diffusion tensor and tractography images were acquired using a high-resolution diffusion tensor sequence (named as Diffusion High-Res, TE = 83 ms, and TR = 8200 ms). A DTI diffusion scheme was used, and a total of 49 diffusion sampling directions were acquired. The b-value was 700 s/mm$^2$. The in-plane resolution was 2.16 mm. The slice thickness was 1.8 mm. DTI data were analyzed with FSL, Medinria, and Leonardo programs for obtaining tractography images.

### 2.2. Genetics

The index case was subjected to whole exome sequencing (WES, Macrogen-Korea). Exomes were captured using the Agilent SureSelect Human All Exome V6, followed by paired-end sequencing on Illumina HiSeq 2500 platform. The bioinformatic analysis was done in-house at the NDAL laboratory of Boğaziçi University. Reads were aligned to human reference genome GRCh37 via Burrows-Wheeler Aligner (BWA) 1, downstream processing of the data was performed with SAMtools 2. Single nucleotide variations (SNV) and small indels were called for each sample by the HaplotypeCaller tool of Genome Analysis Toolkit (GATK) 3. Structural and functional annotation of the variations was performed by using ANNOVAR 4. Minor allele frequencies (MAF) of the variants were obtained from several data-sets consisting of dbSNP138, 1000 Genomes Project 18 and The Exome Aggregation Consortium (ExAC) 5. Variant filtration was performed based on the MAF values; variations present in the population with a frequency greater than 1% were considered as polymorphisms. Visualization of the sequence of interest was performed by Integrative Genomics Viewer (IGV) 6.

**Table 1**
Three Tesla MRI protocol used for the study.

| Sequences/Parameters | 3D-MPRAGE | 3D-SPACE (with VFAM) |
|---|---|---|
| TR/TE (ms) | *2130/3.45* | 3000/579 |
| TI (ms) | *1100* | – |
| Slice thickness (mm) | *0.8* | 0.6 |
| FOV (mm) | *230 × 230* | 240 × 240 |
| Acquisition time (min) | *5* | 5 |
| NEX | *1* | 2 |
| Number of slices | *240* | 240 |
| Flip angle (°) | *8* | 100 |
| Imaging plane | *Sagittal* | Sagittal |
| Distance factor | – | – |
| PAT factor | *2* | 2 |
| PAT mode | *GRAPPA* | GRAPPA |
| Voxel size (mm) | *0.8 × 0.8 × 0.8* | 0.6 × 0.6 × 0.6 |
| FA mode | – | T2 variant |

*Abbreviations:* time of inversion; 3D-SPACE: three-dimensional sampling perfection with application-optimized contrasts using different flip angle evolutions; 3D-MPRAGE: 3D T1W magnetization prepared rapid acquisition gradient-echo; STIR: short tau inversion-recovery; NEX: number of excitations; FOV: field of view; PAT: parallel acquisition technique; GRAPPA: generalized autocalibrating partially parallel acquisitions.

### 2.3. Electrophysiology

Electrophysiology results from the MM patient have been compared with health control subjects (n = 2). During the experimental protocols, all the subjects were blindfolded with an eye band to prevent visual feedback from the environment. Electrophysiology experiments were performed in Koç University Neurophysiology Laboratory.

#### 2.3.1. Equipment

TMS was delivered using Magstim 200$^2$ stimulator (Magstim Co., Whitland, UK) with a figure-of-eight-shaped magnetic coil. Electrical stimulation was delivered using constant current stimulator (model DS7A, Digitimer Ltd, Hertfordshire, UK). Electromyography (EMG) analysis was done using Spike2 v7 (Cambridge Electronic Design, CED, UK). CED 1902 Quad System MKIII amplifier and CED 3601 Power 1401 MKII DAC were used for recording with 2000 Hz sampling frequency and recording was filtered with a band pass filter of 20–500 Hz. Force, on the other hand, was measured with Biopac Software (BIOPAC Systems Inc. CA, USA) using clench force transducer.

