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Kallmann syndrome type 2 associated with a rare missense mutation in the *FGFR1* gene: a clinical case report

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Kallmann syndrome (KS) is a rare congenital form of isolated hypogonadotropic hypogonadism (IHH) associated with anosmia or hyposmia due to impaired migration of GnRH and olfactory neurons during embryogenesis.

Objective — to describe the diagnostic work-up and clinical course of a rare case of KS type 2 associated with a mutation in the *FGFR1* gene and to substantiate the initial hormone replacement therapy strategy to optimize early detection and management algorithms in pediatric endocrinology practice.

Materials and methods. A systematic analysis of 23 contemporary peer-reviewed sources (PubMed/MEDLINE, Scopus, Web of Science) was performed with emphasis on clinical manifestations, genotype—phenotype correlations and differential diagnosis. The clinical case of a 17-year-old Ukrainian boy was reported in accordance with CARE guidelines and with informed parental consent. Comprehensive evaluation included medical history, physical examination, hormonal profiling, bone-age radiography, brain MRI with contrast, olfactometry, scrotal ultrasound, karyotyping and targeted next-generation sequencing (targeted next-generation sequencing (tNGS) panel for hypogonadotropic hypogonadism/ Disorders of Sex Development) of 93 genes performed in a certified laboratory (Labcorp/Invitae, USA).

Results and discussion. Molecular genetic analysis identified a rare heterozygous missense variant rs1064793123 in the *FGFR1* gene (c.1019C>T). This study presents the first comprehensive clinical characterization of this variant with new phenotypic manifestations, additional evidence of pathogenicity, and practical algorithms for pediatric endocrinology in Ukraine.

Conclusions. The case emphasizes the need for mandatory assessment of olfactory function in all adolescents with delayed puberty and early initiation of replacement therapy to prevent psychosocial and somatic complications.

Keywords: Kallmann syndrome 2 type, fibroblast growth factor receptor 1 (Kallmann syndrome gene 2), anosmia, *FGFR1* mutation, clinical case.

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Kallmann syndrome (KS, MIM147950) is a rare genetically determined disease (with an incidence of 1 : 4000 in males, 1 : 8000 in females) [2], which is characterized by a combination of congenital isolated hypogonadotropic hypogonadism due to insufficient secretion of gonadotropin-releasing hormone (GnRH) and anosmia/hyposmia due to aplasia/hypoplasia of the olfactory bulbs and olfactory tracts [7]. The exact official number of cases of Kallmann syndrome in Ukraine is not available in open sources. The Ukrainian Registry of Disorders of Sexual Development (DSD) as of 2022 describes 682 cases with various forms of DSD, including 4 patients with the classic clinical picture of Kallmann syndrome and genetic confirmation [2].

According to the 2015 European Consensus on Congenital Hypogonadotropic Hypogonadism [5], the diagnosis of KS is established in the presence of: clinical and laboratory signs of hypogonadotropic hypogonadism (low/inadequately normal levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and sex steroids in the absence of puberty); objectively confirmed anosmia/hyposmia using olfactometry, magnetic resonance imaging (MRI) of the olfactory bulbs; exclusion of other causes of central hypogonadism (pituitary tumors, post-traumatic changes, infectious processes, etc.).

The association between hypogonadism and anosmia was first noted in 1856 by the Spanish anatomist Aureliano Maestre de San Juan, who described the complete absence of olfactory bulbs, underdeveloped testicles, micropenis, and absence of pubic hair in an autopsy of a 40-year-old man. In 1861, the Austrian pathologist Richard Ladislaus Heschl published a similar case with «bean-sized testicles», a «feminine» type of laryngeal anatomy, and anosmia. The syndrome, as a distinct clinical and hereditary phenotype, was first described in detail in 1944 by the German-American psychiatrist and geneticist Franz Josef Kallmann in his work «The Genetic Aspects of Primary Eunuchoidism» (American Journal of Mental Deficiency). F.J. Kallmann analyzed three family clusters (12 affected individuals) and proved the hereditary nature of the combination of hypogonadotropic hypogonadism with anosmia (and, sometimes, color blindness). It was in his honor that the syndrome received its modern name. In the 1950s, the Swiss anatomist Georges de Morsier additionally documented hypoplasia or aplasia of the olfactory bulbs and tracts in patients with hypogonadism. After the discovery of GnRH in the 1970s, it became clear that the basis is an isolated deficiency of its secretion due to impaired migration of GnRH neurons from the olfactory placode [15].

