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Heterozygous variants in *DCC*

Beyond congenital mirror movements

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Abstract

Objective

To perform a comprehensive characterization of a cohort of patients with congenital mirror movements (CMMs) in Sweden.

Methods

Clinical examination with the Woods and Teuber scale for mirror movements (MMs), neuroimaging, navigated transcranial magnetic stimulation (nTMS), and massive parallel sequencing (MPS) were applied.

Results

The cohort is ethnically diverse and includes a total of 7 patients distributed in 2 families and 2 sporadic cases. The degree of MMs was variable in this cohort. MPS revealed 2 novel heterozygous frameshift variants in DCC netrin 1 receptor (*DCC*). Two siblings harboring the pathogenic variant in c.1466_1476del display a complex syndrome featuring MMs and in 1 case receptive-expressive language disorder, chorea, epilepsy, and agenesis of the corpus callosum. The second *DCC* variant, c.1729delG, was associated with a typical benign CMM phenotype. No variants in *DCC*, *NTN1*, *RAD51*, or *DNAL4* were found for the 2 sporadic CMM cases. However, one of these sporadic cases had concomitant high-risk myelodysplastic syndrome and a homozygous variant in ERCC excision repair like 2 (*ERCC6L2*). Reorganized corticospinal projection patterns to upper extremities were demonstrated with nTMS.

Conclusions

The presence of chorea expands the clinical spectrum of syndromes associated with variants in *DCC*. Biallelic pathogenic variants in *ERCC6L2* cause bone marrow failure, but a potential association with CMM remains to be studied in larger cohorts.

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Glossary

ACC = agenesis of the corpus callosum; **CMM** = congenital mirror movement; **CST** = corticospinal tract; **HC** = healthy control; **MDS** = myelodysplastic syndrome; **MM** = mirror movement; **MPS** = massive parallel sequencing; **nTMS** = navigated transcranial magnetic stimulation; **WES** = whole-exome sequencing; **WGS** = whole-genome sequencing.

Congenital mirror movements (CMMs) constitute a group of nonprogressive movement disorders with aberrant mirroring in contralateral extremities on intentional movements. CMMs manifest in childhood with predominant involvement of the upper extremities, persist throughout life, and are typically observed in the absence of other neurologic symptoms. Pathogenic variants in DDC netrin 1 receptor (*DCC*), *RAD51*, and netrin-1 (*NTN1*) are associated with CMM.[1–3] Only 1 consanguineous large CMM family harboring a homozygous variant in dynein axonemal light chain 4 (*DNAL4*) has been reported so far[4]; some CMM cases/families lack detectable mutations.[1] Mutations in *DCC* are associated with a spectrum of neurologic syndromes resulting from disrupted commissural connections in the brain and spinal cord.[3] *DCC* encodes a netrin-1 receptor involved in developmental axon guidance across the midline,[5,6] which is the likely cause of abnormal ipsilateral cortical projections. The netrin-1 receptor consists of 4 extracellular immunoglobulin-like (Ig1-4), 6 fibronectin 3-like (FN1-6) domains, a transmembrane domain, and 3 intracellular domains (P1-3). Heterozygous pathogenic variants in *DCC* are associated with isolated mirror movements (MMs), agenesis of the corpus callosum (ACC), abnormal development of nociceptive topognosis, and reorganized projections of the corticospinal tracts (CST), either as isolated phenomena or in combination.[7,8] Biallelic *DCC* mutations cause the severe developmental split-brain syndrome.[9]

Here, we present a cohort of 7 patients with CMM, of which 5 were found to carry heterozygous truncating variants in *DCC*. One of these variants was associated with ACC, chorea, epilepsy, and expressive aphasia, suggesting that pathogenic variants in *DCC* may cause a broader spectrum of phenotypes than previously known. One sporadic CMM case with concomitant myelodysplastic syndrome (MDS) harbors a homozygous variant in ERCC excision repair like 2 (*ERCC6L2*).