#### 2.3.2. Preparation

Subjects were comfortably seated in an armchair where their forearm forms a 90-degree angle to the upper body which was vertical to the ground. The forearms were fixed to the armchair slightly to prevent the contribution of other muscle groups. The

bipolar EMG was recorded from the thenar muscle group (abductor pollicis brevis – flexor pollicis brevis – opponens pollicis) using standard Ag/AgCl surface electrodes. One of the electrodes was placed on the abductor muscle belly and the other electrode on the flexor belly (on medial of thumb metacarpal bone), while the ground electrode was placed on the knuckles. The surface EMG was recorded from the left and right homologous muscle pairs, simultaneously for all the experiments.

*2.3.3. Maximum contractions*

Subjects were asked to hold clench force transducer and perform maximum voluntary contractions (MVC) through the opposition of the thumb against digiti minimi. MVC of the right hand, left hand and both hands were measured in a random order with two methods; force transducer and EMG. While force transducer is optimum to test whole grasping muscles in a combined manner, EMG is suitable to test the recorded muscle activity only. Therefore, during MVC, force was used to assess more generalized activity and EMG was recorded to evaluate the activity of thenar group muscles.

*2.3.4. TMS*

The subjects were asked to keep their arms and hands relaxed during TMS. The stimulation site on the head was found using suprathreshold stimuli around the C3 and C4 region according to the international 10–20 system. To activate the thenar group muscles, the figure-of-eight-shaped coil was oriented 45-degrees relative to the nasion-inion line. The optimum location to be stimulated, then, was found as the location where passive motor evoked potential (MEP) was easily detectable compared to the background noise. After the minimum TMS intensity that evoked consistent MEPs was found and noted as threshold intensity, the stimulus intensity was increased by 15% which was used as suprathreshold intensity. Then, 20 supra-threshold stimuli were delivered to both hemispheres separately with an interstimulus interval of 10–15 s. Each hemisphere was stimulated either during both hands were contracted or completely relaxed. In addition, another 5 higher intensity stimuli, i.e. 30% above the threshold intensity, were delivered to both hemispheres separately to investigate the ipsilateral activation while subjects were voluntarily contracting their both hands. Applied examination procedures have been summarized in Fig. 1A.

*2.3.5. H-reflex study*

Bipolar electrical stimulating electrodes were placed on the median nerve. The anode was placed on the distal part while the cathode was placed the proximal to the anode on the wrist. To test the integrity of the primary afferent fibers, monosynaptic H-reflex

