

Brief Reports

Congenital Mirror Movements Due to RAD51: Cosegregation with a Nonsense Mutation in a Norwegian Pedigree and Review of the Literature

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Abstract

Background: Autosomal dominant congenital mirror movements (CMM) is a neurodevelopmental disorder characterized by early onset involuntary movements of one side of the body that mirror intentional movements on the contralateral side; these persist throughout life in the absence of other neurological symptoms. The main culprit genes responsible for this condition are *RAD51* and *DCC*. This condition has only been reported in a few families, and the molecular mechanisms linking *RAD51* mutations and mirror movements (MM) are poorly understood.

Methods: We collected demographic, clinical, and genetic data of a new family with CMM due to a truncating mutation of *RAD51*. We reviewed the literature to identify all reported patients with CMM due to *RAD51* mutations.

Results: We identified a heterozygous nonsense mutation c.760C>T (p.Arg254*) in eight subjects: four with obvious and disabling MM, and four with a mild phenotype. Including our new family, we identified 32 patients from 6 families with CMM linked to *RAD51* variants.

Discussion: Our findings further support the involvement of *RAD51* in CMM pathogenesis. Possible molecular mechanisms involved in CMM pathogenesis are discussed.

Keywords: Mirror movement, *RAD51*, motor control, corticospinal tract, corpus callosum, neurodevelopment

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Conflict of interest: The authors report no conflict of interest related to this paper.

Ethics statement: Written informed consent was obtained from all included family members in accordance with the ethical agreement 2012/1451 of the Regional Ethical Committee in Norway. This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki. The authors' institutional ethics committee has approved this study and all patients have provided written informed consent. All patients that appear on video have provided written informed consent; authorization for the videotaping and for publication of the videotape was provided.

Introduction

Mirror movements (MM) are characterized by involuntary movements of one side of the body that mirror intentional movements on the contralateral side.¹ They can be a manifestation of various

congenital or acquired neurological disorders.^{2,3} Autosomal dominant congenital mirror movements (CMM) are characterized by early onset MM that persist throughout life in the absence of other neurological symptoms.¹ Since CMM predominantly affects the hands, difficulty

carrying out activities of daily living is limited to tasks that require independent movements of the two hands, but patients can also experience chronic upper limb pain.^{4,5} The pathophysiology is related to abnormal development of the motor network and likely involves corticospinal tract abnormalities leading to bilateral downstream transmission of the motor command and altered interhemispheric communication resulting in bilateral activation of primary motor areas.^{6–10}

The main culprit genes responsible for this condition are *RAD51* and *DCC*.^{11–14} Only a few families and sporadic cases have been linked to *RAD51* mutations. Here, we report a new family with autosomal dominant CMM with a *RAD51* mutation and review the literature for previously reported patients. We also discuss the possible pathogenic molecular mechanism in CMM-*RAD51* patients.

Methods

Subjects

A family with CMM was identified during an ongoing study of genetic movement disorders in Norway. Affected subjects, obligatory carriers, and possibly affected family members (taking the pedigree into account) were invited to participate in the study. We collected demographic, clinical, and genetic data. Clinical evaluation and patient phenotyping including movement scoring was performed by a single physician (J.K.) who was blinded to the genotypes. Movements were rated according to the Woods and Teuber MM scale,¹⁵ where 0 means absence of MM; 1, barely discernible but repetitive movement; 2, either slight but unsustained repetitive movement or stronger but briefer repetitive movement; 3, strong and sustained repetitive movement; and 4, movement equal to that observed in the intended hand. Written informed consent was obtained from all included family

members in accordance with the ethical agreement 2012/1451 of the Regional Ethical Committee in Norway.

Mutation analysis and genotyping

DNA was extracted from peripheral blood lymphocytes using standard techniques (QIAamp DNA Blood Mini Kit, Qiagen). The *RAD51* and *DCC* genes exons and their flanking intronic sequences were amplified and sequenced by Sanger sequencing. Genotyping was done independently by a single investigator (OT) that was unaware of the phenotype.

