Neurological Sciences (2019) 40:207–208
https://doi.org/10.1007/s10072-018-3567-z

LETTER TO THE EDITOR

Horizontal gaze palsy with progressive scoliosis: is scoliosis linked to *ROBO3* mutations?

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Received: 11 April 2018 / Accepted: 10 September 2018 / Published online: 14 September 2018

Dear sir,

In our recent paper by Ungaro et al. [1], we dealt briefly with the etiology of the progressive scoliosis in patients with horizontal gaze palsy with progressive scoliosis (HGPPS). Therefore, in order to give a better explanation on the putative correlation between *ROBO3* mutations and scoliosis in HGPPS, we reviewed 50 articles reported in literature related with HGPPS and scoliosis from 2004 to 2017. Consistent with previous reports, no genotype–phenotype correlation exists but some features have to be stressed, allowing us some speculations about the pathogenesis of scoliosis in HGPPS. HGPPS is a rare autosomal recessive disorder characterized by congenital absence of normal horizontal eye movements and progressive scoliosis through childhood and adolescence, with no other associated neurological or behavioral abnormalities. It is caused by the mutation of *ROBO3* gene on chromosome 11 and is associated with the failure of corticospinal and somatosensory neuronal tracts to decussate in the medulla [2]. In HGPPS syndrome, scoliosis is the most common sign in terms of disability because of major functional limitation by which affected patients come to medical evaluation. It has highlighted that scoliosis begins as early as the second year of life, continuing to progress during childhood and even after skeletal maturity. Although the scoliosis enacts a substantial medical problem for all affected individual, it remains unclear whether the physiopathology of scoliosis is musculoskeletal or neurogenic. Since ROBO3 is necessary for hindbrain axons to appropriately cross the midline [3], a neurogenic mechanism has been postulated by Jen et al. [4], even though currently it is undefined how and why *ROBO3* mutations during development causes progressive scoliosis after birth and in light of our knowledge, it is not possible to state that scoliosis is linked to *ROBO3* mutations. To date, due to intrafamilial variability of the clinical features of the pathology and whereas little is known about the function of various ROBO3 domains or actions of alternative splice forms of ROBO3 in the human brainstem [5], a phenotype–genotype correlation in HGPPS has not been obvious. In fact, it is unclear if *ROBO3* mutations alter ligand recognition, protein folding, or targeting and whether resultant changes in protein function might have a differential effect on developing nerve fiber tract decussation and/or on clinical expression such as scoliosis. Since scoliosis has a highly variable clinical course amongst patients diagnosed with HGPPS, a targeted next-generation sequencing (NGS) approach could be performed in order to elucidate the possible contribution of other genes adolescent scoliosis idiopathic correlated (AIS), such as *CHL1*, *LOC642891*, *CHD7*, *DSCAM*, and *CNTNAP2* [6], and/or susceptibility factors or disease modifiers. In fact, NGS technology has been advocated as the standard of care in patients presenting with heterogeneous clinical phenotypes that could result from a wide variety of genetic causes.

Compliance with ethical standards

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

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