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CORRESPONDENCE

Between SCA5 and SCAR14: delineation of the *SPTBN2* p.R480W-associated phenotype

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We read with interest the article by Elsayed et al. [1] describing a family with autosomal recessive congenital ataxia due to a homozygous 5-bp deletion in the β3-spectrin gene (*SPTBN2*). In-frame heterozygous variants of this gene had previously been identified as the cause of autosomal dominant adult-onset SCA5 (MIM#600224) (Suppl.Tab.1) [2–4]. The authors postulated the existence of *SPTBN2* genotype-phenotype correlates, suggesting that loss of function mutations would act recessively, producing a severe congenital ataxic phenotype associated with cognitive impairment and variable additional neurological signs. This hypothesis was partially supported by three subsequent studies, reporting homozygous missense, nonsense and splicing *SPTBN2* variants, all resulting in an analogous congenital ataxia syndrome, defined as SCAR14 (MIM#615386) (Suppl.Tab.1) [5–7]. Elsayed and colleagues [1] also mentioned a previously reported patient affected by a severe infantile-onset cerebellar ataxia with developmental delay, carrying the heterozygous missense variant c.1438C>T (p.R480W) in the *SPTBN2* gene [8]. Based on previous literature data on heterozygous *SPTBN2* mutation carriers (presenting the typical SCA5 phenotype of adult-onset, slowly progressive pure cerebellar ataxia), they speculated that either a second-site SCA5 modifier or an undetected *SPTBN2* variant in trans (e.g., deep intronic or in a non-coding regulatory region) should contribute to the phenotypic manifestation.

In this regard, we would like to report an additional case of congenital severe cerebellar ataxia and intellectual impairment carrying the same *SPTBN2* p.R480W variant. This is a 2-year-old girl, the third child of healthy non-consanguineous parents. She was born by cesarean section after an uncomplicated full-term pregnancy and was referred to the neuropsychiatric clinic because of generalized hypotonia, global developmental delay, and alternating esotropia. At age 12 months, she said her first words and got head control, but could not sit without support. Two months later, her developmental quotient was calculated to be 56. She progressively developed a cerebellar syndrome with gait ataxia and dysarthria. Brain MRI performed at age 1 year 10 months showed global cerebellar hypoplasia with enlarged interfolial spaces, in the absence of any brainstem or supratentorial abnormalities (Suppl.Fig.1A). Molecular analysis consisted of a next-generation sequencing (NGS) panel of 50 genes causative of different forms of non-progressive cerebellar ataxia (with the exclusion of Joubert Syndrome genes), using TruSeq Custom Amplicon (TSCA) technology on a MiSeq platform (Illumina, San Diego, CA, USA). As in the case reported by Jacob et al. [8], this child was heterozygous for *SPTBN2* p.R480W missense variant (NM_006946). This variant was not detected in either of the unaffected parents, suggesting de novo occurrence (Suppl. Fig.1B). Potential heterozygous deletions involving one or more exons were ruled out using a custom script tool aimed at detecting significant differences in read depth from NGS data. The p.R480W variant (rs397514749) is not present in population databases, affects a highly conserved amino acid, and multiple in silico tools consistently predict it as

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deleterious on the gene product (Suppl.Fig.1C-D). Interestingly, Parolin-Schnekenberg and coworkers recently performed a genetic screening in a cohort of children diagnosed with ataxic cerebral palsy, and identified this same heterozygous variant in one case, confirming its pathogenicity using in vitro models [9]. Based on all these evidences, the variant can be classified as pathogenic according to ACMG guidelines.

Comparing the three reported cases heterozygous for *SPTBN2* p.R480W, a common phenotype of congenital ataxia emerges, which closely resembles the SCAR14 phenotype. In particular, all three subjects presented in the neonatal age with abnormal ocular movements and developmental delay, later evolving into ataxia and intellectual disability. Additional neurological signs have been occasionally detected, including hyperreflexia, facial myokymia, and intention tremor (Suppl.Tab.1). Brain imaging shows hypoplastic cerebellum with a shrunken appearance or overt cerebellar atrophy.

In the attempt to identify meaningful genotype-phenotype correlates, we compared the impact of p.R480W on β3-spectrin stability with that of SCA5-associated heterozygous missense variants p.L253P and p.T472M, by assessing their induced thermodynamic change with the FoldX algorithm [10]. Both p.R480W and p.T472M fall within the second spectrin repeat of the protein, which is thought to be involved in dimer formation needed for correct assembly of the tetrameric α-β-spectrin complex [9], while p.L253P resides in the calponin homology domain (Suppl.Fig.2). Interestingly however, p.R480W is predicted to significantly increase protein stability ($\Delta\Delta G = -1.52$ kcal/mol), while SCA5 missense variants were either destabilizing the protein (p.L253P, $\Delta\Delta G = 2.79$ kcal/mol) or rather neutral (p.T472M, $\Delta\Delta G = -0.40$ kcal/mol). The thermodynamic changes caused by these mutations may affect the overall dimerization capability of the protein by either stiffening or making excessively flexible the whole protein structure, yet the observation that *SPTBN2* heterozygous p.R480W is able to produce such a severe clinical presentation compared to adult-onset SCA5 cases still remains to be understood.

In conclusion, the presented case further supports the existence of a specific *SPTBN2* p.R480W-associated phenotype, which resembles SCAR14 but is associated to the de novo occurrence of this variant in the heterozygous state. These findings highlight the complexity of monogenic disorders, providing useful information for both clinical management and genetic counselling of *SPTBN2*-mutated patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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