Methods

This study was approved by the Regional Ethical Board in Stockholm. Patients or legal guardians gave oral and written consent to the study. MMs were evaluated with the Woods and Teuber scale (range 0–4),[10] beside standard neuroimaging, genetic analyses, and neurophysiologic studies. In addition, brain MRI, tractography, and volumetric brain assessment were performed in 4 patients (I:1 and II:1 in family 1 and sporadic cases 6 and 7) and in age- and sex-matched healthy controls (HCs) (supplemental material, links.lww.com/NXG/A331). Whole-exome sequencing (WES) was performed on the index case in family 1. Whole-genome sequencing (WGS) was applied for the index case of family 2 and patients 6 and 7. In both families, segregation was performed after a candidate variant was confirmed with Sanger sequencing. Variants in the candidate genes reported in association with CMM—*DCC*, *NTN1*, *RAD51*, and *DNAL4*—were sought. Navigated transcranial magnetic stimulation (nTMS) was applied in patient I:1 from family 1 and patient 6 to assess reorganization of corticomotor projection patterns (for method description, see appendix e-1, links.lww.com/NXG/A331).

Results

Clinical features and neuroimaging

Briefly, all patients presented with variable degree of childhood-onset MM. Clinical features, neuroimaging, and nTMS findings are summarized in the table. MMs were pronounced in patient 6 (video 1) and mild in family 2 (video 2). Pedigrees of both families 1 and 2 are shown in figure e-1, links.lww.com/NXG/A329.

Family 1

The index case (patient II:1) is a 9-year-old girl whose MMs were noticed during an examination for developmental mile stones. At age 9 years, these MMs became spontaneously less pronounced. Her father (I:1) and younger sister (II:2) also displayed MMs.

Family 2

The index case (patient II:2) is a 7-year-old boy with involuntary movements investigated at age 3 years for delayed speech and language development. His brother (patient II:1) also has MMs and dyslexia but no language impairment. Brain MRI for patient II:1 was normal (figure 1); his guardian declined cognitive assessment. At age 6 years, patient II:2 presented with seizures, and brain CT revealed complete ACC, but no evidence of cortical abnormalities (figure 1). Of note, the anterior, posterior, and hippocampal commissures were present. EEG demonstrated focal motor seizures originating in the left hemisphere with bilateral spreading during sleep, responsive to treatment with valproic acid. A speech-language assessment concluded that he had receptive-expressive language disorder (*International Classification of Diseases, Tenth Revision*: F80.2). Reading and writing skills were reportedly delayed, but no formal dyslexia assessment had been performed due to the young age. The cognitive assessment with Wechsler Intelligence Scale for Children Fifth Edition (WISC-V) revealed that full-scale IQ was 79–91, verbal IQ was significantly lower than performance IQ, and impaired processing speed and executive functions. Examination at age 7 years demonstrated mild chorea and MMs; no other motor abnormalities were found.

Table Summary of patients with congenital mirror movements (CMM)

	Family 1			Family 2			
Case	**Patient I:1**	**Patient II:1[b]**	**Patient II:2**	**Patient II:1**	**Patient II:2[b]**	**Patient 6**	**Patient 7**
Current age, years/sex	54/M	9/F	4/F	9/M	7/M	24/M	59/F
Ethnic background	Iranian	Iranian	Iranian	Caucasian/ Kenyan	Caucasian/Kenyan	East African	Swedish
Variant/ mutation	c.1729delG in *DCC* (exon 11)	c.1729delG in *DCC* (exon 11)	c.1729delG in *DCC* (exon 11)	c.1466_ 1476del in *DCC* (exon 9)	c.1466_1476del in *DCC* (exon 9)	Homozygous 10-kb deletion in exon 11 of *ERCC6L2*	None
Phenotype	CMM	CMM	CMM	CMM Dyslexia	CMM Receptive-expressive language disorder, athetosis, and epilepsy	CMM	CMM
Woods and Teuber scale (range 0–4)	3	2	3	2	1	4	2
TMS	Reorganized corticomotor projections	NA	NA	NA	NA	Reorganized corticomotor projections	NA
Comorbidity	Hypothyroidism and hypertension	None	None	Cold and vibration urticaria[a]	Cold urticaria[a]	MDS and stem cell transplantation GVHD BIH	None
Neuroimaging	WMA	Normal	NA	Normal	ACC	Normal	Normal

