Hypogonadotropic Hypogonadism (HH) and Related Disorders

HH Panel Gene List: *ANOS1, CDH7, CYP19A1, DUSP6, ESR1, FEZF1, FGF17, FGF8, FGFR1, GNRH1, GNRHR, HS6ST1, IL17RD, KISS1, KISS1R, LEP, LEPR, LHB, LHCGR, NR0B1, NR5A1, NSMF, POLR3B, PROK2, PROKR2, PROP1, SEMA3A, SEMA3E, SOX10, SPRY4, TAC3, TACR3, WDR11*

Clinical Features:

Hypogonadotropic hypogonadism (HH) is defined as delayed or absent pubertal development due to impaired gonadotropin secretion. In normal development, gonadotropin-releasing hormone (GnRH) neurons form in the olfactory epithelium and migrate to the hypothalamus. During puberty, GnRH is released, which stimulates the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland. Disruption of any stage of this process can lead to HH. Such disruptions include genetic disorders, brain/pituitary tumors or radiation, head trauma, certain drugs, and chronic systemic illness. Idiopathic HH (IHH) is characterized by low gonadotropin and sex steroid levels in the absence of other hormone deficiencies or hypothalamic-pituitary tract abnormalities.

Individuals with IHH usually present with incomplete or absent pubertal development. Over 90% of females with IHH present with primary amenorrhea. Males may have cryptorchidism, testicular atrophy, and microphallus. During childhood, individuals with IHH may have a eunuchoid body habitus (i.e., an arm span that exceeds height by > 5 cm).[1] However, gonadotropin deficiency left untreated may ultimately lead to retarded bone maturation, osteopenia, and osteoporosis in adulthood.[2] In the presence of a partial or total loss of smell (hyposmia or anosmia), IHH is referred to as Kallmann syndrome (KS). Approximately 60% of individuals with IHH have a defective sense of smell. Individuals with KS may have hearing loss, synkinesia, and/or cleft lip/palate. Up to 30% of males with KS also exhibit renal agenesis. Several genes have been known to cause both normosmic and anosmic HH.[1]

Several genes have other clinical features in addition to IHH or Kallmann syndrome. Individuals who have KS due to variants in the *CHD7* gene may also have phenotypic features of CHARGE syndrome.[3] Variants in the *LEP* and *LEPR* genes are associated with early onset extreme food seeking behavior and severe obesity.[4,5] Additionally, males with variants in the X-linked *NR0B1* gene may cause HH secondary to adrenal failure due to congenital adrenal hypoplasia (AHC). Most female carriers of *NR0B1* variants have normal adrenal function and no evidence of IHH. Males with variants in the *LHCGR* gene may experience Leydig cell hypoplasia with IHH or pseudohermaphroditism, whereas females may experience amenorrhea and infertility.[6]

Management of IHH may include administration of gonadal steroids to stimulate development of secondary sex characteristics followed by infertility treatment in adulthood.[1] Early intervention can prevent low bone density and related complications, and also provides the opportunity for early family planning. Additionally, IHH reversal has been reported in

approximately 10% of males following treatment with gonadal steroids, gonadotropin, or GnRH.[7]

The HH/Kallman related disorders panel may clarify a clinical diagnosis or identify a genetic diagnosis for HH/Kallman or a related disorder. If a genetic diagnosis is found, genetic testing and recurrence risk information would be available for at-risk family members. In addition, having an identified genetic diagnosis may or may not impact medical management or treatment of the condition.

Genetics:

Variants in some of these genes cause Kallmann syndrome, whereas variants in other genes result in normosmic IHH (nIHH). In several instances, a single gene may cause nIHH as well as Kallmann syndrome, frequently referred to as HH with or without anosmia. HH is a genetically heterogeneous condition. Many genes causing HH with or without anosmia demonstrate variable expressivity and reduced penetrance. Loss-of-function variants in the *KISS1, KISS1, ESR1* and *LHCGR* genes are associated with HH, but gain-of-function variants have been associated with central precocious puberty (CPP), which leads to premature development of secondary sexual characteristics, acceleration in linear growth, and bone age advancement.[8,9,10] Oligogenic inheritance has been proposed for some HH-related genes.[11]

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: *KISS1R, POLR3B, SEMA3E,* and *SOX10* genes, no copy number testing.

