Published online: 2019-08-26

Commentary

Single nucleotide polymorphism of BMP4 Gene: A risk factor of non-syndromic cleft lip with or without cleft palate

The authors are to be congratulated for a very focused study on one of the most promising elements of craniofacial cleft aetiology: Bone morphogenetic protein 4 (BMP4). But while they point out a relationship between alterations in the BMP4 gene the mechanism by which BMP4 deficiency might affect the closure of facial tissues is not addressed.

Access this article online	
Quick Response Code:	Website: www.ijps.org
	DOI: 10.4103/0970-0358.163054

How to cite this article: Carstens MH. Single nucleotide polymorphism of BMP4 Gene: A risk factor of non-syndromic cleft lip with or without cleft palate. Indian J Plast Surg 2015;48:164-5.

I wish to point out previously published studies by Zhang which are most enlightening because they describe a feedback loop mechanism between sonic hedgehog (SHH), the protein product of which maintains the stability of eptithelium and BMP4 as an antagonist to SHH.[1,2] Many developmental fields of the face contain one or more membranous bones, all of which are synthesized by the surrounding soft tissues and all of which are composed of mesenchyme derived from neural crest. The very process of membranous osteogenesis releases BMP4 as a soluble protein product; this takes place in all fields. The production is biochemically quantitative — the larger the bone product, the more BMP4 is produced. Thus, any reduction in the gross volume of mesenchyme will result in a quantitative diminution of the amount of BMP4. Thus, neural crest deficits in a give developmental field, be they due to a reduction in the total number of neural crest cells available within the field, or due to an alteration in the physiologic function of a normal neural crest population, will result in a reduced BMP4 signal from that field.

The importance of the papers by Zhang is that the effect of BMP4 deficit on SHH is clearly defined. Normal production of BMP4 inhibits SHH, thus permitting the fusion of craniofacial soft tissue units. Failure to inhibt SHH means that such units cannot fuse, even if they are tightly juxtaposed.

In common cleft lip the locus of the problem is a deficit within premaxilla, the most distal component of which, the frontal process, lies within the piriform margin. This is universally reduced — even in the so-called microform cleft lip in which the nasal stigmata are present while the lip may have a minimal to no alterations in its anatomy. The BMP4 signal migrates from deep to superficial and from cranial to caudal. Thus, as the degree of BMP4 deficit increases, the height of the lip notch will ascend toward the piriform fossa and superficial orbicularis gap will deepen into the underlying deep orbicularis oris.

Nature is parsimonious in her mechanisms; once she has one firmly in place, it is likely to be repeated elsewhere. Thus we find the BMP4/SHH "loop" in palate and well as lip and most likely, in all other areas of facial fusion. The importance of this mechanism is that it gives all specialists dealing with facial clefts and simple and powerful means to envision the reasons underlying the pathologic findings. It also prompts cleft surgeons to think about the problem from a developmental perspective and to utilize surgical concepts which preserve the integrity of the embyologic units to maximize growth potential and minimize the need for revisionary surgery.

Michael H. Carstens

Department of Surgery, Saint Louis University, Saint Louis, MO 63130, USA, Department of Surgery, National Autonomous University of Nicaragua Leon, Nicaragua, Department of Surgery, Military Teaching Hospital "Dr. Alejando Dávila Bolaños", Managua, Nicaragua

Address for correspondence:
Dr. Michael H. Carstens,
Department of Surgery, Military Teaching Hospital
"Dr. Alejando Dávila Bolaños", Managua, Nicaragua.
E-mail: michaelcarstens@mac.com

REFERENCES

1. Zhang Y, Zhang Z, Zhao X, Yu X, Hu Y, Geronimo B, *et al.* A new function of BMP4: Dual role for BMP4 in regulation of Sonic hedgehog expression in the mouse tooth germ. Development 2000;127:1431-43.
2. Zhang Z, Song Y, Zhao X, Zhang X, Fermin C, Chen Y. Rescue of cleft palate in Msx1-deficient mice by transgenic Bmp4 reveals a network of BMP and Shh signaling in the regulation of mammalian palatogenesis. Development 2002;129:4135-46.