endocrines

MDPI

Review

Genetic Etiology of Idiopathic Hypogonadotropic Hypogonadism

Ali Kemal Topaloglu [1,2,*] and Ihsan Turan [3]

[1] Department of Neurobiology and Anatomical Sciences, University of Mississippi Medical Center, Jackson, MS 39216, USA
[2] Division of Pediatric Endocrinology, Department of Pediatrics, University of Mississippi Medical Center, Jackson, MS 39216, USA
[3] Division of Pediatric Endocrinology, Faculty of Medicine, Cukurova University, Adana 01230, Turkey; ituran@cu.edu.tr
* Correspondence: ktopaloglu@umc.edu

Abstract: Idiopathic hypogonadotropic hypogonadism (IHH) is a group of rare developmental disorders characterized by low gonadotropin levels in the face of low sex steroid hormone concentrations. IHH is practically divided into two major groups according to the olfactory function: normal sense of smell (normosmia) nIHH, and reduced sense of smell (hyposmia/anosmia) Kallmann syndrome (KS). Although mutations in more than 50 genes have been associated with IHH so far, only half of those cases were explained by gene mutations. Various combinations of deleterious variants in different genes as causes of IHH have been increasingly recognized (Oligogenic etiology). In addition to the complexity of inheritance patterns, the spontaneous or sex steroid-induced clinical recovery from IHH, which is seen in approximately 10–20% of cases, blurs further the phenotype/genotype relationship in IHH, and poses challenging steps in new IHH gene discovery. Beyond helping for clinical diagnostics, identification of the genetic mutations in the pathophysiology of IHH is hoped to shed light on the central governance of the hypothalamo-pituitary-gonadal axis through life stages. This review aims to summarize the genetic etiology of IHH and discuss the clinical and physiological ramifications of the gene mutations.

Keywords: hypogonadotropic hypogonadism; puberty; genetic etiology

Citation: Topaloglu, A.K.; Turan, I. Genetic Etiology of Idiopathic Hypogonadotropic Hypogonadism. *Endocrines* **2022**, *3*, 1–15. https://doi.org/10.3390/endocrines3010001

Academic Editor: Alessandro Genazzani

Received: 18 October 2021
Accepted: 16 December 2021
Published: 24 December 2021

1. Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) refers to instances of hypogonadotropic hypogonadism (HH) that have no known etiology. IHH is divided into two categories with normal olfaction (normosmic idiopathic hypogonadotropic hypogonadism (nIHH), and hyposmia or anosmia (Kallmann Syndrome (KS)) and can be congenital or acquired [1]. The most frequent presentation of IHH is a pubertal delay, defined as the absence or inadequacy of mammary gland development in a 13-year-old girl, or the inability to attain a testicular volume of 4 mL in a 14-year-old boy. Micropenis and/or cryptorchidism may be the first sign of IHH in male newborns. Typically, clinical symptoms of IHH do not appear in girls until they are in their early teen years [2]. Constitutional delay in growth and puberty (CDGP) is by far the most frequent cause of delayed puberty, which is not an illness in and of itself, rather an individual variation of timing at the older end. The diagnosis of CDGP can only be made by excluding IHH, which often requires prolonged follow-up periods. Genetic factors are thought to account for 50–80 percent of pubertal timing [3]. From this perspective, IHH and CDGP can be considered severely or mildly affected conditions on the same scale. As accepted, new gene discovery studies have initially reported most severe variants in the functionally crucial genes. Researchers have recently associated more genes with IHH in complex pedigrees, often lacking proper genotype-phenotype segregations. This is probably due to a combination of oligogenic etiology [4] and clinical recovery [5], among other factors.

Despite a long history of research on the topic, it remains unclear what triggers pubertal development. The genetic underpinnings of IHH may provide clues to this enigma. Over the past decades, an exponential number of new IHH genes have been published. The improvement of DNA sequencing has been the mainstay for these studies. The development of Sanger sequencing in 1977 by Frederick Sanger and the first commercialization by Applied Biosystems in 1986 was the beginning of a new era. Subsequently, next-generation sequencing (NGS) technology enormously escalated the production of genetic data. Since 2010, molecular genetic analyses based on NGS entered medical practice and furthered research possibilities. NGS has allowed the systematic identification of variants on a large scale and accelerated the pace of gene discovery and disease diagnosis on a molecular level, particularly for the rare Mendelian disease [6]. The exponentially increased number of articles published in Pubmed about the genetics of normosmic IHH and Kallmann Syndrome is presented in Figure 1.

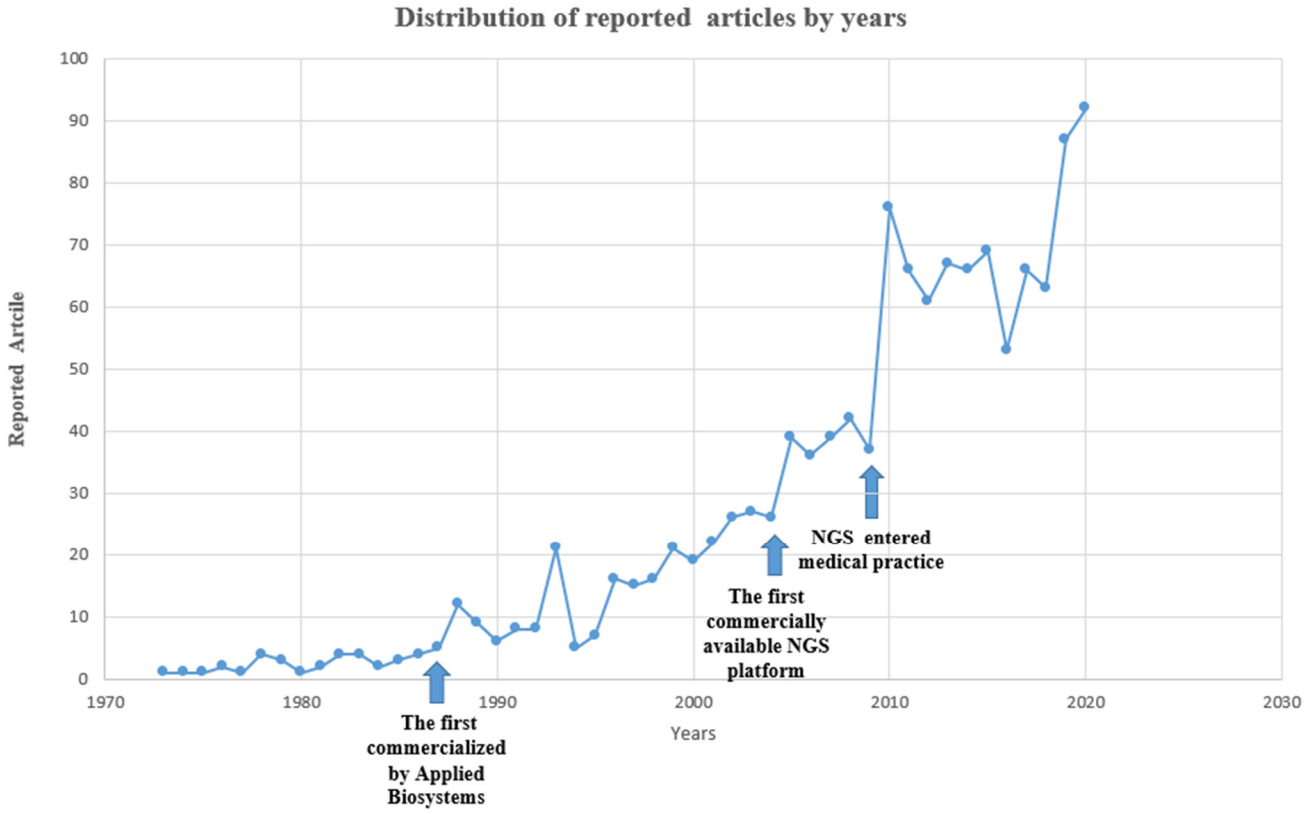

Figure 1. The exponential increase in the number of articles published in Pubmed over the past several decades regarding mutations in IHH genes.

Preparing this review article, we identified relevant articles from the earliest available online indexing up to November 2021 through systematic searches in the PubMed/MEDLINE database. The search strategy included the following keywords: "idiopathic hypogonadotropic hypogonadism" OR "Kallmann syndrome" OR "puberty" AND "gene" OR "puberty" AND "mutation." The search results were manually reviewed. Up until present, nearly 60 genes have been reported to be associated with IHH (Table 1). However, the genes reported so far may explain approximately 50% of all seemingly inherited cases [1]. Oligogenicity has been reported for IHH based on Mendelian inheritance [4,7–9]. The increasing use of next-generation sequencing in clinical practice has been revolutionary for genetic-based studies (e.g., elucidating disease physiology, rapid diagnosis, or new gene discoveries) [10]. While it has been known that the oligogenic inheritance was about 10–20% in IHH, recent studies have reported that this rate may be much higher, up to 70% [11].

The genes involved in the physiology of IHH can be divided into two main categories: neurodevelopmental and neuroendocrine. However, it has been increasingly reported that these two groups may be intertwined. Thus, a KS-related gene may also be responsible for nIHH (or vice versa) [11–13]. Those neurodevelopmental genes closely related to the KS genes are mainly associated with fibroblast growth factor (FGF) signaling, GnRH neuron migration, and olfactory bulb structure. They may occasionally be observed with additional clinical features, such as synkinesia, dental agenesis, hearing loss, and digital bony abnormalities [1,14,15]. Neuroendocrine genes, which represent the normosmic side of the disease (nIHH), are fundamentally related to the function of the hypothalamo-pituitary-gonadal axis. Mutations identified in familial nIHH cases provided a better understanding of the physiology of the HPG axis [16]

The aim of the manuscript is to review the genetic etiology of IHH. We presented the genes associated with IHH in two sections as with or without phenotype numbers of OMIM.