The pathogenesis of KS is due to mutations in genes (*ANOS1, FGFR1, PROKR2*, etc.) that disrupt the migration of GnRH neurons from the olfactory placode to the hypothalamus [6, 14, 18].

Currently, more than 30 different genes are associated with KS [14], which explain about 50 % of cases of the disease (Table 1).

One of the most important recent discoveries in the genetic component of Kallmann syndrome is that it can be inherited in different patterns and is not always monogenic. In 10—20 % of cases, oligogenicity is observed, when the patient has mutations in two or more different genes at the same time. This helps to explain the great variability of symptoms even among members of the same family with the same underlying mutations. In KS, the phenomenon of spontaneous recovery (reversion/spontaneous resumption of endogenous gonadotropin secretion even after discontinuation of treatment) is also considered, which is observed in 10—20 % of cases after a course of puberty induction, emphasizing the need for continuous medical supervision [12, 24].

Objective — to describe the diagnostic work-up and clinical course of a rare case of Kallmann syndrome type 2 caused by a mutation in the *FGFR1* gene and to justify the initial hormone replacement strategy to optimize early detection and management algorithms in pediatric endocrinology practice.

Materials and methods

Presented in accordance with the CAse REport (CARE) standards [20] and with the informed consent of the child's legal representatives, the clinical case is a description of Kallmann syndrome type 2 associated with a heterozygous mutation in the *FGFR1* gene, confirmed by molecular genetic methods in a certified laboratory Labcorp/Invitae (USA). Genetic diagnostics were performed using targeted next-generation sequencing tNGS of 93 genes (Hypogonadotropic panel/Panel of sexual development disorders). The genetic study was approved by the child's parents and the ethics committee of the Dnipro State Medical University (Protocol No. 18 dated 04/17/2025).

The main method of the study was a clinical examination of the patient during inpatient treatment with analysis and interpretation of the obtained clinical, anamnestic, laboratory and instrumental data. The list of additional paraclinical examination methods was compiled in accordance with the Order of the Ministry of Health of Ukraine No. 254 dated April 27, 2006 «Protocol for providing medical care to boys with delayed sexual development»; «Protocol for the provision of medical care to boys with cryptorchidism», as well as in accordance with the expert consensus of the European Consensus Statement/Clinical Practice Guidelines of the Endocrine Society on the optimization of clinical strategies for the early detection and treatment of hypogonadotropic hypogonadism [4, 5].

The search for scientific publications was carried out in the international scientometric databases PubMed (MEDLINE), Scopus, Web of Science and Google Scholar. The search query was formed using Boolean logical operators (AND, OR) and contained combinations of the following keywords (MeSH

Table 1
Genes associated with the development of Kallmann syndrome and isolated hypogonadotropic hypogonadism

