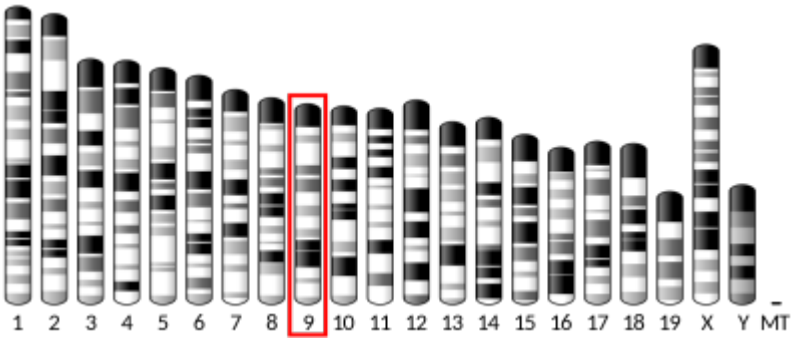
BBS9 gene in nonsyndromic craniosynostosis

Mutations in several genes account for a small number of Nonsyndromic craniosynostosis (NCS) patients; thus, the molecular etiopathogenesis of NCS remains largely unclear.



In 2012 Justice et al., conducted, the first genome-wide association study for nonsyndromic sagittal craniosynostosis (sNSC) using 130 non-Hispanic case-parent trios of European ancestry (NHW). They found robust associations in a 120-kb region downstream of BMP2 flanked by rs1884302 (P = 1.13 × 10(-14), odds ratio (OR) = 4.58) and rs6140226 (P = 3.40 × 10(-11), OR = 0.24) and within a 167-kb region of BBS9 between rs10262453 (P = 1.61 × 10(-10), OR = 0.19) and rs17724206 (P = 1.50 × 10(-8), OR = 0.22). They replicated the associations to both loci (rs1884302, P = 4.39 × 10(-31) and rs10262453, P = 3.50 × 10(-14)) in an independent NHW population of 172 unrelated probands with sNSC and 548 controls. Both BMP2 and BBS9 are genes with roles in skeletal development that warranted functional studies to further understand the etiology of sNSC [1)].

Sewda et al., identified a novel BBS9 variant that further shows the potential involvement of BBS9 in the pathogenesis of craniosynostosis (CS) [2)]

A study of Barba et al., aimed at characterizing the molecular signaling implicated in the aberrant ossification of cranial sutures in NCS patients. Comparative gene expression profiling of NCS patient sutures identified a fused suture-specific signature, including 17 genes involved in primary cilium signaling and assembly. Cells from fused sutures displayed a reduced potential to form primary cilia compared to cells from control patent sutures of the same patient.

They identified specific upregulated splice variants of the Bardet Biedl syndrome-associated gene 9 (BBS9), which encodes a structural component of the ciliary BBSome complex. BBS9 expression increased during in vitro osteogenic differentiation of suture-derived mesenchymal cells of NCS patients. Also, Bbs9 expression increased during in vivo ossification of rat sutures. BBS9 functional knockdown affected the expression of primary cilia on patient suture cells and their osteogenic potential. Computational modeling of the upregulated protein isoforms (observed in patients) predicted that their binding affinity within the BBSome may be affected, providing a possible explanation for the aberrant suture ossification in NCS [3)].

Previous genome-wide association study of sagittal nonsyndromic craniosynostosis identified associations with variants downstream from BMP2 and intronic in BBS9. Because no coding variants in BMP2 were identified, Justice et al., hypothesized that conserved non-coding regulatory elements may alter BMP2 expression. In order to identify and characterize noncoding regulatory elements near

BMP2, two conserved noncoding regions near the associated region on chromosome 20 were tested for regulatory activity with a Renilla luciferase assay. For a 711 base pair noncoding fragment encompassing the most strongly associated variant, rs1884302, the luciferase assay showed that the risk allele (C) of rs1884302 drives higher expression of the reporter than the common allele (T). When this same DNA fragment was tested in zebrafish transgenesis studies, a strikingly different expression pattern of the green fluorescent reporter was observed depending on whether the transgenic fish had the risk (C) or the common (T) allele at rs1884302. The in vitro results suggest that altered BMP2 regulatory function at rs1884302 may contribute to the etiology of sagittal nonsyndromic craniosynostosis. The in vivo results indicate that differences in regulatory activity depend on the presence of a C or T allele at rs1884302 [4].

References

1)
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