2. IHH-Associated Genes with OMIM Phenotype Number

ANOS1 (HH1, #308700): This gene, formerly known as *KAL1*, is located on the X chromosome and encodes an extracellular glycoprotein called anosmin-1 [17]. The extracellularly secreted anosmin-1 enhances FGF activity by promoting FGF8-FGFR1 complex formation, which is required for neuronal migration [15] Patients with deleterious *ANOS1* variants have absent or severely reduced migration of GnRH cells into the hypothalamus. *ANOS1* mutations are seen in male individuals with KS. To date, various mutations have been reported ranging from missense to frameshifts caused by insertion/deletion [18,19]. Accompanying clinical signs may include bimanual synkinesia (mirror movements) and unilateral renal agenesis [20]. In addition, the association of rarely reported clinical signs, such as deafness and vas deferens agenesis, has not been fully clarified.

Fibroblast growth factor family and related genes: *FGFR1* (HH2 #1479850), *FGF8* (HH6 #612702), *HS6ST1* (HH15 #614880), *SPRY4* (HH17 #615266), *IL17RD* (HH18 #615267), *DUSP6* (HH19 #615269), *FGF17* (HH20 #615270), *FLRT3* (HH21 #615271), and *KLB* (2017): FGFR1 signaling is involved in the morphogenesis of olfactory bulbs. It is required for normal migration, differentiation, and/or survival of GnRH neurons. However, isolated defects in GnRH neuronal migration that occur without the development of olfactory bulbs affected may also be due to FGFR1 mutations. To date, numerous mutations associated with both KS and nIHH have been reported [12,14,21–24]. Thus, this gene should be prioritized in screening panels for both forms of HH [25].

FGF8 is a ligand of *FGFR1,* which is involved in GnRH neuron ontogenesis. Falardeau et al. reported missense mutations in *FGF8* in six IHH patients with variable olfactory function. They also showed that the hypomorphic homozygous *Fgf8* mice lack GnRH neurons and olfactory bulbs in the hypothalamus [26]. The study of Miraoui and colleagues identified heterozygous *FGF17* mutations in both normosmic IHH and KS patients [27]. *FGF17* has a similar sequence to that of *FGF8* and is a critical *FGFR1* ligand that plays a role in GnRH neuron ontogeny. Bone defects, cleft lip-palate, and dental agenesis are commonly associated with the FGF group gene mutations [20]. In addition, it has been reported that *IL17RD, DUSP6, SPRY4*, and *FLRT3* have essential roles in the development of GnRH neurons [27].

KLB encodes for beta-klotho a co-receptor in FGF21 signaling. The majority of patients with *KLB* mutations have various metabolic defects. *Klb* knockout mice showed a milder hypogonadal phenotype [28].

HS 6-O-sulfotransferase 1 is a sulfation enzyme that catalyzes the transfer of sulfate and is involved in cell-cell communication and neuronal migration. Inactivating *HS6ST1* mutations have been identified with oligogenicity in both KS and nIHH. C. elegans studies have shown that *HS6ST1* regulates neural branching required for FGF8-mediated *FGFR1* signaling [29]. Recently, a heterozygous HS6ST1 variant was shown to be segregated with

self-limited delayed puberty, which is effectively synonymous to CDGP in a large pedigree. Accompanying mouse studies corroborated human findings [30].

PROKR2 (HH3 #244200) and *PROK2* (HH4 #610628): *PROK2* and *PROKR2* encode a peptide consisting of 81 amino acids called prokineticin 2 and its G-protein-dependent receptor, respectively. Both serve as origins for neuronal precursors and are involved in various biological processes, including olfactory bulb morphogenesis and sexual maturation [31]. Studies have shown that *Prokr2* knockout mice exhibited a significant reduction in olfactory bulb size, while asymmetric olfactory bulb development was observed in *prok2* knockout mice [32,33]. *PROK2* and *PROKR2* mutations cause phenotypic diversity ranging from KS to nIHH. Patients with *PROK2* or *PROKR2* mutations have been reported with clinical features, such as fibrous dysplasia, synkinesis, and epilepsy. In addition to the known AR and AD transmission model, both genes are associated with oligogenic inheritance [13,34,35].

CHD7 (HH5 #612370): Chromodomain helicase DNA-binding protein 7 (*CHD7*) mutations are the main causes of CHARGE syndrome, comprising Coloboma, Heart anomalies, choanal Atresia, Retardation, Genital defects, and Ear anomalies [36]. The hypothesis that KS and nIHH may be a milder allelic variant of the CHARGE syndrome has emerged with studies that identified *CHD7* mutations in HH patients without CHARGE features [37,38]. Studies in *Chd7*-deficient mice show that this gene affects the GnRH neuron migration pathway from beginning to end [39]. Accordingly, patients with HH phenotype should be examined for possible *CHD7* mutations, even if they do not have any CHARGE syndrome characteristics. *CHD7* should be tested in the presence of clinical features, such as coloboma, abnormal ears, deafness, and/or semicircular canal hypoplasia/aplasia [36].

GNRHR (HH7 #146110) and *GNRH1* (HH12 #614841): The GnRH receptor encoded by the *GNRHR* belongs to the G-protein-coupled receptor family consisting of seven helical transmembrane domains. In 1997, de Roux and coworkers reported that inactivating mutations in *GNRHR* cause nIHH [40]. *GNRHR* mutations with an autosomal recessive inheritance pattern have a prevalence of approximately 40% in familial cases and 17% in sporadic cases in nIHH [41]. Mutations have been observed in patients with a broad spectrum of reproduction ranging from partial to complete GnRH resistance [42]. *GNRH1* encodes gonadotropin-releasing hormone, a hypothalamic decapeptide, and plays an essential role in regulating vertebrate reproduction [43]. The essential role of GnRH in human reproduction was confirmed by inactivating *GNRH1* mutations, which were reported as the cause of IHH in the same period by two independent research groups [44,45]. The detection of different mutations of the amino acid arginine at position 31 (p.Arg31Cys and p.Arg31His) that affect the GnRH decapeptide sequence has shown that this region could be a "hot spot" [45,46].

KISS1R (HH8 #614837) and *KISS1* (HH13 #614842): *KISS1R* encodes the kisspeptin receptor, a G-protein-coupled receptor. Autosomal recessive *KISS1R* mutations were first identified in 2003 by two independent research groups using linkage analysis in familial multiplex IHH cases [47,48]. Subsequently, loss-of-function *KISS1R* mutations have also been reported in partial or complete nIHH patients with different studies [48]. Studies have shown that *KISS1* and its receptor are expressed in the mouse hypothalamus and are an essential neuroendocrine regulator of gonadotropin secretion [49,50].

In 2012, Topaloglu et al. identified a homozygous *KISS1* mutation in a large consanguineous family with normosmic IHH. This study reported an inactivating mutation affecting the fourth amino acid of the mature Kisspeptin−10, which has a highly conserved residue [51]. As with other ligands (i.e., *GNRH1* and *TAC3*), mutations in *KISS1* are rarer in the etiology of IHH in comparison to their receptor counterparts.

NSMF (HH9 #614838): *NSMF*, the NMDA receptor synaptonuclear signaling and neuronal migration factor, is expressed in olfactory and GnRH cells during embryonic development. It has been shown to guide olfactory axonal projection and GnRH migration in mice studies. *NSMF* mutations have been identified in both KS and normosmic IHH

patients, some associated with other known IHH genes, such as *TACR3*, *HS6ST1*, *FGFR1*, and *ANOS1* [52,53].

TAC3 (HH10 #614839) and *TACR3* (HH11 #614840): Neurokinin B is encoded by tachykinin precursor 3 (*TAC3*), and neurokinin B receptor is encoded by tachykinin receptor 3 (*TACR3*), a member of the rhodopsin family of G-protein-coupled receptors. Together with kisspeptin and dynorphin, neurokinin B forms KNDy neurons in the hypothalamic arcuate nucleus (ARC) and regulates the secretion of GnRH, which is required for mammalian reproduction [54]. In 2009, Topaloglu and colleagues using single nucleotide polymorphism analyses based on autozygosity mapping, identified the first inactivating homozygous *TAC3* and *TACR3* mutations in nine patients from four independent families with IHH phenotype [16,55]. Later studies determined that *TACR3* mutations were common [56,57]. Clinical reversibility is a phenomenon with unclear mechanisms, seen in approximately 10% of IHH patients. Gianetti et al. reported a clinical reversibility rate of 83% in their *TAC3*/*TACR3* cohort. In contrast, the presence of micropenis and cryptorchidism, which is an indication of severe congenital phenotype, was observed in male infants with *TACR3* mutations. These observations may be due to the plasticity of neurokinin B signaling through the reproductive life stages.

WDR11 (HH14 #614858): *WDR11* encodes WD repeat-containing protein 11 and is associated with both KS and nIHH. The interaction of EMX1, a homeodomain transcription factor involved in the development of olfactory neurons, and WDR11 have been demonstrated by murine studies [58]. *WDR11*/*PROKR2* coexistence has been reported in association with pituitary stalk interruption syndrome [59].

SEMA3A (HH16 #614897) and *SEMA3E* (2015): *SEMA3A* encodes semaphorin 3A, an axonal guide molecule that interacts with neuropilins. Neuropilin-plexin-A1 complex, which is involved in axonal growth during embryonic development, is activated by semaphorin 3A. Cariboni et al. seminally reported that *SEMA3A* is the critical player in semaphorin signaling during GnRH neuron development [60]. Studies have shown that mice lacking *SEMA3A* expression have defects in the olfactory system and migration of GnRH cells, thus having a Kallmann-like phenotype [61,62]. Similarly, *SEMA3E*, another member of the same SEMA3 family and encoding semaphorin 3E, is a secreted protein involved in axonal growth [63]. Studies have shown that mutations in both genes are related to IHH with oligogenic inheritance [64].