Gene	Full name (HGNC/ NCBI Gene, 2026)	Main role in the pathogenesis of KS/IHH	Inheritance pattern and mutation features	Additional associated features
I. Major genes				
ANOS1 (*KAL1*)	Anosmin 1 (Kallmann syndrome 1 gene)	Extracellular glycoprotein; ensures adhesion and migration of GnRH neurons and olfactory axons	X-linked recessive (mainly affects males)	Renal anomalies (unilateral renal agenesis), synkinesia (mirror hand movements)
FGFR1 (*KAL2*)	Fibroblast Growth Factor Receptor 1 (Kallmann syndrome 2 gene)	FGF receptor; critical for proliferation, migration of GnRH neurons and development of olfactory bulbs	Autosomal dominant (often *de novo*)	Cleft lip/palate, skeletal anomalies, dental agenesis
CHD7	Chromodomain Helicase DNA-binding Protein 7	Chromatin remodeler; regulates hypothalamic and olfactory system development	Autosomal dominant	CHARGE syndrome (coloboma, heart defects, choanal atresia, ear anomalies)
PROKR2 and *PROK2*	Prokineticin Receptor 2 and Prokineticin 2	Signaling pathway for GnRH neuron migration and olfactory tract formation	Autosomal dominant or recessive (often oligogenic)	Classic KS or normosmic IHH, sometimes obesity
II. Other significant genes				
FGF8 and *FGF17*	Fibroblast Growth Factor 8 and 17	Ligands of *FGFR1*; stimulate induction and migration of GnRH neurons	Autosomal dominant or digenic	KS/nIHH, sometimes hypothalamic defects
SOX10	SRY-Box Transcription Factor 10	Regulates development of the neural crest and olfactory system	Autosomal dominant	Sensorineural hearing loss, Waardenburg syndrome (pigmentary anomalies)
WDR11	WD Repeat Domain 11	Interaction with *EMX1*; development of hypothalamus and olfactory bulbs	Autosomal dominant	KS with or without anosmia
HS6ST1	Heparan sulfate 6-O-sulfotransferase 1	Modification of heparan sulfate (FGF co-receptor); enhances FGF signaling	Autosomal dominant or oligogenic	KS, sometimes additional endocrine disorders
SEMA3A	Semaphorin 3A	Repulsive axonal guidance of olfactory axons and GnRH neurons	Autosomal dominant or digenic	KS, hyposmia
III. Additional (candidate / oligogenic) genes				
FEZF1	Fez Family Zinc Finger 1	Transcription factor; forebrain neuron specification and GnRH migration	Autosomal recessive	Normosmic IHH or KS
NSMF (*NELF*)	NMDA Receptor Synaptonuclear Signaling and Neuronal Migration Factor (Nasal Embryonic LHRH Factor)	Migration of GnRH neurons from the nasal placode	Autosomal dominant, recessive or digenic	KS/nIHH, sometimes reversible hypogonadism
DUSP6	Dual Specificity Phosphatase 6	Negative regulator of MAPK/ERK pathway (downstream of *FGFR1*)	Autosomal dominant (HH19), often digenic with *FGFR1*	KS/nIHH
SPRY4	Sprouty RTK Signaling Antagonist 4	Negative regulator of RTK/FGF signaling	Often digenic/ oligogenic	Phenotype enhancement in gene combinations
FLRT3	Fibronectin Leucine Rich Transmembrane Protein 3	Modulation of FGF receptors and cell adhesion during neuronal migration	Often digenic (with *FGFR1*)	KS/nIHH in oligogenic context

terms): «Kallmann syndrome», «fibroblast growth factor receptor 1 (Kallmann syndrome gene 2)», «hypogonadotropic hypogonadism», «secondary hypogonadism», «anosmia», «hyposmia». Inclusion criteria: original studies, clinical case reports, literary, narrative and systematic reviews regarding Kallmann syndrome. Excluded: theses, letters, works without full text. 87 records were identified, 52 were retained after duplicate removal, 34 after screening, and 23 articles were included after full-text analysis.

Patient information

The *patient G.D.O.*, a boy born on July 30, 2008 (17 years 6 months at last visit).

Chief complaints and history

Main complaints: delayed sexual development, growth retardation, complete lack of sense of smell (actively detected during a targeted survey).

Born from the first pregnancy, full-term delivery, birth weight 3200 g. Early development without features. No family history of similar disorders.

