

## Review Article

# Male Hypogonadism-Areview of Secondary Hypogonadism with Special Emphasis on Hypogonadotropic Hypogonadism

Kulvinder Kochar Kaur<sup>1\*</sup>, Gautam Nand Allahbadia<sup>2</sup> and Mandeep Singh<sup>3</sup>

<sup>1</sup>Department of Reproductive neuroendocrinology Centre for human reproduction, India

<sup>2</sup>Department of Reproductive neuroendocrinology, Rotunda-A Centre for Human, India

<sup>3</sup>Departmen of Neurology, Swami Satyanand Hospital, India

## \*Corresponding author

Kulvinder Kochar Kaur, Centre For Human Reproduction,721,G.T.B. Nagar,Jalandhar, Punjab, India-144001, E-mail: kulvinder.dr@gmail.com

Submitted: 15 March 2014

Accepted: 06 May 2014

Published: 08 May 2014

ISSN: 2333-6692

## Copyright

© 2014 Kaur et al.

## OPEN ACCESS

## Keywords

- Lowtestosterone
- Hypogonadotropic hypogonadism
- Kallmann syndrome
- Normosmic IHH
- KAL1
- FGF8
- FGFR1
- PROK2
- PROKR2
- CHD7
- WDR11
- SEMA3A
- PulsatileGnRH therapy
- Testosterone enanthate

## Abstract

Male hypogonadism refers to low serum testosterone (T) (<200-250ng/dl) checked at 8am in fasting subjects. Secondary hypogonadism with low normal gonadotropins can be due to congenital or acquired causes. Congenital hypogonadotropic hypogonadism (CHH) is considered when low serum inhibin B levels are found to accompany low S. FSH/LH and T. The differential diagnosis of CHH includes pituitary tumours /pituitary infiltration, juvenile hemochromatosis and other anterior pituitary functional disorders ruled out by neuroimaging and detailed hormone testing respectively. The abuse of anabolic steroids/opioids/corticosteroids which may result in hormonal changes similar to those seen in CHH need to be excluded. However confusion may result in case of constitutionally delayed pubertal growth in adolescents. Following detailed family history a genetic study performed helps to segregate the two commonest forms namely anosmic/hyposmic Kallmann Syndrome (KS) or normosmic IHH. Till date 9 genes (KAL1 (Kallmann syndrome 1)/FGF8(fibroblast growth factor 8)/ FGFR1(fibroblastgrowthfactor receptor1)/HS6ST1(Heparan -6-O -transferase 1)/PROK2(prokineticin 2)/ PROKR2 (prokineticinreceptor2)/CHD7(chromodomain 7)/WDR11/SEMA3A(semanaphorin 3A)) have been found to be associated with KS and further for nIHH the "ones associated with GnRH function" (KISS1(Tumor metastasis suppressor)/KISSR1(KISS1 receptor)/GNRH(gonadotropin releasing hormone)/GNRHR (gonadotropin releasing hormone receptor)/TAC3(tachykinin 3)/TAC3R (tachykinin receptor3) only 30%-32%of these genes account for KS and isolated GnRH deficiency respectively. Treatment protocol is individualized according to patients requirements; ranging from Tenanthate /pulsatile GnRH therapy/rFSH-hCG or in some specific cases kisspeptin 10 agonists are prospectively being tried as future therapeutic options. Still a lot of work needs to be done on transcription factors considering genetic overlap between midline disorders like septooptic dysplasia, holopresencephaly in KS" given the developmental role of transcription factors in forebrain development as causative genes for KS.

## INTRODUCTION

Male hypogonadism usually refers to a low testosterone level. Since the definition of low testosterone (T) varies from various laboratories, in general values <200-250ng/dl are considered low and values between 250-350ng/dl considered borderline low. Considering that normally testosterone levels follow a diurnal rhythm and at about 8am are about 30%higher than the serum levels later in the day, especially in younger men, one

should repeat or confirm low testosterone values at 8am [1-3]. Also glucose ingestion induces a significant reduction in total and free T levels in men which is similar across spectrum of glucose tolerance. This decrease in T appears to be because of a direct testicular defect, but the absence of compensatory changes in LH suggest an additional central component, hence men found to have low nonfasting T levels should be reevaluated in the fasting state [4]. Besides that it should be confirmed that sample is obtained

during normal health and not during any acute illness or state of decompensation. Once one encounters low testosterone levels then one should check serum FSH and LH levels-

**I)** if raised LH and FSH (hypergonadotropic) found, namely- Primary hypogonadism -then cause lies in testis and one has to evaluate for any testicular disorder like.

i) Karyotypic abnormalities like Klinefelters syndrome XXY- most common

ii) Toxin exposure, chemotherapy

iii) Congenital defect in testosterone biosynthesis (in cryptorchidism) [5]

iv) Orchitis (mumps, autoimmune)

v) Testicular trauma/infarction

vi) Haemochromatosis

vii) Medications that inhibit androgen biosynthesis eg ketoconazole

ix) Increase in temperature of testicular environment

**II)** Low or normal range LH/FSH (hypogonadotropic)-namely **Secondary hypogonadism**-one has to evaluate for gonadotroph suppression/Hypothalamo-Pituitary process which may be **A) Congenital-a)** anosmic-Kallmanns Syndrome

b) normosmic-Idiopathic Hypogonadotropic Hypogonadism (nIHH)

**B) Acquired-Causing gonadotroph suppression**

i) Medications (opioids, corticosteroids) [6-8]

ii) Obesity/insulin resistance [9, 10]

iii) Type 2 diabetes mellitus [11]

iv) Obstructive sleep apnea [12-14]

v) Ageing [15]

vi) Hemochromatosis [16, 17]

vii) Hyperprolactinaemia [18]

viii) Anabolic steroid abuse

ix) Alcohol abuse [19]

x) Human immune deficiency virus infection [20]

xi) Chronic medical conditions (cirrhosis, rheumatoid arthritis, renal failure [21-26]

xii) Severe primary hypothyroidism [27]

xiii) Anorexia nervosa [28]

xiv) Constitutional Delay of Growth of Puberty [29]

xv) Acute illness

xvi) Estrogen excess [30-32]

