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Case Report

A Clinical Case of Hypogonadism and Anosmia Associated with a New Mutation of the *KAL1/ANOS1* Gene

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Abstract

Kallmann syndrome (KS) is a genetic disease characterized by the association of anosmia or hyposmia and congenital hypogonadotropic hypogonadism (CHH). Different genes can be involved in KS, and the most frequent allelic variant in the X-linked form occurs in the *KAL1/ANOS1* gene. Differential diagnosis is made with other rare genetic diseases as CHARGE syndrome (CS) which includes hypogonadism, hyposmia, and several organ defects including eyes and heart defects. Here we report a patient with a clinical diagnosis of KS in which a new genetic gene variant was found. The patient showed hypogonadotropic hypogonadism and anosmia. The genetic analysis showed a heterozygous variant in the region 8q12.2 of the *CHD* gene (p.L2806V: c.84716C>G) and a hemizygous X-linked variant in the Xp22.31 region of the *KAL1/ANOS1* gene (p.R46H: c.137G>A). This latest is a newly identified variant and has never been described so far.

Keywords: Kallmann Syndrome; *KAL1/ANOS1* Mutations; *CHD7* Mutations; CHARGE Syndrome; Congenital Hypogonadotropic Hypogonadism; Anosmia

Introduction

Kallmann syndrome (KS) is a genetic disorder characterized by the association of GnRH deficiency resulting in congenital hypogonadotropic hypogonadism (CHH) and anosmia or hyposmia. CHH is an uncommon and clinically heterogeneous group of disorders characterized by isolated gonadotropin deficiency of varying degree with normal pituitary function leading to absent or incomplete puberty and infertility [1, 2]. The first genetic cause of KS was identified in 1991 and the estimated incidence of this syndrome is 1:30,000 in men and 1:125,000 in women [3, 4]. The severity of the disease in patients with KS significantly varies among individuals, depending on different affected genes and modes of inheritance [5, 6]. The most frequent allelic variant in the X-linked form occurs in the *KAL1/ANOS1* gene. The *KAL1/ANOS1* gene encodes anosmin 1, a glycoprotein of embryonic extracellular matrices that is involved in fibroblast growth factor (FGF) signaling [7, 8]. Other inherited patterns can be classic Mendelian ones (autosomal dominant or recessive) or more complex as in multifactorial/multigenic diseases [5]. KS is associated with numerous candidate genes and mutations can explain approximately 50% of all cases. Differential diagnosis is often made with other rare genetic diseases such as CHARGE syndrome (CS) which includes hypogonadism, hyposmia, and several organ defects. CS is a rare autosomal dominant syndrome caused by mutations of the Chromodomain helicase DNA binding protein 7 (*CHD7*) gene [9]. The estimated incidence of CS is

1:8500 live births [3]. Signs associated with CS include Coloboma, Heart defects, Atresia of choanae, Retardation of growth and development, Genital and urinary defects, Ear anomalies, and deafness. Subjects with these characteristics should be screened for mutations in *CHD7*. Mutations of the *CHD7* gene have also been described in approximately 6% of patients with CHH [1].

Here we report a clinical case of a patient with a clinical diagnosis of KS in which a new genetic *KAL1/ANOS1* gene variant was found to be associated with a rare mutation of the *CHD7* gene.

Case presentation

A 48-year-old male patient was referred to our endocrinology service for evaluation of hypogonadism. The medical history of the patient started when he was 17 years old. At that time patient was diagnosed with hypogonadotropic hypogonadism (LH <0.07mUI/mL; FSH <0.3 mUI/mL, Testosterone 3.17 ng/dL) and anosmia wherefore placed on testosterone replacement therapy to induce its pubertal development. At the time of the visit to our service, the patient reported a lack of compliance with intramuscular testosterone therapy over the years and was therefore placed again on therapy. Testosterone was topically administered at a dose of 40 mg per day and dose adjustments were made according to its hematic testosterone levels. No genetic tests had been conducted until our visit on suspicion of KS. Patient characteristics are reported in Table 1.

Sex	Male
Age at diagnosis	17 years old
Clinical features	Hypogonadotropic hypogonadism and anosmia
Laboratory before testosterone replacement	LH <0.07mUI/mL (0.8-8.6); FSH <0.3 mUI/mL (1.55-9.74), Testosterone 3.17 ng/dL (95-1042)
on testosterone replacement (last visit)	LH <0.21 mUI/mL, (0.8-8.6); FSH <0.66 mUI/mL, (1.55-9.74); Testosterone 540.00 ng/dL (132-813)
MR imaging	Absence of the olfactory bulbs and the olfactory sulcus in the left frontobasal area
Genetic analysis	Heterozygous variant in the region 8q12.2 of the CHD gene (p.L2806V: c.84716C>G) Hemizygous X-linked variant in the Xp22.31 region of the KAL1/ANOS1 gene (p.R46H: c.137G>A)
Therapy (last visit)	Testosterone 40 mg per day

Table 1: Characteristics of the patient.

