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BmpR1A is a major type 1 BMP receptor for BMP-Smad signaling during skull development

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Abstract

Craniosynostosis is caused by premature fusion of one or more sutures in an infant skull, resulting in abnormal facial features. The molecular and cellular mechanisms by which genetic mutations cause craniosynostosis are incompletely characterized, and many of the causative genes for diverse types of syndromic craniosynostosis have not yet been identified. We previously demonstrated that augmentation of BMP signaling mediated by a constitutively active BMP type IA receptor (ca-BmpR1A) in neural crest cells (ca1A hereafter) causes craniosynostosis and superimposition of heterozygous null mutation of Bmpr1a rescues premature suture fusion (ca1A;1aH hereafter). In this study, we superimposed heterozygous null mutations of the other two BMP type I receptors, Bmpr1b and Acvr1 (ca1A;1bH and ca1A;AcH respectively hereafter) to further dissect involvement of BMP-Smad signaling. Unlike caA1;1aH, ca1A;1bH and ca1A;AcH did not restore the craniosynostosis phenotypes. In our in vivo study, Smad-dependent BMP signaling was decreased to normal levels in mut;1aH mice. However, BMP receptor-regulated Smads (R-Smads; pSmad1/5/9 hereafter) levels were comparable between ca1A, ca1A;1bH and ca1A;AcH mice, and elevated compared to control mice. Bmpr1a, Bmpr1b and Acvr1 null cells were used to examine potential mechanisms underlying the differences in ability of heterozygosity for Bmpr1a vs. Bmpr1b or Acvr1 to rescue the mut phenotype. pSmad1/5/9 level was undetectable in Bmpr1a homozygous null cells while pSmad1/5/9 levels did not decrease in Bmpr1b or Acvr1 homozygous null cells. Taken together, our study indicates that different levels of expression and subsequent activation of Smad signaling differentially contribute each BMP type I receptor to BMP-Smad signaling and craniofacial development. These results also suggest differential involvement of each type 1 receptor in pathogenesis of syndromic craniosynostoses.

Keywords: Acvr1; BMP Smad signaling; Bmpr1a; Bmpr1b; Craniosynostosis.