Abbreviations: ACC = agenesis of the corpus callosum; BIH = benign intracranial hypertension; CMM = congenital mirror movement; GVHD = graft-versus-host disease; MDS = myelodysplastic syndrome; NA = not assessed; TMS = transcranial magnetic stimulation; WMA = white matter abnormality.
[a] Both siblings and their mother are affected by cold urticaria. The mother does not have any mirror movements. A genetic variant in *ADGRE2* was found in the index case of family 2, but it did not segregate with urticaria. Patients 6 and 7 are sporadic cases.
[b] Index case in each family.

Patients 6 and 7 are apparent sporadic cases. Of interest, patient 6 developed pancytopenia at age 21 years; further investigations with bone marrow aspiration revealed MDS and the presence of 1 pathogenic somatic *TP53* variant in about 20% of bone marrow cells. Taken together, this high-risk MDS motivated stem cell transplantation and a targeted analysis of *ERCC6L2*.

Neuroimaging and nTMS

Volumetric analyses in patient I:1 in family 1 and patients 6 and 7 did not reveal any differences compared with HCs. Volumetric assessment in patient II:1 from family 1 was not possible to perform due to movement artifacts. Reorganized corticospinal projection patterns to upper extremities were demonstrated on nTMS (figure 2, supplemental material, links.lww.com/NXG/A331).

Genetics

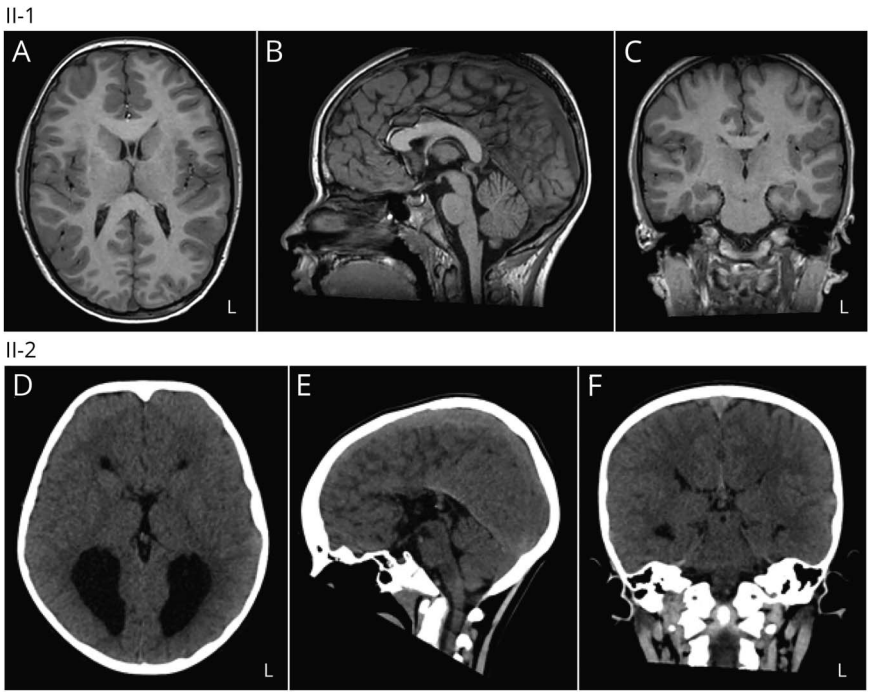
WES revealed the novel variant c.1729delG p.Glu577Argfs*12 in *DCC* (NM_005215.3, exon 11) in the index case of family 1, which segregates with disease (table and figure e-2, links.lww.com/NXG/A330). WGS detected the novel variant c.1466_1476del p.Val489Glufs*15 in *DCC* (NM_005215.3, exon 9) in the index case of family 2. This variant is also present in his older brother but absent in their mother; the father was not available for genetic testing. Both variants are located in exons encoding the fibronectin type III-like (FN3) domains 2 and 1, respectively. This region of the protein interacts with netrin-1 that specifically binds to the 4–6th FN3 domains,[3] and these domains are more frequently associated with ACC.