First visit to an endocrinologist in 2011 (at the age of 3 years), regarding bilateral cryptorchidism, in connection with which the child underwent testicular orchiopexy with an interval of one year.

Since 2017 — regular observation: hypoplasia of the left testicle, low LH with normal free testosterone.

Since 2022 — progressive growth retardation (height –1.85...–2.1 σ) and absence of pubertal signs (Tanner G1P1). Basal gonadotropic hormones and testosterone are persistently low.

In March 2025 (age 16.7 years), a test was performed with diphereline 0.1 mg i.m. — basal LH/FSH low, after loading, luteinizing hormone — 6.91 mIU/ml (reference 0.5—8.0 mIU/ml), follicle-stimulating hormone — 2.08 mIU/ml (reference 0.61—7.9 mIU/ml), 4 hours after loading luteinizing hormone — 3.19 mIU/ml (reference 0.5—8.0 mIU/ml), follicle-stimulating hormone — 3.19 mIU/ml (0.61—7.9 mIU/ml), which was verified as the absence of a pubertal reaction in the classical sense for a test with an agonist.

03/17/2025 — MRI of the brain with contrast: no pathological changes (olfactory tubercles and sulci are not described as hypoplastic).

04/14/2025 — olfactometry: complete anosmia on both sides.

Clinical findings (January 21—22, 2026)

Height 161.5 cm (–1.8 σ for age), +2 cm over the last year; body weight 57.6 kg; body mass index 22.1 kg/m^2. Body structure normosthenic, proportional. Skin clean, vitiligo on the left elbow joint.

Sexual development: F1Ax2P2G2 (Penis length-5Testicular volum4), corresponds to 11—12 years. External genitalia are formed according to the male type, testicles are reduced (ultrasound examination (US) of the scrotum: right testicle 26 × 13 mm, left testicle 26 × 12 mm).

Bone age (radiography of the hand and wrist 01/21/2026, protocol: paraarticular enostal compaction (paraarticular enostosis) is determined in the area of the hook bone) — 12.5—13.0 years.

Passport age 17.6 years; physical development corresponds to 13.9 years.

Diagnostic work-up

Hormonal profile (dynamics of key indicators):

LH 0.56—0.86 mIU/ml (low), FSH 0.69—1.12 mIU/ml (low/lower limit).

Total testosterone 0.36—2.84 nmol/l (significantly below normal), free testosterone 0.13—6.07 pg/ml (mostly low). Anti-Mullerian hormone 14.9 ng/ml (elevated), inhibin B 98 pg/ml (normal). According to the results of the test with triptorelin at a dose of 0.1 mg, the diagnosis of secondary hypogonadism was confirmed.

Thyroid stimulating hormone (TSH) — 7.875 μIU/ml (confirms subclinical hypothyroidism), Thyroxine free (fT4) — 2.08 ng/dl, Antibodies to thyroperoxidase (Ab-TPO) — 166.9 IU/ml (confirms chronic autoimmune thyroiditis).

Hematological and biochemical parameters — without significant deviations.

Comorbidity: chronic autoimmune thyroiditis, subclinical hypothyroidism (TSH up to 7.875 μIU/ml); steatotic liver disease associated with metabolic dysfunction, skeletal abnormalities.

Cytogenetic examination: karyotype 46XY.

Molecular genetic examination was performed in August 2025. As a result of the examination, three heterozygous variants of uncertain clinical significance (VUS) were identified: FGFR1, SPECC1L and TNK2.

A detailed analysis of the most relevant mutation SNV rs1064793123 of the FGFR1 gene c.1019C>T (p.Thr340Met) discovered by us for the first time is provided in Table 2.

The other two VUS (SPECC1L c.514G>A (p.Asp172Asn and TNK2 c.3058C>T p.Arg1020Trp) are less relevant for the KS phenotype.

