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# Parathyroid Hormone-Related Protein in the Hand or Out of Hand?

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In humans, the parathyroid hormone like hormone (*PTHLH*) gene is located on the short arm of chromosome 11. The protein encoded by this gene is parathyroid hormone-related protein (PTHrP). PTHrP is normally produced in many tissues and acts at those sites in a paracrine manner. Knockout mice of the PTHLH or the parathyroid hormone (PTH) receptor 1 (PTHR1) genes and transgenic mice overexpressing PTHR1 in chondrocytes revealed the physiologic action of PTHrP in endochondral bone formation [1]. These results demonstrated that PTHrP controls the pace of growth plate development by delaying the premature differentiation of chondrocytes. Therefore, haploinsufficiency of *PTHLH* accelerates the premature differentiation of chondrocytes, without maintaining a sufficient pool of chondrocytes for normal bone size to be attained [2,3]. Furthermore, haploinsufficiency of *PTHLH* has been identified as a cause of brachydactyly type E (BDE), which is commonly associated with short stature [4-6].

Bae and colleagues [7] reported a novel mutation in *PTHLH* in a mother and son who presented with brachydactyly in the current issue of *Endocrinology and Metabolism*. However, the affected mother and son did not show short stature, and her breast development was normal. A review of previously reported patients showed that intrafamilial variability occurs in the digits affected in all patients with *PTHLH* mutation-related BDE [8]. Of the 27 reported patients, eight had normal height and only three had dental anomalies. The reason for this phenotypic variability in patients with *PTHLH* mutation-related BDE remains unclear. Very interestingly, PTHrP and PTH both interact with PTHR1. However, PTHrP has a much broader spectrum of effects and it shows more complex biological behavior. There are three splice-variant isoforms of PTHrP: PTHrP 1-139, 1-143, and 1-173. The physiologic significance of these distinct transcripts is uncertain. In addition, post-translational processing events result in N-terminal, mid-region, and C-terminal peptides, depending on the cleavage site. The existence of these peptides suggests the possibility of distinct receptors. Moreover, some biological actions of PTHrP are cell surface-independent [9]. This complexity means that many questions have remained unanswered to this day. Bae and colleagues [7] reported that a novel c.169 C>T mutation yielded a stop codon at position 57. Further studies are needed to elucidate the biological function and tissue-specificity of the protein encoded by this mutation, which were not addressed in the current study.

Finally, Bae and colleagues [7] performed whole exome sequencing in their study. PTHrP-PTHR1 signaling activates the Gsα (stimulatory G-protein)-cAMP (cyclic adenosine monophosphate)-PKA (protein kinase A)-PDE4D (phosphodiesterase 4D) pathway. Mutations in genes involved in this pathway cause pseudohypoparathyroidism and pseudopseudohypoparathyroidism (by *GNAS* [guanine nucleotide binding protein, alpha stimulating] alterations) and acrodysostosis (by *PRKAR1A* [protein kinase cAMP-dependent type I regulatory subunit alpha] or *PDE4D* mutations). All these diseases are associated with BDE. Therefore, target gene sequencing would be reasonable to identify the

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genetic cause in a family that presents with BDE.

In conclusion, this study published in *Endocrinology and Metabolism* reminds readers of the important role of PTHrP in human skeletal development. The protein is clearly secreted in our hands, but extensive understanding of this complex protein is still not in our hands. Further investigations are needed to understand the relevance of mutant PTHLH proteins and phenotypic variability in patients with *PTHLH* mutations.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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