Title: Isolated Gonadotropin-Releasing Hormone (GnRH) Deficiency *GeneReview* – Less Common Genetic Causes

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FGF8

Gene structure. *FGF8* comprises six coding exons which are alternatively spliced into four isoforms.

Pathogenic variants. Pathogenic variants of *FGF8* are predominantly missense variants.

Normal gene product. The normal gene product is FGF8, one of the main ligands for FGFR1 which is involved in neuronal patterning, survival of neural cells, and GnRH neuron development.

Abnormal gene product. Abnormal *FGF8* gene product results in impaired activation of the FGFR1 receptor. *Fgf8* hypomorphic mice have olfactory bulb dysgenesis and reduced number of Gnrh neurons in the hypothalamus [Falardeau et al 2008].

GNRH1

Gene structure. *GNRH1* comprises three coding exons and one alternative splice variant.

Pathogenic variants. Pathogenic frameshift variants of *GNRH1* causing autosomal recessive normosmic IGD as well as missense variants in oligogenic cases have been described.

Normal gene product. *GNRH1* encodes a secreted preprohormone that cleaved to a biologically active decapeptide, GnRH, which in turn stimulates the pituitary to secret the two glycoprotein gonadotropin hormones, LH and FSH, which control steroidogenesis and gametogenesis in the gonads.

Abnormal gene product. Abnormal *GNRH1* gene product due to pathogenic truncating variants in *GNRH1* results in an aberrant peptide lacking biologic activity [Bouligand et al 2009, Chan et al 2009].

HS6ST1

Gene structure. *HS6ST1* comprises two coding exons and has no alternative splice variants.

Pathogenic variants. *HS6ST1* pathogenic variants include missense variants either in the heterozygous or homozygous state and cause IGD in an oligogenic inheritance pattern.

Normal gene product. *HS6ST1* encodes for a type II integral membrane protein that functions as a heparin sulfate biosynthetic enzyme and is responsible for 6-O-sulfation of heparan sulfate. Heparan sulfate, an extracellular glycosaminoglycan, has been shown to be crucial for neural development and heparin 6-O sulfation is required for function of both anosmin-1 and FGFR1 signaling, both of which are critical for GnRH neuronal migration.

Abnormal gene product. Abnormal HS6ST1 protein function disrupts GnRH neuronal migration by compromising anosmin-1 and FGF signaling during neural development.

KISS1

Gene structure. *KISS1* comprises two coding exons and has no alternative splice variants.

Pathogenic variants. Homozygous missense *KISS1* pathogenic variants cause normosmic IGD in an autosomal recessive inheritance pattern, but are exceedingly rare. Rare heterozygous variants have also been associated with IGD suggesting a likely oligogenic inheritance in those individuals.

Normal gene product. *KISS1* encodes for kisspeptin, a secreted peptide that is a potent stimulus for GnRH secretion in all mammalian species through KISS1R, its cognate receptor.

Abnormal gene product. Abnormal *KISS1* gene products result in diminished or absent kisspetin signaling through the receptor resulting in secondary GnRH deficiency and consequent hypogonadotropism.

KISS1R

Gene structure. *KISS1R* comprises five coding exons and one alternative splice variant.

Pathogenic variants. *KISS1R* pathogenic variants, typically nonsense or missense variants, cause normosmic IGD in an autosomal recessive inheritance pattern. These pathogenic variants are extremely rare. Occasionally, heterozygous pathogenic variants are also seen in persons with IGD, suggesting an oligogenic inheritance pattern.

Normal gene product. *KISS1R* encodes for the kisspeptin receptor, KISS1R, a G protein-coupled transmembrane receptor for kisspeptin.

Abnormal gene product. Abnormal *KISS1R* gene products result in diminished or absent kisspetin signaling through the receptor resulting in secondary GnRH deficiency and consequent hypogonadotropism.