**B) Secondary hypogonadism-b) Acquired causing damage**

i) Sellar or infiltrative lesion

ii) Metastatic lesion

iii) Traumatic (head injury)

iv) Radiation

v) Surgery

vi) Stalk Severance

vii) Apoplexy

We will concentrate on secondary hypogonadism, laying emphasis on IHH. As for other conditions the therapeutic aim, is to treat the underlying cause e.g. hyperprolactinaemia with dopamine agonist; primary hypothyroidism with levothyroxine and panhypopituitarism with replacement therapies like levothyroxine, hydrocortisone, and possibly GH and desmopressin (DDAVP). In some cases of hemochromatosis, hypogonadism has been reported to reverse with iron depletion therapy [17]. Since testosterone therapy in patients with sleep apnea can adversely affect ventilatory drive and worsen sleep apnea an attempt should be made to thoroughly investigate the etiology of sleep apnea. Often correcting disturbances in sleep cycle can result in normalization of serum testosterone [13, 14]. Kisspeptin 10 (kp10) is known to increase LH pulse frequency and LH secretion in hypotestosteronic men with type 2 DM (T2DM), and potential novel role of KP agonists is under investigation to enhance endogenous T in T2DM with central hypogonadism [33]. Phase 2 trials are being conducted using enclomiphene citrate (Androxal) (one of trans diastereoisomers of clomiphene citrate for men with dysfunctional hypothalamic-pituitary activity. Wiehle found enclomiphene citrate (6.25mg, 12.5mg and 25mg) consistently increased serum total testosterone into the normal range and increased FSH and LH above normal range specially with 25mg dosage. The increase in FSH suggested spermatogenesis was also being affected besides Leydig cell function with increased testosterone and LH. The effect on LH and testosterone persisted for at least 1 week after stopping treatment. So it may have a therapeutic role in men with hypogonadism, due to ageing, obesity, diabetes, insulin resistance, however it may be unsuitable in increasing T in pituitary tumours, craniopharyngeomas, haemochromatosis and congenital GnRH deficiency [34].

Hypogonadotropic hypogonadism (HH) is a failure of sexual development, or reproductive function due to abnormalities in the pituitary secretion of gonadotrophins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). This profile can result from deficiencies in gonadotropin releasing hormone (GnRH) production by the hypothalamus or by defects in the GnRH receptor function at the pituitary level. Congenital hypogonadotropic hypogonadism (CHH) refers to a group of disorders featuring complete or partial pubertal failure due to insufficient gonadotropin secretion. CHH can be associated with anosmia/hyposmia (Kallmanns Syndrome) (KS) or is apparently isolated without anosmia (normosmic HH) (nHH). This phenotype is related to failure of embryonic migration of GnRH and olfactory neurons [35]. Anatomically KS can be defined by olfactory bulb aplasia and accumulation of GnRH neurons outside the brain together with the premature termination of olfactory and terminal nerve fibres. KS is genetically heterogeneous [36]. Loss of function mutations in KAL1, FGFR1 (fibroblast growth factor receptor 1), FGF8 (fibroblast growth factor 8), or CHD7 (chromodomain 7)

underlie either Xlinkedrecessive or autosomal dominant form of the disease [37-42]. The discovery of Kallmann syndrome1 (KAL1)gene has led to a pathophysiological model co-relating GnRH deficiency with abnormal olfactory bulb development in X linked KS. This gene comprises 14 exons spanning across 210kb on Xp22.3, escapes inactivation, and encodes a protein anosmin sharing homology with molecules involved in neuronal migration and axonal path finding [43]. In fact in humans since Kallman phenotype can be associated with other syndromic diseases like CHARGE syndrome [44, 45] and can display neural crest(NC) associated defects involving craniofacial dysmorphisms, cleft palate, dental agenesis, synkinesis, lack of mirror movements, deafness, ocular albinism, cerebellar defects and dementia [46, 47] besides the presence of KS and lack of pubertal onset, Forni demonstrated that NC gives rise to the olfactory ensheathing cells (OEC) [48], that provide essential growth and guidance to olfactory sensory neurons axons [49], as well as subpopulation of GnRH 1 neurons, olfactory and vomeronasal cells .This data demonstrates that both Schwann cells and OEC'S share a common developmental origin and conditions like KS which impact olfaction as well as sexual development are actually neurocristopathies [48]. Developmental abnormalities in this migratory journey like those demonstrated with the deletion of the KAL 1 gene results in KS [43,50]. Recently the fibroblast growth factor (FGF)signaling pathway genes (FGF8 and FGFR1) [40,41,51], PROK2 signaling pathway genes (PROK2 and PROKR2) [52-57], reviewed in [58], and CHD7 [42], WDR11 [59] and SEMA 3A [60,61] have joined the KAL1 gene as genetic pathways that have an identical neurodevelopment function and cause KS in humans .In contrast IHH also occurs in subjects with a normal sense of smell (nIHH) wherein their GnRH deficiency is secondary to impaired function of genes, that govern the neuroendocrine function of GnRH neurons, including KISS1(tumor metastasis receptor) (MIM603286) and KISS1R (KISS1 receptor) [MIM604161], TAC3(tachykinin 3) [MIM162330] TACR3 (tachykinin receptor 3[MIM162332] [62-65] reviewed in [66]), GNRH 1(gonadotrophin releasing hormone 1; MIM 152760), GNRHR (gonadotropin releasing hormone receptor; MIM 138850) [67-72]. However, mutations in some genes (eg FGF8/FGFR1/PROK2/PROKR2/CHD7) have an overlapping function and can be seen in both KS and nIHH. Lewkowitch-Shpuntoff et al studied the olfactory phenotype in 286 IHH of which 201 were male subjects and found of the IHH cohort 31.5% were anosmic, 33.6%hyposmic and 34.9% normosmic. Within the hyposmic cohort 7/11 subjects exhibited olfactory structure abnormalities on MRI, and 39.5%harboured mutations in genes involved in either GnRH neuronal migration or secretion .Thus they concluded that IHH subjects display a broad spectrum of olfactory phenotypes with one third having a hyposmic phenotype, who harbor mutations in genes affecting GnRH neuronal migration and its secretion and this suggests a pathophysiological overlap between KS and nIHH. Hence accuracy of olfactory phenotype can inform pathophysiology and guide genetic testing [73].

