Acta Biomed 2019; Vol. 90, N. 4: 577-579 DOI: 10.23750/abm.v90i4.7170

Case report

A case of Kallmann syndrome associated to a novel missense mutation of the FGFR1 gene

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Summary. *Background:* Loss-of-function mutations of fibroblast growth factor receptor 1 gene (*FGFR1*) have been reported so far. These mutations have been described in the extracellular domain, consisting of three Ig-like domains in the single transmembrane helix and in the intracellular region, containing a tyrosine kinase domain and cause about 10% of all cases of Kallmann syndrome. *FRGR1* mutations could be associated with non reproductive phenotype such as cleft palate and dental agenesis and a wide spectrum of reproductive phenotype. *Case Report:* The patient, 17 years and 11 months old, was a Bulgarian male referred to our Pediatric Endocrinology Unit for pubertal failure and hyposmia. Clinical evaluation revealed a highpitched voice, gynecomastia and obesity. Hormonal study revealed hypogonadotropic hypogonadism. Molecular analysis, performed by Next Generation Sequencing and confirmed by Sanger sequencing, led to the identification of a novel and previously undescribed mutation c.1058 C>G (p. S353C) in heterozygous state on exon 8 of the *FGFR1* gene. *Conclusion:* The novel mutation, that we found in a boy with Kallman syndrome, could destabilize the D3 immunoglobulin like receptor domain that is crucial for the FGF-FGFR interaction. (www.actabiomedica.it)

Key words: Kallman syndrome, mutation, FGFR1 gene

Background

Congenital hypogonadotropic hypogonadism (CHH) is a cause of pubertal failure. It is usually due to inadequate secretion of pituitary gonadotropins, while testicular/ovarian endocrine and exocrine functions are normal. When CHH is combined with anosmia or hyposmia, it is considered Kallmann syndrome (KS) (1). The KS prevalence has been estimated at 1/8000 in males and 1/40.000 in females (2) and it accounts for approximately 40% of the total CHH cases. It is due to an abnormal embryonic development of the peripheral olfactory system characterized by impaired olfactory neuron axon elongation and GnRH cells migration (3). We report a case of a boy with KS caused by a novel mutation on *FGFR1* gene.

Case report

A Bulgarian boy, 17 years and 11 months old, referred to our Pediatric Endocrinology Unit for pubertal failure and hyposmia. His stature: 171.6 cm (-0.69 SDS), upper segment: 84.3 cm, lower segment: 87.3 cm and arm span 180 cm. His weight was 92 Kg (1.83 SDS) with BMI of 31.24 kg/m^2 (2.22 SDS). Clinical evaluation revealed a high-pitched voice, gynecomastia, obesity and valgus knees. Penile length 3.2 cm, bilateral volume testes about 2 ml and pubic hair Tanner III stage. No evidence of dysmorphic features; he had a double upper urinary tracts. Hormonal basal study revealed low values of FSH (0.29 mUI/ml), LH (0.09 mUI/ml) and testosterone (0.2 ng/ml) for sex and chronological age. GnRH stimulation test elicited

a prepubertal LH response with LH and FSH peaks of 1.18 mUI/mL and 2.43 mUI/mL respectively. The karyotype was 46,XY. Brain magnetic resonance imaging was normal. A subjective smell test confirmed hysposmia. According to this clinical and hormonal picture we hypothesized a Kallmann Syndrome and started gonadotropin therapy. After obtained an informed consent, we performed an extensive NGS mutational analysis by a specific platform including the following genes: CHD7, DUSP6, FEZF1, FGF17, FGF8, FGFR1, FLRT3, GnRH1/2, GnRHR, HS6ST1, IL-17RD, ANOS1 (KAL1), KISS1, PROK2, PROKR2, SEMA3A, SEMA3E, SEMA7A, SOX2, SOX10, SPRY4, TAC3, TACR3, WDR11. The raw data for all of the above genes were then analyzed by filtering the sequence's variants using a specific mutational reference panel for each gene (1000 Genes Project, Roche illumina data bank). The *fgfr1 gene* gave the highest score, and the final Sanger sequencing confirmed the presence of a c.1058 C>G transition in heterozygous state located on exon 8 leading to a Serine to Cystine change never previously described.

