

Review Form 3

Journal Name:	Journal of Advances in Medicine and Medical Research
Manuscript Number:	Ms_JAMMR_130750
Title of the Manuscript:	Genetic Insights into Pediatric Achalasia Cardia: A Pilot Study on Family Pedigrees and Risk Assessment in High-Consanguinity and Close Tight Populations
Type of the Article	Original Research Article

PART 1: Comments

	Reviewer's comment	Author's Feedback <i>(Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
Please write a few sentences regarding the importance of this manuscript for the scientific community. A minimum of 3-4 sentences may be required for this part.	This manuscript provides novel insights into the genetic underpinnings of pediatric congenital achalasia cardia, particularly within high-consanguinity populations, where autosomal recessive inheritance patterns are prevalent. By integrating whole-genome sequencing (WGS), targeted gene analysis (KIT, RET, ANO1, and SCN5A), and functional assays (Western blotting, immunohistochemistry), the study elucidates the molecular mechanisms underlying esophageal dysmotility and neuromuscular dysfunction. The identification of pathogenic variants and their correlation with disease severity, inheritance patterns, and consanguinity rates contributes to the growing body of literature on genetic predisposition to rare esophageal motility disorders. Furthermore, the findings highlight the critical role of genetic screening and risk assessment models in early detection, clinical management, and precision medicine, reinforcing the need for genetic counseling strategies to mitigate recurrence risk in at-risk populations. This research establishes a foundation for future genome-wide association studies (GWAS) and functional genomics investigations, facilitating the development of targeted therapeutic interventions in pediatric achalasia.	All respect for this comment.
Is the title of the article suitable? (If not please suggest an alternative title)	The current title, "Genetic Insights into Pediatric Achalasia Cardia: A Pilot Study on Family Pedigrees and Risk Assessment in High-Consanguinity and Close-Tight Populations," is informative but somewhat lengthy and could be more concise while maintaining scientific clarity. The phrase "Close-Tight Populations" is unconventional in scientific literature and could be reworded for better clarity. Suggested Alternative Titles: Genetic Insights into Pediatric Achalasia Cardia: Inheritance Patterns and Risk Assessment in High-Consanguinity Populations	Genetic Insights into Pediatric Achalasia Cardia: A Pilot Study on Family Pedigrees and Risk Assessment in Highly Consanguineous and Closely Related Populations. Sure.

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Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here.	The abstract of the article is comprehensive and presents the key components of the study, including background, methods, results, and conclusions. However, there are areas that can be improved for clarity, conciseness, and better readability. Recommended Additions: When emphasizing the genetic basis of congenital achalasia, it may benefit from a stronger emphasis on clinical implications, such as how the findings contribute to early diagnosis, targeted interventions, or genetic counseling and The inclusion of a few important statistics will strengthen the scientific impact.	The <i>KIT</i> and <i>RET</i> mutation frequency was compared between affected and non-affected members using a chi-squared test ($P < 0.001$). Differences in neural crest cell migration and protein expression were analyzed using unpaired t-tests ($P = 0.05$). Logarithm of the odds (LOD) score was calculated for linkage in affected families. Sure , we added this comments to abstract.
Is the manuscript scientifically, correct? Please write here.	The manuscript is scientifically sound and presents a methodologically rigorous study on the genetic basis of pediatric congenital achalasia cardia in high-consanguinity populations. The study incorporates genetic analyses, pedigree assessments, and statistical validations, making its conclusions credible and relevant. However, certain aspects require minor refinements to ensure absolute accuracy and clarity. The manuscript shows that in cases of achalasia, the O+ blood group is overrepresented. However, blood group susceptibility to congenital esophageal disorders is not well known in the available literature. Recommendation: Rather than concluding a direct association, the study should note that more research is needed to confirm the potential link between blood groups and congenital achalasia.	Many thanks, please verify our comment in the limitation part [Several Limitations of this cohort should be emphasized, this study's small sample size limits generalizability, and no unaffected control group was included for comparison. <u>More diverse cohorts are needed to validate the results. Future studies should include a larger sample to evaluate whether blood group antigens interact with genetic mutations (e.g., <i>RET</i>, <i>KIT</i>, <i>ANO1</i>) or other risk factors.</u>]
Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form.	The references are generally sufficient and relevant, but the manuscript would benefit from the inclusion of more recent (2020–2024) studies on genetics, precision medicine, and functional genomics of esophageal motility disorders. Some older references (1980s–1990s) could be replaced or supplemented with newer studies that reflect advancements in genomic analysis and molecular diagnostics. Consider adding 4–6 additional references from recent journals to strengthen claims regarding genetic risk factors, functional genomics, and therapeutic implications.	<ol style="list-style-type: none">Orlando, L. A., & Tan, P. (2021). Family history assessment significantly enhances delivery of precision medicine: a comprehensive evaluation. <i>Genome Medicine</i>, 13(3). GENOMEMEDICINE.BIOMEDCENTRAL.COM.Grabowski, A., Korlacki, W., Pasierbek, M., Pułtorak, R., Achteik, F., and Ilewicz, M. (2017). Pediatric achalasia: Single-center study of interventional treatment. <i>Przegląd Gastroenterologiczny</i>, 12(2), 98-104. Two recent references were added, many thanks for this comment.
Is the language/English quality of the article suitable for scholarly communications?	The manuscript is scientifically structured and follows a formal academic tone that is appropriate for scholarly communication. Technical terminology is used correctly, making the article suitable for an audience specializing in genetics, gastroenterology, and medical research. Sentence structure and coherence are generally good, and the logical flow of sections is well maintained. Some long and complex sentences make it difficult to understand. Some statements can be simplified without losing scientific rigor. Some sentences are repetitive and can be facilitated to be concise. It is suitable for academic publishing, but some sentences require grammar improvement and word choice optimization. Technical clarity is good, but small improvements in sentence structure, conciseness, and coherence will improve readability. The manuscript will benefit from professional language editing to ensure that scientific findings are communicated with maximum clarity and precision.	Dear Reviewer, thank you for your constructive feedback and for acknowledging the scientific structure, academic tone, and technical accuracy of our manuscript. We appreciate your insightful comments regarding sentence complexity, redundancy, and language optimization, as they will help improve the clarity and readability of our work. We have reviewed the manuscript for grammatical accuracy and improved word choices where necessary. This includes refining technical expressions to ensure consistency and precision in scientific communication.To further enhance readability and coherence, we have implemented professional language editing, ensuring that the manuscript is presented with maximum clarity.
<u>Optional/General</u> comments	Your study makes an important contribution to genetic research and has clinical value in early diagnosis/genetic counseling. Improving fluency, simplifying sentences, and standardizing statistical reporting will make the text much more powerful.	

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PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Are there ethical issues in this manuscript?	<u>(If yes, Kindly please write down the ethical issues here in details)</u>	