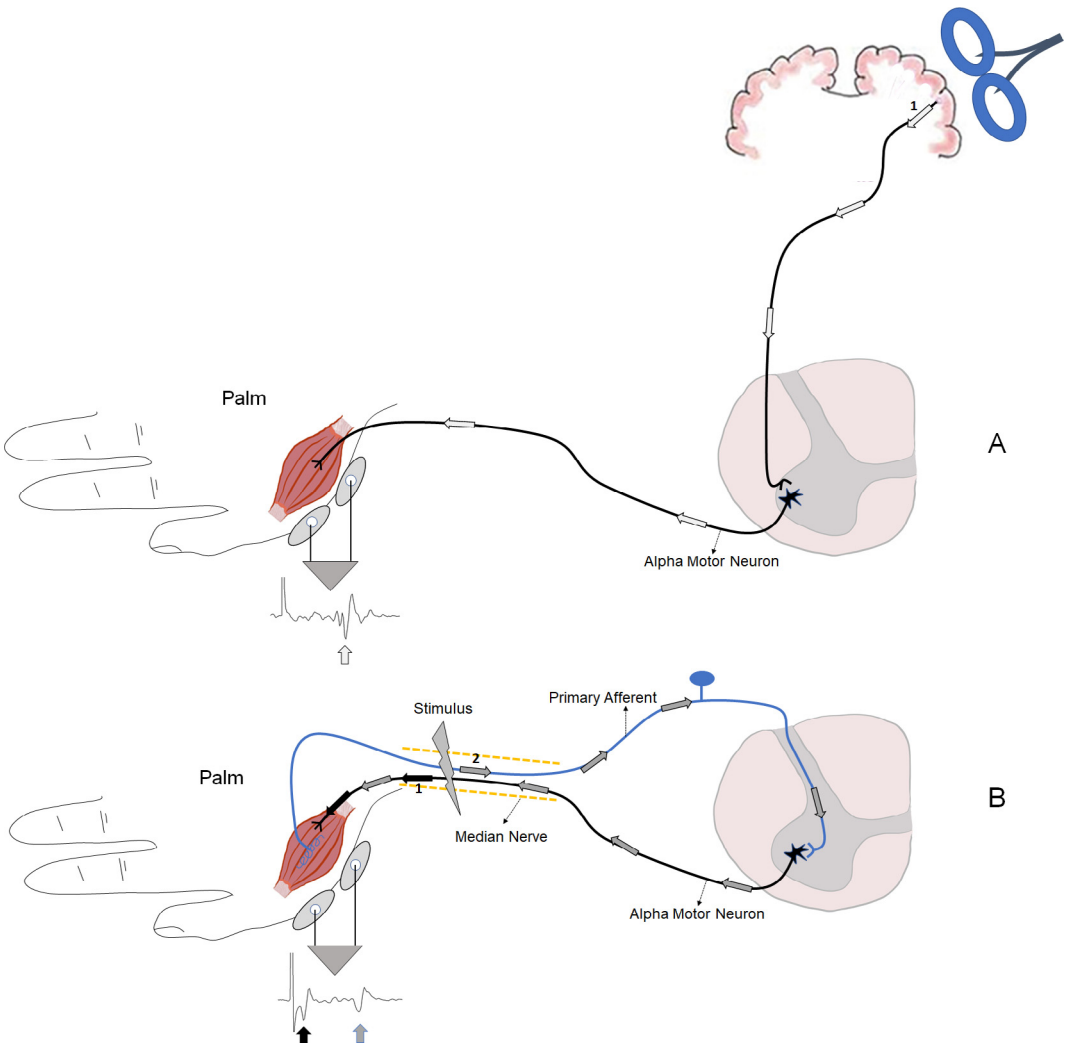


**Fig. 1.** The protocols used in the patient for electrophysiology. A) TMS application which was used to detect MEPs to assess corticospinal tract conduction and decussation. The white arrow shows the MEP producing activity path arising from the motor cortex by TMS coil. B) H-reflex by stimulating the primary afferents in the median nerve to assess local wiring in the spinal cord level. The black arrow indicates M-response direction while gray arrow shows H-reflex path.

[18] was studied in both MM subject and the control group (during no voluntary muscle activity). Through the electrical stimulation of the primary afferent fibers at the median nerve with square pulses of 1 ms width, H-reflex was obtained (Fig. 1B). In addition to the H-reflex, maximum direct motor response (maximum M-response) through stimulation of alpha motor fibers at the median nerve was used to standardize the amplitude of H-reflex. The recorded peak-to-peak amplitude of the H-reflex was normalized using the maximum M-response. The left and right hand median nerves of the subjects were stimulated to evoke H-reflex with an amplitude of around 10% of the maximum M-response obtained from that hand. In total, 20 stimuli were delivered for each hand with an interstimulus interval of 10 s and average responses of 20 stimuli were evaluated.

## 3. Results

In this study, we present examination results of CT, MRI, and DTI to assess the anatomy of a MM patient. Also, whole exome sequencing from the case subject and his parents were performed to clarify the genetical background of this case. Lastly, we showed physiological outcome of the anatomical differences of MM compared to control group using TMS, H-reflex and maximal contractions recorded using surface EMG and clench force transducer.

### 3.1. Radiology

The CT of the patient showed the absence of a spinous process of C5, a fusion of the body of the C5-C6 vertebrae, a hypoplastic dens and an upward bulging of the floor of the posterior cranial fossa adjacent to the foramen magnum (platybasia) (Fig. 2A). MRI showed a syrinx cavity which extended between C3 and C4 level of the spinal cord (Fig. 2B).

Further, DTI of both right and left corticospinal tract showed minimal decussation at the lower medulla oblongata (Fig. 3B and D) compared to control (Fig. 3A and C). The majority of the corticospinal fibers descended in the anterior funiculus. Further, the MM case shows disorganization of the corticospinal fibers at brainstem level and loss of continuity at cervical levels were observed (Fig. 3D and F) compared to control (Fig. 3C and E).