However Moya-Plana found isolated congenital anosmia (ICA) and olfactory bulb agenesis without gonadotropin deficiency and found three PROKR2 mutations previously described for KS and one new PROK2 mutation, and incomplete penetrance on

investigation of families, on screening for KAL1/FGF8/FGFR1/PROK2/PROKR2 which suggests the considerable complexity of GnRH neuron development in humans [74].

The discovery of mutations in FGF8-FGFR1 in CHH has demonstrated a previously unappreciated role of FGF8-FGFR1 signaling in GnRH ontogeny. Subsequently Chung et al have established FGF8 as critical for both GnRH as well as olfactory system development [75]. Besides those ears, eyes, kidneys and limbs are also influenced by FGF8 [76-79] all of which can be affected in CHH [80]. Among the >15 genes implicated in CHH, mutations in FGF8-FGFR1 account for 12% of cases and importantly KAL1 and HS6ST1 (Heparan sulfate-6-O-sulfotransferase 1[MIM 604846]-two genes known to be mutated in CHH, also encode important components of FGF8-FGFR1 signaling. KAL1 encodes anosmin 1, which enhances FGF1 signaling by direct physical interactions with the FGFR-FGF-heparansulfate proteogly can (HSPG) complex on the cell surface. HS6ST1, which encodes a heparansulfotransferase enzyme, was found mutated in CHH and that heparan6-O-sulfation was required for anosmin function in vivo [81]. Based on the fact that multiple genes from FGF family are mutated in CHH, Miraoui studied 386 individuals from CHH group with 155 controls to study role of "FGF8 syn expression group" and found except for FGF18 [MIM 6063726] and SPRY2 (Sprouty homolog2) [MIM602466], all other genes were found to be mutated in CHH individuals FGF17(n=3 individuals), IL17RD(Interleukin 17 receptor D)[MIM6068807](n=8)DUSP6(Dual Specificity phosphatase 6)[MIM602748] (n=5), SPRY4(Sprouty homolog 4)(Drosophila)[MIM607984](n=4), FLRT3(Fibronectin leucine rich transmembrane protein 3)[MIM604808](n=3)while FLRT3 is an enhancer, as compared to others which are inhibitors. They further concluded mutations in IL17RD were found only in KS individuals and were strongly linked to hearing loss individuals (6/8). Further mutations in genes encoding components of FGF pathway are associated with complex modes of CHH inheritance, and act primarily as contributors to an oligogenic genetic architecture underlying CHH [82].

Since genetic testing is becoming complex and costly Costa-Barbosa et al suggested prioritizing genetic testing in patients with KS using clinical phenotypes. For example certain clinical features commonly associated with genetic causes are synkinesia (KAL1), dental agenesis(FGF8/FGFR1), digital bony abnormalities(FGF8/FGFR1) and hearing loss (CHD7) and these can be useful to prioritize genetic screening, although renal agenesis and cleft lip and palate did not emerge as statistically significant predictors [83].This is in slight contrast with the report of Dode et al where they report associations of renal agenesis with KAL1 and cleft lip/palate with FGF8/FGFR1 mutations which was not found in this study [40,84].

However before coming to a diagnosis of CHH one must rule out the differential diagnosis of pituitary tumours, or pituitary infiltration by neuroimaging studies like MRI [85,86], juvenile hemochromatosis by serum iron and serum ferritin levels [87], and a systemic disorder that by undermining nutritional status could affect gonadotropin secretion and pubertal development like anorexia nervosa, celiac disease [88]. Anterior pituitary function must be thoroughly evaluated to

rule out hyperprolactinemia [18,85], primary hypothyroidism, GH, ACTH and investigate adrenal axis or somatotrope axis specifically when pubertal delay is accompanied with statural retardation and rule out multiple hormone deficiencies. Indeed diagnosis of any associated endocrinopathy of this type will reorient the etiologic diagnosis towards a specific lesional organetic disorder [89-94] which will thus conclude that the HH is isolated. The most likely differential diagnosis before 18 year is constitutional delay of puberty. Since IHH may present as delayed puberty it becomes essential to know how to distinguish constitutional delay of growth of puberty (CDGP) from isolated HH with definitive diagnosis of IHH awaiting lack of spontaneous puberty by 18years. Although basal gonadotropins and GnRH Stimulation tests have limited diagnostic specificity, with overlap in gonadotropin levels between adolescents with CDGP and IHH, Stimulation tests using more potent GnRH agonists (especially leuprolide acetate) and/or human chorionic gonadotropin (hCG) may have better discriminatory value, but small study size, lack of replication of diagnostic thresholds, and prolonged protocols limit clinical application. Basal inhibin B may offer a simple discriminatory test, however in a recent metaanalysis Harrington J2012 didn't find any reliable diagnostic test and recommended this an important area for future investigation ([29] for review and figure 1).

In paediatric endocrinology this differential diagnosis is far more difficult as CHH is rare whereas CDGP is infrequent [95]. Serum inhibin B levels in CHH males correlate with testicular volume and thus with clinical severity of gonadotropin deficiency [39,96,97] and with very broad and overlapping values this single marker is not dependent. In view of all difficulties classical clinical features distinguishing CHH from CDGP are still of practical value, especially observing testicular volume over time, in patients receiving exogenous testosterone. In male patient with pubertal delay and low gonadotropins presence of micropenis and/or cryptorchidism practically rules it out since they are rarely seen in CDGP and favours CHH [95,98]. Signs of a particular etiology are also useful like anosmia etc figure 2(see [99] for review).

Recently a novel syndrome has been defined known as TUBB3E410 K Syndrome where one of the eight missense mutations in TUBB3 gene, that encodes the neuronal specific protein  $\beta$  tubulin isotype 3, have congenital fibrosis of the extraocular muscles, facial weakness developmental delay, and possible peripheral neuropathy. This occurs due to c.1228G >A resulting in a TUBB3E410K amino acid substitution which directly alters a kinesin motor protein binding site. In detailed phenotype of eight unrelated individuals Chew confirmed electrophysiology that a progressive sensorimotor polyneuropathy does indeed segregate with the mutation and expand the TUBB3E410K phenotype to include KS, stereotyped midface hypoplasia, intellectual disabilities and in some cases vocal cord paralysis, tracheomalacia and cyclic vomiting. Neuroimaging reveals a thin corpus callosum, and anterior commissure, hypoplastic to absent olfactory sulci, olfactory bulbs and oculomotor and facial nerves, which support underlying abnormalities in axon guidance and maintenance [100].