In patient 6, a homozygous 10-kb large deletion with intronic breakpoints around exon 11 (coordinates hg19: chr9: 98690859-98700947) was identified in *ERCC6L2*. Mutations in *ERCC6L2* are associated with autosomal recessive bone marrow failure and susceptibility to acute myeloid leukemia.[11] No candidate variants in *DCC, RAD51, NTN1*, or *DNAL4* were found for patients 6 and 7.

Discussion

To date, 31 *DCC* mutations have been described, but clear-cut genotype-phenotype correlations are not possible to establish at the moment.[3,12] Herein, we provide data on 2 novel truncating variants in *DCC* associated with isolated MMs and in 1 case with ACC, chorea, epilepsy, and receptive-expressive language disorder. The presence of chorea in association with

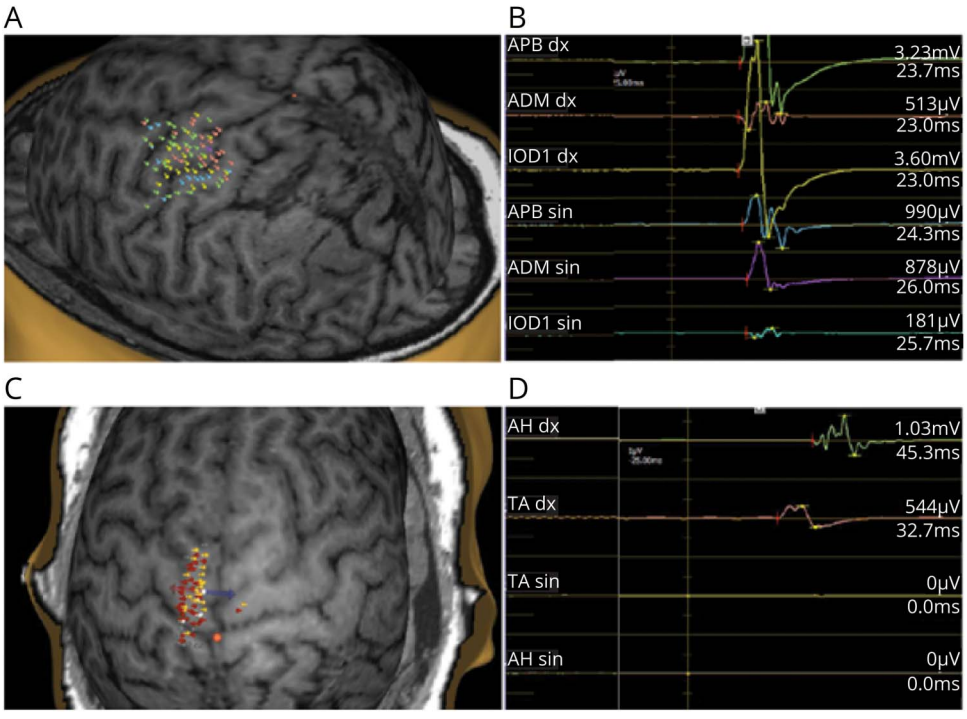
Figure 1 Neuroimaging of family 2 in a cohort with CMM