NSMF (*NELF*)

Gene structure. *NSMF* comprises 16 coding exons and has ten protein-coding alternative splice variants.

Pathogenic variants. *NSMF* pathogenic variants include missense variants and splice variants, either in the heterozygous or compound heterozygous state and cause IGD in an oligogenic inheritance pattern.

Normal gene product. *NSMF* encodes for nasal embryonic LHRH factor, a protein involved in guidance of olfactory axon projections and migration of GnRH neurons.

Abnormal gene product. The precise pathophysiologic role of *NSMF* pathogenic variants is not clear, but abnormal *NSMF* gene products are postulated to result in disruption of embryonic migration of GnRH neurons [Xu et al 2011].

PROK2

Gene structure. *PROK2* comprises four coding exons, including an alternative exon 3.

Pathogenic variants. Pathogenic variants of *PROK2* include missense and nonsense variants, as well as alterations of translation start sites.

Normal gene product. The normal gene product is prokineticin-2, the main ligand of PROKR2.

Abnormal gene product. *PROK2* pathogenic variants resulted in diminished signaling through the PROKR2 receptor [Cole et al 2008, Martin et al 2011].

SEMA3A

Gene structure. *SEMA3A* comprises 17 coding exons and has five alternative protein-coding splice variants.

Pathogenic variants. *SEMA3A* pathogenic variants implicated in IGD include heterozygous deletions and missense/frameshift variants, and cause IGD in an oligogenic inheritance pattern.

Normal gene product. *SEMA3A* is a member of the semaphorin family and encodes a protein with an Ig-like C2-type (immunoglobulin-like) domain, a PSI domain and a Sema domain. This secreted protein can function as either a chemorepulsive agent, inhibiting axonal outgrowth, or as a chemoattractive agent, stimulating the growth of apical dendrites.

Abnormal gene product. Abnormal *SEMA3A* protein results in impaired embryonic migration of the GnRH neurons due to dysfunctional axonal guidance.

TAC3

Gene structure. *TAC3* comprises five coding exons and has two protein-coding alternative splice variants.

Pathogenic variants. Homozygous pathogenic missense, nonsense and frameshift *TAC3* variants cause normosmic IGD in an autosomal recessive inheritance pattern. Rare heterozygous *TAC3* variants have also been associated with IGD suggesting a likely oligogenic inheritance in these patients.

Normal gene product. *TAC3* encodes for neurokinin B, a neuropeptide that is secreted by neurons, a subset of which also coexpress kisspeptin. While the precise role of TAC3 in regaultion of GNRH secretion is still unclear.

Abnormal gene product. Abnormal *TAC3* gene products result in diminished or absent neurokinin B signaling through its cognate receptor, TACR3, and results in secondary GnRH deficiency and consequent hypogonadotropism.

WDR11

Gene structure. *WDR11* comprises 29 coding exons and has no alternative protein-coding splice variants.

Pathogenic variants. *WDR11* pathogenic variants implicated in IGD include heterozygous missense variants and cause IGD in an oligogenic inheritance pattern.

Normal gene product. WDR11 interacts with EMX1, a homeodomain transcription factor involved in the development of olfactory neurons and hence governs GnRH neuronal migration.

Abnormal gene product. Abnormal WDR11 protein abolishes the interaction of WDR11 with EMX1 and disrupts GnRH neuronal migration.

Other Less Common Genetic Causes

The following genes have only been reported recently and only in a single study. These will not be described here; readers are directed to the references indicated:

AXL [Salian-Mehta et al 2014]

CCDC141 [Hutchins et al 2016]

DUSP6 [Miraoui et al 2013]

FEZF1 [Kotan et al 2014]

FGF17 [Miraoui et al 2013]

FLRT3 [Miraoui et al 2013]

POLR3B [Richards et al 2017]

SEMA3E [Cariboni et al 2015]

SPRY4 [Miraoui et al 2013]

SRA1 [Kotan et al 2016]

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