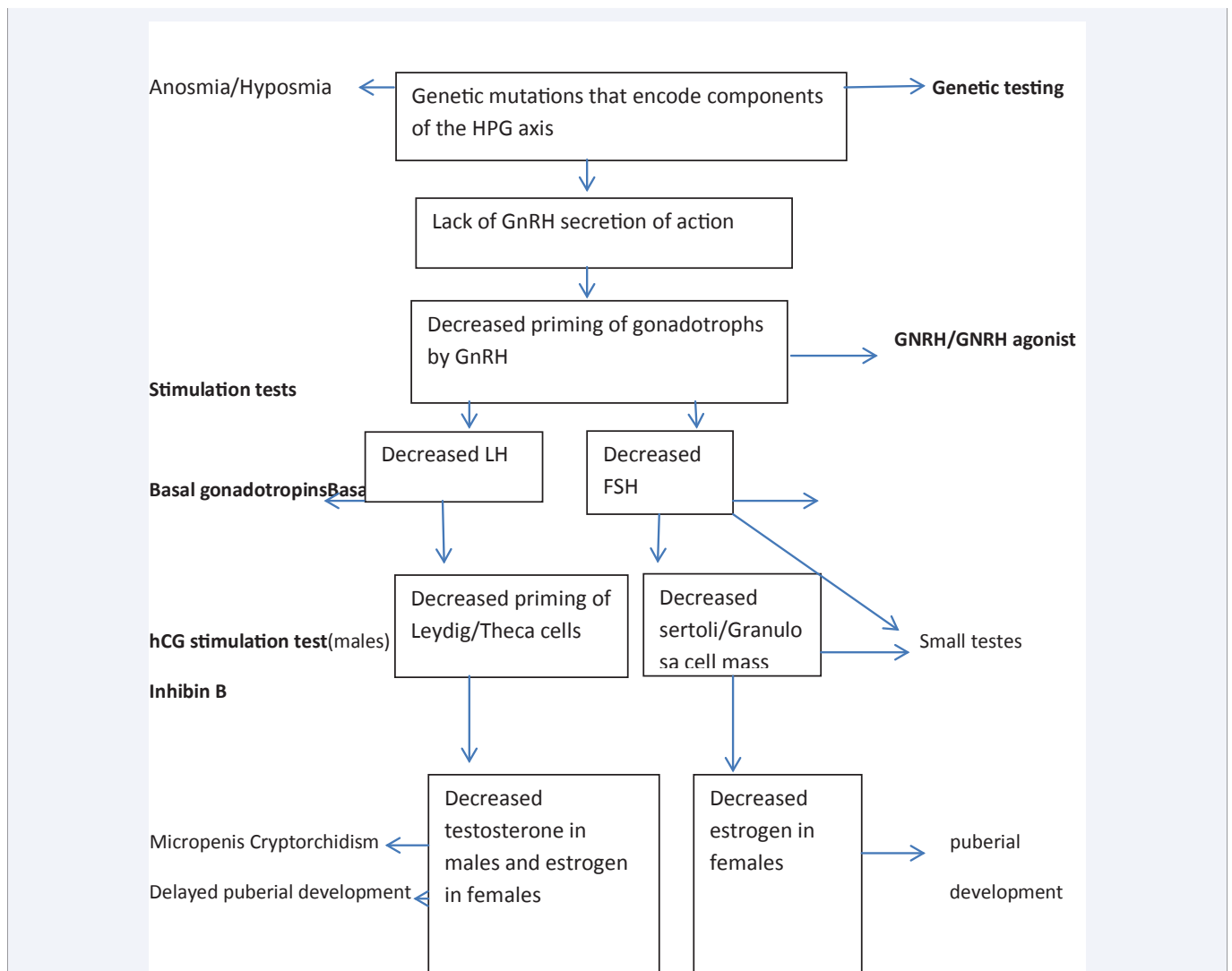
KS combined pituitary hormone deficiency (CPHD), and septo-optic dysplasia (SOD) all result from developmental

defects of the anterior midline in the human forebrain. It has been recently shown that deficient migration of GnRH neurons is also a feature in forebrain formation defects [101]. Hence Raivio studied 103 patients with either CPHD (n=35), or SOD (n=68) and investigated them for mutations in genes implicated in the etiology of KS (FGFR1, FGF8, PROKR2, PROK2 and KAL1). Mutations in FGFR1/FGF8/PROKR2 contributed to 7.8% of their patients with CPHD/SOD which suggests a significant genetic overlap between conditions affecting the development of anterior midline in the human forebrain. Of the SOD 3 patients had heterozygous mutations in FGFR1, with these either shown to alter receptor signaling (Ps450F, Pp483S) or predicted to affect splicing (c.216G >A, p.T72T) that was shown to affect splicing and ligand signaling activity. Four patients with CPHD/SOD were found to harbor heterozygous rare loss of function variants in PROKR2 (p.R85G, p.R85H, p.R268C) [102]. To further study the role of PROKR2/PROK2, McCabe further studied 422 patients of congenital hypopituitarism (CH) and detected that variations in PROKR2 but not PROK2 are associated with CH and SOD. They detected 5PROKR2 variants in 11 patients with SOD/CH: novel p.G371R and previously reported p. A51T, p.R85L, p.L173R and p.R268C-the latter three being known as functionally deleterious variants. Surprisingly, although 1 patient with SOD was heterozygous for the p.L173 Rvariant, his phenotypically unaffected mother was homozygous for the variant [103]. Midline defects are encountered in all three disorders, namely KS [MIM; 147950], SOD[MIM;182230] and holoprosencephaly [HPE; MIM 236100], a complex brain malformation that affects both the forebrain and face. In SOD mutations have been identified in number of transcription factor genes such as SOX2, HESX1, SOX3, and OTX2, which are essential for normal forebrain development [104], and also in HPE genes like SHH, SIX3, TGIF1, TDGF1, FOXH1 and GLI2 have been found to be mutated [105,106]. Hence Vaaralahti 2012 studied 19 subjects (18 males) with KS without known KS genes and screened them for mutations in SOX2, SHH, SIX3, TGIF1, TDGF1, FOXH1, GLI2 and GLI3. One male carried 2 heterozygous missense changes, one in SIX3 (c.428G>A, p.G143D) and the other in GLI2 (c.2509G>A, p.E837 K). Both of these genes have been implicated in etiology of HPE and none was present in 200 control subjects. Thus they concluded that KS and HPE may display a genetic overlap and in view of this the involvement of genes implicated in the etiology of midline defects in patients with KS warrants further studies [107].