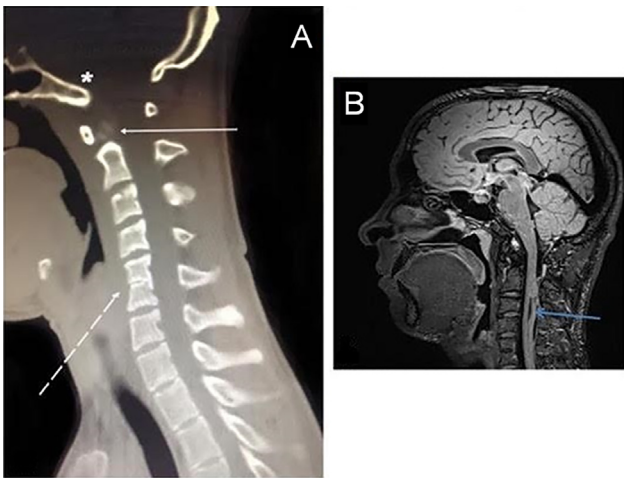


**Fig. 2.** Imaging of the brain and upper level of vertebrae. A) Cervical CT showed the absence of a spinous process of C5, a fusion of the body of C5-C6 vertebrae, hypoplastic dens, and platybasia. B) MRI showed syrinx cavity which extended between C3 to C4 level of the spinal cord.

### 3.2. Genetics

Whole exome sequencing analysis revealed a heterozygous missense variation in the deleted in colorectal carcinoma (DCC) gene (NM_005215, c.1337G > A, p.Arg446His) in the index case. The variation is reported in dbSNP (rs138053380), 1000G (MAF = 0.0002) and in the ExAC database (MAF = 0.00007415) (Fig. 4).

### 3.3. Electrophysiology

The MEPs and H-reflexes were recorded from thenar muscles by using EMG. Also, MVCs were recorded by using both EMG and force transducer. The electrical stimulation of the median nerve did not evoke contralateral H-reflex activity in the control group. However, in the MM subject, the contralateral H-reflex activity was observed in both hands. We observed 25% H-reflex activity from right hand stimulation to left hand and almost 75% H-reflex activity from left hand to right hand, as amplitude (Fig. 5A). Similarly, only 3% and 1% contralateral muscle activity was measured in the control group during left hand and right hand contraction respectively, while 8% (during right hand contraction) and 6% (during left hand contraction) contralateral muscle activity was seen in MM subject in the force measurement during MVC (Fig. 5B). EMG recording also showed the contralateral activity in the MM subject in the MVC experiment. The left hand MVC was contaminated with the right-hand activity by 20%. In contrast, 10% contralateral activity in the left hand was observed when the right hand was maximally contracted. However, there were only slight insignificant contralateral muscle activities were observed in the control subjects (Fig. 5C). Similar results were also obtained in TMS study. Supra-threshold TMS evoked only slight ipsilateral responses which were not larger than 4% in control subjects for any side of the head. However, the present MM case had ipsilateral MEPs as large as 23% and 15% of its contralateral activity during right and left hemisphere stimulation, respectively (Fig. 5D).

## 4. Discussion

This patient showed a rare association of MM, with abnormal absence and fusion of upper cervical vertebrae and abnormal orientation of the floor of the posterior cranial fossa. A syrinx cavity was observed between C3 and C4 level of the spinal cord. Further, unilateral median nerve stimulation showed bilateral evoked H-reflex activities having similar latencies and were distributed bilaterally. Also, sensory deficit (asterognosia) was observed.

### 4.1. The pathophysiological mechanism of mirror movements

The exact pathophysiological mechanism of MM has not been elucidated. Schnitzler, Kessler (19) described MM as structural abnormalities of the corticospinal or transcallosal pathways, and functional deficits of the interhemispheric inhibition of motor planning processes, which leads to the inability to perform independent hand movements. Two hypotheses have been proposed. First, MM may arise from the same hemisphere as the voluntary, crossed corticospinal component by an uncrossed fast-conducting corticospinal counterpart that also descends from the same hand area of the primary motor cortex to the ipsilateral side of the spinal cord. This abnormal ipsilateral projection could depend on either a branching of crossed corticospinal fibers or a separate ipsilateral corticospinal projection (Fig. 6A and B) [6,19]. This hypothesis was also supported by TMS. Stimulation of one side of the head resulted in larger bilateral MEP compared to control. This could be due to abnormal ipsilateral corticospinal projection as strong

