SMAD6

(SMAD Family Member 6) is a Protein Coding gene.

It belongs to the SMAD family of signaling molecules. It acts as an inhibitory SMAD, meaning that it negatively regulates signaling pathways activated by transforming growth factor-beta (TGF-beta) and bone morphogenetic proteins (BMPs). SMAD6 plays a role in various biological processes such as cell proliferation, differentiation, and apoptosis,

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SMAD6 encodes an intracellular inhibitor of the bone morphogenetic protein (BMP) signaling pathway. Until now, SMAD6 deficiency has been associated with three distinctive human congenital conditions, i.e., congenital heart diseases, including left ventricular obstruction and conotruncal defects, craniosynostosis, and radioulnar synostosis. Intriguingly, a similar spectrum of heterozygous loss-of-function variants has been reported to cause these clinically distinct disorders without a genotype-phenotype correlation. Even identical nucleotide changes have been described in patients with either a cardiovascular phenotype, craniosynostosis or radioulnar synostosis. These findings suggest that the primary pathogenic variant alone cannot explain the resultant patient phenotype [1)].

SMAD6 mutations led to poorer mathematics, performance intelligence quotient, full-scale intelligence quotient, and motor coordination, even after controlling for exogenous factors. Genetic testing may be critical for advocating early adjunctive neurodevelopmental therapy [2)]

Mechanisms to explain the remarkable diversity of phenotypes associated with SMAD6 variants remain obscure [3)].

Among 101 infants tested in the Department of Pediatric Neurosurgery, French Referral Center for Craniosynostosis, Hôpital Femme Mère-Enfant Hospices Civils de Lyon, University of Lyon, Department of Genetics, Lyon University Hospitals, INSERM U1028, CNRS UMR5292, Centre de Recherche en Neurosciences de Lyon, Department of Pediatric Cranio-Maxillo-Facial Surgery, Hôpital Femme Mère Enfant, Université Claude Bernard Lyon 1, Lyon, and Department of Genetics, Robert Debré Hospital, Inserm 1132, Université de Paris Cité, Paris, France, 13 carried a total of 13 variants; that is, 12.9% of the infants carried a variant in genes known to be involved in craniosynostosis. Seven infants carried SMAD6 variants, 2 in FGFR2, 1 in TWIST1, one in FREM1, one in ALX4, and one in TCF12. All variants were detected at the heterozygous level in genes associated with autosomal dominant craniosynostosis. Also, neurodevelopmental testing showed especially delayed acquisition of language in children with than without variants in SMAD6. In conclusion, a high percentage of young children with isolated midline craniosynostosis, especially in isolated trigonocephaly, carried SMAD6 variants. The interpretation of the pathogenicity of the genes must take into account incomplete penetrance, usually observed in craniosynostosis. The results highlight the interest in molecular analysis in the context of isolated sagittal and/or metopic craniosynostosis to enhance an understanding of the pathophysiology of midline craniosynostosis [4)].

1)
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