FEZF1 (HH22 #616030): In 2014, a study combining autozygosity mapping and whole-exome sequencing identified homozygous loss-of-function and nonsense *FEZF1* mutations in two independent consanguineous families with KS. The inheritance pattern is autosomal recessive, and mutations are extremely rare. Studies have shown that *Fez-1* deficient mice have a smaller olfactory bulb and no GnRH neuron in their brains due to impaired axonal projection of olfactory receptor neurons. FEZ family zinc finger 1 (encoded by *FEZF1*) corroborates the presence of protease required for GnRH neurons to enter the brain and reach their ultimate destination [65,66].

NDNF (HH25 #618841): *NDNF* is a member of the fibronectin-3 superfamily. WES data from a cohort of 240 probands with IHH were screened for rare variants in FN3 domain-containing proteins. Four apparently pathogenic variants in *NDNF* were identified in four KS probands. In a functional study, delayed GnRH neuron migration and altered olfactory axonal projections to the olfactory bulb were shown by knockdown of the zebrafish ortholog of NDNF [67].

SMCHD1 (#603457): *SMCHD1*, structural maintenance of chromosome flexible hinge domain containing 1, is an epigenetic regulator gene expressed in the olfactory epithelium. In 2017, Shaw et al. identified missense SMCHD1 mutations in a patient with arrhinia (or absence of the nose). The vast majority of patients had HH, and seven subjects lacked olfactory structures [68]. In a recent study, rare variants of this gene in the spectrum of HH-related disease were reported [69].

SOX10 (#613266): *SOX10*, a member of the SOX family, encodes a transcription factor expressed by GnRH neuron precursors. Inactivating mutations cause Waardenburg syn-

drome, a rare genetic condition that can cause pigmentation anomalies of the skin, hair, and/or eyes, and hearing loss. Studies have shown that the olfactory ensheathing cells are absent in *SOX10* knockout mice. *SOX10* has been reported to be associated with KS. Inactivating *SOX10* variants have been observed in approximately one-third of KS patients with deafness (80) [70].

LEP (#614962), *LEPR* (#614963), and *PCSK1* (#600955): Mutations in LEP (encoding leptin) or LEPR (encoding leptin receptor), and PCSK1 (proprotein convertase subtilisin/kexin type 1), account for less than 5% in nIHH [71,72]. These patients have obesity in addition to IHH. It is well-known that energy balance is important for the onset of puberty. Leptin is a fat-derived hormone and regulates food intake and energy expenditure associated with body weight. Therefore, starving and/or loss of body fat suppress reproduction and lead to infertility. Leptin and its receptor are involved in the control of human reproduction [1,73,74]. In mice studies, leptin treatment induced the onset of puberty in normal females and reversed hypogonadism in those with starvation-induced leptin deficiency [75,76].

NR0B1 (#300200): *NR0B1* (the nuclear receptor subfamily 0, group B, member 1) is a pleiotropic gene with X-linked inheritance. *NR0B1* is involved with a syndromic form of IHH associated with primary adrenal insufficiency due to congenital adrenal hypoplasia. It encodes an orphan receptor expressed in the adrenal cortex and gonads [77].

CPE (#619326): Carboxypeptidase E (*CPE*) plays a critical role in the biosynthesis of peptide hormones and neuropeptides within the endocrine and central nervous systems, such as alfa-MSH. A 21-year-old woman was reported to have childhood-onset obesity, impaired intellectual disability, type 2 diabetes, and hypogonadotropic hypogonadism [78]. More recently, a homozygous nonsense variant of CPE was reported in three siblings with the same phenotype with appropriate genotype-phenotype segregations [79].

HESX1 (#182230): Homeobox gene expressed in embryonic stem cells 1 (*HESX1*) encodes a transcription repressor important for cell proliferation and differentiation. The study of Newbern et al. identified heterozygous missense mutations in three patients with an impaired sense of smell out of a total of 217 HH individuals [80].

DMXL2 (#616113): *DMXL2* encodes the synaptic protein DmX-like protein 2. Tata et al. showed that *DMXL2* causes a highly complex syndrome associated with HH and polyendocrine deficiencies and polyneuropathies in three siblings with homozygous deletion. A low *DMXL2* expression in mice leads to partial gonadotropic axis deficiency resulting in reduced fertility [81].

OTUD4 (2013), *RNF216* (#212840), *STUB1* (#615768), and *PNPLA6* (#215470): OTU domain-containing protein 4 (encoded by *OTUD4*), E3 ubiquitin-protein ligase RNF216 (encoded by *RNF216*), and carboxy terminus of Hsp70-interacting protein (encoded by *STUB1*) play roles in ubiquitination. Homozygous mutations in the *OTUD4* and *RNF216* were identified in a consanguineous family with Gordon Holmes syndrome characterized by cerebellar ataxia and normosmic IHH [82]. Shi et al. identified a homozygous mutation in *STUB1* in siblings with IHH and ataxia [83]. Genetic research using WES also showed *PNPLA6* mutations to cause both Gordon Holmes and Boucher–Neuhauser syndromes. Neuropathy target esterase encoded by *PNPLA6* is a protein involved in phospholipid metabolism. *PNPLA6* deficiency results in an impaired gonadotropin release and delayed neurodegeneration [84,85].

POLR3A (#607694) and *POLR3B* (#614381): *POLR3A*, the largest of the 17 subunits that make up RNA polymerase III (Pol III), and *POLR3B*, the second-largest subunit, together form the catalytic center of the enzyme, which transcribes small untranslated RNAs such as tRNA [86]. Recessive mutations in these genes have been reported in association with the 4H syndrome, which is characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism [87,88].

3. The Genes Associated with IHH without Phenotype Numbers of OMIM

Reported mutations in many different genes can explain up to 50% of the causes of genetic cases with IHH. That is the reason why research into new genes that cause IHH is still exciting. Considering that more specific and functionally crucial genes are discovered first, future research will likely elucidate more complex genes. Recent reports of new puberty gene discoveries often lack proper genotype-phenotype segregations in given pedigrees, possibly as a result of oligogenic inheritance, variable penetrance, and clinical heterogeneity of the disease.

SOX3 (2014): *SOX3* encodes a transcription factor involved in pituitary morphogenesis. Previously, duplications and deletions of alanine residues *SOX3* were associated with X-linked panhypopituitarism. Subsequently, two different reports identified an in-frame deletion of the polyalanine tract in *SOX3* in IHH patients without other pituitary hormone deficiencies [89].

AXL (2014): *AXL*, a member of TAM family, receptor tyrosine kinases, is differentially expressed in GnRH neuronal cells and implicated in GnRH neuron migration and/or survival. Four *AXL* variants were detected in four patients with Kallmann syndrome or nIHH [90].

IGSF10 (2016): Using candidate gene sequencing and WES, Howard et al. identified rare mutations in the *IGSF10* in six families with self-limited delayed puberty. The potential role of immunoglobulin superfamily member 10 (IGSF10) in the regulation of GnRH neuronal migration was demonstrated, with its strong expression in embryonic nasal mesenchyme during GnRH neuronal migration. IGSF10 knockdown has been shown to impair GnRH neuron migration in zebrafish. Patients with *IGSF10* mutations were normosmic, despite impaired migration of GnRH. Notably, rare variants in *IGSF10* were also identified in a few patients with functional hypothalamic amenorrhea [91].

SRA1 (2016): *SRA1* was the first gene discovered to function through both protein and non-coding functional RNA products [92]. Nuclear receptors, such as SF-1 and LRH-1, are co-regulated *SRA1* products. *SRA1* is required by *NR0B1* to synergistically enhance SF-1 transcriptional activity (85). Using the autozygosity mapping and WES, *SRA1* mutations in three independent families with IHH were identified [93].

PLXNA1 (2017): Plexin-A1 protein, encoded by *PLXNA1*, is a coreceptor of SEMA3A, SEMA3C, SEMA3F, and SEMA6D. Marcos et al. found the *PLXNA1* variants in a large cohort of KS. These studies revealed 13 heterozygous missense variants in 15 patients from 13 pedigrees. [94]. More recently, Kotan et al. identified 10 variant in *PLXNA1* s in nine patients from seven independent families, seven of whom were normosmic. They concluded that *PLXNA1* variants cause not only anosmic but also normosmic IHH [11].

CCDC141 (2018): *CCDC141* encodes the coiled-coil domain-containing protein 141, a cytoskeletal associated protein expressed in GnRH neurons. Turan et al. reported inactivating *CCDC141* mutations in four independent families with IHH [95]. Knockdown of *Ccdc141* resulted in reduced embryonic GnRH neuronal migration [96]. In another extensive cohort report, 14 variants were detected in 12 unrelated pedigrees. The allele frequency of *CCDC141* RSVs was significantly higher in CHH patients compared to the controls. However, *CCDC141* pathogenic variants were insufficient to cause IHH alone, as 75% of patients had additional IHH gene variants [97].

IRF2BPL (2019): *IRF2BPL* encodes probable E3 ubiquitin-protein ligase that is included within the proteasome-mediated ubiquitin-dependent degradation of target proteins, and probably plays a role in the development of the central nervous system and neuronal maintenance. Functional analyses of the gene indicated its pivotal role in pubertal timing [98]. Mancini et al. reported one in-frame deletion and one missense variant in two independent families with delayed puberty [99].

AMH and *AMH2R* (2019): In a recent study, AMH has been shown to be expressed in migratory GnRH neurons in both mouse and human fetuses. AMH acts as a pro-motility factor for GnRH neurons. Furthermore, inactivating heterozygous mutations were identified in *AMH* and its receptor *AMH2R* in a large cohort of IHH [100].