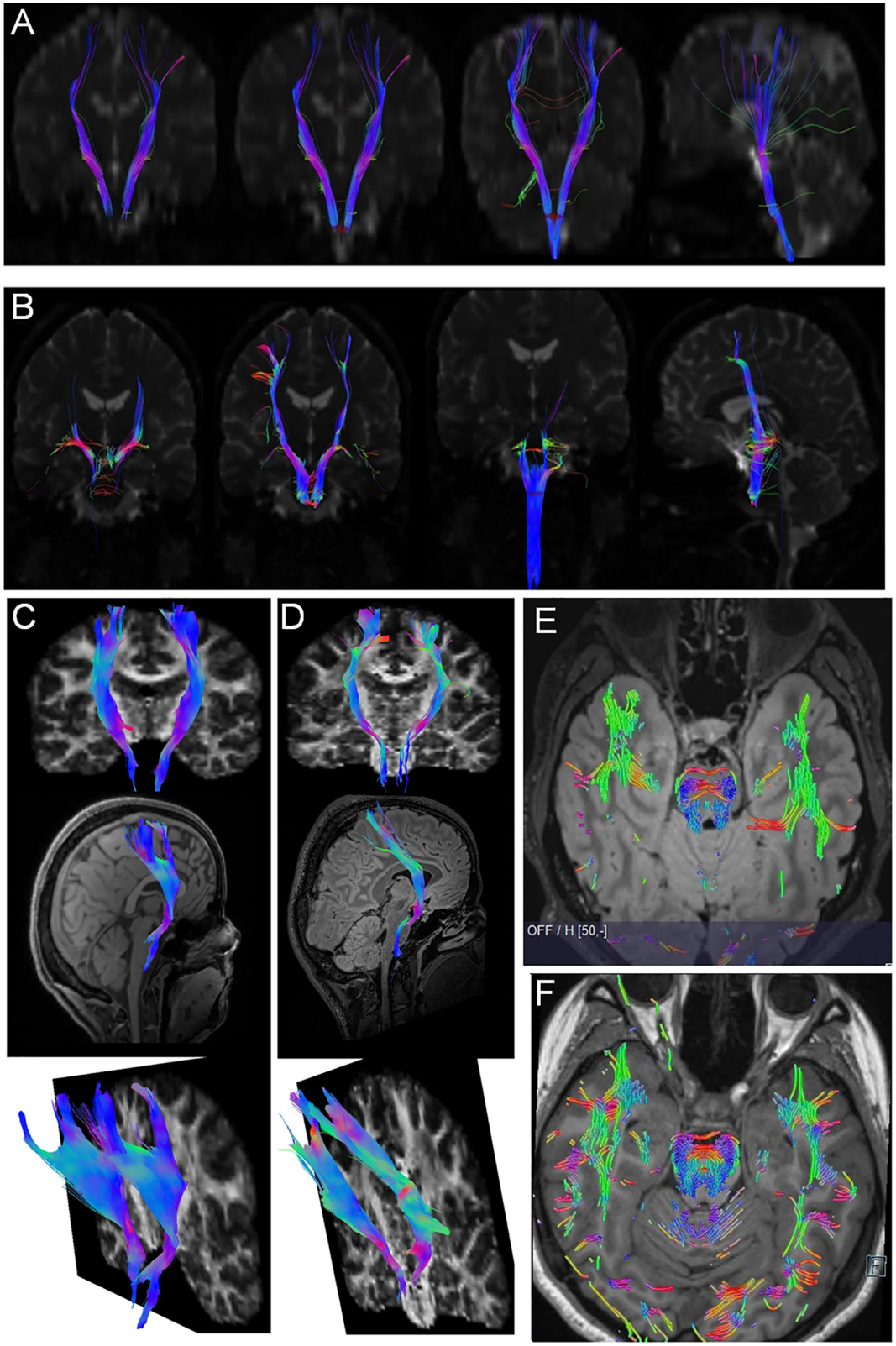


**Fig. 3.** DTI imaging to present decussation, continuity and organization of the corticospinal fibers. A) Normal decussation from a volunteer control subject is observed. B) The present MM case shows a significant reduction of decussation and integrity of the corticospinal fibers at the lower medulla oblongata level. C) No abnormal continuity of the corticospinal tract is seen in the control subject. D) Loss of continuity of corticospinal fibers at brainstem level were observed in the MM patient. E) There are no significantly disorganized corticospinal fibers in the control subject. F) Disorganization of the corticospinal fibers can be clearly identified in the MM case.

ipsilateral MEP was observed. In addition, MVC recordings showed bilateral clenching of the hand which could be due to the same reason discussed, abnormal ipsilateral projection.

