REVIEW

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Genetics of Idiopathic Hypogonadotropic Hypogonadism

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ABSTRACT

Idiopathic hypogonadotropic hypogonadism (IHH) comprises a group of disorders characterized by deficient secretion or action of gonadotropin-releasing hormone (GnRH), leading to impaired pubertal development and infertility. Traditionally, IHH is classified into Kallmann syndrome, associated with anosmia, and normosmic IHH, in which olfactory function is preserved. The condition exhibits marked genetic heterogeneity. Advances in next generation sequencing have significantly expanded the genetic landscape of IHH, with pathogenic variants identified in over 60 genes, accounting for up to 50% of cases. Oligogenic inheritance is increasingly recognized, occurring in 10-20% of individuals. The potential for spontaneous or treatment-induced clinical recovery in a subset of patients, along with phenotypic overlap with constitutional delay of growth and puberty, presents additional diagnostic challenges. Despite these complexities, genetic studies of IHH have provided critical insights into fundamental neuroendocrine processes, most notably the recent elucidation of the Kisspeptin, Neurokinin B, Dynorphin neurons as the GnRH pulse generator. These discoveries have also informed the development of targeted therapies, exemplified by the recent FDA approval of fezolinetant, a neurokinin B receptor antagonist, for the treatment of menopausal vasomotor symptoms.

Keywords: Hypogonadotropic hypogonadism, delayed puberty, genetics, etiology

Introduction

In vertebrates, gonadotropin releasing hormone (GnRH)-secreting neurons develop outside the central nervous system, originating from the nasal placode. They migrate along olfactory-derived vomeronasal axons to their final location in the hypothalamus (1).

The activity of the hypothalamic-pituitary-gonadal (HPG) axis demonstrates significant variability across the human lifespan (2). During early adolescence, a gradual reactivation of this neuroendocrine axis initiates the development of secondary sexual characteristics and the maturation of the reproductive system, marking the onset of puberty. This complex developmental process typically starts around 10 to 11 years of age in girls and boys respectively and spans from two to five years. Epidemiological data suggest that approximately 50% to 75% of the variation in the age at onset of puberty is influenced by genetics (3). The failure to undergo pubertal progression results in sexual immaturity and infertility, a clinical state referred to as hypogonadism. When this condition arises from anatomical malformations or functional impairments that compromise the secretion of GnRH or the subsequent release of pituitary gonadotropins, it is specifically classified as hypogonadotropic hypogonadism (HH).

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Idiopathic Hypogonadotropic Hypogonadism

The term idiopathic HH (IHH) refers to a condition characterized by delayed or absent sexual maturation due to deficient secretion or action of GnRH, in the absence of any identifiable anatomical or functional cause. IHH is traditionally categorized into two main forms: Kallmann syndrome (KS), which is associated with anosmia or hyposmia, and normosmic IHH (nIHH), in which olfactory function remains intact. IHH may be either congenital or acquired, with congenital cases comprising the majority of those that have a hereditary basis. In female individuals, clinical signs typically do not become evident until the early adolescent years. In contrast, male infants may exhibit signs of reproductive dysfunction at birth due to the critical activity of the HPG axis between the sixteenth and twenty-second weeks of gestation, a period during which androgen production is essential for the proper virilization of the male fetus with a 46,XY karyotype. As a result, congenital IHH in males may present with micropenis and/or undescended testes (cryptorchidism) at birth. In some cases, the degree of under-virilization is sufficient to warrant evaluation for a "disorder of sexual development". The brief reactivation of the HPG axis during early infancy, commonly referred to as "minipuberty", occurring approximately between four and sixteen weeks of life, presents a valuable diagnostic window during which both male and female infants with congenital IHH may be identified (4). KS is typically attributed to aberrant embryonic development and/or disrupted migration of GnRH-secreting neurons. During embryogenesis, these GnRH neurons originate from the nasal placode and migrate along olfactory axons to reach the hypothalamus. Consequently, the close developmental association between GnRH and olfactory neurons underlies the characteristic clinical presentation of HH accompanied by anosmia or hyposmia. In addition to reproductive and olfactory deficits, individuals with KS frequently exhibit a spectrum of non-reproductive congenital anomalies, including cleft palate, unilateral renal agenesis, limb malformations such as split hand/foot malformation and shortened metacarpals, sensorineural hearing loss, and mirror movements (synkinesia) (5). In contrast nIHH refers to those IHH cases in which patients have an intact sense of smell (6). nIHH arises from dysfunction of the GnRH neurons that are properly located within the hypothalamus. These cases typically lack any associated congenital anomalies.

Caution is warranted when employing the classifications of KS and nIHH, as the distinction between these entities can be ambiguous. This is exemplified by mutations in the *FGFR1* gene, which could be associated with either phenotype. Mutations in *CCDC141* or *IGSF10*, although typically associated with nIHH, have been shown *in vitro* to impair the migration of GnRH neurons, an abnormality more commonly linked to the KS phenotype. These findings underscore the complexity of the underlying molecular mechanisms and challenge the traditional dichotomy between KS and nIHH (7,8).

Pubertal delay is the most typical presentation of IHH. Pubertal delay is defined as absence of breast development (Tanner breast stage 1) in a girl at age 13 years or failure to achieve a testicular volume of 4 mL in a boy by age 14 years (9). By far the most common cause of delayed puberty is constitutional delay in growth and puberty (CDGP), also known as self-limited delayed puberty, which is not a disease *per se* but a maturational delay in development at the extreme of the population standards. CDGP accounts for pubertal delay in two third of boys and one third of girls (10). As CDGP is a diagnosis of exclusion, it must be carefully considered in the differential diagnosis of IHH. Differentiating between these two conditions frequently necessitates prolonged clinical observation and extensive diagnostic evaluation.

Studies have shown that some variants in established puberty-related genes, including *TAC3* and *TACR3*, are present in both individuals with nIHH and those with CDGP within the same families. These findings suggest that CDGP may represent a milder, transient manifestation of the same genetic defect underlying IHH, indicating a shared pathophysiological continuum between the two conditions (11). Clinicians often initiate a low-dose sex steroid regimen to "jump-start" pubertal development in patients suspected of having CDGP. It is now well established that approximately 10-20% of individuals with IHH experience clinical recovery, occurring either spontaneously or, more commonly, following sex steroid replacement therapy (12,13). These observations suggest that CDGP and IHH may share underlying pathophysiological mechanisms. This supports the concept of a phenotypic continuum ranging from normal pubertal timing to severe forms of IHH, with CDGP representing an intermediate point along this spectrum. On the other hand, a recent study found that the common genetic variants associated with pubertal timing in the general population contribute substantially to the genetic basis of CDGP, but only minimally to that of IHH (14). Furthermore, a more recent study involving 71 CDGP subjects revealed no mutations in genes associated with nIHH, such as *GNRHR, TAC3,* and *TAC3R*. This study revealed new candidate genes for CDGP, most notably *INHBB*, encoding the beta B subunit of inhibin, which is associated with age at menarche (15). In yet another study *MC3R* loss-of-function variants were overrepresented in patients with CDGP in comparison to IHH (16). Collectively, these recent studies suggest that the genetic architecture underlying CDGP and IHH may be distinct. Currently identified genetic defects explain up to 50% of all IHH cases (5,17). To date, mutations in nearly 60 genes have been implicated in the pathogenesis of IHH. A comprehensive list of currently known IHH-associated genes

