**Background:** Mutations in *CHD7* cause a rare multi-organ 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 embryonic 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 anomnic 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.Asn7855Ser, 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.

**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 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.

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

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**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 | p.Arg459Cys | Uncertain significance (BP1) | 0.9989 | 0.0001769 | M1338 | normosmic | |
| c.3778G>A | p.Gly1260Ser | Uncertain significance (PM1, PM2, PP1, BP1) | 0.9987 | - | - | |
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 | 0.0002082 | 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, PP1, BP1) | 0.9993 | 0.0 | - | hyposmic | FGFR1 | p.Pro700Leu, c.2096,2097insG |
P6 | c.1676C>T | p.Ser559Leu | Uncertain significance (PM2, BP1) | 0.9988 | 0.00004856 | - | normosmic | |
P7 | c.7170T>G | p.Asp2390Glu | Uncertain significance (BP4) | 0.9294 | 0.0002522 | - | normosmic | PCSK1 | p.Ala37Gly, c.1110C>G RAB3GAP2 | p.Gly137Glu, c.4118G>A |
P8 | c.1534C>G | p.Pro515Ala | Uncertain significance (PM2, BP1) | 0.8196 | - | - | normosmic | AXL | p.Ala886Glu, c.2657C>A PCSK1 | p.Ile487Val, c.1459A>G |