The second hypothesis is alternative or complementary, suggesting that MM may result from an abnormal activation of both hemispheres during intended one-handed movement (Fig. 6C and

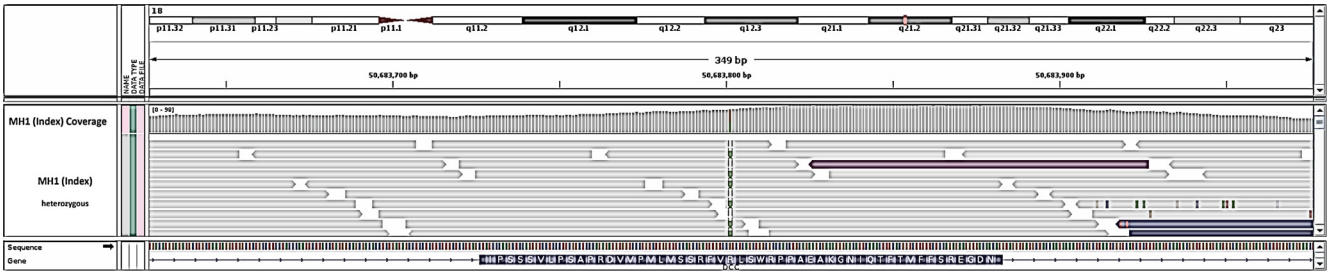


**Fig. 4.** Image view using Integrative Genomics Viewer (IGV) demonstrates an altered 'A' nucleotide in approximately half of the reads indicating heterozygosity in the c.1337 for the index.

