BMP4 mutations as a novel cause of normosmic hypogonadotropic hypogonadism

A. Kemal TOPALOGLU[1,*], Ruken YILDIRIM[2], Leman Damla KOTAN[3], Gamze AKKUS[4], Ihsan TURAN[5], Edip UNAL[6], Mehmet TASTAN[3], Semine OZDEMIR DILEK[3], Fatih GURBUZ[3], Bilgin YUKSEL[3]

[1]University of Mississippi Medical Center, Department of Pediatrics, Division of Pediatric Endocrinology and Department of Neurobiology and Anatomical Sciences, Jackson, Mississippi, USA
[2]Diyarbakir Pediatric Hospital, clinic of Pediatric Endocrinology, Diyarbakir, Turkey
[3]Cukurova University, Faculty of Medicine, Division of Pediatric Endocrinology, Adana, Turkey
[4]Department of Endocrinology and Metabolism, Antakya State Hospital, Hatay, Turkey
[5]Sanliurfa Training and Research Hospital, Clinic of Pediatric Endocrinology, Sanliurfa, Turkey
[6]Dicle University, Faculty of Medicine, Department of Pediatric Endocrinology, Diyarbakir, Turkey
[*]Address for Correspondence: Topaloglu, MD at aktopaloglu@gmail.com

Background: *BMP4*, a member of the bone morphogenetic protein family which is part of the transforming growth factor-beta superfamily, is involved in the embryonic development of various organ and tissues including the cranio-facial structures, olfactory, pituitary, eyes, heart, and kidneys. Mutations in this gene are associated with orofacial cleft and microphthalmia in human patients. *BMP4* plays an important role in the embryonic development of the GnRH neurons (Forni et al., 2013, Layman et al 2011) and anterior pituitary by regulating diverse cellular responses, such as cell differentiation, migration, adhesion, and proliferation (Massague et al 2000). *BMP4* also has been described as inhibiting FSH production particularly (Nicol et al 2008). Recently, a heterozygous truncating mutation was described in a 6 years old prepubertal child with combined pituitary hormone deficiency (Rodriguez-Contreras et al 2019). Mutations in the BMP genetic network including *BMP4* were reported to be found in patients with hypogonadotropic hypogonadism (HH) in a meeting abstract (Cassatella et al., ASHG 2013). However, no detailed description of *BMP4* mutations in the etiology of HH has been found in the literature. Here we present three independent patients with isolated HH apparently due to deleterious sequence variants in *BMP4*.

Methods: We screened the whole exome sequencing data from 215 HH patients from Turkey.

Results: We identified apparently deleterious rare *BMP4* sequence variants in three independent patients with HH. All patients were normosmic. The patients did not have deficiencies of other pituitary hormones. Variant p.N150K was found in homozygosity in a patient from a consanguineous family. Interestingly, this same variant has been reported to cause renal hypodysplasia in heterozygosity as well as homozygosity in two independent patients (Weber et al 2008). Co-occurrence of HH with kidney anomalies are well known. In all three patients both FSH and LH were similarly deficient, i.e. there was not a particularly more pronounced deficiency of FSH over LH.

Patient number	DNA change	Protein change	Zygosity	Minor allele frequency in gnomAD	CADD score
P1	NM_001202.3:c.450C>G	NP_001193.2:p.Asn150Lys	Homozygous	0.00001	22.5
P2	NM_001202.3:c.41G>A	NP_001193.2:p.Cys14Tyr	Heterozygous	0.00001	24.9
P3	NM_001202.3:c.751C>T	NP_001193.2:p.His251Tyr	Heterozygous	0.00001	29.6

Conclusion: These results strongly suggest that inactivating variants in *BMP4* are novel causes of normosmic hypogonadotropic hypogonadism. This phenotype is consistent with previously described role of BMP4 in the ontogeny of the GnRH neurons and the anterior pituitary.