SEMA3F and *PLXNA3* (2021): Variants in members of class 3 semaphorins, SEMA3A, SEMA3E, and SEMA3G, have been associated with IHH [61,63,101]. Additionally, heterozygous variants in *PLXNA1* were reported to cause KS and nIHH [11,94]. Kotan et al. recently screened whole-exome sequencing data from a cohort of 216 probands with congenital hypogonadotropic hypogonadism for rare variants in *SEMA3F* and *PLXNA3.* They identified 10 monoallelic variants in 15 patients from 11 unrelated families. Further studies suggested that SEMA3F signaling via *PLXNA3* is essential for the guidance of migrating GnRH neurons [102].

RAB3GAP1, *RAB3GAP2*, *RAB18*, and *TBC1D20*: Martsolf syndrome and Warburg Micro syndrome are phenotypically overlapping disorders characterized by intellectual disability, eye anomalies (i.e., congenital cataract, optic atrophy), and hypogonadism. *RAB3GAP1* (RAB3 GTPase-activating protein 1), *RAB3GAP2* (RAB3 GTPase-activating protein 2), *RAB18* (RAS-associated protein RAB18), and *TBC1D20* (TBC1 domain protein, member 20) mutations have been associated with these syndromes [103]. Disease-causing variants in these genes directly (*RAB18*) or indirectly (*RAB3GAP1*, *RAB3GAP2*, and *TBC1D20*) cause dysfunction of a GTPase, resulting in a rare syndromic presentation of IHH [104,105].

4. Concluding Remarks

The contributions from human genetics to our current understanding of GnRH neuron function have been enormous. The unprecedented identification of kisspeptin (*KISS1*, *KISS1R*) and neurokinin B (*TAC3*, *TACR3*) ligand-receptor gene pair mutations in human families with IHH have paved the way to the identification of the long-sought GnRH pulse generator as the KNDy neurons in the arcuate (infundibular) nucleus. This reverse translational pathway of discovery, thanks to the improvement of genetic sequencing technology, promises to continue to deliver even more insights into the central control of reproduction. Most notably, what triggers the GnRH pulse generator to reawaken after childhood remains an enigma. Close to 60 genes have been reported to date to be associated with IHH. However, gene discoveries have been noticeably more complex in recent years, probably due to more complex variants and phenotypes. It is exciting for clinical as well as basic neuroendocrinologists to note that continued gene discoveries for IHH will likely help further our understanding of the complex regulation of the HPG axis throughout human life stages.

Table 1. Genetic causes of idiopathic hypogonadotropic hypogonadism.

Gene	HGNC ID	Clinical Phenotype	Gene Function	Phenotype Number of OMIM (or Ref.)
AMH	464	KS, nIHH	GnRH neuron migration	Malone et al. [100]
AMHR2	465	nIHH	GnRH neuron migration	Malone et al. [100]
ANOS1	6211	KS, nIHH	GnRH neuron migration	308700
AXL	905	KS, nIHH	GnRH neuron migration	109135
CCDC141	26821	nIHH	GnRH neuron migration	Turan et al. [95]
CHD7	20626	KS, nIHH, CHARGE	GnRH neuron migration	612370
CPE	2303	nIHH	Neuropeptide biosynthesis	Alsters et al. [78]
DCC	2701	KS, nIHH	GnRH neuron migration	Bouilly et al. [106].
DLG2	2901	DP	Neuroendocrine regulation	Jee et al. [107]
DMXL2	2938	nIHH, PEPNS	ATPase regulation	616113
DUSP6	3072	KS, nIHH	GnRH neuron migration	615269

Table 1. *Cont.*

Gene	HGNC ID	Clinical Phenotype	Gene Function	Phenotype Number of OMIM (or Ref.)
FEZF1	22788	KS	GnRH neuron migration	616030
FGF17	3673	KS, nIHH, DWS	GnRH neuron development	615270
FGF8	3686	KS, nIHH	GnRH neuron development	612702
FGFR1	3688	KS, CPHD, SOD, SHFM, HS	Neuroendocrine regulation, Hypothalamus/pituitary development	147950
FLRT3	3762	KS	GnRH neuron migration	615271
FSHB	3964	nIHH	Hypothalamus/pituitary development	229070
GNRH1	4419	nIHH	Neuroendocrine regulation	614841
GNRHR	4421	nIHH	Neuroendocrine regulation	146110
HESX1	4877	KS, CPHD, SOD	Hypothalamus/pituitary development	182230
HS6ST1	5201	KS, nIHH	GnRH neuron migration	614880
IGSF10	26384	DP	GnRH neuron migration	Howard et al. [91]
IL17RD	17616	KS, nIHH	GnRH neuron migration	615267
IRF2BPL	14282	DP	Ubiquitination	Mancini et al. [99]
KISS1	6341	nIHH	Neuroendocrine regulation	614842
KISS1R	4510	nIHH	Neuroendocrine regulation	614837
KLB	15527	KS, nIHH	GnRH neuron development	Xu et al. [28]
LEP	6553	nIHH, Obesity	Neuroendocrine regulation	614962
LEPR	6554	nIHH, Obesity	Neuroendocrine regulation	614963
LHB	6584	nIHH	Hypothalamus/pituitary development	228300
NDNF	26256	KS	GnRH neuron migration	618841
NR0B1	7960	nIHH, CAH	Hypothalamus/pituitary development	300200
NSMF	29843	KS	GnRH neuron migration	614838
NTN1	8029	KS, nIHH	GnRH neuron migration	Bouilly et al. [106]
OTUD4	24949	nIHH, GHS	Ubiquitination	212840
PCSK1	8743	nIHH, Obesity	Hypothalamus/pituitary development	600955, 162150
PLXNA1	9099	KS, nIHH	GnRH neuron migration	601055
PLXNA3	9101	KS, nIHH	GnRH neuron migration	Kotan et al. [102]
PNPLA6	16268	nIHH, GHS, BNS	Phospholipid homeostasis	215470, 603197
POLR3A	30074	4H	DNA-dependent RNA polymerase	607694
POLR3B	30348	4H	DNA-dependent RNA polymerase	614381
PROK2	18455	KS, nIHH	GnRH neuron migration	610628
PROKR2	1836	KS, nIHH, CPHD, MGS	GnRH neuron migration	244200
RAB18	14244	WMS 3	GTPase regulation	614222
RAB3GAP1	17063	WMS 1	GTPase regulation	600118
RAB3GAP2	17168	MS	GTPase regulation	212720
RNF216	21698	nIHH, GHS	Ubiquitination	212840
SEMA3A	10723	KS	GnRH neuron migration	614897
SEMA3E	10727	KS, nIHH	GnRH neuron migration	608166

Table 1. *Cont.*

Gene	HGNC ID	Clinical Phenotype	Gene Function	Phenotype Number of OMIM (or Ref.)
SEMA3F	10728		GnRH neuron migration	Kotan et al. [102]
SMCHD1	29090	nIHH, CPHD, BAMS	DNA methylation	Shaw et al. [68]
SOX10	11190	KS, WS	Hypothalamus/pituitary development	613266
SOX3	11199	nIHH	Pituitary development	
SPRY4	15533	KS	GnRH neuron migration	615266
SRA1	11281	nIHH	Neuroendocrine regulation	Kotan et al. [93]
STUB1	11427	Spinocerebellar ataxia	Ubiquitination	615768
TAC3	11521	nIHH	Neuroendocrine regulation	614839
TACR3	11528	nIHH	Neuroendocrine regulation	614840
TBC1D20	16133	WMS 4	Vesicle-mediated transport regulation	615663
WDR11	13831	KS, CPHD	GnRH neuron migration	614858

KS: Kallmann Syndrome; nIHH: Normosmic Idiopathic Hypogonadotropic Hypogonadism; DP: delayed puberty; PEPNS: Polyendocrine Polyneuropathy Syndrome; DWS: Dandy-Walker Syndrome; SOD: septo-optic dysplasia; SHFM: split hand/foot malformation; HS: Hartsfield Syndrome; CAH: Adrenal hypoplasia congenital; GHS: Gordon Holmes syndrome; BNS: Boucher-Neuhauser Syndrome; CPHD: combined pituitary hormone deficiencies; MGS: morning glory syndrome; WMS 3-1-4: Warburg Micro Syndrome 3-1-4; MS: Martsolf syndrome; BAMS: Bosma Arhinia Microphthalmia Syndrome; WS: Waardenburg syndrome.

Author Contributions: A.K.T. and I.T. conceptualized and wrote this article. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Topaloglu, A.K. Update on the Genetics of Idiopathic Hypogonadotropic Hypogonadism. *J. Clin. Res. Pediatric Endocrinol.* **2017**, *9*, 113–122. [CrossRef]
2. Semple, R.K.; Topaloglu, A.K. The recent genetics of hypogonadotrophic hypogonadism—Novel insights and new questions. *Clin. Endocrinol.* **2010**, *72*, 427–435. [CrossRef]
3. Gajdos, Z.K.; Henderson, K.D.; Hirschhorn, J.N.; Palmert, M.R. Genetic determinants of pubertal timing in the general population. *Mol. Cell. Endocrinol.* **2010**, *324*, 21–29. [CrossRef] [PubMed]
4. Sykiotis, G.P.; Plummer, L.; Hughes, V.A.; Au, M.; Durrani, S.; Nayak-Young, S.; Dwyer, A.A.; Quinton, R.; Hall, J.E.; Gusella, J.F.; et al. Oligogenic basis of isolated gonadotropin-releasing hormone deficiency. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 15140–15144. [CrossRef] [PubMed]
5. Sidhoum, V.F.; Chan, Y.M.; Lippincott, M.F.; Balasubramanian, R.; Quinton, R.; Plummer, L.; Dwyer, A.; Pitteloud, N.; Hayes, F.J.; Hall, J.E.; et al. Reversal and relapse of hypogonadotropic hypogonadism: Resilience and fragility of the reproductive neuroendocrine system. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 861–870. [CrossRef]
6. Ng, S.B.; Nickerson, D.A.; Bamshad, M.J.; Shendure, J. Massively parallel sequencing and rare disease. *Hum. Mol. Genet.* **2010**, *19*, R119–R124. [CrossRef] [PubMed]
7. Quaynor, S.D.; Kim, H.G.; Cappello, E.M.; Williams, T.; Chorich, L.P.; Bick, D.P.; Sherins, R.J.; Layman, L.C. The prevalence of digenic mutations in patients with normosmic hypogonadotropic hypogonadism and Kallmann syndrome. *Fertil. Steril.* **2011**, *96*, 1424–1430.e1426. [CrossRef]
8. Pitteloud, N.; Quinton, R.; Pearce, S.; Raivio, T.; Acierno, J.; Dwyer, A.; Plummer, L.; Hughes, V.; Seminara, S.; Cheng, Y.Z.; et al. Digenic mutations account for variable phenotypes in idiopathic hypogonadotropic hypogonadism. *J. Clin. Investig.* **2007**, *117*, 457–463. [CrossRef]