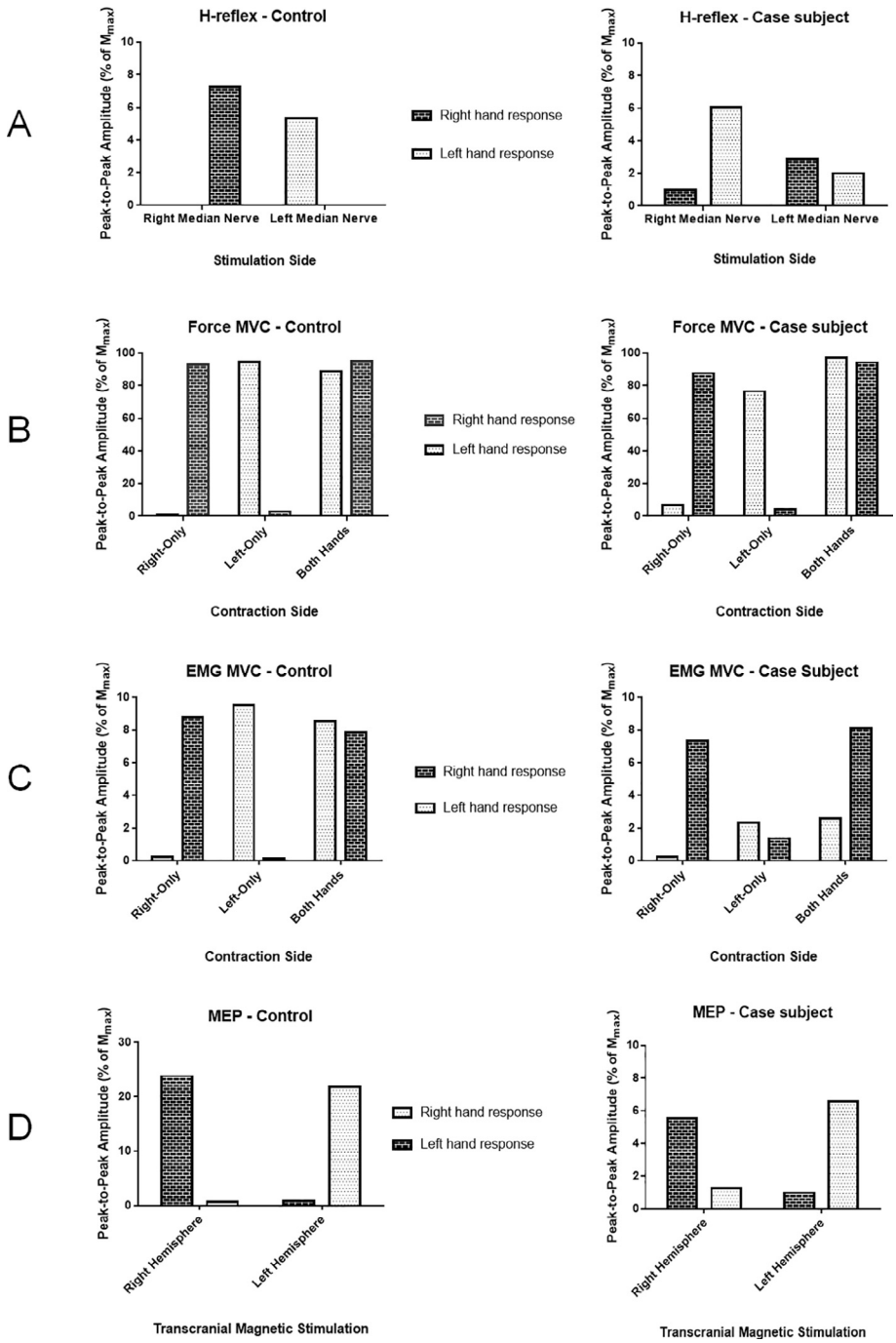


**Fig. 5.** The experimental output from various physiological recordings. A) The H-reflex activity recorded from thenar muscles using EMG. B) Clench force recording of MVC. C) EMG activity by MVC in thenar muscles. D) TMS induced-MEP recordings using EMG.

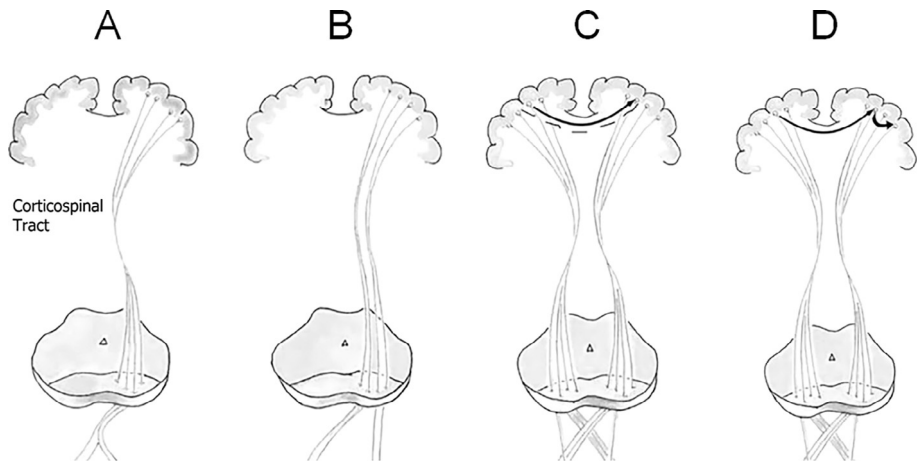


**Fig. 6.** Schematic illustration showing the proposed hypotheses of mirror movement arising from the ipsilateral motor cortex. A) This abnormal ipsilateral projection could depend on either a branching of crossed corticospinal fibers or B) a separate ipsilateral corticospinal projection. The mirror movement may result from an abnormal activation of both hemispheres during intended unimanual movement. C) By reduced transcallosal inhibition (dashed line) or increased facilitations (solid line) from the ipsilateral primary motor cortex to the contralateral primary motor cortex. D) By the altered effects of interhemispheric inhibition on intracortical inhibitory or excitatory circuit rather than the effects of corticospinal neurons.

D) [6,19]. The second mechanism proposed is that both motor cortices may be activated during an intended unimanual movement [6,19]. It has been proposed that interhemispheric inhibition and facilitation of the contralateral motor cortex via the corpus callosum may assist synchronous bilateral movements as well as suppress unwanted movements during the unimanual motor performance [19]. The interhemispheric inhibition is thought to be mediated via excitatory transcallosal projections, which then activate the local inhibitory interneurons in the primary motor cortex [20].

