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Reply to *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 appreciate the valuable comments regarding our recent case report on a 15-year-old girl presenting with scoliosis, growth retardation, facial dysmorphism, and delayed puberty, who was found to carry the heterozygous NM_002470.4(MYH3):c.326G>A (p.Arg109His) variant.[1] We welcome the opportunity to address the concerns raised and to further clarify aspects of our study, as constructive scientific dialogue is important for refining our understanding of the pathophysiology of scoliosis.

We acknowledge that the pathogenicity of the genetic variant has not been definitively established. MYH3 variants have been implicated in a variety of phenotypic presentations, ranging from severe congenital syndromes to milder musculoskeletal abnormalities.[2,3] Our patient exhibited subtle facial dysmorphism and musculoskeletal abnormalities. She did not present any additional dysmorphic features beyond those described in our report. Given her unusual phenotype, the diagnosis was even more challenging, and this may be one of the reasons why a diagnosis was made at age 15. Our case study contributes to expanding the known clinical spectrum and raises the possibility that this specific variant may have incomplete penetrance or variable expressivity. Importantly, our work does not suggest a causal relation between the MYH3 variant and rapidly progressing scoliosis, but it raises the possibility that scoliosis may be one of the clinical presentations of the disease. Therefore, we suggest that a rapidly developing scoliosis, coupled with other relevant clinical signs, should be taken into account as a possible indicator of syndromes that require additional investigation.[4,5]

No information on first-degree relatives or on the clinical history of the patient are reported in the original work because the primary objective of our case report is to highlight how a musculoskeletal deformity, such as scoliosis, may serve as a clinical marker of underlying pathological conditions warranting further investigation, rather than to provide a complete characterization of this specific case of MYH3 variant. The patient was referred to our rehabilitation service at the University Hospital of Padua due to rapidly progressing scoliosis. As part of a broader study investigating idiopathic scoliosis, a neurophysiological assessment was conducted, allowing for a more comprehensive evaluation of the patient's condition.[5] This initial assessment prompted additional investigations, including genetic testing, thereby discovering the genetic variant. No genetic testing was done earlier because (we can only assume since the patient was followed elsewhere) the patient presented with subtle manifestations that had never been further investigated before our evaluation for musculoskeletal deformity. Although earlier testing might have been beneficial, the patient's initial clinical features were not immediately suggestive of a known syndromic condition. Nonethless, we are happy to address the reviewer's concerns by reporting that both the mother and grandmother carried the same MYH3 variant but exhibited only mild musculoskeletal manifestations, without scoliosis or significant dysmorphism. Other first-degree relatives were unavailable for genetic testing.

While it would indeed be interesting to investigate or rule out additional chromosomal defects in conjunction with the MYH3 variant, this is outside of the scope of our investigation, which focuses on reporting the specific musculoskeletal manifestations and correlation with EEG activation in the patient. These future assessments fall outside the scope of our case report.

Cardiac and pulmonary assessments, including echocardiography and pulmonary function tests, were within nor-

mal limits at the time of evaluation. However, given the potential for scoliosis progression to affect cardiopulmonary function, long-term follow-up remains essential. Additionally, considering the role of MYH3 in muscle function, further studies could explore whether this variant might contribute to neuromuscular dysfunction affecting respiration or cardiovascular health.[3]

Finally, we acknowledge that the interpretation of EEG spectral analysis in scoliosis remains an emerging area of research.[6] While our findings suggest altered sensorimotor processing, further studies are needed to validate EEG as a reliable biomarker in the pathophysiology of scoliosis.[5,6] Specifically, prospective studies comparing EEG spectral analysis in scoliosis patients versus controls, along with additional neurophysiological and biomechanical assessments, could provide more robust evidence regarding the potential role of altered cortical activity in the pathogenesis of scoliosis.

In conclusion, this case highlights the importance of thorough evaluations in patients with atypical musculoskeletal presentations, as scoliosis may be an early marker of underlying conditions requiring further investigation. We hope our response provides clarity and contributes to an ongoing discussion on this topic.

List of abbreviations

AIS, Adolescent Idiopathic Scoliosis
EEG, Electroencephalography

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Conflict of interest

The authors declare no conflicts of interest.

Ethics approval

All methods were carried out in accordance with the guidelines of the 2008 Helsinki Declaration. Ethical approval was obtained in April 2023 (5627/AO/22).

Availability of data and materials

All data generated or analyzed during this study can be provided upon request.

Contributions

SM and EF, Development of the study design, supervision, MCM, MP, EP, PC, MR, and EF, data collection, data interpretation, MCM, MR, and EF, writing, MCM, MR, and EF, data analysis.

Informed consent

All patients participating in this study signed a written informed consent form.

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