Abstracts

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Heterozygous Variants in DCC: Beyond Congenital Mirror Movements

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), neuro-imaging, 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. 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.

Practical Guidelines to Manage Discordant Situations of SMN2 Copy Number in Patients With Spinal Muscular Atrophy

Objective Assessment of SMN2 copy number in patients with spinal muscular atrophy (SMA) is essential to establish careful genotype-phenotype correlations and predict disease evolution. This issue is becoming crucial in the present scenario of therapeutic advances with the perspective of SMA neonatal screening and early diagnosis to initiate treatment, as this value is critical to stratify patients for clinical trials and to define those eligible to receive medication. Several technical pitfalls and interindividual variations may account for reported discrepancies in the estimation of SMN2 copy number and establishment of phenotype-genotype correlations.

Methods We propose a management guide based on a sequence of specified actions once SMN2 copy number is determined for a given patient. Regardless of the method used to estimate the number of SMN2 copies, our approach focuses on the manifestations of the patient to recommend how to proceed in each case.

Results We defined situations according to SMN2 copy number in a presymptomatic scenario of screening, in which we predict the possible evolution, and when a symptomatic patient is genetically confirmed. Unexpected discordant cases include patients having a single SMN2 copy but noncongenital disease forms, 2 SMN2 copies compatible with type II or III SMA, and 3 or 4 copies of the gene showing more severe disease than expected.

Conclusions Our proposed guideline would help to systematically identify discordant SMA cases that warrant further genetic investigation. The SMN2 gene, as the main modifier of SMA phenotype, deserves a more in-depth study to provide more accurate genotype-phenotype correlations.