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Callosal agenesis and congenital mirror movements: outcomes associated with *DCC* mutations

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ABBREVIATION

ACC Agenesis of the corpus callosum

DCC Deleted in colorectal cancer gene

ABSTRACT

Pathogenic variants in the gene encoding deleted in colorectal cancer (*DCC*) are the first genetic cause of isolated agenesis of the corpus callosum (ACC). Here we present the detailed neurological, brain magnetic resonance imaging (MRI), and neuropsychological characteristics of 12 individuals from three families with pathogenic variants in *DCC* (aged 8–50y), who showed ACC and mirror movements (*n*=5), mirror movements only (*n*=2), ACC only (*n*=3), or neither ACC nor mirror movements (*n*=2). There was heterogeneity in the

neurological and neuroimaging features on brain MRI, and performance across neuropsychological domains ranged from extremely low (impaired) to within normal limits (average). Our findings show that ACC and/or mirror movements are associated with low functioning in select neuropsychological domains and a *DCC* pathogenic variant alone is not sufficient to explain the disability.

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Case Series

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What this paper adds

- Neuropsychological impairment severity is related to presence of mirror movements and/or agenesis of the corpus callosum.
- A *DCC* pathogenic variant in isolation is associated with the best prognosis.

Recently we reported that monoallelic pathogenic variants in the deleted in colorectal cancer gene (*DCC*) cause isolated agenesis of the corpus callosum (ACC) with or without mirror movements.[1] This is the first known genetic cause for isolated ACC. ACC can be isolated or associated with other structural brain anomalies and multiple congenital syndromes[2,3] due to genetic and environmental aetiologies.[3] Mirror movements are characterized by involuntary movements on one side of the body mirroring voluntary movements on the other, and may present in isolation or as part of a syndrome.[2] In patients with *DCC* pathogenic variants, mirror movements are thought to be due to reduced crossing of the corticospinal tracts at the level of the pyramidal decussation, as we have shown using diffusion tensor imaging.[1] *DCC* is important for commissural tract development, including the corpus callosum, for

information transfer between left and right hemispheres, and crossing of corticospinal tracts for transmission of motor signals to the contralateral side.[4,5]

Here we detail a spectrum of neurological, neuroimaging, and neuropsychological features in a series of individuals with *DCC* pathogenic variants from our gene discovery study.[1] Other than determining the clinical spectrum, our aim was to identify diagnostic features to aid in determining prognosis.

METHOD

Participants

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This study involves 12 individuals aged 8 to 50 years from families 1, 2, and 4 previously reported as having a *DCC* pathogenic or likely pathogenic variant[1] (American College of Medical Genetics and Genomics/Association for Molecular Pathology criteria[6]) for whom comprehensive neurological, neuroimaging, and neuropsychological data were available. Informed consent was obtained from all participants/guardians. Approval was given by local Human Research and Ethics Committees.

Family 1 included two females in generation 3 (III-2: 46y; III-4: 50y), without mirror movements or ACC, the daughter of III-2 (IV-2: 11y) with partial ACC, and both daughters of III-4 (IV-1: 33y; IV-3: 24y) with complete ACC. Family 2 included a female (II-1: 50y) and three of her four sons (III-1: 12; III-2: 10y; III-3: 8y) who have mirror movements and complete ACC. Family 4 included a female (II-1: 44y), her daughter (III-2:12y), and her son (III-1: 10y) who have mirror movements; the son also has isolated partial ACC.

Neurological features

Clinical information was obtained from medical records and neurological examination where possible. Families 2 and 4 underwent examination of their mirror movements including the Woods and Teuber classification.[7] Woods and Teuber classify mirror movements in the contralateral limb on a 0 to 4 scale as follows: 0, no clearly imitative movement; 1, barely discernible 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 expected for the intended hand. A total score for the upper limbs was determined by addition of scores for finger flexion/extension, wrist flexion/extension, and forearm pronation/supination. Topognosis assessment for sensory coupling was performed using von Frey filaments. Sensory coupling is the perception of a sensation in the

contralateral limb to that being stimulated. Assessment for sensory coupling was performed by stimulation with a 5.07 von Frey nylon filament (10g force) in the upper limb on the tip of the index finger, the volar aspect of the thumb, the volar aspect of the wrist, and the cubital fossa.

