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Letter to the Editor

Comment to the Description of a Novel Cohesinopathy in Chronic Intestinal Pseudo Obstruction

TO THE EDITOR: We read with great interest the article "A novel cohesinopathy causing chronic intestinal pseudo obstruction in 2 siblings and literature review" by Venkatesh et al[1] reporting on a gene mutation in 2 patients with a clinical phenotype of chronic intestinal pseudo-obstruction (CIPO). The topic of the genetic analysis in rare forms of severe gut dysmotility is extremely cogent in the neurogastroenterology area especially because the management of CIPO is still largely ineffective and mainly centered on general measures (hydro-electrolyte balance and adequate caloric support often via parenteral nutrition). Thus, investigating genetic and molecular mechanisms may unveil novel therapeutic approaches for this orphan disorder. In any affected patient, either adult or pediatric, CIPO is characterized by a marked derangement of gut propulsion, mimicking a mechanical sub-occlusion, in the absence of any anatomical cause of obstruction. The severity of the clinical presentation is typically associated with disabling digestive symptoms, which contribute to poor quality of life and increased mortality. In the last years, several genetic causes have been identified in different subsets of CIPO patients. Heterozygous mutations in the *ACTG2* gene were found in patients with CIPO characterized by degeneration of enteric smooth muscle, as well as in the "megacystis, microcolon, and intestinal hypoperistalsis" syndrome.[2-5] X-linked CIPO has been ascribed to *filamin A* gene mutations.[6,7] *TYMP, POLG*, and *LIG3* genes have been demonstrated in recessive forms of mitochondrial CIPO.[8-10] Finally, homozygous mutations in *SGOL1* and *RAD21* genes, encoding for members of the cohesin complex, have been identified in another subset of CIPO in association with additional clinical manifestations, ie, chronic atrial and intestinal dysrhythmia (CAID),[11] or cardiac defect and long Barrett esophagus in Mungan's syndrome,[12,13] respectively. Both *SGOL1* and *RAD21* mutations are known to be causative of these 2 forms of "cohesinopathy" underlying CIPO.

In this context, Venkatesh et al[1] identified a homozygous variant in *SGOL1* in 2 siblings using next-generation sequencing analysis. The mutation was correctly interpreted to be causative, although the authors did not inform whether a target gene panel analysis, whole exome or whole genome sequencing was performed. These methodological approaches are of critical importance to exclude the presence of other putative variants of interest. Moreover, the identified variant (p.Lys23Glu) is exactly the same of that reported by Chetaille et al[11] who showed a causative homozygous variant in several Canadian pedigrees with patients affected by CIPO and atrial dysrhythmia (hence CAID, as previously mentioned). We address this in order to avoid possible misinterpretation by the reader. It would be always important to report the genomic coordinates and the dbSNP ID of a variant, as in the current case (rs199815268). This finding facilitates comparison between studies and can help identifying clinical convergence and/or differences among CIPO patients. Furthermore, the segregation of the selected variants should be pursued when possible in order to confirm that the pattern(s) of inheritance is/are correct. Since there was no report of consanguinity in the family reported by Venkatesh et al,[1] it would be very important to prove that both parents were heterozygous carriers, maybe again due to a founder effect in the corresponding geographical area, as observed in the original paper by Chetaille et al[11] in the described Canadian families.

In conclusion, we commend Venkatesh et al[1] for their effort aimed at identifying CIPO-causative variants, which is a pivotal approach to better understand the molecular defects underlying this difficult and highly challenging condition. However, data regarding mutations of any detected variants should be carefully detailed to provide a clear-cut understanding for all readers.

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