## MANAGEMENT

The initial goal of treatment for adolescents and young men who present with CHH is to induce physical and behavioral development matching that of normal healthy subjects of same age. This includes development of secondary sex characters like pubic and axillary hair, increase in penis size, voice masculinization and development of muscle mass. Further one aims at correcting the delay in bone maturation and deficient bone mineralization, enhance libido and modify sex behavior. Mostly effective testosterone replacement therapy can lead to a spectacular improvement in quality of life, which demonstrates a causal relationship between testosterone deficiency and these patients' symptoms.

Although it is more physiological to achieve such benefits with

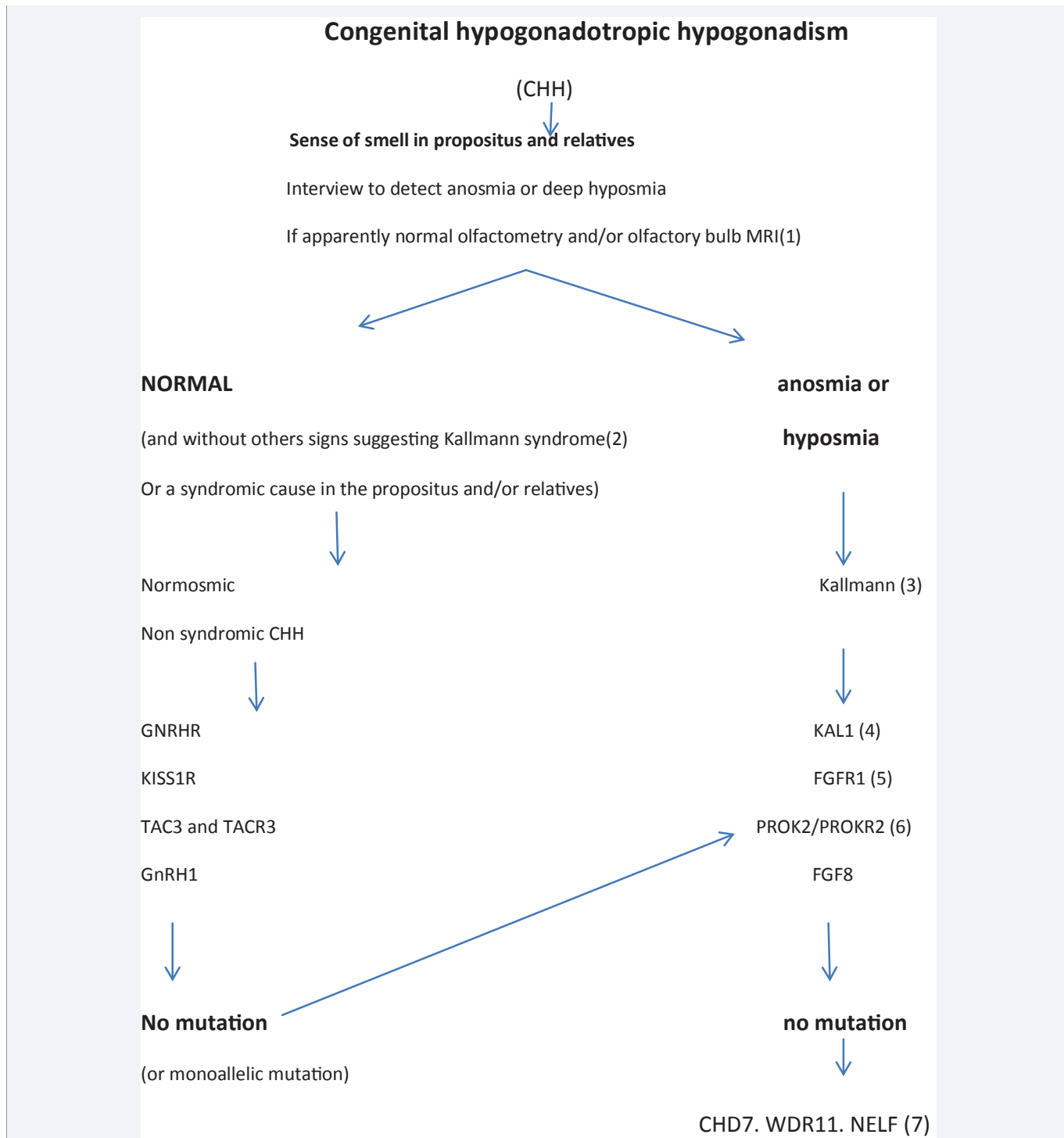


**Figure 1** Courtesy ref 73-In a subset of adolescents with IHH (and Kallmanns syndrome), mutations in genes that encode critical components of the HPG axis lead to either a lack of GnRH secretion, or action. The etiologies in the remaining cases are undetermined. The lack of GnRH action leads to a deficiency of both priming and hormonal secretion of the gonadotropins in the pituitary and of the leydig/theca cells of the gonads. These characteristics of the H-P-G axis form the physiological basis for the diagnostic tests (indicated in bold face) and typical characteristics (indicated in italic anosmia/hyposmia, small testes, micropenis, cryptorchidism) used to identify patients with a higher likelihood of IHH than CDGP.

