CHD7 mutations in patients with anosmic or normosmic idiopathic hypogonadotropic hypogonadism.

Leman Damla KOTAN[1,*], Ahmet ANIK[2], Eda MENGEN[3], Ihsan TURAN[4], Gamze AKKUS[5], Elif OZSU[6], Abdullah BEREKET[7], M. Nuri OZBEK[8], Bilgin YUKSEL[1], A. Kemal TOPALOGLU[9]

[1]Cukurova University, Faculty of Medicine, Division of Pediatric Endocrinology, Adana, Turkey
[2]Adnan Menderes University, Faculty of Medicine, Department of Pediatric Endocrinology, Aydin, Turkey
[3]Department of Pediatrics, Division of Pediatric Endocrinology, Ankara Children's Hematology and Oncology Training Hospital, Ankara, Turkey
[4]Sanliurfa Training and Research Hospital, Clinic of Pediatric Endocrinology, Sanliurfa, Turkey
[5]Department of Endocrinology and Metabolism, Antakya State Hospital, Hatay, Turkey
[6]Pediatric Endocrinology, Samsun Obsteric and Children Hospital, Samsun, Turkey,
[7]Marmara University, Division of Pediatric Endocrinology, Istanbul, Turkey
[8]Department of Pediatrics, Division of Pediatric Endocrinology and Metabolism, Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey
[9]University of Mississippi Medical Center, Department of Pediatrics, Division of Pediatric Endocrinology and Department of Neurobiology and Anatomical Sciences, Jackson, Mississippi, USA
[*]Address for Correspondence: PhD Kotan at dkotan@cu.edu.tr

Background: Mutations in *CHD7* cause a rare multi-organ system disorder, CHARGE syndrome (CS). Genital hypoplasia has been described in ~60-80% of reported cases because of idiopathic hypogonadotropic hypogonadism (IHH), which is a result of inadequate GnRH secretion in the hypothalamus. As *CHD7* is implicated in embriyonic olfactory development and GnRH migration, in patients with CS may have IHH and anosmia, mimicking anosmic IHH (Kallmann syndrome). However, in line with the large phenotypic spectrum of *CHD7*, mutations have also been reported in IHH patients without typical CS features. Therefore, we aimed to identify the phenotype of those IHH patients who do not meet any CS criteria and with variants of uncertain significance in *CHD7*.

Methods: Rare sequence variants (RSVs) in *CHD7* were screened in anosmic and normosmic IHH patients without CS classification or criteria. Identified RSVs were evaluated according to ACMG/AMP standards. gnomAD was used to identify variants with MAF <0.01%. DANN score and pathogenicity were determined using VarSome and InterVar. Only those variants with “uncertain significance” (VUS) classification was included in the study.

Results: Eight missense VUS alterations (p.Arg459Cys, p.Gly1260Ser, p.Ala2733Thr, p.Asn785Ser, p.Arg886Trp, p.Ser559Leu, p.Asp2390Glu, and p.Pro515Ala) were detected in *CHD7* from eight unrelated IHH patients without CS criteria. Six of eight patients with VUS were normosmic while two patients were hyposmic. Five of eight patients had also IHH related gene variants including *SEMA3E*, *WDR11*, *FGFR1*, *PCSK1*, *RAB3GAP2*, and *AXL* in the heterozygous state.

Patient	*CHD7* cDNA level	*CHD7* Protein level	ACMG/AMP Variant Classification	DANN	gnomAD frequency	CHD7 Database Mutation ID	Olfaction	Additional IHH gene variants
P1	c.1375C>T c.3778G>A	p.Arg459Cys p.Gly1260Ser	Uncertain significance (BP1) Uncertain significance (PM1, PM2, PP3, BP1)	0.9989 0.9987	0.0001769 -	M1338 -	normosmic	-
P2	c.1375C>T	p.Arg459Cys	Uncertain significance (BP1)	0.9989	0.0001769	M1338	normosmic	*SEMA3E* p.Gly89Ser, c.265G>A
P3	c.8197G>A	p.Ala2733Thr	Uncertain significance (BP1)	0.9986	0.00002082	M694	hyposmic	*WDR11* p.Met769Val, c.2305A>G
P4	c.2354A>G	p.Asn785Ser	Uncertain significance (PM1, PM2, BP1)	0.8933	-	-	normosmic	-
P5	c.2656C>T	p.Arg886Trp	Uncertain significance (PM1, PM2, PP3, BP1)	0.9993	0.0	-	hyposmic	*FGFR1* p.Pro700fs, c.2096_2097insG
P6	c.1676C>T	p.Ser559Leu	Uncertain significance (PM2, BP1)	0.9988	0.000004856	-	normosmic	-
P7	c.7170T>G	p.Asp2390Glu	Uncertain significance (BP4)	0.9294	0.00002522	-	normosmic	*PCSK1* p.Ala37Gly, c.110C>G *RAB3GAP2* p.Gly1373Glu, c.4118G>A
P8	c.1543C>G	p.Pro515Ala	Uncertain significance (PM2, BP1)	0.8196	-	-	normosmic	*AXL* p.Ala886Glu, c.2657C>A *PCSK1* p.Ile487Val, c.1459A>G

Conclusion: Based on our data, RSVs of uncertain significance in *CHD7* according to ACMG/AMP criteria may be associated with hyposmic or normosmic IHH. The discovery of the increasing number of RSVs in *CHD7* in patients with IHH indicate that this gene is becoming a major genetic etiology in IHH. High rate of additional gene variants in other IHH genes (62,5%) were also observed. But this may be associated with oligogenic inheritance in both anosmic and normosmic IHH. For this reason, we think that it is important not to ignore the missense variants in genes known to be usually due to disease-causing truncating mechanisms, such as *CHD7*. These findings confirm that *CHD7* variants can lead to a broad spectrum of phenotypes. Accordingly, patients with IHH phenotype regardless of their olfactory function should be tested for possible *CHD7* mutations, even if they do not have CS characteristics. In addition, major and minor criteria of CHARGE syndrome should be rechecked if *CHD7* mutations are detected to allow for more optimal patient management.

58ESPE RFC8-005
Pituitary, neuroendocrinology and puberty
Leman Damla Kotan
Poster presented at: ESPE 2019 VIENNA
PosterSessionOnline.com