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Before scoliosis can be attributed to the variant c.326G>A in MYH3, its pathogenicity must be proven

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Dear Editor,

We were interested to read the article by Maccarone *et al.* about a 15-year-old girl with scoliosis, growth retardation, facial dysmorphism and delayed puberty.[1] Genetic testing revealed the heterozygous variant NM_002470.4(MYH3): c.326G>A (p.Arg109His) in MYH3. The patient benefited from a Lyon ARTbrace after refusing surgical correction of scoliosis.[1] The study is noteworthy, but several points should be discussed.

The first point is that the pathogenicity of the variant NM_002470.4(MYH3):c.326G>A is uncertain. The variant has not been reported in PubMed or Google Scholar. There is also no report on the pathogenicity of the variant in dbSNP.[2] Also according to ClinVar, the variant was only reported in the index study, but not observed in significant frequency in large population cohorts (gnomAD).[3] After in silico analyses, the variant was classified as probably pathogenic, due to this lack of evidence for the pathogenicity of the variant, biochemical and functional studies are required to prove its pathogenicity.

Secondly, MYH3 mutations usually manifest as arthrogryposis 2A, also known as Freeman-Sheldon syndrome or whistling face syndrome (mask-like face, small mouth with whistling appearance, low-set ears, broad nasal bridge, long philtrum, H-shaped dimple on the chin, windmill wing hand position and severe talipes equinovarus deformity),[4] arthrogryposis 2B3, also known as Sheldon-Hall syndrome (multiple congenital contractures, triangular face, downturned palpebral fissures, small mouth, high-arched palate, muscle weakness),[5] spondylo-carpo-tarsal synostosis syndrome type 1A or 1B,[6] or single or multiple pterygia. There is also a study of 10 families with carriers of MYH3 variants who presented with some atypical phenotypic features such as small mouth with dowslanting corners, camptodactyly, broad chest, increased distance between the nipples, enlarged knee joints with contractures and pterygia, flat feet, prominent philtrum, ptosis. clinodactyly of the 5th finger, multiple cervical and thoracic vertebral fusions, rudimentary disc spaces, rib crowding, posterior vertebral fusions, and lunotriquetral fusion.[7] Were any of these features also present in the index patient?

The third point is that it was not reported whether first-degree relatives other than the mother and grandmother were also clinically affected and whether family members other than the mother and grandmother were also carriers of the MYH3 variant. Knowing the exact segregation of the variant within the family is crucial not only for determining pathogenicity, disease progression and outcome, but also for genetic counseling. If the phenotype segregates with the genotype within a family, this indicates that the genotype is responsible. If only one patient is found in a family, the correlation between genotype and phenotype is less strong.

The fourth point is that it is incomprehensible why the index patient did not undergo genetic testing earlier than the age of 15. Short stature and facial dysmorphism must have occurred earlier than at age 15, which should have indicated a genetic defect. Has she also undergone a CGH array to rule out microdeletions or microduplications? Since the patient showed atypical features of a MYH3 mutation (delayed puberty, short stature), an additional chromosomal defect should definitely be ruled out.

The fifth point: It was not reported whether the scoliosis had a secondary effect on cardiac or pulmonary function. Since pulmonary or cardiac impairment due to scoliosis or thoracic deformity strongly influences the outcome, it is important to examine these patients prospectively for cardiac or pulmonary involvement.[8] Was there any evidence of diastolic dysfunction or impaired respiratory function? Were echocardiography and pulmonary function tests normal?

The sixth point is that the interpretation of EEG spectral analysis is highly speculative.[1] Whether the Fourier transformation of raw EEG signals can really detect altered motor innervation of axial muscles and altered processing of sensory input in scoliosis patients remains speculative.

In summary, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the con-

clusions and corroborate the study's message. Before scoliosis can be attributed to the c.326G>A variant in MYH3, its pathogenicity must be proven. Patients with a MYH3 mutation not only require treatment for scoliosis and thoracic deformity, but also cardiac and pulmonary examinations to ensure that cardiac and respiratory involvement is not overlooked.

Availability of data and material

All data are available from the corresponding author.

Consent to participation

Not applicable.

Consent for publication

Not applicable.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval

Not applicable.

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