9. Boehm, U.; Bouloux, P.M.; Dattani, M.T.; De Roux, N.; Dode, C.; Dunkel, L.; Dwyer, A.A.; Giacobini, P.; Hardelin, J.P.; Juul, A.; et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism—Pathogenesis, diagnosis and treatment. *Nat. Rev. Endocrinol.* **2015**, *11*, 547–564. [CrossRef]
10. Chong, J.X.; Buckingham, K.J.; Jhangiani, S.N.; Boehm, C.; Sobreira, N.; Smith, J.D.; Harrell, T.M.; McMillin, M.J.; Wiszniewski, W.; Gambin, T.; et al. The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities. *Am. J. Hum. Genet.* **2015**, *97*, 199–215. [CrossRef] [PubMed]
11. Kotan, L.D.; Isik, E.; Turan, I.; Mengen, E.; Akkus, G.; Tastan, M.; Gurbuz, F.; Yuksel, B.; Topaloglu, A.K. Prevalence and associated phenotypes of PLXNA1 variants in normosmic and anosmic idiopathic hypogonadotropic hypogonadism. *Clin. Genet.* **2019**, *95*, 320–324. [CrossRef] [PubMed]
12. Pitteloud, N.; Acierno, J.S., Jr.; Meysing, A.; Eliseenkova, A.V.; Ma, J.; Ibrahimi, O.A.; Metzger, D.L.; Hayes, F.J.; Dwyer, A.A.; Hughes, V.A.; et al. Mutations in fibroblast growth factor receptor 1 cause both Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 6281–6286. [CrossRef]
13. Pitteloud, N.; Zhang, C.; Pignatelli, D.; Li, J.D.; Raivio, T.; Cole, L.W.; Plummer, L.; Jacobson-Dickman, E.E.; Mellon, P.L.; Zhou, Q.Y.; et al. Loss-of-function mutation in the prokineticin 2 gene causes Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17447–17452. [CrossRef]
14. Dode, C.; Levilliers, J.; Dupont, J.M.; De Paepe, A.; Le Du, N.; Soussi-Yanicostas, N.; Coimbra, R.S.; Delmaghani, S.; Compain-Nouaille, S.; Baverel, F.; et al. Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome. *Nat. Genet.* **2003**, *33*, 463–465. [CrossRef]
15. Hardelin, J.P.; Dode, C. The complex genetics of Kallmann syndrome: KAL1, FGFR1, FGF8, PROKR2, PROK2, et al. *Sex. Dev.* **2008**, *2*, 181–193. [CrossRef] [PubMed]
16. Topaloglu, A.K.; Reimann, F.; Guclu, M.; Yalin, A.S.; Kotan, L.D.; Porter, K.M.; Serin, A.; Mungan, N.O.; Cook, J.R.; Imamoglu, S.; et al. TAC3 and TACR3 mutations in familial hypogonadotropic hypogonadism reveal a key role for Neurokinin B in the central control of reproduction. *Nat. Genet.* **2009**, *41*, 354–358. [CrossRef]
17. Franco, B.; Guioli, S.; Pragliola, A.; Incerti, B.; Bardoni, B.; Tonlorenzi, R.; Carrozzo, R.; Maestrini, E.; Pieretti, M.; Taillon-Miller, P.; et al. A gene deleted in Kallmann's syndrome shares homology with neural cell adhesion and axonal path-finding molecules. *Nature* **1991**, *353*, 529–536. [CrossRef]
18. Pedersen-White, J.R.; Chorich, L.P.; Bick, D.P.; Sherins, R.J.; Layman, L.C. The prevalence of intragenic deletions in patients with idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. *Mol. Hum. Reprod.* **2008**, *14*, 367–370. [CrossRef] [PubMed]
19. Oliveira, L.M.; Seminara, S.B.; Beranova, M.; Hayes, F.J.; Valkenburgh, S.B.; Schipani, E.; Costa, E.M.; Latronico, A.C.; Crowley, W.F., Jr.; Vallejo, M. The importance of autosomal genes in Kallmann syndrome: Genotype-phenotype correlations and neuroendocrine characteristics. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 1532–1538. [CrossRef]
20. Tsai, P.S.; Gill, J.C. Mechanisms of disease: Insights into X-linked and autosomal-dominant Kallmann syndrome. *Nat. Clin. Pract. Endocrinol. Metab.* **2006**, *2*, 160–171. [CrossRef]
21. Pitteloud, N.; Meysing, A.; Quinton, R.; Acierno, J.S.; Dwyer, A.A., Jr.; Plummer, L.; Fliers, E.; Boepple, P.; Hayes, F.; Seminara, S.; et al. Mutations in fibroblast growth factor receptor 1 cause Kallmann syndrome with a wide spectrum of reproductive phenotypes. *Mol. Cell. Endocrinol.* **2006**, *254–255*, 60–69. [CrossRef] [PubMed]
22. Trarbach, E.B.; Costa, E.M.; Versiani, B.; De Castro, M.; Baptista, M.T.; Garmes, H.M.; De Mendonca, B.B.; Latronico, A.C. Novel fibroblast growth factor receptor 1 mutations in patients with congenital hypogonadotropic hypogonadism with and without anosmia. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 4006–4012. [CrossRef]
23. Pitteloud, N.; Acierno, J.S., Jr.; Meysing, A.U.; Dwyer, A.A.; Hayes, F.J.; Crowley, W.F., Jr. Reversible kallmann syndrome, delayed puberty, and isolated anosmia occurring in a single family with a mutation in the fibroblast growth factor receptor 1 gene. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 1317–1322. [CrossRef]
24. Xu, N.; Qin, Y.; Reindollar, R.H.; Tho, S.P.; McDonough, P.G.; Layman, L.C. A mutation in the fibroblast growth factor receptor 1 gene causes fully penetrant normosmic isolated hypogonadotropic hypogonadism. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 1155–1158. [CrossRef] [PubMed]
25. Raivio, T.; Sidis, Y.; Plummer, L.; Chen, H.; Ma, J.; Mukherjee, A.; Jacobson-Dickman, E.; Quinton, R.; Van Vliet, G.; Lavoie, H.; et al. Impaired fibroblast growth factor receptor 1 signaling as a cause of normosmic idiopathic hypogonadotropic hypogonadism. *J. Clin. Endocrinol. Metab.* **2009**, *94*, 4380–4390. [CrossRef] [PubMed]
26. Falardeau, J.; Chung, W.C.; Beenken, A.; Raivio, T.; Plummer, L.; Sidis, Y.; Jacobson-Dickman, E.E.; Eliseenkova, A.V.; Ma, J.; Dwyer, A.; et al. Decreased FGF8 signaling causes deficiency of gonadotropin-releasing hormone in humans and mice. *J. Clin. Investig.* **2008**, *118*, 2822–2831. [CrossRef] [PubMed]
27. Miraoui, H.; Dwyer, A.A.; Sykiotis, G.P.; Plummer, L.; Chung, W.; Feng, B.; Beenken, A.; Clarke, J.; Pers, T.H.; Dworzynski, P.; et al. Mutations in FGF17, IL17RD, DUSP6, SPRY4, and FLRT3 are identified in individuals with congenital hypogonadotropic hypogonadism. *Am. J. Hum. Genet.* **2013**, *92*, 725–743. [CrossRef]
28. Xu, C.; Messina, A.; Somm, E.; Miraoui, H.; Kinnunen, T.; Acierno, J., Jr.; Niederlander, N.J.; Bouilly, J.; Dwyer, A.A.; Sidis, Y.; et al. KLB, encoding beta-Klotho, is mutated in patients with congenital hypogonadotropic hypogonadism. *EMBO Mol. Med.* **2017**, *9*, 1379–1397. [CrossRef]