pulsatile GnRH administration or with combined gonadotropin therapy (human chorionic gonadotropin and FSH) [108,109] with both therapies effectively inducing testicular growth and secretion of testosterone and estradiol [108]. We have to consider availability of GnRH infusion pumps, cost of treatment, patients requirements especially if patient presents as a partner of an infertile couple with spermatogenesis in view. Since long term treatment is required even in west mostly testosterone therapy as (injectable esters) is generally preferred for convenience of infrequent injections and cost, DHT is not preferred as it can't be aromatized to estradiol and hence can't serve the dual purpose of testosterone esters used for decades now as first line treatment. TN enanthate is one of the cheaper preparations, used at a dose of 200-250 mg once every 2 or 3 weeks. Although these doses depend on age at diagnoses and local practices, Pediatric endocrinologists who see these patients at a younger age, initially prescribe lower doses, gradually increasing for fear

of inducing abrupt virilization and bone maturation which could cause behavioral and relational problems. Endocrinologists see adult CHH patients at a later stage when main signs/symptoms are of severe hypogonadism, and usually require full dose. Although two approaches are not comparable patient should be counseled that he will need longterm androgen therapy. Once full virilization has been induced by exogenous testosterone, males whose testes have significantly increased in size (<5% cases) should be reevaluated off androgen replacement therapy to identify those with reversible forms [110,111] who no longer require treatment.

Patients who wish to have an increase in testicular volume or fertility in developing countries like ours where most centres don't have the facilities of infusion pump the approach of combination therapy with initial rFSH with the idea of stimulating proliferation of immature sertoli cells which are



**Figure 2** With permission from dr Young courtesy ref79-Molecular studies performed in male patients of CHH categorized on the basis of smell 1)MRI,2)Bimanual synkinesis,tooth agenesis,hearing impairment ,renal agenesis,cleft lip/palate,high atched palate,pes cavus,ptosis,absent nasal cartilage,hand /foot skeletal abnormalities and iris coloboma 3)Step by step strategy based on familial history and putative mode of disease inheritance (pedigree),and the presence of additional clinical anomalies as mentioned above that may direct the geneticist towards a particular Kallmann gene 4 and 5)For instance 4)KAL 1 is analyzed especially in Kallmann men with mirror movements(bimanual synkinesis) and/or for kidney agenesis and/or when the pedigree suggests an X linked mode of inheritance,whereas 5)in subjects displaying cleft lop/palate FGFR1 mutations are searched in firstline whatever the apparent mode of inheritance 6)in subjects with monoallelic,PROK2 or PROKR2 mutations ,search for mutations in other CHH genes to demonstrate a digenic or oligogenic mode of inheritance 7)Analysis of other large genes mentioned below performed in second line ,given their lower or unknown prevalence among normosmic CHH and Kallmann men.Sizes of the genes currently sequenced in CHH patients:GNRH1;three exons,GNRHR;three exons,KISS1R;five exons,TAC3;six exons;TACR3;five exons;KAL1;fourteen exons,FGF8,six exons;FGFR1,18exons;PROKR2 ,two exons;PROK2 ,four exons;CHD7;38exons;WDR11 ;29 exons;NSMF(NMDA receptor synaptonuclear signaling and neuronal migration factor -formerly known as NELF);16 exons.

under control of FSH initial doses of 1.5iu/Kg (180-450u/week) x2months -2.8yrs Puberty is then initiated with hCG 500iu-4000 iu/week, 1-3times/week sc and after onset of hCG treatment if patient can't afford can shift to highly purified FSH. Raivio found this induced prepubertal testes growth with increase in serum inhibin B levels, and 6/7 prepubertal boys displayed sperms despite extremely small initial testis primed with rFSH [111].

GnRH treatment is successful in inducing virilization and spermatogenesis in men with IHH; however a small subset of IHHmen, fail to reach a normal testicular volume and produce sperm on this therapy [112]. Pitteloud in studying 76 IHH men undergoing GnRH therapy for 12-24 months to define predictors of outcome of long term GnRH therapy concluded anosmia was not an independent predictor, however favorable predictors of achieving an adult testicular size and consequently optimizing spermatogenesis are prior history of sexual maturation, with a baseline inhibin(B) > 60pg/ml along with absence of cryptorchidism [113].

Further extending this study on GnRH treatment, Sykiotis et al studied 90 patients and classified patients into four groups according to the response obtained to long term physiological pulsatile GnRH release .1) 67/90 subjects displayed normal expected response, with normal serum T (270-1100ng/dl, LH (4.2-17IU/L) and FSH (1.8-14IU/L) and had sperm in their ejaculate and were labeled as typical responders. In rest 23 patients(26%)three distinct patterns were seen 2)10men remained hypogonadotropic and hypogonadal with low normal LH/FSH, serum T, <200ng/dl and no sperm despite GnRH doses upto 800ng/Kg-and thus labeled Group1 with triple defect with GnRH deficiency, pituitary resistance and testicular failure.3) 8men achieved normal serum T and produced sperms but did so with high LH (>17IU/L and FSH >14IU/L and thus labeled Group 2 with dual defect, GnRH deficiency and testicular resistance.4) 5men remained azoospermic after atleast 21 months despite achieving normal serum T, LH and FSH and thus labeled Group 3 with GnRH deficiency with azoospermia. Although typical responders showed mutations in all the IHH genes tested, atypical responders displayed mutations exclusively in KAL1 Gene [114]. Although Sinisi et al reported a case with homozygous mutation in PROKR2 gene Val274 Asp which presented as reversible KS along with persistent oligozoospermia [115].

Dwyer 2013 conducted a randomized open label prospective trial to see if there is any benefit of giving recombinantFSH (rFSH) pretreatment for 4 months followed by pulsatile GnRH therapy vs GnRH therapy alone in a group of CHH patients with prepubertal testis (<4ml), no cryptorchidism, and no prior gonadotropin therapy and found rFSH increased inhibin B levels into normal range (29+-9-107+-41pg/ml) and doubled testicular volume from 1.1-2.2ml. Histological analysis showed proliferation of sertoli cells (SC) and spermatogonia, a decreased SC to germ cell ratio from 0.74 to 0.35 and SC cytoskeletal rearrangements. Although with pulsatile GnRH similar hormones and significant testicular growth was exhibited, all men receiving rFSH developed sperm in their ejaculate (7/7 vs 4/6in GnRH only group) and showed trends towards higher maximal sperm counts and hence concluded that rFSH not only appears to maximize the SC population, but also induces morphologic changes, suggesting