Differential diagnosis

In an adolescent with a clinical picture of delayed sexual development, growth retardation, a history of cryptorchidism, and confirmed anosmia, differential diagnosis is performed with the following conditions (Table 3).

Thus, analysis of data regarding «red flags» [11], such as the combination of a history of cryptorchidism, hypogonadotropic hypogonadism, objectively confirmed anosmia, delayed bone age, and the presence of SNV rs1064793123 of the *FGFR1* gene, demonstrated compliance with the diagnostic criteria for Kallmann syndrome type 2 and excluded other alternative diagnoses.

Therapeutic intervention

1. *Sex steroid replacement therapy* is the most common treatment, focusing on the development of external signs of puberty but not on testicular growth or stimulation of fertility. The patient was prescribed a prolonged-release form of testosterone enanthate 50 mg intramuscularly once a month, with subsequent dose titration to mimic natural puberty and maximize growth potential, gradually increasing the dose to the adult dose over 18—24 months [17].
2. *Gonadotropin therapy* — This method stimulates the gonads to produce their own hormones, which is a more physiological approach. For boys, injections of human chorionic gonadotropin (hCG), which acts like LH, are used, sometimes in combination with FSH. The sequential approach involves priming boys with very small testes (less than

Table 2
Analysis of the missense mutation SNV rs1064793123 in the *FGFR1* gene

Genetic Component	Description
Nomenclature and variant characteristics	NM_023110.3(FGFR1):c.1019C > T, p.(Thr340Met)/T340M. Type: missense (single nucleotide variant — SNV). Exon: 8. dbSNP: rs1064793123
Population frequency of the variant	Absent in gnomAD (AF = 0) — a rare variant not observed in healthy populations
Localization of the variant in the *FGFR1* protein structure	Extracellular Ig-like domain III (D3) — the key region for FGF ligand binding and *FGFR1* receptor dimerization
Molecular nature of the amino acid substitution	Substitution of polar hydrophilic threonine (Thr) with non-polar hydrophobic methionine (Met) at position 340
Structural and functional consequences at the protein level	Disruption of local domain structure, decreased receptor stability, impaired FGF-8/FGF-17 binding and conformational changes required for tyrosine kinase domain activation («loss-of-function» effect)
In silico analysis results	GeneDx: supports a deleterious effect. Invitae Evidence Modeling (structural, functional, spatial properties, conservation, thermodynamic stability): negative predictive value ≈80 % regarding functional impairment
Impact on the conserved amino acid residue	Disrupts the highly conserved residue p.Thr340 (other variants altering this residue have already been described in *FGFR1*-associated disorders)
Clinical significance according to ClinVar (VCV000418207.7, as of 2026)	Conflicting classification: Likely pathogenic (Hartsfield syndrome [12]) / Variant of Uncertain Significance (VUS) (Labcorp, Invitae, GeneDx — for hypogonadotropic hypogonadism type 2 with/without anosmia and Pfeiffer syndrome)
Association with the gene and disease	The FGFR1 gene is responsible for autosomal dominant Kallmann syndrome type 2 (MedGen UID: 289648)
Reported clinical cases	The T340M variant has previously been identified in patients with the phenotype of Kallmann syndrome/normosmic IHH [13–16]. In the Chinese cohort [14], similar *FGFR1* mutations were accompanied by additional features: dental agenesis, hearing impairment, and limb defects
Significance of the variant for the patient	The clinical phenotype (hypogonadotropic hypogonadism, cryptorchidism, anosmia, delayed bone age) fully correlates with the *FGFR1* «loss-of-function» effect. Heterozygosity is consistent with autosomal dominant inheritance