29. Tornberg, J.; Sykiotis, G.P.; Keefe, K.; Plummer, L.; Hoang, X.; Hall, J.E.; Quinton, R.; Seminara, S.B.; Hughes, V.; Van Vliet, G.; et al. Heparan sulfate 6-O-sulfotransferase 1, a gene involved in extracellular sugar modifications, is mutated in patients with idiopathic hypogonadotrophic hypogonadism. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 11524–11529. [CrossRef]
30. Howard, S.R.; Oleari, R.; Poliandri, A.; Chantzara, V.; Fantin, A.; Ruiz-Babot, G.; Metherell, L.A.; Cabrera, C.P.; Barnes, M.R.; Wehkalampi, K.; et al. HS6ST1 Insufficiency Causes Self-Limited Delayed Puberty in Contrast With Other GnRH Deficiency Genes. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 3420–3429. [CrossRef]
31. Cheng, M.Y.; Leslie, F.M.; Zhou, Q.Y. Expression of prokineticins and their receptors in the adult mouse brain. *J. Comp. Neurol.* **2006**, *498*, 796–809. [CrossRef] [PubMed]
32. Martin, C.; Balasubramanian, R.; Dwyer, A.A.; Au, M.G.; Sidis, Y.; Kaiser, U.B.; Seminara, S.B.; Pitteloud, N.; Zhou, Q.Y.; Crowley, W.F., Jr. The role of the prokineticin 2 pathway in human reproduction: Evidence from the study of human and murine gene mutations. *Endocr. Rev.* **2011**, *32*, 225–246. [CrossRef]
33. Matsumoto, S.; Yamazaki, C.; Masumoto, K.H.; Nagano, M.; Naito, M.; Soga, T.; Hiyama, H.; Matsumoto, M.; Takasaki, J.; Kamohara, M.; et al. Abnormal development of the olfactory bulb and reproductive system in mice lacking prokineticin receptor PKR2. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 4140–4145. [CrossRef] [PubMed]
34. Abreu, A.P.; Trarbach, E.B.; De Castro, M.; Frade Costa, E.M.; Versiani, B.; Matias Baptista, M.T.; Garmes, H.M.; Mendonca, B.B.; Latronico, A.C. Loss-of-function mutations in the genes encoding prokineticin-2 or prokineticin receptor-2 cause autosomal recessive Kallmann syndrome. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 4113–4118. [CrossRef] [PubMed]
35. Cole, L.W.; Sidis, Y.; Zhang, C.; Quinton, R.; Plummer, L.; Pignatelli, D.; Hughes, V.A.; Dwyer, A.A.; Raivio, T.; Hayes, F.J.; et al. Mutations in prokineticin 2 and prokineticin receptor 2 genes in human gonadotrophin-releasing hormone deficiency: Molecular genetics and clinical spectrum. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 3551–3559. [CrossRef] [PubMed]
36. Vissers, L.E.; Van Ravenswaaij, C.M.; Admiraal, R.; Hurst, J.A.; De Vries, B.B.; Janssen, I.M.; Van der Vliet, W.A.; Huys, E.H.; De Jong, P.J.; Hamel, B.C.; et al. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat. Genet.* **2004**, *36*, 955–957. [CrossRef]
37. Kim, H.G.; Kurth, I.; Lan, F.; Meliciani, I.; Wenzel, W.; Eom, S.H.; Kang, G.B.; Rosenberger, G.; Tekin, M.; Ozata, M.; et al. Mutations in CHD7, encoding a chromatin-remodeling protein, cause idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. *Am. J. Hum. Genet.* **2008**, *83*, 511–519. [CrossRef]
38. Xu, C.; Cassatella, D.; Van der Sloot, A.M.; Quinton, R.; Hauschild, M.; De Geyter, C.; Fluck, C.; Feller, K.; Bartholdi, D.; Nemeth, A.; et al. Evaluating CHARGE syndrome in congenital hypogonadotropic hypogonadism patients harboring CHD7 variants. *Genet. Med.* **2018**, *20*, 872–881. [CrossRef]
39. Layman, W.S.; Hurd, E.A.; Martin, D.M. Reproductive dysfunction and decreased GnRH neurogenesis in a mouse model of CHARGE syndrome. *Hum. Mol. Genet.* **2011**, *20*, 3138–3150. [CrossRef]
40. De Roux, N.; Young, J.; Misrahi, M.; Genet, R.; Chanson, P.; Schaison, G.; Milgrom, E. A family with hypogonadotropic hypogonadism and mutations in the gonadotropin-releasing hormone receptor. *N. Engl. J. Med.* **1997**, *337*, 1597–1602. [CrossRef] [PubMed]
41. Beranova, M.; Oliveira, L.M.; Bedecarrats, G.Y.; Schipani, E.; Vallejo, M.; Ammini, A.C.; Quintos, J.B.; Hall, J.E.; Martin, K.A.; Hayes, F.J.; et al. Prevalence, phenotypic spectrum, and modes of inheritance of gonadotropin-releasing hormone receptor mutations in idiopathic hypogonadotropic hypogonadism. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 1580–1588. [CrossRef]
42. Beneduzzi, D.; Trarbach, E.B.; Min, L.; Jorge, A.A.; Garmes, H.M.; Renk, A.C.; Fichna, M.; Fichna, P.; Arantes, K.A.; Costa, E.M.; et al. Role of gonadotropin-releasing hormone receptor mutations in patients with a wide spectrum of pubertal delay. *Fertil. Steril.* **2014**, *102*, 838–846. [CrossRef]
43. King, J.A.; Millar, R.P. Evolutionary aspects of gonadotropin-releasing hormone and its receptor. *Cell. Mol. Neurobiol.* **1995**, *15*, 5–23. [CrossRef]
44. Bouligand, J.; Ghervan, C.; Tello, J.A.; Brailly-Tabard, S.; Salenave, S.; Chanson, P.; Lombes, M.; Millar, R.P.; Guiochon-Mantel, A.; Young, J. Isolated familial hypogonadotropic hypogonadism and a GNRH1 mutation. *N. Engl. J. Med.* **2009**, *360*, 2742–2748. [CrossRef]
45. Chan, Y.M.; De Guillebon, A.; Lang-Muritano, M.; Plummer, L.; Cerrato, F.; Tsiaras, S.; Gaspert, A.; Lavoie, H.B.; Wu, C.H.; Crowley, W.F., Jr.; et al. GNRH1 mutations in patients with idiopathic hypogonadotropic hypogonadism. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 11703–11708. [CrossRef]
46. Mengen, E.; Tunc, S.; Kotan, L.D.; Nalbantoglu, O.; Demir, K.; Gurbuz, F.; Turan, I.; Seker, G.; Yuksel, B.; Topaloglu, A.K. Complete Idiopathic Hypogonadotropic Hypogonadism due to Homozygous GNRH1 Mutations in the Mutational Hot Spots in the Region Encoding the Decapeptide. *Horm. Res. Paediatr.* **2016**, *85*, 107–111. [CrossRef]
47. Seminara, S.B.; Messager, S.; Chatzidaki, E.E.; Thresher, R.R.; Acierno, J.S., Jr.; Shagoury, J.K.; Bo-Abbas, Y.; Kuohung, W.; Schwinof, K.M.; Hendrick, A.G.; et al. The GPR54 gene as a regulator of puberty. *N. Engl. J. Med.* **2003**, *349*, 1614–1627. [CrossRef]
48. Cerrato, F.; Shagoury, J.; Kralickova, M.; Dwyer, A.; Falardeau, J.; Ozata, M.; Van Vliet, G.; Bouloux, P.; Hall, J.E.; Hayes, F.J.; et al. Coding sequence analysis of GNRHR and GPR54 in patients with congenital and adult-onset forms of hypogonadotropic hypogonadism. *Eur. J. Endocrinol.* **2006**, *155*, S3–S10. [CrossRef]
49. Navarro, V.M.; Tena-Sempere, M. Neuroendocrine control by kisspeptins: Role in metabolic regulation of fertility. *Nat. Rev. Endocrinol.* **2011**, *8*, 40–53. [CrossRef]

