Hypogonadotropic Hypogonadism (HH) Panel

Panel Gene List:
ANOS1, CHD7, CYP19A1, DUSP6, ESR1, FEZF1, FGF17, FGF8, FGFR1, FLRT3, FSHB, GNRH1, GNRHR, HS6ST1, IL17RD, KISS1, KISS1R, LEPR, LEP, LHB, LHCGR, NR0B1, NR5A1, NSMF, POLR3B, PROK2, PROKR2, PROP1, SEMA3A, SEMA3E, SOX10, SPRY4, TAC3, TACR3, WDR11, XRCC4

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 cryptoorchidism, 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). However, gonadotropin deficiency left untreated may ultimately lead to retarded bone maturation, osteopenia, and osteoporosis in adulthood. 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.

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. Variants in the LEP and LEPR genes are associated with early onset extreme food seeking behavior and severe obesity. 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.

Management of IHH may include administration of gonadal steroids to stimulate development of secondary sex characteristics followed by infertility treatment in adulthood. 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.

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, KISS1R, 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: FLRT3, KISS1R, and XRCC4 genes, no copy number testing. For the FGF8, KISS1, LHB, NR5A1, and PROK2 genes only whole gene deletion/duplications can be detected.

Clinical 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, NSMF, NR0B1, TAC3, or TACR3 genes. Variants in the genes CYP19A1, DUSP6, ESR1, FEZF1, FGF17, FGF8, FLRT3, FSHB, GNRH1, HS6ST1, IL17RD, LEP, LEPR, LHB, LHCGR, NR5A1, POLR3B, PROP1, SEMA3A, SEMA3E, SOX10, SPRY4, TAC3, TACR3, WDR11, and XRCC4 are rare, as they have only been reported in a small subset of families.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOS1</td>
<td>Kallmann syndrome interval gene 1</td>
<td>XLR</td>
<td>KS</td>
<td>5-10% of KS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-6% of IHH</td>
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<tr>
<td>CHD7</td>
<td>Chromodomain helicase DNA binding protein 7</td>
<td>AD</td>
<td>HH with or without anosmia, CHARGE</td>
<td>10% of KS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6% of IHH</td>
</tr>
<tr>
<td><strong>Gene</strong></td>
<td><strong>Gene Name</strong></td>
<td><strong>Gene Description</strong></td>
<td><strong>Inheritance</strong></td>
<td><strong>Syndrome</strong></td>
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<tr>
<td><strong>CYP19A1</strong></td>
<td>Cytochrome P450, family 19, subfamily A, polypeptide 1</td>
<td>AD and AR</td>
<td>Aromatase deficiency / Aromatase excess deficiency</td>
<td>Rare14</td>
</tr>
<tr>
<td><strong>DUSP6</strong></td>
<td>Map kinase phosphatase 3</td>
<td>AD</td>
<td>HH with or without anosmia</td>
<td>Rare; 1-4% of IHH15</td>
</tr>
<tr>
<td><strong>ESR1</strong></td>
<td>Estrogen receptor 1</td>
<td>AR</td>
<td>Estrogen resistance / precocious puberty</td>
<td>Rare16</td>
</tr>
<tr>
<td><strong>FEZF1</strong></td>
<td>Family zinc finger protein 1</td>
<td>AR</td>
<td>KS</td>
<td>Rare17</td>
</tr>
<tr>
<td><strong>FGF17</strong></td>
<td>Fibroblast growth factor 17</td>
<td>AD</td>
<td>HH with or without anosmia</td>
<td>Rare; 1-4% of IHH15</td>
</tr>
<tr>
<td><strong>FGF8</strong></td>
<td>Fibroblast growth factor 8</td>
<td>AD</td>
<td>HH with or without anosmia</td>
<td>Rare; 1-4% of IHH15</td>
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<tr>
<td><strong>FGFR1</strong></td>
<td>Fibroblast growth factor receptor 1</td>
<td>AD</td>
<td>HH with or without anosmia</td>
<td>8-16% of KS1,8 6% of IHH2,13,18</td>
</tr>
<tr>
<td><strong>FLRT3</strong></td>
<td>Fibronectin-like domain-containing leucine-rich transmembrane protein 3</td>
<td>AD</td>
<td>HH with anosmia</td>
<td>Rare15</td>
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<tr>
<td><strong>FSHB</strong></td>
<td>Follicle-stimulating hormone, beta polypeptide</td>
<td>AR</td>
<td>HH without anosmia</td>
<td>Rare39-42</td>
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<tr>
<td><strong>GNRH1</strong></td>
<td>Gonadotropin-releasing hormone 1</td>
<td>AR</td>
<td>HH</td>
<td>Rare8</td>
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<tr>
<td><strong>GNRHR</strong></td>
<td>Gonadotropin-releasing hormone receptor</td>
<td>AR</td>
<td>HH</td>
<td>16-40% of nIHH12</td>
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<tr>
<td><strong>HS6ST1</strong></td>
<td>Heparan sulfate 6-Osulfotransferase 1</td>
<td>AD</td>
<td>HH with or without anosmia</td>
<td>Rare19</td>
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<tr>
<td><strong>IL17RD</strong></td>
<td>Interleukin 17 receptor D</td>
<td>AD</td>
<td>KS</td>
<td>Rare; 1-4% of IHH15</td>
</tr>
<tr>
<td><strong>KISS1</strong></td>
<td>Kisspeptin</td>
<td>AR</td>
<td>HH</td>
<td>5% of nIHH212,18,22 2% of IHH12</td>
</tr>
<tr>
<td><strong>KISS1R</strong></td>
<td>KISS1 receptor, G protein-coupled receptor 54</td>
<td>AR</td>
<td>HH</td>
<td>5% of nIHH212,18,22 2% of IHH12</td>
</tr>
<tr>
<td><strong>LEP</strong></td>
<td>Leptin</td>
<td>AR</td>
<td>HH, Congenital leptin deficiency</td>
<td>Rare23</td>
</tr>
<tr>
<td><strong>LEPR</strong></td>
<td>Leptin receptor</td>
<td>AR</td>
<td>HH, Congenital leptin deficiency</td>
<td>Rare5</td>
</tr>
<tr>
<td><strong>LHB</strong></td>
<td>Luteinizing hormone, beta polypeptide</td>
<td>AR</td>
<td>HH with or without anosmia</td>
<td>Rare24</td>
</tr>
<tr>
<td><strong>LHCGR</strong></td>
<td>Luteinizing hormone, choriongonadotropin receptor</td>
<td>AD and AR</td>
<td>Leydig cell hypoplasia with HH or pseudohermaphroditism / precocious puberty</td>
<td>Rare25</td>
</tr>
<tr>
<td><strong>NR0B1</strong></td>
<td>Nuclear receptor subfamily 0, group B, member 1</td>
<td>XLR</td>
<td>HH, Congenital adrenal hyperplasia</td>
<td>&lt;3% of nIHH1,26</td>
</tr>
</tbody>
</table>
NR5A1  | Nuclear receptor subfamily 5, group A, member 1 | AD | 46,XY disorder of sexual development with or without adrenal insufficiency | Rare27