is presented in Table 1. In a subset of patients or pedigrees, more than one pathogenic variant in different IHH-associated genes is identified, a phenomenon referred to as oligogenic inheritance or etiology. This mode of inheritance is estimated to account for 10-20% of all IHH cases (18,19,20,21). With the increased application of comprehensive, unbiased genetic approaches, such as whole exome sequencing (WES), it has become evident that oligogenic inheritance is more prevalent in Mendelian disorders than previously recognized (22). From the diagnostic point of view designing a panel of genes for targeted exome sequencing may prove to be practical in aiding timely differential diagnosis of delayed puberty. Such gene panels may prioritize genes more commonly implicated in patients with IHH or CDGP, and in our view, should at minimum include *FGFR1, ANOS1, CHD7, PROKR2, GNRHR, KISS1R, TAC3, TACR3, FGF8, FGF17, PROK2, CCDC141, SEMA3A, IGSF10, INHBB, MC3R*, and *IL17RD (5,15,16,23,24)*.

Genes Associated with IHH

Kallmann syndrome (KS) associated genes

X-linked recessive, autosomal dominant (AD), and autosomal recessive (AR) inheritance patterns have all been described in association with KS. However, KS frequently occurs as a sporadic condition. Even in familial cases, considerable intrafamilial phenotypic variability is commonly observed, with individuals harboring the same genetic mutation exhibiting a wide range of clinical manifestation (25,26,27). Based on the presence of specific associated clinical features, genetic screening can be prioritized for particular gene(s): synkinesia (*ANOS1*), dental agenesis (*FGF8/FGFR1*), digital bony abnormalities (*FGF8/FGFR1*) and hearing loss (*CHD7*, *SOX10*) (28). A shared pathophysiological mechanism among genes implicated in KS involves the interaction of fibroblast growth factor signaling, prokineticin signaling, and Anosmin-1 with heparan sulfate glycosaminoglycan moieties within extracellular signaling complexes. These interactions are thought to facilitate the proper migration of GnRH neurons during embryonic development (29,30).

Table 1. The list of genes associated with idiopathic hypogonadotropic hypogonadism

Gene	HGNC ID	Approved name	OMIM phenotype	Phenotype MIM number
AMH	464	Anti-Müllerian hormone	Persistent Mullerian duct syndrome, type I	261550
AMHR2	465	Anti-Müllerian hormone receptor type 2	Persistent Mullerian duct syndrome, type II	261550
ANOS1	6211	Anosmin 1	Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1)	308700
ARHGAP5	675	Rho GTPase activating protein 5		
ARHGAP35	4591	Rho GTPase activating protein 35		
AXL	905	AXL receptor tyrosine kinase		
CCDC141	26821	Coiled-coil domain containing 141		
CHD7	20626	Chromodomain helicase DNA binding protein 7	Hypogonadotropic hypogonadism 5 with or without anosmia	612370
			CHARGE syndrome	214800
CPE	2303	Carboxypeptidase E	BDV syndrome	619326
DCC	2701	DCC netrin 1 receptor	Colorectal cancer, somatic	114500
			Esophageal carcinoma, somatic	133239
			Gaze palsy, familial horizontal, with progressive scoliosis, 2	617542
			Mirror movements 1 and/or agenesis of the corpus callosum	157600
DLG2	2901	Discs large MAGUK scaffold protein 2		
DMXL2	2938	Dmx like 2	Deafness, autosomal dominant 71*	617605
			Polyendocrine-polyneuropathy syndrome*	616113
			Developmental and epileptic encephalopathy 81	618663
DUSP6	3072	Dual specificity phosphatase 6	Hypogonadotropic hypogonadism 19 with or without anosmia	615269
FEZF1	22788	FEZ family zinc finger 1	Hypogonadotropic hypogonadism 22, with or without anosmia	616030
FGF8	3686	Fibroblast growth factor 8	Hypogonadotropic hypogonadism 6 with or without anosmia	612702

Table 1. Continued

Gene	HGNC ID	Approved name	OMIM phenotype	Phenotype MIM number
FGF17	3673	Fibroblast growth factor 17	Hypogonadotropic hypogonadism 20 with or without anosmia	615270
FGFR1	3688	Fibroblast growth factor receptor 1	Hypogonadotropic hypogonadism 2 with or without anosmia	147950
			Encephalocraniocutaneous lipomatosis, somatic mosaic	613001
			Hartsfield syndrome	615465
			Jackson-Weiss syndrome	123150
			Osteoglophonic dysplasia	166250
			Pfeiffer syndrome	101600
			Trigonocephaly 1	190440
FLRT3	3762	Fibronectin leucine rich transmembrane protein 3	Hypogonadotropic hypogonadism 21 with anosmia	615271
FSHB	3964	Follicle stimulating hormone subunit beta	Hypogonadotropic hypogonadism 24 without anosmia	229070
GNRH1	4419	Gonadotropin releasing hormone 1	Hypogonadotropic hypogonadism 12 with or without anosmia*	614841
GNRHR	4421	Gonadotropin releasing hormone receptor	Hypogonadotropic hypogonadism 7 without anosmia	146110
HESX1	4877	HESX homeobox 1	Growth hormone deficiency with pituitary anomalies	182230
			Pituitary hormone deficiency, combined, 5	182230
			Septooptic dysplasia	182230
HS6ST1	5201	Heparan sulfate 6-O-sulfotransferase 1	Hypogonadotropic hypogonadism 15 with or without anosmia	614880
IGSF10	26384	Immunoglobulin superfamily member 10		
IL17RD	17616	Interleukin 17 receptor D	Hypogonadotropic hypogonadism 18 with or without anosmia	615267
IRF2BPL	14282	Interferon regulatory factor 2 binding protein like	Neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures	618088
KISS1	6341	KiSS-1 metastasis suppressor	Hypogonadotropic hypogonadism 13 with or without anosmia*	614842
KISS1R	4510	KISS1 receptor	Hypogonadotropic hypogonadism 8 with or without anosmia	614837
			Precocious puberty, central, 1*	176400
KLB	15527	Klotho beta		
LEP	6553	Leptin	Obesity, morbid, due to leptin deficiency	614962
LEPR	6554	Leptin receptor	Obesity, morbid, due to leptin receptor deficiency	614963
LHB	6584	Luteinizing hormone subunit beta	Hypogonadotropic hypogonadism 23 with or without anosmia	228300
NDNF	26256	Neuron derived neurotrophic factor	Hypogonadotropic hypogonadism 25 with anosmia	618841
NHLH2	7818	Nescient helix-loop-helix 2	Hypogonadotropic hypogonadism 27 without anosmia*	619755
NR0B1	7960	Nuclear receptor subfamily 0 group B member 1	46XY sex reversal 2, dosage-sensitive	300018
			Adrenal hypoplasia, congenital	300200
NSMF	29843	NMDA receptor synaptonuclear signaling and neuronal migration factor	Hypogonadotropic hypogonadism 9 with or without anosmia	614838
NTN1	8029	Netrin 1	Mirror movements 4	618264
OTUD4	24949	OTU deubiquitinase 4		