Review of the literature

We conducted a review of published studies to identify all reported patients with CMM due to *RAD51* mutations. We searched the PubMed database using the terms “*RAD51* and mirror movements” from 1980 to September 2016. The reference lists of papers thus retrieved were also scanned for relevant articles.

Results

Study of the New *RAD51*-MM family

The characteristics of the patients are shown in Table 1. By direct sequencing of the *RAD51* coding sequence (NM_002875.4), we identified a heterozygous nonsense mutation c.760C>T (p.Arg254*) in the eight subjects (Figure 1). Among them, four had obvious MM in their hands that disturbed their activities of daily living (subjects #1, #2, #3, #4). The remaining four mutation carriers had no complaints despite having mild MM when attempting to perform strictly unilateral movements (subjects #5, #6, #7; #8) (Video 1). No other non-neurological phenotype cosegregated with the *RAD51* variants.

Table 1. Patient Characteristics

Patient-Sex/Age	MM Severity ¹ / Location	Asymmetry	Associated Disorders	Functional Disability
1-M/59	3/UL	No	No	Difficulties in fine bimanual activities
2-F/5	3/UL	No	No	Difficulties in fine bimanual activities
3-F/3	3/UL; 1/LL	No	No	Difficulties in fine bimanual activities
4-F/22	3/UL; 1/LL	No	No	Difficulties in fine bimanual activities
5-F/70	1/UL	R>L	Chronic fatigue	None
6-M/45	1/UL	R>L	No	None
7-M/44	1/UL	L>R	No	Chronic UL pain
8-M/43	1/UL	R>L	No	None

Abbreviations: F, Female; L, Left; LL, Lower Limbs; M, Male; MM, Mirror Movements; R, Right; UL, Upper Limbs.

¹According to the Woods and Teuber MM severity scale: (0: No MM; 1: Barely discernible but repetitive MM; 2: Either slight but sustained MM, or stronger, but briefer MM; 3: Strong and sustained repetitive MM; 4: MM equal to that observed in the intended hand).