In May 2019 patient history was collected and a physical examination was made at our outpatient clinic. Laboratory examination confirmed hypogonadotropic hypogonadism while cortisol circadian rhythm (ACTH 16 pg/mL, normal values (nv) 7.4-64.3; cortisol 188 nmol/L, nv 123-626) and thyroid function (TSH 0.70 mcUI/mL, nv 0.46-4.68; FT4 1.04 ng/dL, nv 0.78-2.19) showed no abnormalities. Testosterone dose was adjusted during the last visit with the achievement of adequate testosterone values (LH <0.21 mUI/mL, nv 0.8-8.6; FSH <0.66 mUI/mL, nv 1.55-9.74; Testosterone 540.00 ng/dL, nv 132-813).

A blood sample for genetic evaluation of the patient was collected after obtaining informed consent to explain the origin of the syndrome. Genes implicated in KS were amplified and verified by Sanger direct sequencing after the next-generation sequencing (NGS) of related genes using Illumina Nextera Rapid Capture Custom Enrichment kits (Illumina, San Diego, CA). NGS sequencing revealed the presence of two different gene allelic variants: a heterozygous variant in the region 8q12.2 of the *CHD g*ene (p.L2806V: c.84716C>G) and a hemizygous X-linked variant in the Xp22.31 region of the *KAL1/ANOS1* gene (p.R46H: c.137G>A) (Figure 1). This latest is a newly identified variant and has never been described so far. The patient had no other further suspected signs or symptoms of genetic disease or CS.

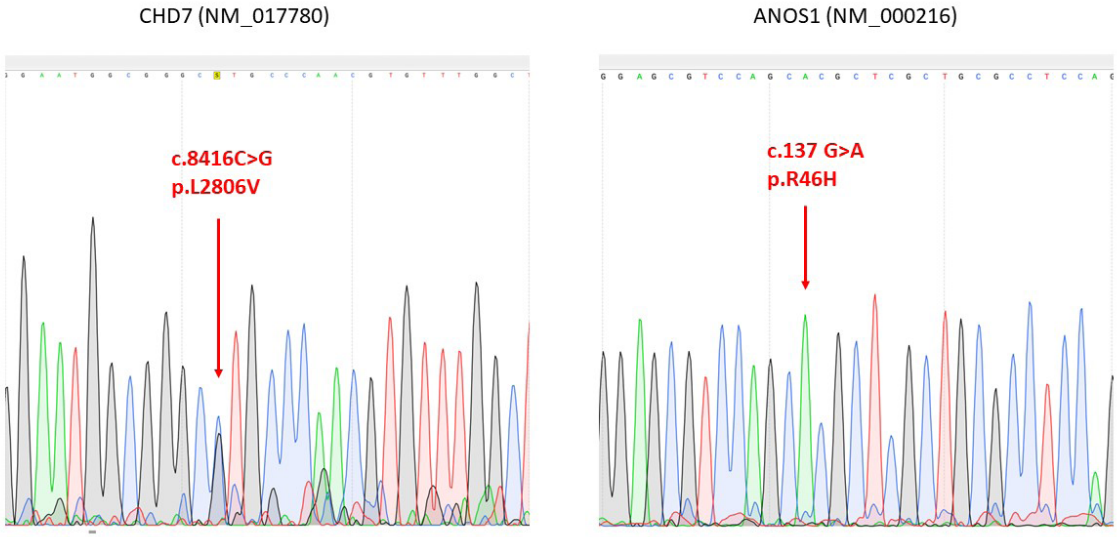

Figure 1: DNA sequence analysis showing a heterozygous variant in the region 8q12.2 of the *CHD* gene and a hemizygous X-linked variant in the Xp22.31 region of the *KAL1/ANOS1* gene.

The patient also underwent a cardiological examination and an echocardiogram which did not show any signs or symptoms of the disease. Ophthalmological and ear, nose, and throat evaluations showed no signs of CS.

Magnetic resonance (MR) imaging of the olfactory bulb and of the pituitary gland revealed a bilateral absence of the olfactory bulbs and the absence of the olfactory sulcus in the left frontobasal area, which was compatible with the diagnosis of KS (Figure 2).