Table 3
Differential diagnosis of Kallmann syndrome in the presented patient

No.	Differential diagnosis	Key differences from the present case	Reason for exclusion
1	Constitutional delay of growth and puberty (CDGP)	Normal sense of smell, positive family history of delayed puberty, normal or pubertal response to GnRH stimulation test, spontaneous puberty after age 18 years	Complete anosmia confirmed by olfactometry, absent LH response to triptorelin stimulation test, persistently low gonadotropins and testosterone, pathogenic *FGFR1* variant
2	Isolated hypogonadotropic hypogonadism without anosmia (normosmic IHH)	Absence of olfactory impairment	Confirmed bilateral anosmia by olfactometry
3	Panhypopituitarism/pituitary or hypothalamic tumors/traumatic or infectious hypogonadism	Other pituitary hormone deficiencies (TSH, adrenocorticotropic hormone (ACTH) and growth hormone (GH)), pathological findings on MRI	Normal brain MRI, no other pituitary hormone deficiencies (fT4 and cortisol levels within reference ranges or not reported as decreased)
4	Syndromic forms of hypogonadism: · Prader-Willi syndrome (PWS) · Bardet-Biedl syndrome (BBS) · CHARGE syndrome · Hartsfield syndrome (HS)	Obesity + hypotonia (PWS); polydactyly, retinopathy, obesity (BBS); coloboma, choanal atresia, heart defects (CHARGE); holoprosencephaly and diabetes insipidus (HS)	Absence of characteristic extragonadal features, normal body mass index 22.1 kg/m², normal echocardiography
5	Hypergonadotropic hypogonadism (Klinefelter syndrome 47, XXY, anorchia after orchiopexy, testicular failure) [17]	Elevated LH and FSH, small testicular volume, high FSH	Low LH and FSH, normal/elevated anti-Müllerian hormone (14.9 ng/mL), normal male karyotype 46, XY
6	Functional (hypogonadotropic) hypogonadism	Excessive physical activity, anorexia, chronic systemic diseases, hyperprolactinemia	No corresponding history, normal hematological and biochemical parameters (including TSH within reference range)

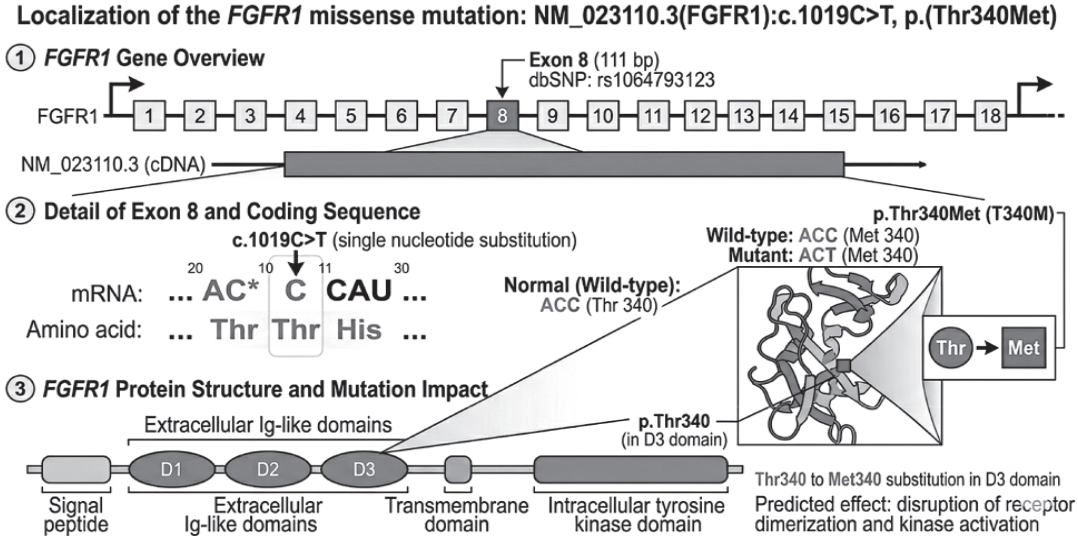

Figure. **Molecular and genetic features of type 2 KS [3, modification of authors]**

4 mL) with FSH for several months before adding hCG, which promotes Sertoli cell proliferation [25].