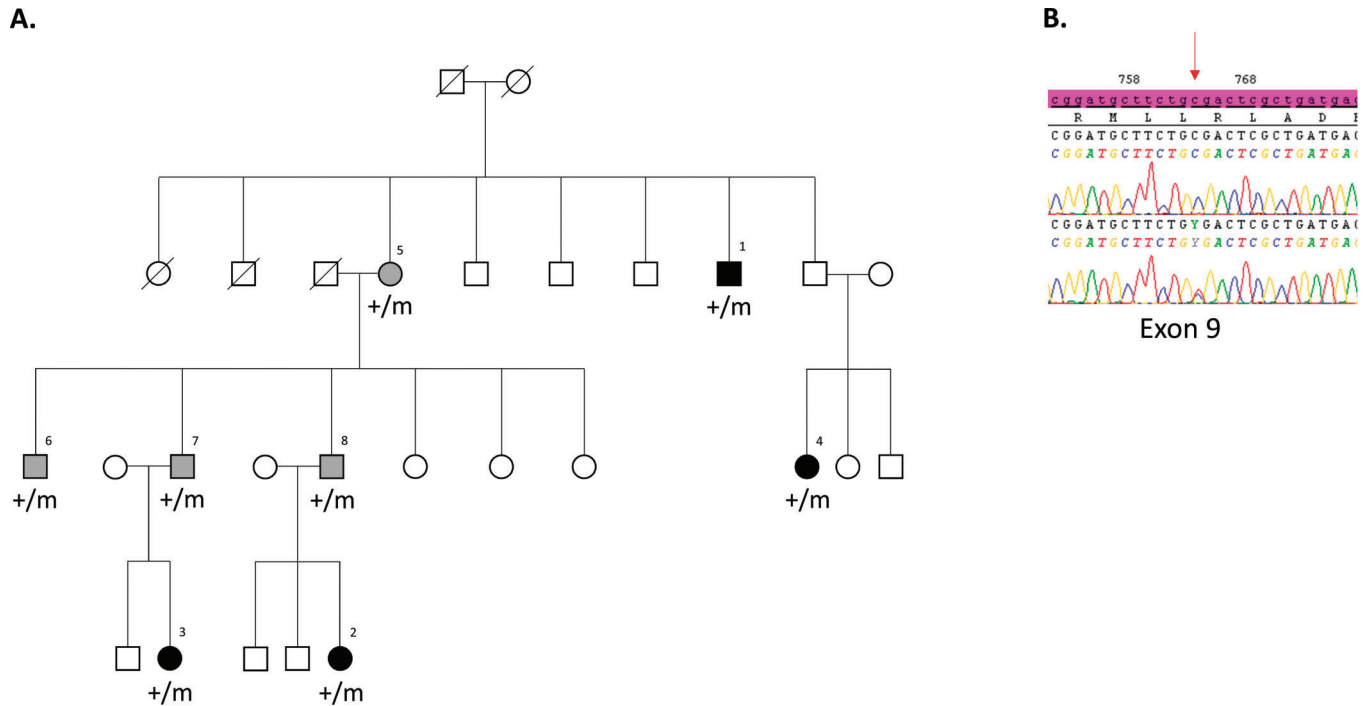


Figure 1. Identification of the R254* Mutation in the Norwegian Family. (A) Segregation of the mutation. Black symbols represent individuals with strong congenital mirror movements, and gray symbols represent individuals with mild congenital mirror movements. Circles indicate females; squares, males; symbols with a diagonal line, deceased; m: mutated allele, +: wild-type allele. (B) Sequence profile of the mutation in the heterozygous state in a congenital mirror movement patient compared with an unaffected subject. The red arrow points to sequence changes; electrophoregrams were obtained with SeqScape software (v2.6, Applied Biosystems).



Video 1. Illustrative video of severe and mild mirror movements. Two patients (subjects #2 and #3) with severe mirror movements (severity score = 3), and then a patient (subject #7) with mild mirror movements (severity score = 1). The red arrow indicates the side of the voluntary movement.

Review of the literature

We retrieved 11 papers that were analyzed in detail. Including our new family, we identified 32 CMM patients from 6 families with

variants of *RAD51* as summarized in Table 2.^{12,14,16} Thirty patients had a clearly pathogenic mutation, and two had missense variants that are possibly pathogenic.

Table 2. Summary of Reported CMM Patients with *RAD51* Mutations

Families	Reference	Patient Origin	Number of Patients (M/F)	Asymptomatic Carriers (M/F)	Variants	In Silico Predictions (SIFT/Polyphen-2)	CADD score	ExAC frequency	Final prediction	
1	12	France	9 (7/2)	7 (3/4)	c.760C>T/ p.Arg254*	-	13.368440	42	0	Pathogenic
2	12	Germany	2 (1/1)	0	c.855dup/ p.Pro286Thrfs*37	-	8.263609	35	0	Pathogenic
3	16	USA	11 (6/5)	1 (0/1)	c.749G>A/ p.Arg250Gln	Deleterious/ possibly damaging	7.716175	35	0	Pathogenic
4	14	Italy	1 (0/1)	2 (1/1)	c.140A>G/ p.His47Arg	Deleterious/ benign	2.124248	17.01	8,238.10 ⁶	Possibly pathogenic
5	14	France	1 (0/1)	1 (0/1)	c.406A>T/ p.Ile136Phe	Deleterious/ benign	3.953950	23.6	0	Possibly pathogenic
6 ¹		Norway	8 (4/4)	1 (1/0)	c.760C>T/ p.Arg254*	-	13.368440	42	0	Pathogenic

Abbreviations: CADD, Combined Annotation Dependent Depletion; CMM, congenital mirror movements; ExAC, Exome Aggregation Consortium; F, Female; M, Male.
¹Present report

Discussion

We report a new CMM family with a *RAD51* truncating mutation, providing further support for the involvement of *RAD51* in CMM pathogenesis. A review of all published cases of *RAD51*-linked CMM raises the possibility of a molecular pathogenesis other than mere haploinsufficiency.