Table 1. Continued

Gene	HGNC ID	Approved name	OMIM phenotype	Phenotype MIM number
PCSK1	8743	Proprotein convertase subtilisin/kexin type 1	Obesity, susceptibility to, BMIQ12	612362
			Endocrinopathy due to proprotein convertase 1/3 deficiency	600955
PLXNA1	9099	Plexin A1	Dworschak-Punetha neurodevelopmental syndrome	619955
PLXNA3	9101	Plexin A3		
PLXNB1	9103	Plexin B1		
PNPLA6	16268	Patatin like domain 6, lysophospholipase	Laurence-Moon syndrome*	245800
			Boucher-Neuhauser syndrome	215470
			Oliver-McFarlane syndrome	275400
			Spastic paraplegia 39, autosomal recessive	612020
POLR3A	30074	RNA polymerase III subunit A	Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism	607694
			Wiedemann-Rautenstrauch syndrome	264090
POLR3B	30348	RNA polymerase III subunit B	Charcot-Marie-Tooth disease, demyelinating, type 1I	619742
			Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism	614381
POU6F2	21694	POU class 6 homeobox 2	Wilms tumor susceptibility-5	601583
PROK2	18455	Prokineticin 2	Hypogonadotropic hypogonadism 4 with or without anosmia	610628
PROKR2	15836	Prokineticin receptor 2	Hypogonadotropic hypogonadism 3 with or without anosmia	244200
RAB18	14244	RAB18, member RAS oncogene family	Warburg micro syndrome 3	614222
RAB3GAP1	17063	RAB3 GTPase activating protein catalytic subunit 1	Martsolf syndrome 2	619420
			Warburg micro syndrome 1	600118
RAB3GAP2	17168	RAB3 GTPase activating non-catalytic protein subunit 2	Martsolf syndrome 1	212720
			Warburg micro syndrome 2	614225
RNF216	21698	Ring finger protein 216	Cerebellar ataxia and hypogonadotropic hypogonadism	212840
SEMA3A	10723	Semaphorin 3A	Hypogonadotropic hypogonadism 16 with or without anosmia	614897
SEMA3E	10727	Semaphorin 3E		
SEMA3F	10728	Semaphorin 3F		
SMCHD1	29090	Structural maintenance of chromosomes flexible hinge domain containing 1	Bosma arhinia microphthalmia syndrome	603457
			Facioscapulohumeral muscular dystrophy 2, digenic	158901
SOX2	11195	SRY-box transcription factor 2	Microphthalmia, syndromic 3	206900
			Optic nerve hypoplasia and abnormalities of the central nervous system	206900
SOX3	11199	SRY-box transcription factor 3	Intellectual developmental disorder, X-linked, with isolated growth hormone deficiency	300123
			Panhypopituitarism, X-linked	312000
SOX10	11190	SRY-box transcription factor 10	PCWH syndrome	609136
			Waardenburg syndrome, type 2E, with or without neurologic involvement	611584
			Waardenburg syndrome, type 4C	613266
SOX11	11191	SRY-box transcription factor 11	Intellectual developmental disorder with microcephaly and with or without ocular malformations or hypogonadotropic hypogonadism	615866

Table 1. Continued

Gene	HGNC ID	Approved name	OMIM phenotype	Phenotype MIM number
SPRY4	15533	Sprouty RTK signaling antagonist 4	Hypogonadotropic hypogonadism 17 with or without anosmia	615266
SRA1	11281	Steroid receptor RNA activator 1		
STUB1	11427	STIP1 homology and U-box containing protein 1	Spinocerebellar ataxia 48	618093
			Spinocerebellar ataxia, autosomal recessive 16	615768
TCF12	11623	Transcription factor 12	Hypogonadotropic hypogonadism 26 with or without anosmia	619718
			Craniosynostosis 3	615314
TAC3	11521	Tachykinin precursor 3	Hypogonadotropic hypogonadism 10 with or without anosmia	614839
TACR3	11528	Tachykinin receptor 3	Hypogonadotropic hypogonadism 11 with or without anosmia	614840
TBC1D20	16133	TBC1 domain family member 20	Warburg micro syndrome 4	615663
WDR11	13831	WD repeat domain 11	Hypogonadotropic hypogonadism 14 with or without anosmia	614858
			Intellectual developmental disorder, autosomal recessive 78	620237

ANOS1

The first gene identified as causative for KS is *ANOS1* (31). Formerly known as *KAL1* it is located on the short arm of the X chromosome (Xp22.3) (OMIM: 300836) (32). Ten to 20 percent of males with KS carry *ANOS1* mutations or intragenic microdeletions are present (33, 34). The extracellular glycoprotein it encodes, anosmin-1, plays a role in the adhesion of GnRH cells and axon migration during organogenesis (35). Anomin-1 exerts its biological effects mainly through signal modulation of *FGFR1* via its third fibronectin-like type 3 (FnIII) domain and the N-terminal region (36). The migratory defect of olfactory and GnRH neurons is the central mechanism underlying the clinical features of *ANOS1* mutations (37). In its first observation, in a 19-week-old male human fetus with a deletion in *ANOS1*, GnRH neurons could not migrate to their normal positions in the brain (38). In KS cases associated with *ANOS1* mutations, penetrance has been reported to be almost complete (39,40). Additional clinical findings include bimanual synkinesis, unilateral renal agenesis, vas deferens agenesis, and deafness (28,41).

FGFR1, *FGF8* and related genes (*FGF17*, *IL17RD*, *DUSP6*, *SPRY4*, *FLRT3*, and *KLB*)

FGFR1 encodes a receptor belonging to the tyrosine kinase superfamily. It regulates central developmental processes, such as neuronal proliferation, differentiation, and migration critical for embryonic development. *FGFR1* is the first gene in which mutations were identified for the AD form of KS (42). However, over time, *FGFR1* has also been found to be associated with nIHH (43,44). Around 10% of patients with KS were found to have inactivating mutations in *FGFR1* (29,43,45). Loss-of-function mutations in *FGFR1* were detected in 7% of 134 nIHH patients (46). To date numerous insertions/deletions, missense, and nonsense mutations have been reported with AD, AR, *de novo*, and oligogenic inheritance (29,47,48). Loss of *FGFR1* function elicit reproductive abnormalities ranging from severe AD KS through fully penetrant nIHH to delayed puberty (43,44,45,49,50). *FGFR1* mutations have been associated with cleft palate, synkinesis, and tooth agenesis, and asymptomatic carriers have been reported in some familial cases (5,51).