(A–C) Brain MRI of patient II:1 at age 9 years showing normal anatomy, including the corpus callosum. A small cavum septum pellucidum is noted as a normal variant. From left to right: 3D T1-weighted axial, coronal, and sagittal 1-mm isotropic slices. (D–F) Nonenhanced brain CT of patient II:2 at age 6 years showing agenesis of the corpus callosum, giving rise to a racing car sign. From left to right: axial, coronal, and sagittal 3-mm thick slices centered at the posterior commissure. CMM = congenital mirror movement.

the variant c.1466_1476del expands the clinical spectrum of CMM. Normal corpus callosum morphometry in a sibling with MMs and dyslexia harboring the same variant illustrates a striking intrafamilial variability. Epilepsy associated with *DCC* mutations has been described in 1 patient in a report by Marsh et al.,[3] but seizures ceased at age 2 years. The contralateral spread of focal epileptic activity observed in our patient with ACC is intriguing because the corpus callosum constitutes the

Figure 2 nTMS of patient 6 in a cohort with CMM



Motor evoked potentials (MEP) after MRI navigated TMS in the hand area in the left hemisphere (A). Motor responses were elicited from both right (contralateral) (EMG Ch1. APB dx, Ch2. ADM dx, Ch3. IOD1 dx) and left (ipsilateral) sides (EMG channel Ch4. APB sin, Ch5. ADM sin, Ch6. IOD1 sin). Stimulation in left leg motor area (C) elicited motor responses only in the contralateral side (D) (EMG Ch1. AH dx, Ch2. TA dx). APB = Abductor pollicis brevis, ADM = Abductor digiti minimi, IOD1 = 1st dorsal interossei, AH = Abductor Hallucis, TA = Tibialis anterior.

major pathway for bilateral synchrony,[13] suggesting propagation through noncanonical routes. Notably, a previous study reports that ACC associated with truncating *DCC* variants was frequently observed in 2 families of Northern African origin, with a clear preference for females.[7] ACC in association with *DCC* mutations entails a better prognosis than without variants in this gene, illustrating the importance of etiologic diagnosis for the prognosis of complex syndromes.[3] The occurrence of aggressive MDS in association with a homozygous variant in *ERCC6L2* in a young patient with CMM is striking. *ERCC6L2* has been thought to have role in DNA-damage response.[11] However, any possible association between CMM and the reported homozygous variant in *ERCC6L2* may be just coincidental. Of interest, *RAD51* encodes a protein involved in repair of DNA double-strand breaks. Heterozygous variants in *RAD51* have been associated with a very rare form of Fanconi anemia.[14] Our findings are in keeping with the variable intrafamilial expressivity for variants in *DCC*, but still the factors modulating this variability remain to be determined.[3] WGS did not identify any other variants in the 3 other CMM genes or syndromic forms of MMs in 2 sporadic cases, reflecting genotypic heterogeneity and the need for refined sequencing tools. We used MRI-navigated TMS to perform focal cortical stimulation of hand motor cortex, but even when stimulating with higher certainty it is still difficult to approach the legs' homunculus.[15] Our findings describe reorganized CST to upper extremities, while typical contralateral pathways to the lower extremities, are in accordance with previous studies.[16]

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Disclosure

The authors report no disclosures. Go to Neurology.org/NG for full disclosure.

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Appendix Authors

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Mominul Islam, MD, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden	Study concept and design; interpretation of neurophysiologic studies and clinical data; and revising the manuscript
Marie Lindefeldt, MD	Astrid Lindgren's Hospital, Stockholm, Sweden	Patient care; interpretation of data; and revising the manuscript
Ann Nordgren, MD, PhD	Karolinska University Hospital, and Karolinska Institutet, Stockholm, Sweden	Study concept and design; interpretation of genetic studies and clinical data; and revising the manuscript
Tobias Granberg, MD, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden	Obtaining and interpreting neuroimaging data and revising the manuscript
Bianca Tesi, MD, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden	Interpretation of genetic studies and clinical data and revising the manuscript
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Martin Paucar, MD, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden	Patient care; study concept and design; analysis and interpretation of data; study supervision and coordination; and revising the manuscript

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