Discussion

In this case, the presence of CHH in association with defective sense of smell allowed the clinical diagnosis of KS. KS is characterized by a variable degree of hypogonadism and olfactory dysfunction, among unrelated patients and within the same family (2). A subgroup of these patients can present a specific non-reproductive phenotypes, including involuntary upper limb mirror movements (bimanual synkinesis), congenital ptosis, abnormal eye movements, agenesis of the corpus callosum, hearing impairment, unilateral (occasionally bilateral) renal agenesis, cleft lip or palate, hypodontia and obesity (4). KS can occur sporadically or be hereditary. Hereditary cases have been well documented with different inheritance: X chromosome-linked recessive, autosomal dominant and autosomal recessive (5). Several genes are involved in etiology of KS: mutations in KAL1 gene cause X-linked forms; FGFR1, FGF8, CHD7, HS6ST1, SOX10, SEMA3A, WDR11 and IL17RD are correlated to autosomal dominant form; PROKR2, PROK2 and FEZF1 are described in association with autosomal recessive and oligogenic forms (6, 7). FGFs (fibroblast growth factors) and their receptors (FGFRs) comprise a large family of signaling molecules that have been shown to play crucial roles as growth factors in vertebrate and invertebrate embryonic development. FGFR gene family consists of four highly related genes (FGFR1-FGFR4) that have distinct binding affinities with FGF ligands. FGFR1 protein is a transmembrane receptor with an extracellular region of three immunoglobulin-like domains (8). In response to FGF stimulation a variety of signaling proteins are phosphorylated, leading to activation of downstream signaling pathways (9,10). In our case, molecular analysis led to the identification of a novel and previously undescribed mutation c.1058 C>G (p. S353C) in heterozygous state on exon 8 of the fibroblast growth factor receptor 1 gene. The in silico analysis demonstrated that the mutation is located on the D3 immunoglobulin like receptor domain that is crucial for the FGF-FGFR interaction. The mutation c.1058 C>G (p.S353C) determines a rearrangement of the H bond pattern with Thre 340 leading to a repositioning of the adiacent Tyr 339 (Figure 1). Based on this preliminary evaluation there could be a significative possibility that such change could destabilize the D3 domain, hampering its function and determining a lost of efficiency in the ligand receptor interaction.

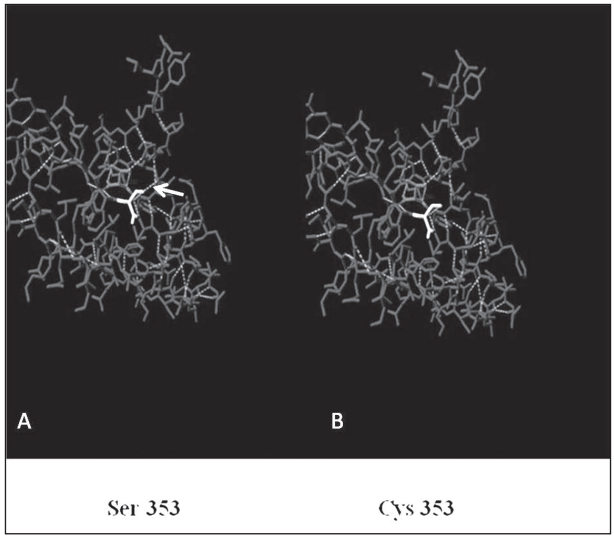

Figure 1. The mutation c. 1058 C>G (p.S353C) determines a rearrangement of the H bond pattern with Thre 340 leading to a repositioning of the adiacent Tyr 339

Experiments are in progress to prove this hypothesis. Our findings, expanding the number of the molecular defects on the FGFR1 responsible of KS, strenght the role of this gene in the pathogenesis of the disease and confirm the high molecular heterogeneity of this syndrome.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 9 March 2018
Accepted: 6 October 2018
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