broader developmental roles [116]. This maybe in accordance with the results of study of Pitteloud where he found while studying 25 patients of IHH that when analyzed for degree of pubertal/testicular development (TV <or =3ml) Group 1 men showed sharp increases in serum FSH compared to men with some prior evidence of partial puberty (TV>3ml, Group II. Group I exhibited a decreased LH response to GnRH on day2, compared to day1 which did not recover until day5 (1-4 vs 5-7days). GroupII exhibited a robust and equivalent LH response to GnRH throughout 7days of study. The mutations identified were in 4 different locations on genetic studies (DAX1, KAL1, GNRH1, FGFR1) in this cohort. Hence they concluded GnRH deficient men undergoing GnRH induced sexual maturation displayed an inverse responsiveness to GnRH and baseline testicular size and I (B) levels. This observation implied that increasing seminiferous tubule maturity represents the major constraint on FSH responsiveness to GnRH in early puberty. In contrast LH responsiveness to GnRH correlated directly with duration of GnRH exposure. Although attenuated pituitary gonadotropin responses were noted in 2 subjects harboring DAX1 mutations it is consistent with their known pituitary defects and this model of IHH helps study the normal physiology of puberty which one can't dissect out in normal adolescent boys with intact H-P-G axis [117].

Still controversy exists on the sexuality and intimate relations of men with severe CHH accompanied by cryptorchidism and micropenis [118]. Since there is a negative prognostic value of cryptorchidism and low testicular volume for the future fertility of patients with severe CHH, a trial of earlier gonadotropin therapy during the neonatal or normal pubertal period is warranted and just may prove beneficial, both in terms of testicular hypertrophy and in terms of future fertility [119-122]. Not only do we learn how to manage these patients but these patients of IHH have served as good models to make us understand the role of testosterone, estradiol feedback at hypothalamic and pituitary level in normal men as one cannot use human model to study the control of GnRH secretion in human model otherwise.

## ROLE OF ESTRADIOL

Trabados studying 91 men of IHH, with 63 controls and 45 patients of Klinefelters syndrome found male hypogonadism in CHH is associated with profound E2 insufficiency which can be overcome by aromatizable androgen (Testosterone) or combined gonadotropin (FSH-hCG) therapy, but not dihydrotestosterone (DHT) contrary to Klinefelters syndrome [108]. This E2 deficiency is also associated with abnormal bone development, teenage growth spurt and osteopenia or osteoporosis. Reports that altered E2 production (aromatase loss of function mutations), and responsiveness (E2 receptor inactivating mutations) are associated with adverse skeletal effects in men strongly suggest that E2 are critically important for male sexual development and bone mineral density acquisition [123-125]. Further Rochira reported 4 cases of tall stature without growth hormone deficiency who had a impaired response of GH to GHRH-ARG as compared to normal subjects and who had significantly lower IGF1 levels as compared to normal subjects and both IGF1 peak and concentrations were not modified by estrogen therapy in men with aromatase deficiency and concluded insulin as the

cause of tall stature rather than GH for the marked increase in height due to nonclosure of epiphyses [126]. Besides that for normal physiology, Pitteloud 2008 showed that for Inhibition of LH secretion by T in men aromatization is required for its pituitary effect but not its hypothalamic effect as shown by studying 11 men with GnRH deficiency and 21 normal (NL) men and using ketoconazole for medical castration and inhibition of aromatase. They showed that in NLmen KC caused a3fold increase in mean LH, which was stable on d6-7 with no add back. Addition of T reduced LH levels (34-17iu/l) by slowing GnRH frequency pulses, whereas LH amplitude increased from 6.9 to12.1 IU/L, E2 add back suppressed LH levels from 36.4-19IU/L, by slowing GnRH pulse frequency (11.4-8.6pulses/12h but had no effect on LH amplitude). In IHH men restoring normal T levels caused no suppression of mean LH levels/LH amplitude. E2 add back normalized mean LH levels and decreased LH levels and decreased LH amplitude from 14.7 to 12IU/L and thus concluding both T and E2 have independent effects on LH 2) Inhibition of LH by T requires aromatization for its pituitary but not hypothalamic effect 3) E2 has dual sites of feedback, but its predominant effect is at the hypothalamus [127].

Further since Kp 10 is a potent stimulator of LH and increases pulse frequency in men and thereby LH and testosterone levels in normal men there may be a potential role of Kp agonists in HH due to KISS 1/KISS1R mutations [128,63]. Although TAC3/TAC3R mutations also are associated with IHH administration of NKB was not accompanied by increase in serum LH and testosterone levels, hence role of NKB doesn't appear to be useful in treating these patients presenting with TAC3/TACR3 mutations [129,130].

## CONCLUSION

Despite finding so many early developmental genes like KAL1, FGF8, FGFR1, NELF, CHD7, PROK2, PROKR2, H6SST1, SEMA3A in a study of a large cohort of GnRH deficient patients (n=397) at the Massachusetts general hospital at least roughly 32% have been linked to at least one gene mutation (when studying all genes including those involved in GnRH function like (KISS1/KISSR1, GnRH/GnRHR/TAC3/TACR3) whereas just for KS mutations in any of the 9 genes identified thus far have been found only in approximately 30% patients [131,132] Still a lot of controversial issues remain regarding role of PROK signaling as highlighted in [58] regarding absence of PROK receptors on GnRH neurons, mode of inheritance-digenic/oligogenic [133] with presence of PROK2 mutations even in normosmic HH and thus extending the role beyond olfactory bulb development and GnRH neuronal migration and absence of any defect in homozygous mutations while most of human presentations being in heterozygous mutations. Further recently that there may be an ethnic role is highlighted by greater presence of PROKR2 mutations in KS patients from Maghreb as compared to European origin patients (23.3%vs 5.1%) [134]. Further more work needs to be done on other transcription factors as has been shown for SOX10 i.e., loss of function mutations in SOX 10 is associated with KS along with deafness [135]. Similar work needs to be done for other transcription factors in view of genetic overlap of other midline forebrain disorders like SOD and HPE with KS.