50. Gottsch, M.L.; Cunningham, M.J.; Smith, J.T.; Popa, S.M.; Acohido, B.V.; Crowley, W.F.; Seminara, S.; Clifton, D.K.; Steiner, R.A. A role for kisspeptins in the regulation of gonadotropin secretion in the mouse. *Endocrinology* **2004**, *145*, 4073–4077. [CrossRef]
51. Topaloglu, A.K.; Tello, J.A.; Kotan, L.D.; Ozbek, M.N.; Yilmaz, M.B.; Erdogan, S.; Gurbuz, F.; Temiz, F.; Millar, R.P.; Yuksel, B. Inactivating KISS1 mutation and hypogonadotropic hypogonadism. *N. Engl. J. Med.* **2012**, *366*, 629–635. [CrossRef]
52. Miura, K.; Acierno, J.S., Jr.; Seminara, S.B. Characterization of the human nasal embryonic LHRH factor gene, NELF, and a mutation screening among 65 patients with idiopathic hypogonadotropic hypogonadism (IHH). *J. Hum. Genet.* **2004**, *49*, 265–268. [CrossRef] [PubMed]
53. Kramer, P.R.; Wray, S. Novel gene expressed in nasal region influences outgrowth of olfactory axons and migration of luteinizing hormone-releasing hormone (LHRH) neurons. *Genes Dev.* **2000**, *14*, 1824–1834. [CrossRef]
54. Goodman, R.L.; Lehman, M.N.; Smith, J.T.; Coolen, L.M.; De Oliveira, C.V.; Jafarzadehshirazi, M.R.; Pereira, A.; Iqbal, J.; Caraty, A.; Ciofi, P.; et al. Kisspeptin neurons in the arcuate nucleus of the ewe express both dynorphin A and neurokinin B. *Endocrinology* **2007**, *148*, 5752–5760. [CrossRef]
55. Gianetti, E.; Tusset, C.; Noel, S.D.; Au, M.G.; Dwyer, A.A.; Hughes, V.A.; Abreu, A.P.; Carroll, J.; Trarbach, E.; Silveira, L.F.; et al. TAC3/TACR3 mutations reveal preferential activation of gonadotropin-releasing hormone release by neurokinin B in neonatal life followed by reversal in adulthood. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 2857–2867. [CrossRef]
56. Lander, E.S.; Botstein, D. Homozygosity mapping: A way to map human recessive traits with the DNA of inbred children. *Science* **1987**, *236*, 1567–1570. [CrossRef]
57. Francou, B.; Bouligand, J.; Voican, A.; Amazit, L.; Trabado, S.; Fagart, J.; Meduri, G.; Brailly-Tabard, S.; Chanson, P.; Lecomte, P.; et al. Normosmic congenital hypogonadotropic hypogonadism due to TAC3/TACR3 mutations: Characterization of neuroendocrine phenotypes and novel mutations. *PLoS ONE* **2011**, *6*, e25614.
58. Kim, H.G.; Ahn, J.W.; Kurth, I.; Ullmann, R.; Kim, H.T.; Kulharya, A.; Ha, K.S.; Itokawa, Y.; Meliciani, I.; Wenzel, W.; et al. WDR11, a WD protein that interacts with transcription factor EMX1, is mutated in idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. *Am. J. Hum. Genet.* **2010**, *87*, 465–479. [CrossRef]
59. McCormack, S.E.; Li, D.; Kim, Y.J.; Lee, J.Y.; Kim, S.H.; Rapaport, R.; Levine, M.A. Digenic Inheritance of PROKR2 and WDR11 Mutations in Pituitary Stalk Interruption Syndrome. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 2501–2507. [CrossRef]
60. Cariboni, A.; Davidson, K.; Rakic, S.; Maggi, R.; Parnavelas, J.G.; Ruhrberg, C. Defective gonadotropin-releasing hormone neuron migration in mice lacking SEMA3A signalling through NRP1 and NRP2: Implications for the aetiology of hypogonadotropic hypogonadism. *Hum. Mol. Genet.* **2011**, *20*, 336–344. [CrossRef]
61. Hanchate, N.K.; Giacobini, P.; Lhuillier, P.; Parkash, J.; Espy, C.; Fouveaut, C.; Leroy, C.; Baron, S.; Campagne, C.; Vanacker, C.; et al. SEMA3A, a gene involved in axonal pathfinding, is mutated in patients with Kallmann syndrome. *PLoS Genet.* **2012**, *8*, e1002896. [CrossRef]
62. Young, J.; Metay, C.; Bouligand, J.; Tou, B.; Francou, B.; Maione, L.; Tosca, L.; Sarfati, J.; Brioude, F.; Esteva, B.; et al. SEMA3A deletion in a family with Kallmann syndrome validates the role of semaphorin 3A in human puberty and olfactory system development. *Hum. Reprod.* **2012**, *27*, 1460–1465. [CrossRef] [PubMed]
63. Cariboni, A.; Andre, V.; Chauvet, S.; Cassatella, D.; Davidson, K.; Caramello, A.; Fantin, A.; Bouloux, P.; Mann, F.; Ruhrberg, C. Dysfunctional SEMA3E signaling underlies gonadotropin-releasing hormone neuron deficiency in Kallmann syndrome. *J. Clin. Investig.* **2015**, *125*, 2413–2428. [CrossRef] [PubMed]
64. Kansakoski, J.; Fagerholm, R.; Laitinen, E.M.; Vaaralahti, K.; Hackman, P.; Pitteloud, N.; Raivio, T.; Tommiska, J. Mutation screening of SEMA3A and SEMA7A in patients with congenital hypogonadotropic hypogonadism. *Pediatr. Res.* **2014**, *75*, 641–644. [CrossRef]
65. Kotan, L.D.; Hutchins, B.I.; Ozkan, Y.; Demirel, F.; Stoner, H.; Cheng, P.J.; Esen, I.; Gurbuz, F.; Bicakci, Y.K.; Mengen, E.; et al. Mutations in FEZF1 cause Kallmann syndrome. *Am. J. Hum. Genet.* **2014**, *95*, 326–331. [CrossRef]
66. Eckler, M.J.; McKenna, W.L.; Taghvaei, S.; McConnell, S.K.; Chen, B. Fezf1 and Fezf2 are required for olfactory development and sensory neuron identity. *J. Comp. Neurol.* **2011**, *519*, 1829–1846. [CrossRef] [PubMed]
67. Messina, A.; Pulli, K.; Santini, S.; Acierno, J.; Kansakoski, J.; Cassatella, D.; Xu, C.; Casoni, F.; Malone, S.A.; Ternier, G.; et al. Neuron-Derived Neurotrophic Factor Is Mutated in Congenital Hypogonadotropic Hypogonadism. *Am. J. Hum. Genet.* **2020**, *106*, 58–70. [CrossRef] [PubMed]
68. Shaw, N.D.; Brand, H.; Kupchinsky, Z.A.; Bengani, H.; Plummer, L.; Jones, T.I.; Erdin, S.; Williamson, K.A.; Rainger, J.; Stortchevoi, A.; et al. SMCHD1 mutations associated with a rare muscular dystrophy can also cause isolated arhinia and Bosma arhinia microphthalmia syndrome. *Nat. Genet.* **2017**, *49*, 238–248. [CrossRef] [PubMed]
69. Kinjo, K.; Nagasaki, K.; Muroya, K.; Suzuki, E.; Ishiwata, K.; Nakabayashi, K.; Hattori, A.; Nagao, K.; Nozawa, R.S.; Obuse, C.; et al. Rare variant of the epigenetic regulator SMCHD1 in a patient with pituitary hormone deficiency. *Sci. Rep.* **2020**, *10*, 10985. [CrossRef]
70. Pingault, V.; Bodereau, V.; Baral, V.; Marcos, S.; Watanabe, Y.; Chaoui, A.; Fouveaut, C.; Leroy, C.; Verier-Mine, O.; Francannet, C.; et al. Loss-of-function mutations in SOX10 cause Kallmann syndrome with deafness. *Am. J. Hum. Genet.* **2013**, *92*, 707–724. [CrossRef]
71. Strobel, A.; Issad, T.; Camoin, L.; Ozata, M.; Strosberg, A.D. A leptin missense mutation associated with hypogonadism and morbid obesity. *Nat. Genet.* **1998**, *18*, 213–215. [CrossRef] [PubMed]

72. Farooqi, I.S.; Wangensteen, T.; Collins, S.; Kimber, W.; Matarese, G.; Keogh, J.M.; Lank, E.; Bottomley, B.; Lopez-Fernandez, J.; Ferraz-Amaro, I.; et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N. Engl. J. Med.* **2007**, *356*, 237–247. [CrossRef] [PubMed]
73. Wauters, M.; Considine, R.V.; Van Gaal, L.F. Human leptin, from an adipocyte hormone to an endocrine mediator. *Eur. J. Endocrinol.* **2000**, *143*, 293–311. [CrossRef] [PubMed]
74. Farooqi, I.S.; Jebb, S.A.; Langmack, G.; Lawrence, E.; Cheetham, C.H.; Prentice, A.M.; Hughes, I.A.; McCamish, M.A.; O'Rahilly, S. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N. Engl. J. Med.* **1999**, *341*, 879–884. [CrossRef]
75. Ahima, R.S.; Prabakaran, D.; Mantzoros, C.; Qu, D.; Lowell, B.; Maratos-Flier, E.; Flier, J.S. Role of leptin in the neuroendocrine response to fasting. *Nature* **1996**, *382*, 250–252. [CrossRef]
76. Ahima, R.S.; Dushay, J.; Flier, S.N.; Prabakaran, D.; Flier, J.S. Leptin accelerates the onset of puberty in normal female mice. *J. Clin. Investig.* **1997**, *99*, 391–395. [CrossRef] [PubMed]
77. Muscatelli, F.; Strom, T.M.; Walker, A.P.; Zanaria, E.; Recan, D.; Meindl, A.; Bardoni, B.; Guioli, S.; Zehetner, G.; Rabl, W.; et al. Mutations in the DAX-1 gene give rise to both X-linked adrenal hypoplasia congenita and hypogonadotropic hypogonadism. *Nature* **1994**, *372*, 672–676. [CrossRef] [PubMed]
78. Alsters, S.I.; Goldstone, A.P.; Buxton, J.L.; Zekavati, A.; Sosinsky, A.; Yiorkas, A.M.; Holder, S.; Klaber, R.E.; Bridges, N.; Van Haelst, M.M.; et al. Truncating Homozygous Mutation of Carboxypeptidase E (CPE) in a Morbidly Obese Female with Type 2 Diabetes Mellitus, Intellectual Disability and Hypogonadotrophic Hypogonadism. *PLoS ONE* **2015**, *10*, e0131417. [CrossRef] [PubMed]
79. Durmaz, A.; Aykut, A.; Atik, T.; Ozen, S.; Ayyildiz Emecen, D.; Ata, A.; Isik, E.; Goksen, D.; Cogulu, O.; Ozkinay, F. A New Cause of Obesity Syndrome Associated with a Mutation in the Carboxypeptidase Gene Detected in Three Siblings with Obesity, Intellectual Disability and Hypogonadotropic Hypogonadism. *J. Clin. Res. Pediatr. Endocrinol.* **2021**, *13*, 52–60. [CrossRef] [PubMed]
80. Newbern, K.; Natrajan, N.; Kim, H.G.; Chorich, L.P.; Halvorson, L.M.; Cameron, R.S.; Layman, L.C. Identification of HESX1 mutations in Kallmann syndrome. *Fertil. Steril.* **2013**, *99*, 1831–1837. [CrossRef]
81. Tata, B.; Huijbregts, L.; Jacquier, S.; Csaba, Z.; Genin, E.; Meyer, V.; Leka, S.; Dupont, J.; Charles, P.; Chevenne, D.; et al. Haploinsufficiency of Dmxl2, encoding a synaptic protein, causes infertility associated with a loss of GnRH neurons in mouse. *PLoS Biol.* **2014**, *12*, e1001952. [CrossRef] [PubMed]
82. Margolin, D.H.; Kousi, M.; Chan, Y.M.; Lim, E.T.; Schmahmann, J.D.; Hadjivassiliou, M.; Hall, J.E.; Adam, I.; Dwyer, A.; Plummer, L.; et al. Ataxia, dementia, and hypogonadotropism caused by disordered ubiquitination. *N. Engl. J. Med.* **2013**, *368*, 1992–2003. [CrossRef] [PubMed]
83. Shi, C.H.; Schisler, J.C.; Rubel, C.E.; Tan, S.; Song, B.; McDonough, H.; Xu, L.; Portbury, A.L.; Mao, C.Y.; True, C.; et al. Ataxia and hypogonadism caused by the loss of ubiquitin ligase activity of the U box protein CHIP. *Hum. Mol. Genet.* **2014**, *23*, 1013–1024. [CrossRef] [PubMed]
84. Topaloglu, A.K.; Lomniczi, A.; Kretzschmar, D.; Dissen, G.A.; Kotan, L.D.; McArdle, C.A.; Koc, A.F.; Hamel, B.C.; Guclu, M.; Papatya, E.D.; et al. Loss-of-function mutations in PNPLA6 encoding neuropathy target esterase underlie pubertal failure and neurological deficits in Gordon Holmes syndrome. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E2067–E2075. [CrossRef]
85. Synofzik, M.; Gonzalez, M.A.; Lourenco, C.M.; Coutelier, M.; Haack, T.B.; Rebelo, A.; Hannequin, D.; Strom, T.M.; Prokisch, H.; Kernstock, C.; et al. PNPLA6 mutations cause Boucher-Neuhauser and Gordon Holmes syndromes as part of a broad neurodegenerative spectrum. *Brain* **2014**, *137*, 69–77. [CrossRef]
86. Dumay-Odelot, H.; Durrieu-Gaillard, S.; Da Silva, D.; Roeder, R.G.; Teichmann, M. Cell growth- and differentiation-dependent regulation of RNA polymerase III transcription. *Cell Cycle* **2010**, *9*, 3687–3699. [CrossRef]
87. Bernard, G.; Chouery, E.; Putorti, M.L.; Tetreault, M.; Takanohashi, A.; Carosso, G.; Clement, I.; Boespflug-Tanguy, O.; Rodriguez, D.; Delague, V.; et al. Mutations of POLR3A encoding a catalytic subunit of RNA polymerase Pol III cause a recessive hypomyelinating leukodystrophy. *Am. J. Hum. Genet.* **2011**, *89*, 415–423. [CrossRef]
88. Tetreault, M.; Choquet, K.; Orcesi, S.; Tonduti, D.; Balottin, U.; Teichmann, M.; Fribourg, S.; Schiffmann, R.; Brais, B.; Vanderver, A.; et al. Recessive mutations in POLR3B, encoding the second largest subunit of Pol III, cause a rare hypomyelinating leukodystrophy. *Am. J. Hum. Genet.* **2011**, *89*, 652–655. [CrossRef]
89. Izumi, Y.; Suzuki, E.; Kanzaki, S.; Yatsuga, S.; Kinjo, S.; Igarashi, M.; Maruyama, T.; Sano, S.; Horikawa, R.; Sato, N.; et al. Genome-wide copy number analysis and systematic mutation screening in 58 patients with hypogonadotropic hypogonadism. *Fertil. Steril.* **2014**, *102*, 1130–1136.e1133. [CrossRef]
90. Salian-Mehta, S.; Xu, M.; Knox, A.J.; Plummer, L.; Slavov, D.; Taylor, M.; Bevers, S.; Hodges, R.S.; Crowley, W.F., Jr.; Wierman, M.E. Functional consequences of AXL sequence variants in hypogonadotropic hypogonadism. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 1452–1460. [CrossRef]
91. Howard, S.R.; Guasti, L.; Ruiz-Babot, G.; Mancini, A.; David, A.; Storr, H.L.; Metherell, L.A.; Sternberg, M.J.; Cabrera, C.P.; Warren, H.R.; et al. IGSF10 mutations dysregulate gonadotropin-releasing hormone neuronal migration resulting in delayed puberty. *EMBO Mol. Med.* **2016**, *8*, 626–642. [CrossRef]
92. Chooniedass-Kothari, S.; Emberley, E.; Hamedani, M.K.; Troup, S.; Wang, X.; Czosnek, A.; Hube, F.; Mutawe, M.; Watson, P.H.; Leygue, E. The steroid receptor RNA activator is the first functional RNA encoding a protein. *FEBS Lett.* **2004**, *566*, 43–47. [CrossRef] [PubMed]