NSMF  | NMDA receptor synaptonuclear signaling and neuronal migration factor | AD | HH with or without anosmia | <2% of KS/IHH<sup>11</sup>

POLR3B  | Polymerase III, RNA, subunit b | AR | Hypomyelinating leukodystrophy with or without oligodontia and HH | Rare28,29

PROK2  | Prokinectin 2 | AD and AR | HH with or without anosmia | 5-10% of KS<sup>12</sup> 3-6% of IHH<sup>12</sup>

PROKR2  | Prokinectin receptor 2 | AD and AR | HH with or without anosmia | 5-10% of KS<sup>12</sup> 3-6% of IHH<sup>30</sup>

PROP1  | G protein-coupled receptor 73like 1 | AR | HH | Rare31,32

SEMA3A  | Semaphorin 3A | AD | KS | Rare33

SEMA3E  | Semaphorin 3E | AD | KS | Rare34,35

SOX10  | SRY-box 10 | AD | KS, Waardenburg syndrome | Rare36

SPRY4  | Sprouty, drosophila, homolog 4 | AD | HH with or without anosmia | Rare: 1-4% of IHH<sup>15</sup>

TAC3  | Tachykinin 3 | AR | HH | Rare8

TACR3  | Tachykinin receptor 3 | AR | HH | Rare30, 37

WDR11  | WD repeat domain 11 | AD | HH with or without anosmia | Rare38

XRCC4  | X-ray repair, complementing defective, in Chinese Hamster, 4 | AR | Short stature, microcephaly, and endocrine dysfunction | Rare43,44

REFERENCES:

44. Saito et al. (2016) J. Hum. Genet. : (PMID: 27169690);