FGF8 and *FGF17* are *FGFR1* ligands with similar sequence structures that play a role in GnRH neuron ontogenesis. Mutations in these genes have been reported in IHH patients with varying olfactory functions (52,53). Mice homozygous for the hypomorphic *Fgf8* allele exhibited absent olfactory bulbs and lacked GnRH neurons in the hypothalamus (52). IHH patients harboring *FGF8* variants have also been reported to exhibit additional phenotypic features, including cleft lip and/or palate, a flat nasal bridge, and camptodactyly (54,55). Further screening for *FGF8*-related genes in a group of 388 congenital IHH patients revealed inactivating variants in *FGF17*, *IL17RD*, *DUSP6*, *SPRY4*, and *FLRT3* (53).

KLB encodes β-Klotho, a co-receptor essential for *FGF21* signaling via *FGFR1*. In one study, over 300 IHH patients were screened, identifying 13 individuals with loss-of-function *KLB* variants. Most of these patients exhibited metabolic abnormalities, including insulin resistance or dyslipidemia. Notably, *Klb* knockout mice displayed a milder hypogonadal phenotype compared to the human presentation (56).

HS6ST1

heparan sulfate 6-O-sulfotransferase 1 (HS6ST1) is directly involved in the sulfation of heparan sulfate proteoglycans, which are critical modulators of FGF signaling. The 6-O-sulfation of heparan sulfate chains, catalyzed by *HS6ST1*, is required for optimal binding and activation of FGF ligands (such as *FGF8* and *FGF17*) to their receptor *FGFR1* (57). This interaction is essential for the development, migration, and survival of GnRH neurons during embryogenesis. Mutations in *HS6ST1*, often co-occurring with variants in other known KS genes, have been reported in seven families (58).

PROKR2 and *PROK2*

PROK2 and *PROKR2* encode prokineticin 2, an 81-amino acid peptide, and its G protein-coupled receptor, respectively. Both play critical roles in the development of neuronal precursors and are essential for processes such as olfactory bulb morphogenesis and sexual maturation (59). This ligand-receptor pair has been identified as a strong candidate for the pathogenesis of KS as *PROK2* (60,61) or *PROKR2* knockout mice had defective olfactory bulbs and failed migration of GnRH neurons (62). Subsequent studies identified inactivating variants in *PROKR2* and *PROK2* in patients with KS. The majority of these mutations have been identified in the heterozygous state, although both homozygous and compound heterozygous variants have also been reported (63). Patients with *PROK2* or *PROKR2* mutations have considerable phenotypic variability (61,64,65), ranging from KS to nIHH. A variety of associated clinical features has been reported in affected individuals, including fibrous dysplasia, synkinesia, epilepsy, and Crohn's disease (66). Mutations in *PROKR2* and *PROK2* are frequently identified in combination with variants in other genes, supporting an oligogenic mode of inheritance in IHH.

CHD7

CHARGE syndrome is a multisystem disorder that includes **C**oloboma, Heart anomalies, choanal Atresia, growth Retardation, Genital defects and Ear anomalies (67). *CHD7* mutations are present in the majority of patients with CHARGE syndrome. *CHD7* is a chromatin-remodeling protein essential for the ontogeny of GnRH neurons and the proper targeting of olfactory axons during embryogenesis. Pathogenic *CHD7* mutations disrupt these developmental processes, resulting in a reduced number of hypothalamic GnRH neurons and defective GnRH secretion. There is a range of abnormalities in the GnRH neuron migration pathway in mice with *CHD7* deficiency (68,69). While large *de novo* deletions are noted in classical CHARGE syndrome patients, inherited or *de novo* point mutations may result in KS/nIHH (48,70,71). Thus, IHH patients should be carefully examined for possible clinical features of CHARGE syndrome, such as abnormal ears, deafness, semicircular canal hypoplasia, and coloboma (67).

WDR11

WDR11 in partnership with EMX1, a homeodomain transcription factor, is essential for normal Hedgehog (Hh) signaling and ciliogenesis, both of which are critical for the embryonic development and migration of GnRH neurons. Mutations in *WDR11* disrupt Hh pathway signaling, impairing the formation and function of primary cilia, which are required for the proper migration of GnRH and olfactory neurons (72). By positional cloning, heterozygous mutations were discovered in several patients with KS (73).

CCDC141

CCDC141 encodes a coiled-coil domain containing protein that is expressed in GnRH neurons. We have reported inactivating *CCDC141* variants in four separate families with IHH. Affected individuals exhibit normal olfaction and anatomically normal olfactory bulbs (74). In a rodent nasal explant model, knockdown of Ccdc141 led to impaired embryonic migration of GnRH neurons without affecting olfactory axon outgrowth, thereby producing a nIHH phenotype distinct from other genes implicated in GnRH neuronal migration (7). *CCDC141* Mutations have been identified as a recurrent finding in individuals with CDGP. Among a cohort of 193 patients with CDGP, 21 individuals (6%) were found to carry predicted deleterious variants in *CCDC141* (75).

FEZF1

The protein product of *FEZF1* facilitates the penetration of olfactory receptor neuron axons through the basal lamina of the central nervous system in murine models. As a subset of these axons serves as a migratory scaffold for GnRH neurons, *FEZF1* deficiency results in failed entry of GnRH neurons into the brain (76,77). Through autozygosity mapping and WES of 30 individuals with KS, we discovered homozygous loss-of-function mutations in *FEZF1* in two separate consanguineous families, each with two affected siblings (78). *FEZF1* mutations are apparently extremely rare as no new KS cases have been reported to date.

IGSF10

IGSF10, a member of the immunoglobulin superfamily, was implicated in delayed puberty by Howard et al. (8), who analyzed WES data from over 100 affected individuals and identified pathogenic mutations in six families. Knockdown studies demonstrated reduced GnRH neuronal migration in the GN11 cell line. Despite this impaired migration, patients harboring *IGSF10* mutations exhibited a normal sense of smell. The authors proposed that a reduced number or delayed arrival of GnRH neurons to the hypothalamus results in a milder disruption of the GnRH neuronal network, manifesting as delayed puberty rather than permanent IHH. Notably, *IGSF10* mutations were also identified in adults with functional hypothalamic amenorrhea, a condition considered a mild and reversible form of HH (8).

SEMA3A and related genes (*SEMA3E, SEMA3G, SEMA3F, PLXNA1, PLXNA3 etc)*

The precise targeting of GnRH neurons and olfactory/vomeronasal projections relies on the coordinated activity of axonal guidance cues, including semaphorins which are a large and heterogeneous family of secreted and membrane-bound proteins (79). Mutations in class-3 semaphorin family members, including *SEMA3A*, *SEMA3E*, and *SEMA3G*, have been implicated in the pathogenesis of IHH (80,81,82). *SEMA3* proteins exert their biological functions by binding to Neuropilin co-receptors, forming heteromeric complexes with *PlexinA1-4 (PLXNA1-4)* receptors, thereby initiating plexin-mediated signal transduction pathways (83). Non-synonymous heterozygous variants in *PLXNA1* have been identified in KS individuals (84). More recently we have identified deleterious variants in *SEMA3F* and *PLXNA3* that caused IHH (85).