Imaging features

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Brain MRI and computed tomography (CT) were reviewed to classify:[8,9] (1) ACC type: partial: part of corpus callosum absent or complete: entire corpus callosum absent; (2) anterior, posterior, and hippocampal commissures: absent, small, normal, or dysmorphic; (3) central nervous system anomalies: additional brain abnormalities, including cerebral cortex, brainstem, cerebellum, basal ganglia, ventricles, white matter, hippocampi, pituitary, and vasculature. Anatomical changes commonly associated with ACC (Probst bundles, cingulate gyrus alteration, colpocephaly) were not coded as additional malformations.[10,11]

Neuropsychological profile

Testing was performed by a neuropsychologist using standardized measures to assess cognitive and behavioural domains (Table S1, online supporting information). IQ scores are reported as standard scores (mean 100, SD 15), and cognitive and motor performance scores are reported as centiles (Table S2, online supporting information). Social and behavioural functioning ratings are reported as the level of presenting problems.

RESULTS

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Neurological and imaging features

Table 1 summarizes the participant's genetic, developmental, neurological, and neuroimaging features, and Table S3 (online supporting information) summarizes the neuropsychological features. Mirror movements were present in 7 out of 12 individuals. Woods and Teuber scores were 3 to 9 in the right upper limb and 0 to 9 in the left upper limb; mirror movements were symmetric in four individuals and asymmetric in three (Families 2 and 4; Table 1). Mirror movements were detected in the lower limbs in only one individual (4-II-1). Only two individuals (2-II-1 and 2-III-3) were aware they had mirror movements, although all with mirror movements were aware of upper limb fine motor or coordination difficulties. Sensory coupling in the upper limb was present in three individuals (Table 1).[12] None had been aware of this before formal topognosis testing. No other neurological abnormality was detected.

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Neuroimaging showed complete ACC in 6 out of 12 and partial ACC in 2 out of 12 individuals, as assessed by MRI (*n*=9), computerized tomography (*n*=2), and prenatal ultrasound (*n*=1). Of those with complete ACC, cingulate gyrus absence and colpocephaly were uniformly present. One individual with partial ACC had absence of the rostrum, genu, and anterior body and an enlarged splenium (4-III-1). A thickened corpus callosum was seen in one individual (4-III-2). All individuals in Family 2 had dysmorphic hippocampi, appearing bulky and malrotated. At least one commissure (anterior, posterior, or hippocampal) was present in all individuals, although the hippocampal commissure was frequently absent, and the anterior commissure may have been thickened, thinned, or been dysmorphic (Fig. 1).

Neuropsychological profile

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There were four severity groups for neuropsychological disability depending on the presence or absence of ACC and/or mirror movements (for details see Table S3).

ACC and mirror movements subgroup

The full-scale IQ of the five individuals with complete or partial ACC and mirror movements ranged from extremely low (*n*=1, partial ACC), to borderline (*n*=3, complete ACC), to low average (*n*=1, complete ACC). Compared to full-scale IQ scores, individual scores were comparable (or lower) for auditory selective attention (5/5), divided attention (4/5), and expressive language (3/5). All reported elevated executive functioning problems, social skills deficits, anxiety, and problem behaviours (all four children). In contrast, 4 out of 5 had performed better in semantic verbal fluency and rapid naming, compared to full-scale IQ. Children (aged ≤12y) scored extremely low to borderline for reading, spelling, and mathematics, but the adult was only low for mathematics.

ACC without mirror movements subgroup

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The full-scale IQ of the three individuals with ACC without mirror movements was low average for the child (partial ACC) and one adult (complete ACC), and average for the other adult (complete ACC). Psychomotor speed was consistent with full-scale IQ, although reading was relatively weaker irrespective of age (borderline range). All had strong scores above their full-scale IQ scores for auditory sustained attention, working memory, verbal fluency, cognitive flexibility (2/3), and inhibition (1/3).

Mirror movements without ACC subgroup

Two individuals (one adult, one child in Family 4) had average full-scale IQ scores. Scores were consistent with this level (or better) for memory, language, literacy, numeracy, processing speed, and attention, although auditory sustained attention and executive functioning (inhibition, cognitive flexibility, phonemic fluency) were weaker for the child. Both had high anxiety levels.