In this paper, we report the first CMM family from Norway comprising eight affected members: four with strong MM, and four with a mild phenotype. All affected patients have a heterozygous nonsense mutation of *RAD51*, previously demonstrated to cause CMM in a large, unrelated French family.¹² The exact age of onset is difficult to ascertain in CMM patients, including in the family described here. In our clinical experience, the age of onset corresponds to the period of manual skill development in toddlers, regardless of the culprit gene (*DCC* or *RAD51*). Males with a *DCC* mutation may be more prone to develop MM,^{11,13,14} whereas the sex ratio seems to be well balanced (18 males/14 females) in patients with CMM due to *RAD51* mutations. In the Norwegian family described here, there was considerable intrafamilial variability in MM severity, and the available data were too scarce to properly discuss the penetrance. Typically, penetrance is incomplete, and phenotypic severity varies widely within families with CMM (including *RAD51*-CMM families),¹¹⁻¹⁴ from asymptomatic carriers to subjects with strong, sustained MM. The incomplete penetrance and phenotypic variability of CMM due to *RAD51* mutations may be related neither to age nor sex, but it could be linked to greater expression of *RAD51* from the remaining normal allele or to other genetic, epigenetic, or environmental modifiers. In mildly affected subjects, it can be difficult to distinguish among mild genetically determined “pathologic” MM, physiologic MM, and secondary MM. Indeed, subtle mirroring can be seen in otherwise healthy subjects, particularly in young children or elderly subjects.¹⁷ Mild MM can similarly be observed in patients with various central nervous system (CNS) disorders, including poststroke hemiplegia,¹⁸ amyotrophic lateral sclerosis,¹⁹ multiple sclerosis,²⁰ Parkinson’s disease,²¹⁻²³ essential tremor,^{24,25} Huntington’s disease,²⁶ and corticobasal degeneration.²⁷ In this setting, the MM are acquired and therefore presumably absent before CNS disorder onset.

Since the *RAD51* protein is well known for its important role in DNA repair through homologous recombination,²⁸ its role in a developmental CNS disorder such as CMM was totally unexpected. The first *RAD51* mutations discovered in CMM patients were nonsense or frameshift mutations.¹² In particular, we described a French family carrying the same mutation as the Norwegian family (reported here), and the phenotypes are very similar.¹² CMM patients in the French family exhibited a downregulation of *RAD51* mRNA, corresponding to the degradation of the mutated mRNA by nonsense-mediated decay. Western blot analyses failed to detect any truncated protein in lymphoblastic cells of affected family members. Taking genotypic and phenotypic similarities into account, haploinsufficiency is likely the pathogenic mechanism accounting for CMM in both families. In keeping with this, Exome Aggregation Consortium (ExAC)

data show that *RAD51* is highly intolerant to loss of function (probability of loss of function intolerance = 0.99). Therefore, the prevailing hypothesis has been one of a haploinsufficiency leading to CMM in *RAD51* patients. The recent finding that a missense pathogenic *RAD51* mutation was responsible for CMM in a large family¹⁶ raises the possibility of pathophysiologic mechanisms other than mere haploinsufficiency. Interestingly, a dominant-negative effect of *RAD51* mutations was recently proposed for patients affected with Fanconi's anemia, another disorder linked to *RAD51* mutations.^{29,30} To date, there is no report of a patient with both CMM and Fanconi's anemia. Similarly, none of the *RAD51* pathogenic variants have been described in both disorders. This suggests that CMM and Fanconi's anemia are allelic disorders due to mutations with mechanistically distinct functional effects on *RAD51* activity. Further functional studies are needed to investigate the genotype/phenotype correlation in patients with *RAD51* mutations in depth and clarify the impact of nongenetic factors on the phenotype and penetrance.

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