SEMA3F and *PLXNA3*

SEMA3F and its coreceptor *PLXNA3* play a role in cell migration and axonal guidance (86). WES of 216 patients with IHH identified rare *SEMA3F* and *PLXNA3* variants in 15 individuals. Over half (54%) also carried mutations in other known IHH genes, highlighting the disorder's oligogenic nature. *SEMA3F* variants followed AD inheritance with variable penetrance, while *PLXNA3* variants were X-linked recessive. Six patients exhibited impaired olfaction. The study provided clinical, genetic, and cellular evidence supporting the role of *SEMA3F* signaling deficiency in IHH pathogenesis (85).

PLXNA1

Plexin-A1, a transmembrane coreceptor for semaphorin 3 signaling, is encoded by *PLXNA1* (87). Heterozygous *PLXNA1* variants were identified in 15 of 237 unrelated patients with KS, and impaired plexin-A1 signaling has been linked to oligogenic inheritance in KS (84). Subsequently, by screening the WES data of 215 IHH patients, we identified rare heterozygous *PLXNA1* variants in KS and nIHH patients carrying additional variants in known IHH genes. Thus, the contribution of *PLXNA1* to the oligogenicity of both forms of IHH was confirmed (88).

PLXNB1

The receptor for semaphorin 4D, plays a critical role in GnRH neuronal development. In murine models, disruption of *Sema4D/PLXNB1* signaling results in abnormal GnRH ontogeny. In a cohort of 336 patients with IHH, we were able to detect six rare *PLXNB1* variants in eight individuals with the nIHH (89).

SMCHD1

SMCHD1 encodes an epigenetic repressor that is expressed in the human olfactory epithelium. Shaw et al. (90) identified inactivating mutations in *SMCHD1* as the underlying cause of congenital arhinia in 41 cases. Notably, 97% of affected individuals also exhibited hypogonadal features, including cryptorchidism, microphallus, or amenorrhea, alongside absent olfactory structures and anosmia (90).

SOX10

Inactivating mutations in *SOX10* are responsible for Waardenburg syndrome, a rare condition marked by pigmentation defects and sensorineural hearing loss. In a subset of KS patients presenting with deafness, *SOX10* mutations were identified in about one-third of cases. Consistent with these findings, *Sox10* knockout mice exhibit a complete absence of olfactory ensheathing cells along the olfactory nerve pathway, highlighting the critical role of this gene in olfactory system development (91). A large cohort study of 1309 IHH patients reported that developmental problems due to *SOX10* variants may encompass a phenotypic line from KS to nIHH (92).

SOX2

SOX2 encodes the SRY-related, HMG-box 2 transcription factor protein. A study involving eight IHH patients with heterozygous *SOX2* variants who had severe eye defects found that pathogenic *SOX2* variants were linked to both anosmic and normosmic forms of IHH. Functional analyses indicated that *Sox2* was highly expressed in the hypothalamus of adult mice. The study emphasized that screening for *SOX2* variants should be performed in patients, regardless of the presence of ocular defects, when conducting genetic evaluations for IHH (93).

NDNF

NDNF is a secreted neurotrophic factor involved in the migration of GnRH neurons and is a member of the fibronectin type III (FN3) superfamily. Screening for rare variants in FN3 domain-containing proteins identified three protein-truncating and one missense heterozygous *NDNF* variant among patients with KS. In *NDNF*-null mice, a reduced number of GnRH neurons reached their final destination compared to wild-type $NDNF^{+/+}$ mice (94). More recently, we identified a homozygous protein-truncating variant in *NDNF* in a consanguineous family with KS, highlighting that, in addition to the previously described dominant inheritance, NDNF-related disease can also follow an AR pattern (95).

AMH and *AMHR2*

Anti-Müllerian Hormone (AMH) is expressed in migrating GnRH neurons in mouse and human fetuses during embryonic development and functions as a promotility factor (96). *AMHR2*-deficient mice exhibit aberrant development of the peripheral olfactory system and impaired embryonic migration of GnRH neurons. In humans, heterozygous inactivating variants in *AMH* or *AMHR2* have been associated with IHH. These findings indicate

the critical role of *AMH/AMHR2* signaling in GnRH neuronal migration and its contribution to the pathogenesis of IHH (97).

AXL

AXL receptor tyrosine kinases, members of the TAM (TYRO3/AXL/MERTK) family, play a role in GnRH neuron migration and survival. Studies of sexual maturation in *AXL* null mice reported that TAM function was impaired (98). *AXL* variants have been identified in both anosmic and normosmic IHH probands.

NTN1

Netrin-1, encoded by the *NTN1* gene, plays a crucial role in central nervous system development by guiding axonal and neuronal migration through its receptor DCC. In *DCC*$^{-/-}$ and *NTN1*$^{-/-}$ mouse embryos, GnRH neurons exhibited aberrant trajectories and failed to reach the medial preoptic area, highlighting the importance of NTN1/DCC signaling in proper GnRH neuronal migration (99,100). WES of a cohort of 133 individuals with IHH identified pathogenic variants in *NTN1* and the gene for its receptor, *DCC*. Five heterozygous *DCC* variants were detected in six probands, five of whom had KS and one with nIHH. In addition, co-occurring variants in both *DCC* and *NTN1* were identified in two KS patients, supporting an oligogenic basis for disease pathogenesis (101).

nIHH Associated Genes

Genes implicated in nIHH are particularly informative for understanding the regulation of the HPG axis and the timing of puberty. Genetic analyses of familial nIHH cases have significantly advanced this understanding. In a study of 22 consecutive multiplex families with nIHH, mutations were identified in five genes, *GNRHR*, *TACR3*, *TAC3*, *KISS1R*, and *KISS1*, in 77% of families. Among these, *GNRHR* and *TACR3* mutations were the most frequently observed, each accounting for approximately one-third of the genetically resolved cases (24).

GNRHR and *GNRH1*

GNRH1 and *GNRHR* are the most obvious candidate gene in the etiology of IHH. In 1997, de Roux et al. (102) identified compound heterozygous mutations in *GNRHR* in two siblings with partial nIHH, showing that Gln106Arg impaired GnRH binding while Arg262Gln reduced IP3 signaling. The male sibling exhibited normal gonadotropin levels and LH pulse frequency but reduced pulse amplitude, consistent with partial GnRH receptor dysfunction. Shortly after, Layman et al. (103) reported a family with four siblings carrying compound heterozygous *GNRHR* mutations (p.Arg262Gln and p.Tyr284Cys), further supporting the role of biallelic *GNRHR* mutations in IHH without anosmia or developmental anomalies (103). Subsequent studies found *GNRHR* variants in approximately 5-6% of nIHH cases (104). This relatively high prevalence of *GNRHR* was confirmed in subsequent studies (105). To date over 60 distinct mutations have since been reported (106).