No mirror movements nor ACC subgroup

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Two adults (Family 1) had average full-scale IQ scores. Scores were consistently at this level, except both had specific visual memory weakness and one reported high levels of executive functioning problems.

DISCUSSION

This is the first detailed phenotypic analysis of monoallelic *DCC* pathogenic variants; the first gene identified for isolated ACC.[1] Although showing a severity spectrum, neuropsychological dysfunction was most severe when both mirror movements and ACC were present. By contrast, a *DCC* pathogenic variant without mirror movements or ACC was characterized by largely intact functioning and minimal disability. This highlights a higher disability risk than previously recognized when considering IQ only,[1] emphasizing the importance of neuropsychological assessment in fully determining a neurodevelopmental phenotype.

We showed heterogeneity of neurological and neuroanatomic features in the same pedigree, suggesting variation in both penetrance and expressivity. Assessment for mirror movements is not part of the standard neurological examination in individuals with cognitive or developmental delay. We suggest evaluation for mirror movements should be performed, as its presence may indicate an axonal crossing disorder,[4,12] as is the case in individuals with genetic syndromes such as Kallman[3] or X-linked Klippel-Feil syndrome. It may also be seen in congenital hemiparesis,[7] where it is hypothesized that there is either compensatory ipsilateral corticospinal tract control or reduced contralateral motor inhibition. In individuals with a *DCC* pathogenic variant, mirror movements and sensory coupling are likely to reflect a failure of crossing of fibres in the brainstem and spinal cord, as has been shown in the mouse model of *DCC*.[11]

Our findings inform prognostic and genetic counselling in both prenatal and postnatal settings. Counselling for ACC remains difficult, because of the elevated risk for a wide spectrum of neurodevelopmental and neuropsychological disturbances. Knowledge of whether a fetus or infant has a combination of a *DCC* pathogenic variant with ACC indicates risk of neuropsychological difficulties, with the greatest risk of ACC and mirror movements. Pathological mirror movements cannot be diagnosed until the second decade as they can be a variant of typical development, therefore, their presence in early childhood cannot be used for prognostication. However, our findings suggest neuropsychological disabilities, even if ACC is apparently isolated. Additionally, cognitive, behavioural, and academic disturbances can emerge with age because these domains have a protracted trajectory in typical development. The five individuals with ACC and mirror movements had a pathogenic variant within the NTN1 binding interface, which may be most disruptive for brain development.[1,12] Other than this, we did not identify specific genotype–phenotype correlations, although a larger sample size of this relatively newly-identified genetic cause of ACC is required.

In conclusion, a heterozygous *DCC* pathogenic variant may impact brain connectivity leading to mirror movements and/or ACC. A monoallelic *DCC* pathogenic variant in isolation is insufficient to explain the range of neuropsychological deficits. When both mirror movements and ACC are present, neuropsychological disturbances are greatest. Presumably the combination of mirror movements and ACC reflects a more global disturbance of brain wiring than the presence of a *DCC* variant in isolation. The reason for this variable expressivity is unknown; a situation common to many genetic neurodevelopmental disorders. We suggest there is no distinct *DCC* phenotype per se, but a grading in severity of neuropsychological performance that is a function of underlying brain changes associated with either mirror movements or ACC.

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SUPPORTING INFORMATION

The following additional material may be found in the online:

Table S1: Neuropsychological measures.

Table S2: Scaled score, centiles, and descriptors for IQ measures.

Table S3: Neuropsychological features.

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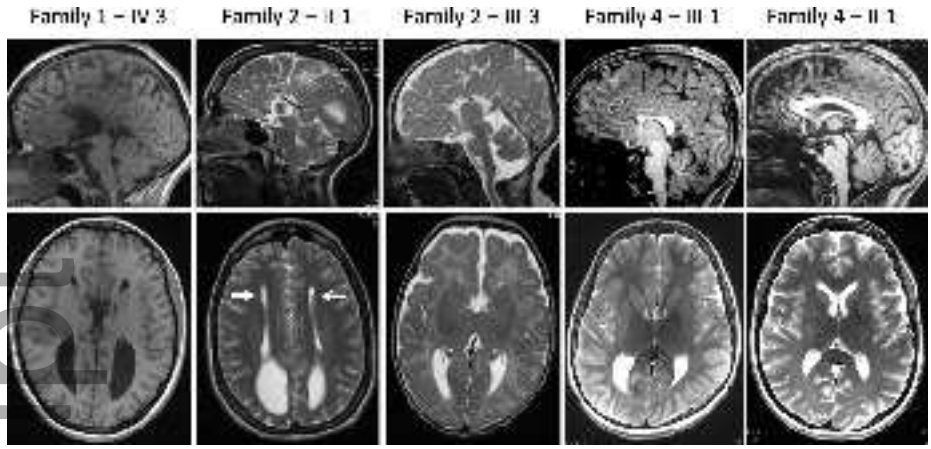
[Figure legend]