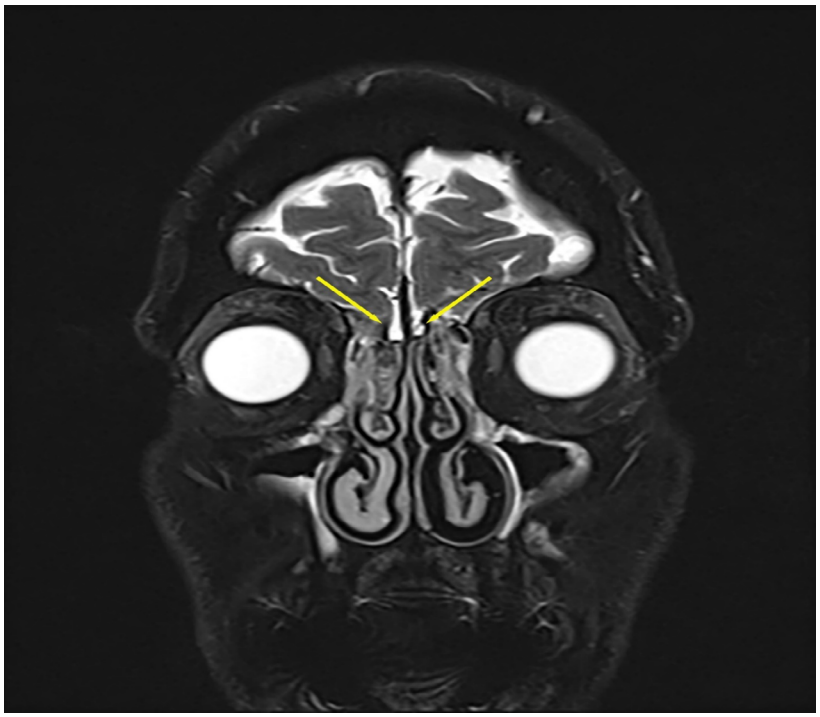

Figure 2: Patient MR image showing the absence (arrows) of the olfactory bulbs and the olfactory sulcus in the left frontobasal area.

It was requested to investigate the presence of KS also in family members, but it was not possible because at the time of the genetic evaluation, the parents had died and there were no siblings to investigate. No other suspected anomalous cases of KS or CS were described in the family.

Discussion

KS is a condition characterized by CHH and an impaired sense of smell of various degrees. KS can have additional signs and symptoms such as cardiovascular disease, metabolic syndrome, osteoporosis, psychological disorders, and renal or dental abnormalities [2, 10, 11]. Several genes mutated in KS affect the migration of GnRH neurons [5]. CHH and anosmia are frequent features also in other rare genetic disorders such as CS and it could be possible that the same embryonic migration process is altered in both syndromes. In particular, *CHD7* gene encodes a protein of the chromodomain family that can play an important role in regulating embryonic development [12]. On the other hand, during embryonic development, GnRH neurons migrate alongside the olfactory axons toward the hypothalamus, and protein products of *KAL1/ANOS1* genes are thought to be involved in this migration process [13, 14].

Both *KAL1/ANOS1* and *CHD7* genes are known to be important causal genes in the development of KS. Mutation in the *CHD7* gene can be found in approximately 75 % of CS patients and in 6-8% of patients with KS [1, 3, 5]. KS and CS are clinically highly variable characteristics and differential diagnosis between these two diseases should be considered in patients with anosmia and hypogonadism. Some authors have hypothesized that CHH can be a variant of CS and that to date the correlation between the CS phenotype and the *CHD*7 mutation in KS is not completely clear [15, 16].

The diagnosis of KS and CS is based on the clinical and hormonal evaluation of the patients, while the genetic analysis is useful for confirming the molecular diagnosis of the two syndromes. Males born with CHH can have micropenis and cryptorchidism. At puberty, male patients may not develop secondary sexual characteristics such as the growth of facial hair and deepening of the voice, while adults can have infertility. In the present case, the patient showed hypogonadotropic hypogonadism and anosmia treated with testosterone replacement to induce pubertal development during his adolescence. The MR confirmed the radiological diagnosis of KS showing the absence of the olfactory bulbs and the olfactory sulcus in the left frontobasal area. Moreover, the patient had been found to harbor two mutations in adulthood in *KAL1/ANOS1* and *CHD7* genes. Until now p.R46H variant in *KAL1/ANOS1* gene has never been reported, while p.L2806V variant was described in the literature to be associated with less severe forms of CS and with incomplete CS features [17, 18]. Our results confirm the incomplete penetrance of this *CHD7* variant which might contribute together with the novel *KAL1/ANOS1* to the KS phenotype of this patient.

In conclusion, here we report a case of KS associated with an unprecedented oligogenic involvement, a new variant in the *KAL1/ANOS1* gene, and a rare heterozygous variant in the *CHD7* gene. KS is a rare condition that must be considered for the management of patients with hypogonadism and anosmia and differential diagnosis should be made with other rare genetic diseases such as CS.

Declaration of Interest: MDP, FM, GDS, FV, and LG have no financial interest to report.

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Patient Consent: Written informed consent has been obtained from the patient for publication of this report.

Author Contribution Statement: M.D.P. collected the data and drafted the case report. G.D.S. is the physician responsible for the patient, collecting the data, and editing the manuscript. F.M. proposed and supervised the case report and edited the manuscript. B.M. and L.P. performed the genetic analysis and contributed to the MS preparation. All authors contributed to the case report editing, reading, and approving the final manuscript.

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