Genotype-phenotype correlations have been observed for specific *GNRHR* mutations. The genetic makeup (homozygous, compound heterozygous, or monoallelic variants) broadly correlates with clinical severity, ranging from complete IHH to milder forms, such as CDGP and functional hypothalamic amenorrhea (104). The homozygous R139C missense mutation in the conserved DRS motif of the GnRH receptor causes complete IHH by severely impairing receptor trafficking to the plasma membrane, a defect reversible with the pharmacological chaperone IN3 (107). In contrast, the heterozygous Gln106Arg mutation is linked to adult-onset IHH (AOHH), where normal pubertal development precedes nIHH. Homozygosity for p.Gln106Arg has also been associated with the fertile eunuch variant of nIHH, characterized by hypogonadism with preserved testicular size and partial virilization (108). These findings highlight how specific *GNRHR* mutations contribute to a broad spectrum of GnRH deficiency phenotypes (5,106).

GNRH1 encodes the GnRH preprohormone. Deletion of *GNRH1* in murine models was shown to result in complete absence of GnRH synthesis, a finding reported well before analogous mutations were identified in humans (109,110). Over a decade after the initial discovery of *GNRHR* mutations, pathogenic *GNRH1* variants were reported in humans (111,112). Bouligand et al. (111) demonstrated that pulsatile GnRH administration for two weeks resulted in synchronous LH pulses, increased levels of estradiol, and a single dominant ovarian follicle. These findings confirmed the hypothalamic origin and pivotal role of GnRH in human reproduction. Affected individuals frequently present with micropenis and cryptorchidism (111,112,113).

KISS1R and *KISS1*

In 2003, kisspeptin emerged as a pivotal central regulator of GnRH neuronal activity following the identification of mutations in a previously little-characterized G protein-coupled receptor, initially termed *GPR54* and later renamed *KISS1R* (kisspeptin receptor) (106). In 2003, two independent research groups concurrently reported homozygosity mapping in familial cases of IHH, resulting in the first identification of pathogenic mutations in *KISS1R* (114,115). Mutant *KISS1R* constructs exhibited impaired receptor function in *in vitro* assays, and *KISS1R*-knockout mice recapitulated the human hypogonadotropic phenotype, confirming the essential role of the kisspeptin signaling pathway in pubertal and reproductive regulation across mammals (114). In a mutational screening study, only five out of 166 (3%) probands with nIHH were found to have rare variants in *KISS1R* (116). The rarity of mutations in *KISS1* and *KISS1R* may be attributed to evolutionary selection pressures, given the critical roles of kisspeptin in placentation, reproductive

function, and metastasis suppression, which likely constrain the transmission of deleterious variants within populations (106). Studying a large, consanguineous family with four sisters with nIHH, we found inactivating mutations altering the 4th amino acid of Kisspeptin-10. Overnight frequent LH sampling did not reveal any LH pulsatility, further confirming the essential role of kisspeptin signaling in the GnRH pulse generator (117). Coutant et al. (118) recently identified homozygous frameshift mutations in *KISS1* within a consanguineous family (118). Molecular analyses confirmed a complete absence of kisspeptin protein. Affected male siblings exhibited congenital gonadotropin deficiency, including bilateral cryptorchidism, micropenis, and absent spontaneous puberty. However, the two older brothers later showed spontaneous reversal of hypogonadism, with normalization of testicular volume and spermatogenesis. These findings indicate that complete kisspeptin deficiency does not preclude delayed GnRH activation or pubertal maturation, highlighting the redundancy and adaptability of upstream neuroendocrine pathways (118). The potential involvement of alternative *KISS1R* ligands, neuroendocrine plasticity, or compensatory pathways, such as neurokinin B (NKB) or glutamatergic signaling, requires further investigation.

TACR3 and *TAC3*

Tachykinin receptor 3, encoded by *TACR3*, mediates the biological actions of neurokinin B (NKB), which is encoded by *TAC3*. Through autozygosity mapping aimed at discovering novel regulators of the HPG axis, we identified homozygous non-synonymous mutations in the coding regions of *TAC3* or *TACR3* in nine individuals from four families presenting with an nIHH phenotype (119). With the additional cases identified in our cohort, it became clear that *TACR3* mutations are almost as common as *GNRHR* mutations (24,120). Similar findings regarding the prevalence of *TACR3* mutations have been reported by other research groups. Gianetti et al. (121) found 19 among 345 (5.5%) cases while a very similar rate (5.2%) was observed by Francou et al. (122) from a cohort of 173 cases of familial and sporadic nIHH. The frequent occurrence of micropenis and cryptorchidism in male patients with *TACR3* mutations suggests that functional *TACR3* signaling is essential for normal fetal gonadotropin secretion, which in turn regulates testicular development, descent, and penile growth (4).

Clinical reversibility, characterized by spontaneous pubertal progression, often following a period of exogenous sex steroid therapy, was observed in approximately 10% of an unselected cohort with nIHH (12). Gianetti et al. (121) reported a significantly higher rate of reversibility of 83% in their cohort of patients with *TAC3*/*TACR3* mutations. In our cohort, four patients from three unrelated and ethnically diverse families exhibited clinical recovery, representing 25% (4/16) of the cases. Notably, all of these families carried the same *TACR3* mutation (p.Thr177Lys). Given the relatively high rate of reversibility, it was hypothesized that CDGP might represent a mild form of IHH linked to *TACR3* mutations. To investigate this, Vaaralahti et al. (123) screened *TAC3* and *TACR3* in 146 Finnish individuals with CDGP but identified no pathogenic variants associated with the phenotype.

Additional clinical studies have enhanced our understanding about the regulation of the HPG axis by Neurokinin B signaling. Young et al. (124) showed that patients with null mutations in *TAC3* could achieve pubertal levels of gonadotropins and sex steroids following repeated administration of exogenous GnRH. This finding indicates that neurokinin B acts at a hypothalamic level, upstream of GnRH secretion, rather than directly influencing pituitary function (124). Furthermore, a genome-wide association study identified a significant association between age at menarche, a surrogate marker of pubertal start, and a single nucleotide polymorphism (rs3733631) located immediately upstream of *TACR3*, supporting a role for neurokinin B signaling in the regulation of pubertal timing at the population level (125).

IRF2BPL (*EAP1*)

Pubertal onset is postulated to be regulated in part by transcriptional factors such as EAP1 (126). In a cohort with familial CDGP, two rare *EAP1* variants (p.Ala221del and p.Asn770His) were identified, both impairing GnRH promoter activation through distinct molecular mechanisms. These findings provide the first link between *EAP1* mutations and CDGP (127).

LEP and *LEPR*

Leptin deficiency with mutations in either *LEP* (encoding leptin) or *LEPR* (encoding the leptin receptor) is associated with IHH (128,129). Administration of leptin in individuals with *LEP* deficiency restores normal pubertal development but does not induce precocious puberty in prepubertal children. This suggests that leptin functions as a permissive, rather than initiatory, factor in the onset of puberty in humans (130). These patients are readily distinguishable from other individuals with IHH due to the characteristic presentation of early-onset obesity and hyperphagia.