However, besides cortex, there are movement-related centers in the central nervous system such as basal ganglia and cerebellum. Cortex innervates basal ganglia in the striatum and innervates the cerebellum through the pons; both are concerned with controlling movements, making them more accurate (cerebellum) or enhancing or suppressing them (basal ganglia).

Further, most of the corticospinal fibers in MM of the present patient descend in the anterior funiculus of the white mater of the spinal cord. It has been shown that extensive distal bilateral axonal arborization extends across the anterior spinal commissure to innervate neurons on both ventromedial and anterior horn motor neurons [21,22]. Thus, an abnormal decussation at spinal cord levels should not be ruled out. Bilateral H-reflex activity could support this abnormal crossing at spinal cord level. Although it is known that H-reflex could be influenced by contralateral muscle or sensory neuron activity, the changes in H-reflex is restricted to be a conditioning activity which is believed to tune sensory-motor neuron connections in locomotion [23,24]. However, in the MM case subject, ipsilateral electrical stimulation produced H-reflex which had similar latency and distributed bilaterally. On contrary, in the normal subjects, reflex responses were confined to the stimulated side. This result suggests a direct crossing and monosynaptic connection of primary sensory neurons with contralateral alpha motor neurons as no further central delay was observed. Yet, more investigations are needed to localize all the anatomic pathways underlying this so-called disorder and their functional relationships.

An association of Klippel-Feil syndrome with MM has been reported [9,25]. The present case like Klippel-Feil syndrome also shows the failure of spine segmentation, odontoid hyperplasia, and platybasia. However, the present case did not show short neck, low hair line, limitations of neck movements as seen in Klippel-Feil syndrome.

### *4.2. Developmental explanation of mirror movement*

In the literature, MM have been reported alone or accompanied by meningocele and myelomeningocele [26,27]. Further, high cervical split spinal cord malformation with C1 posterior arch absence was reported [4,28]. In the patient, we have observed the absence of the spinous process of C5, a fusion of the corpus of C5-C6 vertebrae hypoplastic dens and a syrinx cavity between C3 and C4 level of the spinal cord.

The corticospinal fibers arise from motor neurons of the gray matter of the cerebral cortex and are guided by the axonal guidance molecules, which must be present in the environment to "attract" or to "repel" the axons, and the neuronal receptor molecules which must also be present to guide the axons to their final destination [29]. It has been shown that developmental morphogens such as Sonic hedgehog, bone morphogenetic proteins and Wnts are used by the growth cones to navigate properly. Nugent, Kolpak [30] showed that some human disorders may very well arise because of malformation of a pathway in the human nervous system. In the present study, the minimal crossing at the pyramidal decussation of the patient can be due to the absence of axon guidance molecules or their receptors misguiding the corticospinal fibers to their destinations and the abnormal formations of the vertebral column summarized above may be relevant to an abnormal distribution of these molecules.

Environmental teratogenic factors may cause mutation/deletion in various genes. Depienne, Cincotta (1) studied the genetic causes of MM by comparing the corticospinal tract morphology of patients with the DCC mutation/deletion and RAD51/deletion with normal subjects and demonstrated that each primary motor cortex was abnormally connected to both sides of the spinal cord via separate crossed and fast conducting corticospinal projections [29]. Thus, the development of the decussation is under the control of a host of signaling molecules. Growing understanding of the molecular processes underlying the formation of these structures offers hope for new diagnostic and therapeutic interventions.

The astereognosia observed in the present case can be completely different or a combined entity of MM. There is no effective treatment of the mirror hand syndrome. However, in serious cases callosotomy can be choice of treatment, the decussating fibers can be detected by tractography and selective callosotomy can be achieved by using neuro-navigated microsurgical techniques to avoid complications.

It is concluded that the MM in this patient had motor commands that were distributed to the motor neuron pools on the left and right sides of the spinal cord via abnormally (plus unequally) branched fast-conducting corticospinal tract fibers. Bilaterally evoked H-reflex findings in the patient proposed that these activities were the result of an unequally developed or adapted spinal reflex pathway.

## Conflict of interest

Authors declare that they have no conflict of interest.

## Acknowledgment

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