Test Sensitivity:

Approximately 30% of IHH is familial, and many genes associated with IHH have been identified. Twenty-five to 40% of individuals with KS have variants in the *ANOS1, CHD7, FGFR1, FGF8, PROK2*, or *PROKR2* genes. Together, approximately 50% of individuals with nIHH have variants in the *GNRH1, GNRHR, KISS1, KISS1R, NELF, NR0B1, TAC3,* or *TACR3* genes. Variants in the genes *CYP19A1, DUSP6, ESR1, FEZF1, FGF17, FGF8, GNRH1, HS6ST1, IL17RD, LEP, LEPR, LHB, LHCGR, NR5A1, POLR3B, PROP1, SEMA3A, SEMA3E, SOX10, SPRY4, TAC3, TACR3,* and *WDR11* are rare, as they have only been reported in a small subset of families.

Gene	Protein	Inheritance	Disease Associations	Sensitivity
ANOS1	Kallmann syndrome interval gene 1	XLR	KS	5-10% of KS[20] 3-6% of IHH[21]
CHD7	Chromodomain helicase DNA binding protein 7	AD	HH with or without anosmia, CHARGE	10% of KS[12] 6% of IHH[13]
CYP19A1	Cytochrome P450, family 19, subfamily A, polypeptide 1	AD and AR	Aromatase deficiency / Aromatase excess deficiency	Rare[14]
DUSP6	Map kinase phosphatase 3	AD	HH with or without anosmia	Rare; 1-4% of IHH[15]
ESR1	Estrogen receptor 1	AR	Estrogen resistance / precocious puberty	Rare[16]
FEZF1	Family zinc finger protein 1	AR	KS	Rare[17]
FGF17	Fibroblast growth factor 17	AD	HH with or without anosmia	Rare; 1-4% of IHH[15]
FGF8	Fibroblast growth factor 8	AD	HH with or without anosmia	Rare; 1-4% of IHH[15]
FGFR1	Fibroblast growth factor receptor 1	AD	HH with or without anosmia	8-16% of KS[1,8] 6% of IHH[2,13,18]
GNRH1	Gonadotropin-releasing hormone 1	AR	HH	Rare[8]
GNRHR	Gonadotropin-releasing hormone receptor	AR	HH	16-40% of nIHH[12]
HS6ST1	Heparan sulfate 6-O-sulfotransferase 1	AD	HH with or without anosmia	Rare[19]
IL17RD	Interleukin 17 receptor D	AD	KS	Rare; 1-4% of IHH[15]
KISS1	Kisspeptin	AR	HH	5% of nIHH2[12,18,22] 2% of IHH[12]
KISS1R	KISS1 receptor, G protein-coupled receptor 54	AR	HH	5% of nIHH2[12,18,22] 2% of IHH[12]

LEP	Leptin	AR	HH, Congenital leptin deficiency	Rare[23]
LEPR	Leptin receptor	AR	HH, Congenital leptin deficiency	Rare[5]
LHB	Luteinizing hormone, beta polypeptide	AR	HH with or without anosmia	Rare[24]
LHCGR	Luteinizing hormone, choriogonadotropin receptor	AD and AR	Leydig cell hypoplasia with HH or pseudo-hermaphroditism / precocious puberty	Rare[25]
NR0B1	Nuclear receptor subfamily 0, group B, member 1	XLR	HH, Congenital adrenal hyperplasia	<3% of nIHH [1,26]
NR5A1	Nuclear receptor subfamily 5, group A, member 1	AD	46,XY disorder of sexual development with or without adrenal insufficiency	Rare[27]
NSMF	NMDA receptor synaptonuclear signaling and neuronal migration factor	AD	HH with or without anosmia	<2% of KS/IHH[11]
POLR3B	Polymerase III, RNA, subunit b	AR	Hypomyelinating leukodystrophy with or without oligodontia and HH	Rare[28,29]
PROK2	Prokinectin 2	AD and AR	HH with or without anosmia	5-10% of KS[12] 3-6% of IHH[12]
PROKR2	Prokinectin receptor 2	AD and AR	HH with or without anosmia	5-10% of KS[12] 3-6% of IHH[30]
PROP1	G protein-coupled receptor 73-like 1	AR	HH	Rare[31,32]
SEMA3A	Semaphorin 3A	AD	KS	Rare[33]
SEMA3E	Semaphorin 3E	AD	KS	Rare[34,35]
SOX10	SRY-box 10	AD	KS, Waardenburg syndrome	Rare[36]
SPRY4	Sprouty, drosophila, homolog 4	AD	HH with or without anosmia	Rare; 1-4% of IHH[15]
TAC3	Tachykinin 3	AR	HH	Rare[8]
TACR3	Tachykinin receptor 3	AR	HH	Rare[30, 37]
WDR11	WD repeat domain 11	AD	HH with or without anosmia	Rare[38]

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