NR0B1 (*DAX1*)

NR0B1 belongs to the nuclear receptor superfamily and is classified as an orphan receptor due to the absence of a known endogenous ligand. Mutations in *NR0B1* are known to cause adrenal hypoplasia congenita in combination with IHH (131,132,133,134,135). Adrenal hypoplasia typically presents as adrenal insufficiency during infancy, whereas IHH becomes manifest in affected males who survive into the second decade of life. Nuclear receptors, such as SF-1 and LRH-1, involded in

adrenal and gonadal phyiology and development, are regulated in their transcriptional activity by coregulatory molecules (136). *DAX-1*, lacks a DNA-binding domain and functions exclusively as a coregulator (137). Notably, Dax-1 is predominantly expressed in the arcuate nucleus (ARC) of the hypothalamus. In adult female mice, *DAX-1* is present in at least 70% of Kiss1 neurons within the ARC, which is associated with pubertal development, whereas it is found in fewer than 5% of Kiss1 neurons in the AVPV nucleus, which is exclusively linked to the menstrual cycle (138). These findings suggest that *DAX-1* is selectively involved in the regulation of pubertal onset and the sustained function of the HPG axis. As mentioned earleir, mutations in *NR0B1* result in adrenal hypoplasia congenita together with IHH (131,132). Paradoxically, *NR0B1* mutations can also result in the opposite phenotype, precocious puberty, even within the same kindred (133,134,135). The genetic mechanisms underlying these divergent phenotypic outcomes remain poorly understood, highlighting intriguing genotype-phenotype correlations. This paradox suggests a complex, context-dependent role for *DAX-1* in regulating the HPG axis and pubertal timing.

SRA1

SRA1 was the first gene demonstrated to exert its function through both its protein product and a non-coding, functional RNA transcript (139). These proteins serve as co-regulators for nuclear receptors, including sex steroid receptors, and play a critical role in modulating the activity of SF-1 and LRH-1, the principal regulators of steroid hormone biosynthesis. *SRA1* is required for the synergistic enhancement of SF-1 transcriptional activity by *DAX-1 (NR0B1)*, mutations in which also cause IHH (140). We and others have reported nIHH patients with inactivating *SRA1* mutations (141,142,143).

PNPLA6

Gordon Holmes syndrome (GDHS) is characterized by cerebellar ataxia/atrophy and nIHH, while the related Boucher-Neuhäuser syndrome also includes chorioretinal dystrophy. *PNPLA6*, which encodes neuropathy target esterase (NTE), a key regulator of phospholipid metabolism, was found to carry loss-of-function mutations in six GDHS patients from three unrelated families via autozygosity mapping and WES. Functional studies showed that NTE inhibition in LβT2 gonadotroph cells impaired LH exocytosis in response to GnRH. These findings suggest that NTE dysfunction in GDHS disrupts phospholipid homeostasis, contributing to both neurodegeneration and impaired LH secretion, resulting in nIHH (144).

OTUD4 and *RNF216*

Ubiquitination-related *OTUD4* encodes a deubiquitinase, while *RNF216* encodes a ubiquitin E3 ligase. *OTUD4* and *RNF216* mutations have been identified in patients with GDHS. Patients have progressive ataxia, dementia, and neuronal losses are observed in the cerebellar pathway and hippocampus. Functional studies have shown that knockout of *OTUD4* and *RNF216* in zebrafish causes defects in the eye and cerebellum and that suppression of the two genes together worsens these phenotypes. Hence, inactivating mutations in *OTUD4* and *RNF216* cause neurodegeneration and reproductive failure through dysregulated ubiquitination (145).

STUB1

STUB1 encodes C-terminus of HSC70-inactivating protein, which functions as a E3 ubiquitin ligase. Pathogenic variants of *STUB1* have been associated with GDHS (146).

POU6F2

POU6F2 belongs to a gene family characterized by a bipartite DNA-binding domain, comprising a POU-specific domain and a POU homeodomain. Members of this family function as transcriptional regulators involved in cell type–specific differentiation. Several POU domain–containing proteins have been implicated in the regulation of GnRH neuron expression (147,148). Using WES data from two independent IHH cohorts (331 nIHH, 85 KS; 416 patients in total and 677 nIHH, 632 KS; 1309 patients in total), 12 rare missense variants of *POU6F2* were identified in 15 patients. Functional studies of two different isoforms encoded by *POU6F2* were performed, and the function of isoform 1 was proven as a transcriptional regulator of GNRH1 expression. Thus, pathogenic *POU2F6* variants were shown to be involved in IHH pathogenesis by disrupting normal GnRH migration (149).

DLG2

DLG2 encodes a scaffolding protein that interacts with N-methyl-D-aspartate (NMDA) receptors, which have been implicated in the regulation of sexual maturation in animal models. WES identified a rare missense variant in *DLG2* in a large family with delayed puberty. Functional studies demonstrated that this variant reduces *GnRH* expression *in vitro*, suggesting a potential mechanistic link between *DLG2* and pubertal timing (150). A subsequent study screened the WES data of 336 IHH probands from 290 independent families for rare *DLG2* variants. A total of one homozygous and two heterozygous missense variants were identified in three independent normosmic patients (151).

NHLH2

NHLH2, a basic helix-loop-helix transcription factor family member, mediates leptin-induced activation of POMC in the leptin-melanocortin pathway. Screening of WES data in a large IHH cohort revealed obese patients with rare disease-causing sequence variants. *In silico* and *in vitro* analyses of the findings showed that *NHLH2* binding to the Mc4r promoter

and KISS1 transactivation were reduced, supporting a critical role for *NHLH2* in human puberty and body weight control (152). Remarkably, *NHLH2* knockout mice exhibit a phenotype closely resembling that of patients with rare inactivating *NHLH2* variants, characterized by nIHH and late-onset obesity (153).

CPE

CPE encodes an enzyme responsible for processing neuropeptides, including GnRH, into their biologically active forms within the hypothalamus. Inactivating mutations in *CPE* result in a syndrome characterized by severe obesity, intellectual disability, disrupted glucose homeostasis, and IHH, a phenotype consistent with observations in *CPE* knockout mouse models (154). A subsequent study detected a homozygous non-sense *CPE* mutation in three obese siblings with mental retardation and IHH (155). Comparison with previously reported cases led to the delineation of a distinct clinical entity termed Blakemore-Durmaz-Vasileiou (BDV) syndrome, which is an extremely rare AR disorder characterized by a combination of impaired intellectual development, hyperphagia, and IHH (156).

POLR3A and *POLR3B*

RNA polymerase III regulates fundamental cellular processes through the transcription of small RNAs. Its catalytic core is composed of multiple subunits, including *POLR3A* and *POLR3B*. Pathogenic variants in these subunits have been associated with 4H syndrome (also known as POLR3-related leukodystrophy), a rare disorder characterized by hypomyelination, hypodontia, and IHH (157,158). Mice studies have shown that missense mutations in *POLR3A* and *POLR3B* can variably disrupt development and Pol III function (159). It is still unclear how inactivating mutations in those genes cause IHH.