93. Kotan, L.D.; Cooper, C.; Darcan, S.; Carr, I.M.; Ozen, S.; Yan, Y.; Hamedani, M.K.; Gurbuz, F.; Mengen, E.; Turan, I.; et al. Idiopathic Hypogonadotropic Hypogonadism Caused by Inactivating Mutations in SRA1. *J. Clin. Res. Pediatr. Endocrinol.* **2016**, *8*, 125–134. [CrossRef]
94. Marcos, S.; Monnier, C.; Rovira, X.; Fouveaut, C.; Pitteloud, N.; Ango, F.; Dode, C.; Hardelin, J.P. Defective signaling through plexin-A1 compromises the development of the peripheral olfactory system and neuroendocrine reproductive axis in mice. *Hum. Mol. Genet.* **2017**, *26*, 2006–2017. [CrossRef] [PubMed]
95. Turan, I.; Hutchins, B.I.; Hacihamdioglu, B.; Kotan, L.D.; Gurbuz, F.; Ulubay, A.; Mengen, E.; Yuksel, B.; Wray, S.; Topaloglu, A.K. CCDC141 Mutations in Idiopathic Hypogonadotropic Hypogonadism. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 1816–1825. [CrossRef]
96. Hutchins, B.I.; Kotan, L.D.; Taylor-Burds, C.; Ozkan, Y.; Cheng, P.J.; Gurbuz, F.; Tiong, J.D.; Mengen, E.; Yuksel, B.; Topaloglu, A.K.; et al. CCDC141 Mutation Identified in Anosmic Hypogonadotropic Hypogonadism (Kallmann Syndrome) Alters GnRH Neuronal Migration. *Endocrinology* **2016**, *157*, 1956–1966. [CrossRef]
97. Hou, Q.; Wu, J.; Zhao, Y.; Wang, X.; Jiang, F.; Chen, D.N.; Zheng, R.; Men, M.; Li, J.D. Genotypic and phenotypic spectrum of CCDC141 variants in a Chinese cohort with congenital hypogonadotropic hypogonadism. *Eur. J. Endocrinol.* **2020**, *183*, 245–254. [CrossRef] [PubMed]
98. Heger, S.; Mastronardi, C.; Dissen, G.A.; Lomniczi, A.; Cabrera, R.; Roth, C.L.; Jung, H.; Galimi, F.; Sippell, W.; Ojeda, S.R. Enhanced at puberty 1 (EAP1) is a new transcriptional regulator of the female neuroendocrine reproductive axis. *J. Clin. Investig.* **2007**, *117*, 2145–2154. [CrossRef]
99. Mancini, A.; Howard, S.R.; Cabrera, C.P.; Barnes, M.R.; David, A.; Wehkalampi, K.; Heger, S.; Lomniczi, A.; Guasti, L.; Ojeda, S.R.; et al. EAP1 regulation of GnRH promoter activity is important for human pubertal timing. *Hum. Mol. Genet.* **2019**, *28*, 1357–1368. [CrossRef] [PubMed]
100. Malone, S.A.; Papadakis, G.E.; Messina, A.; Mimouni, N.E.H.; Trova, S.; Imbernon, M.; Allet, C.; Cimino, I.; Acierno, J.; Cassatella, D.; et al. Defective AMH signaling disrupts GnRH neuron development and function and contributes to hypogonadotropic hypogonadism. *Elife* **2019**, *8*, e47198. [CrossRef]
101. Oleari, R.; Andre, V.; Lettieri, A.; Tahir, S.; Roth, L.; Paganoni, A.; Eberini, I.; Parravicini, C.; Scagliotti, V.; Cotellessa, L.; et al. A Novel SEMA3G Mutation in Two Siblings Affected by Syndromic GnRH Deficiency. *Neuroendocrinology* **2021**, *111*, 421–441. [CrossRef] [PubMed]
102. Kotan, L.D.; Ternier, G.; Cakir, A.D.; Emeksiz, H.C.; Turan, I.; Delpouve, G.; Kardelen, A.D.; Ozcabi, B.; Isik, E.; Mengen, E.; et al. Loss-of-function variants in SEMA3F and PLXNA3 encoding semaphorin-3F and its receptor plexin-A3 respectively cause idiopathic hypogonadotropic hypogonadism. *Genet. Med.* **2021**, *23*, 1008–1016. [CrossRef] [PubMed]
103. Borck, G.; Wunram, H.; Steiert, A.; Volk, A.E.; Korber, F.; Roters, S.; Herkenrath, P.; Wollnik, B.; Morris-Rosendahl, D.J.; Kubisch, C. A homozygous RAB3GAP2 mutation causes Warburg Micro syndrome. *Hum. Genet.* **2011**, *129*, 45–50. [CrossRef]
104. Handley, M.T.; Aligianis, I.A. RAB3GAP1, RAB3GAP2 and RAB18: Disease genes in Micro and Martsolf syndromes. *Biochem. Soc. Trans.* **2012**, *40*, 1394–1397. [CrossRef] [PubMed]
105. Handley, M.; Sheridan, E. RAB18 deficiency. In *GeneReviews ((R))*; Adam, M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Mirzaa, G., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1993.
106. Bouilly, J.; Messina, A.; Papadakis, G.; Cassatella, D.; Xu, C.; Acierno, J.S.; Tata, B.; Sykiotis, G.; Santini, S.; Sidis, Y.; et al. DCC/NTN1 complex mutations in patients with congenital hypogonadotropic hypogonadism impair GnRH neuron development. *Hum. Mol. Genet.* **2018**, *27*, 359–372. [CrossRef]
107. Jee, Y.H.; Won, S.; Lui, J.C.; Jennings, M.; Whalen, P.; Yue, S.; Temnycky, A.G.; Barnes, K.M.; Cheetham, T.; Boden, M.G.; et al. DLG2 variants in patients with pubertal disorders. *Genet. Med.* **2020**, *22*, 1329–1337. [CrossRef]