3. *GnRH pulse therapy* is the most physiological method, using a special portable pump. The pump mimics the natural release of gonadotropin-releasing hormone (GnRH) by the hypothalamus, delivering the drug every 90—120 minutes. This method successfully restores the secretion of the pituitary's own hormones (LH and FSH), stimulating virilization and testicular growth simultaneously. Studies show that GnRH pulse therapy may be more effective than hCG for inducing puberty in boys.

Results and discussion

At the time of the description, the patient has just started replacement therapy. Puberty induction, growth acceleration, and improvement of psychoemotional state are expected. Control of blood serum parameters after 1 month (FSH, LH, total/free testosterone, complete blood count); after 3 months — extended control (FSH, LH, total/free testosterone, sex hormone binding globulin (SHBG), prostate-specific antigen (PSA), hematocrit, ALT, AST, bilirubin fractions, complete blood count); after 6 months — breast ultrasound.

Long-term observation is planned in the endocrinology department with control of bone density and fertility (in the future — pulse therapy with gonadotropins or GnRH). Considering the fact that patients with KS have anosmia, it is mandatory to install smoke or gas detectors in residential premises and monitor food expiration dates. At the same time, the presence of pronounced microorchidism, cryptorchidism, low levels of anti-Müllerian hormone and inhibin B, and an unsatisfactory response to previous treatment with hCG indicate an extremely unfavorable prognosis for the course of the disease. To achieve fertility in some patients with KS, assisted reproductive technologies may be used [9, 22].

In this study, we identified a novel mutation in the *FGFR1* gene in a Ukrainian young man with Kallmann syndrome. The presented case meets the classic diagnostic criteria for Kallmann syndrome type 2: 1) hypogonadotropic hypogonadism (low basal LH/FSH and low testosterone); 2) anosmia confirmed by olfactometry; 3) MRI of the pituitary gland with contrast without pathological changes; 4) history of cryptorchidism; 5) missense mutation, genotype CT SNV rs1064793123 of the *FGFR1* gene.

At the same time, the clinical case contains a unique phenotypic spectrum: a combination of classic KS type 2 with steatotic liver disease associated with metabolic dysfunction and paraarticular enostal consolidation of the hook bone.

Mutations in the *FGFR1* (*KAL2*) gene account for 5—10 % of all cases of KS with an autosomal dominant inheritance pattern and incomplete penetrance. The absence of severe skeletal and facial deformities in our patient confirms the incomplete penetrance of mutations in this gene, which is described in the works of T. Hacquart, et al. [10].

The association of the phenotypic manifestations provided by us with the genotype of CT SNV rs1064793123 of the *FGFR1* gene is responsible for autosomal dominant Kallmann syndrome type 2 (MedGen UID: 289648). The pathogenicity of the identified variant was predicted by in silico analysis. The T340M variant has previously been described in patients with the Kallmann syndrome/normosmic IgG phenotype [1, 13, 19]. In a Chinese cohort [16], similar *FGFR1* mutations were accompanied by additional features (tooth agenesis, hearing impairment, limb defects).

The molecular consequences of this mutation are the replacement of a polar hydrophilic threonine (Thr) with a nonpolar hydrophobic methionine (Met) at position 340. This disrupts the local domain structure, receptor stability, FGF-8/FGF-17 binding, and conformational changes required for activation of the

tyrosine kinase domain. The variant disrupts the conserved residue p.Thr340 [3] (Figure).

The absence of other pituitary deficiencies excludes panhypopituitarism. The concomitant autoimmune thyroiditis is probably coincidental, although rare associations with autoimmune diseases have been described. Differentiation was made with constitutional delayed puberty (no response to GnRH agonist challenge, anosmia) and other forms of IgG.