Figure 1: Examples of brain magnetic resonance imaging from each family. Top row: midsagittal T1- or T2-weighted sequences; bottom row: axial T1- or T2-weighted sequences. Scans of 1-IV-3, 2-II-1, and 2-III-3 all show complete agenesis of the corpus callosum with associated absence of the cingulate gyrus and varying degrees of colpocephaly. In addition, 2-II-1 shows two small nodules of anterior periventricular grey matter heterotopia (arrows). 4-III-1 shows partial agenesis of the corpus callosum with absence of the rostrum, genu, and anterior body, thinning of the mid body, and an enlarged splenium. 4-II-1 is normal.

Table 1: Genetic, developmental, neurological, and neuroimaging features

	Family 1					Family 2				Family 4		
	IV-2	**IV-1**	**IV-3**	**III-2**	**III-4**	**III-1**	**III-2**	**III-3**	**II-1**	**III-1**	**III-2**	**II-1**
Phenotype	pACC+ MM–[a]	cACC+ MM–[a]	cACC+ MM–[a]	ACC–MM–[b]	ACC– MM–[b]	cACC+ MM+[c]	cACC+ MM+[c]	cACC+ MM+[c]	cACC+ MM+[c]	pACC+ MM+[c]	ACC– MM+[d]	ACC– MM+[d]
***DCC* mutation**												
Inheritance	Germline					Germline				Germline		
Allele	Monoallelic					Monoallelic				Monoallelic		
cDNA	c.925delA					c.2378T>G				c.2414G>A		
Protein	p.(Thr309Profs*26)					p.(Val793Gly)				p.(Gly805Glu)		
Protein domain	IgC2-3					FN3-4				FN3-4		
Age, y	11	33	24	46	50	12	10	8	50	10	12	44
Development												
Language	N	N	N	N	N	Delay	N	Delay	Delay	Delay	N	N/A
Motor	N	N	N	N	N	Delay	N	Delay	Delay	Delay	Delay	N/A
Education support	N/A	N/A	N/A	N/A	N/A	EI, Aide	Reading	EI	Aide	Aide		
Behavioural diagnosis	N/A	N/A	N/A	N/A	N/A	ADHD	ADHD	ADHD	Childhood ADHD, adult depression	ASD	Anxiety	
Neurology												
Woods and Teuber score	N/A	N/A	N/A	N/A	N/A	R 6, L 5	R 3, L 3	R 9, L 9	R 4, L 3	R 7, L 5	R 6, L 3	R 4, L 0
Sensory coupling	N/A	N/A	N/A	N/A	N/A	-	-	+	+	+	-	-
Seizure disorder	-	-	-	-	-	-	-	-	-	+	-	-
Imaging features												
Corpus callosum	PACC	CACC	CACC	N	N	CACC	CACC	CACC	CACC	PACC	Thick	N
Anterior commissure	N/Ass	N/Ass	N	N/Ass	N/Ass	Thin	Thick	N	Thick	N	N	N

Phenotypes: [a]*DCC* mutation with ACC only, [b]*DCC* mutation without ACC or MM, [c]*DCC* mutation with ACC and MM present, [d]*DCC* mutation with MM only. Reference sequences used are NM_005215.3 and NP_005206.2. IgC2, immunoglobulin-like type C2 domain; FN3, fibronectin type III-like domain; pACC+, partial agenesis of the corpus callosum; cACC+, complete agenesis of the corpus callosum; ACC–, no corpus callosum abnormalities; MM+/–, presence or absence of mirror movements; N, normal; N/A, data not available; EI, early intervention; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; N/Ass, data not assessable.



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