Small GTPase related genes (*RAB18, RAB3GAP1, RAB3GAP2, TBC1D20,* and *DMXL2*)

Mutations in several genes related to small GTPases that include *RAB18, RAB3GAP1, RAB3GAP2, TBC1D20,* and *DMXL2*, have been implicated in IHH, often in conjunction with neurodegenerative features. Small GTPases are critical regulators of intracellular trafficking, particularly in endocytosis and exocytosis. RAB18 is a member of the Ras-related GTPases that play a role in apical endocytosis/recycling between the plasma membrane and early endosomes (160). Mutations in *RAB18* or in any of its essential regulators, *RAB3GAP1, RAB3GAP2,* and *TBC1D20* (161,162,163), are associated with Warburg micro syndrome type 3 (164). Warburg micro and Martsolf syndromes are overlapping clinical entities characterized by IHH, progressive spasticity, severe developmental delay, microcephaly, cortical visual impairment, hypotonia, and optic nerve atrophy. *DMXL2* encodes for rabconnectin-3a, which is a regulator of another intracellular GTPase, RAB3A. Rabconnectin-3a is expressed in exocytosis vesicles in GnRH axons in the median eminence of the hypothalamus (165). Furthermore, inactivating *DMXL2* mutations cause a novel complex syndrome that features IHH and a neurodegenerative phenotype, including cerebellar ataxia and demyelinating polyneuropathy, among other clinical features (165).

ARHGAP35 and *ARHGAP5*

ARHGAP35 which codes for Rho GTPase activating protein 35 and *ARHGAP5* which codes for Rho GTPase activating protein 5 are Rho GTPase activating protein genes. Rare protein-truncating variants (PTVs) in *ARHGAP35* have been reported to result in IHH. Zebrafish modeling has shown that neuronal areas are reduced in mutant embryos lacking the *ARHGAP35* paralog *ARHGAP35*. No changes were observed in the *ARHGAP35* paralog in functional studies, and it was identified as an IHH candidate. These observations suggest a novel role for the p190 RhoGAP proteins in GnRH neuronal development and integrity (166).

FSHB

FSHB encodes the beta subunit of follicle-stimulating hormone (FSH). A homozygous deletion of *FSHB* has been reported in a patient with nIHH, primary amenorrhea, and infertility due to isolated pituitary FSH deficiency (167). Studies have reported mutations in compound heterozygous, missense, and non-sense types (168,169). Mouse studies show that *FSHB*-/- female mice are sterile and hypogonadal (170).

LHB

Luteinizing hormone (LH), encoded by *LHB*, is a glycoprotein hormone essential for the regulation of gonadal function. A homozygous mutation in *LHB* was first identified in a patient with nIHH caused by biologically inactive LH (171,172). Subsequent studies have reported missense mutations, non-sense mutations, and small deletions in *LHB* associated with nIHH (173,174,175). In animal models, targeted disruption of *LHB* in mice resulted in reduced testicular size and decreased testosterone levels in males, while females exhibited a hypogonadal phenotype (176).

Scientific Significance of Identifying Ihh-Associated Genes

Undoubtedly, the most impactful contribution of IHH-associated gene studies has been the elucidation of the long-sought GnRH pulse generator, advancing our fundamental understanding of reproductive neuroendocrine regulation (177,178,179,180). A surge of research into kisspeptin and neurokinin B signaling, catalyzed by the discovery of inactivating mutations in familial cases of nIHH, has led to the characterization of the elusive GnRH pulse generator. Current understanding centers on a population of sex steroid-responsive neurons within the arcuate (infundibular) nucleus that co-express Kisspeptin, NKB, Dynorphin (KNDy), and estrogen receptor alpha (ERα), collectively termed KNDy neurons. Within this network, stimulatory signals from NKB initiate action potentials, which are subsequently attenuated by inhibitory dynorphin signaling. When dynorphin-mediated inhibition is overcome, a new cycle of NKB-induced excitation

ensues, resulting in rhythmic, intermittent action potentials. Each burst drives pulsatile kisspeptin release onto GnRH neuron terminals in the median eminence, thereby triggering GnRH secretion into the portal circulation and ultimately stimulating pituitary gonadotropes. The synchronization of KNDy neuronal activity is thought to be mediated by NKB-neurokinin-3 receptor (NK3R) signaling via ipsilateral and contralateral projections within the KNDy network (178,181,182).

Clinical Significance of Identifying IHH-Associated Genes

A major impact stemming from IHH-associated gene studies may be the translation into new therapeutic modalities. The first therapeutic oppurtunities linked to the identification of IHH genes stemmed from the discovery of *TAC3* and *TACR3* mutations in patients with nIHH (183). Antagonism of neurokinin B signaling has been used in the development of pharmacological therapies targeting two of the most common reproductive health disorders in women globally: menopausal hot flushes and polycystic ovary syndrome (PCOS).

In menopausal women, the decline in ovarian estrogen levels reduces negative feedback on KNDy neurons, causing them to become hypertrophied and to overproduce neurokinin B. KNDy neurons project to the *TACR3*-expressing median preoptic nucleus within the hypothalamus, a key region involved in thermosensory processing and heat-defense mechanisms (184,185). Building on these observations, the Rance laboratory demonstrated that ablation of KNDy neurons in rats leads to a reduction in tail-skin temperature, indicating that NKB promote cutaneous vasodilation, a key physiological component of hot flushes (186). Following clinical trials, fezolinetant, which is a selective *NK3R* antagonist, was approved for the treatment of vasomotor symptoms in menopausal women in 2023 (187,188).

NK3R antagonists also have potential for the treatment of PCOS. In premenopausal women, NK3R antagonism decreases the GnRH pulse frequency leading to reduced basal LH secretion, lower LH/FSH ratio, and the modulation of the temporal dynamics of ovarian sex hormone production over the menstrual cycle (189). The NK3R antagonist, MLE4901, was demonstrated to reduce LH pulse frequency, as well as serum LH and testosterone levels, in women with PCOS (190). These hormonal findings were validated in a recent study involving fezolinetant. However, no significant improvement was observed in menstrual cycle regularity or clinical outcome scores (187). The investigators noted that the 12-week treatment duration in this trial may have been insufficient to elicit measurable changes, as favorable clinical outcomes in PCOS trials are typically observed after 6 to 9 months of therapy (187,191). The use of an NK3R antagonist as a therapeutic agent for PCOS remains a promising strategy, given its potential to modulate the neuroendocrine dysregulation underlying the condition.

Concluding Remarks

Currently, approximately half of the genes underlying IHH remain unidentified. The complexity of genotype-phenotype correlations in IHH, largely due to the established phenomena of oligogenic inheritance and spontaneous or treatment-induced clinical reversibility, poses significant challenges to gene discovery. Nevertheless, advances in next-generation sequencing technologies are expected to drive continued progress in uncovering the genetic basis of IHH. These investigations not only enhance our understanding of fundamental biological processes, such as the recent elucidation of the GnRH pulse generator, but also inform the development of targeted therapeutics, exemplified by the approval of fezolinetant for the treatment of menopausal hot flushes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A. Kemal Topaloğlu, Concept: A. Kemal Topaloğlu, Design: A. Kemal Topaloğlu, Data Collection or Processing: A. Kemal Topaloğlu, Analysis or Interpretation: A. Kemal Topaloğlu, Literature Search: A. Kemal Topaloğlu, Leman Damla Kotan, Writing: A. Kemal Topaloğlu, Leman Damla Kotan.

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