Similar to our clinical observation, in which KS was associated with steatosis liver disease associated with metabolic dysfunction and enostosis, Y. Soejima et al. also reported a similar case of association in latent hypogonadism [23], noting that loss of *FGFR1* function not only disrupts GnRH neuron migration but also affects gonadal steroidogenesis and metabolism (via the *FGF21/FGFR1*/KLB pathway). *FGFR1* affects osteogenesis, therefore variations in bone density/carpal structures are possible, but enostosis is more often associated with osteopoikilosis, melorheostosis or incidental changes.

Literature data, including Ukrainian publications [2], emphasize that in 60 % of cases central hypogonadism is caused by Kallmann syndrome and confirm that early replacement therapy prevents osteoporosis, improves quality of life and psychosocial adaptation.

Conclusions

The presented clinical case demonstrates the importance of including olfactory assessment in the evaluation of any adolescent with delayed sexual development. Since patients may not be aware of their anosmia, formal testing (e.g., using odor panels) is necessary.

Early diagnosis of Kallmann syndrome allows for timely initiation of hormone replacement therapy, prevention of complications, and optimization of fertility prognosis.

Routine genetic testing and a multidisciplinary team approach (endocrinologist, geneticist, otolaryngologist, psychologist) are recommended.

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Синдром Каллмана 2 типу, асоційований з рідкісною міссенс-мутацією гена *FGFR1*: клінічний випадок

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Синдром Каллмана (КС) — рідкісна вроджена форма ізольованого гіпогонадотропного гіпогонадизму (ІГГ), що поєднується з аносмією або гіпосмією внаслідок порушення міграції GnRH-нейронів та нюхових нейронів під час ембріогенезу.

Мета роботи — описати особливості діагностичного пошуку та клінічного перебігу рідкісного випадку синдрому Каллмана 2 типу, асоційованого мутацією гена *FGFR1*, а також обґрунтувати первинну тактику замісної гормональної терапії для оптимізації алгоритмів раннього виявлення та ведення таких хворих у практиці дитячого ендокринолога.

Матеріали та методи. Було проведено систематичний аналіз 23 сучасних рецензованих джерел (PubMed/MEDLINE, Scopus, Web of Science) з акцентом на клінічні прояви, кореляції генотип-фенотип та диференціальну діагностику КС. Клінічний випадок 17-річного українського хлопчика було описано відповідно до рекомендацій CARE та за інформованою згодою батьків. Комплексна оцінка включала анамнестичні дані, фізикальне обстеження, гормональне профілювання, рентгенографію кісткового віку, МРТ головного мозку з контрастуванням, ольфактометрію, ультразвукове дослідження калитки, каріотипування та цільове секвенування наступного покоління (tNGS Панелі: Гіпогонадотропний гіпогонадизм/Розлади статевого розвитку) 93 генів, проведене в сертифікованій лабораторії (Labcorp/Invitae, США).

Результати та обговорення. У роботі представлено перший повний клінічний портрет рідкісного гетерозиготного міссенс-варіанта rs1064793123 гену *FGFR1* —c.1019C>T з новими фенотиповими проявами, додатковими доказами патогенності та практичними алгоритмами для дитячих ендокринологів в Україні.

Висновки. Кейс підкреслює необхідність обов'язкового опитування щодо нюхової функції у всіх підлітків із затримкою статевого дозрівання та раннього початку замісної терапії для запобігання психосоціальним та соматичним ускладненням.

Ключові слова: синдром Каллмана 2 типу, рецептор 1 фактора росту фібробластів (ген 2 синдрому Каллмана), аносмія, мутація *FGFR1*, клінічний випадок.

ДЛЯ ЦИТУВАННЯ • *FOR CITATION*

- Abaturov OE, Nikulina AO, Yenhovatova VA, Turova SV. Kallmann syndrome type 2 associated with a rare missense mutation in the *FGFR1* gene: a clinical case report. Український журнал дитячої ендокринології. 2026;1:23-30. doi: 10.30978/UJPE2026-1-23.
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