## REFERENCES

1. Cooke RR, McIntosh JE, McIntosh RP. Circadian variation in serum free and non-SHBG-bound testosterone in normal men: measurements, and simulation using a mass action model. *Clin Endocrinol (Oxf)*. 1993; 39: 163-171.
2. Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD. Diurnal rhythm of serum total, free and bioavailable testosterone and of SHBG in middleaged men compared with those in younger men. *Clin Endocrinol (oxf)*. 2003; 58: 710-717.
3. Clair P, Claustrat B, Jordan D, Dechaud H, Sassolas G. Daily variations of plasma sex hormone binding globulin capacity, testosterone and leteininh hormone concentrations in healthy rested adult males. *Horm Res* 1985; 21: 220-223.
4. Caronia LM, Dwyer AA, Hayden D, Amati F, Pitteloud N, Hayes FJ. Abrupt decrease in serum testosterone levels after an oral glucose load in men: implications for screening for hypogonadism. *Clin Endocrinol (Oxf)*. 2013; 78: 291-296.
5. Farrer JH, Sikka SC, Xie HW, Constantine D, Rajfer J. Impaired testosterone biosynthesis in cryptorchidism. *Fertil Steril*. 1985; 44: 125-132.
6. Colameco S, Coren JS, Ciervo CA. Continuous opioid treatment for chronic noncancer pain: a time for moderation in prescribing. *Postgrad Med*. 2009; 121: 61-66.
7. Fraser LA, Morrison D, Morley-Forster P, Paul TL, Tokmakejian S, Larry Nicholson R, et al. Oral opioids for chronic non-cancer pain: higher prevalence of hypogonadism in men than in women. *Exp Clin Endocrinol Diabetes*. 2009; 117: 38-43.
8. Morrison D, Capewell S, Reynolds SP, Thomas J, Ali NJ, Read GF, et al. Testosterone levels during systemic and inhaled corticosteroid therapy. *Respir Med*. 1994; 88: 659-663.
9. Mah PM, Wittert GA. Obesity and testicular function. *Mol Cell Endocrinol*. 2010; 316: 180-186.
10. Gascón F, Valle M, Martos R, Ruz FJ, Ríos R, Montilla P, et al. Sex hormone-binding globulin as a marker for hyperinsulinemia and/or insulin resistance in obese children. *Eur J Endocrinol*. 2000; 143: 85-89.
11. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. *J Clin Endocrinol Metab*. 2011; 96: 2341-2353.
12. Santamaria JD, Prior JC, Fleetham JA. Reversible reproductive dysfunction in men with obstructive sleep apnoea. *Clin Endocrinol (Oxf)*. 1988; 28: 461-470.
13. Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID, Sullivan CE. Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. *J Clin Endocrinol Metab*. 1989; 68: 352-358.
14. Matsumoto AM, Sandblom RE, Schoene RB, Lee KA, Giblin EC, Pierson DJ, et al. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnoea, respiratory drives, and sleep. *Clin Endocrinol (Oxf)*. 1985; 22: 713-721.
15. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab*. 1983; 56: 1278-1281.
16. Mcdermot JH, Walsh CH. Hypogonadotropism in men hemochromatosis. *J Clin Endocrinol Metab*. 2005; 90: 2451-2455.
17. Kelly TM, Edwards CQ, Meikle AW, Kushner JP. Hypogonadism in hemochromatosis: reversal with iron depletion. *Ann Intern Med*. 1984; 101: 629-632.

18. Milenkovic L, D'Angelo G, Kelly PA, Weiner RI. Inhibition of gonadotropin hormone releasing hormone by prolactin from GT1 neuronal cell lines through prolactin receptor. *Proc Natl Acad Sci USA*. 1994; 91: 1244-1247.
19. Emanuele MA, Emanuele NV. Alcohol's effects on male reproduction. *Alcohol Health Res World*. 1998; 22: 195-201.
20. Cohan GR. HIV-associated hypogonadism. *AIDS Read*. 2006; 16: 341-345, 348, 352-4.
21. Handelsman DJ, Strasser S, McDonald JA, Conway AJ, McCaughan GW. Hypothalamic-pituitary-testicular function in end-stage non-alcoholic liver disease before and after liver transplantation. *Clin Endocrinol (Oxf)*. 1995; 43: 331-337.
22. Lim VS, Fang VS. Gonadal dysfunction in uremic men. A study of the hypothalamo-pituitary-testicular axis before and after renal transplantation. *Am J Med*. 1975; 58: 655-662.
23. Handelsman DJ, Dong Q. Hypothalamo-pituitary gonadal axis in chronic renal failure. *Endocrinol Metab Clin North Am*. 1993; 22: 145-161.
24. Handelsman DJ, Spaliviero JA, Turtle JR. Hypothalamic-pituitary function in experimental uremic hypogonadism. *Endocrinology*. 1985; 117: 1984-1995.
25. Tengstrand B, Carlström K, Hafström I. Bioavailable testosterone in men with rheumatoid arthritis-high frequency of hypogonadism. *Rheumatology (Oxford)*. 2002; 41: 285-289.
26. Tengstrand B, Carlström K, Hafström I. Gonadal hormones in men with rheumatoid arthritis--from onset through 2 years. *J Rheumatol*. 2009; 36: 887-892.
27. Vagenakis AG, Dole K, Braverman LE. Pituitary enlargement, pituitary failure, and primary hypothyroidism. *Ann Intern Med*. 1976; 85: 195-198.
28. Rigotti NA, Neer RM, Jameson L. Osteopenia and bone fractures in a man with anorexia nervosa and hypogonadism. *JAMA*. 1986; 256: 385-388.
29. Harrington J, Palmert MR. Clinical review: Distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism: critical appraisal of available diagnostic tests. *J Clin Endocrinol Metab*. 2012; 97: 3056-3067.
30. Valensi P, Coussieu C, Kemeny JL, Attali JR, Amouroux J, Sebaoun J. Endocrine investigations in two cases of feminizing Leydig cell tumour. *Acta Endocrinol (Copenh)*. 1987; 115: 365-372.
31. Young S, Gooneratne S, Straus FH 2nd, Zeller WP, Bulun SE, Rosenthal IM. Feminizing Sertoli cell tumors in boys with Peutz-Jeghers syndrome. *Am J Surg Pathol*. 1995; 19: 50-58.
32. Zayed A, Stock JL, Liepman MK, Wollin M, Longcope C. Feminization as a result of both peripheral conversion of androgens and direct estrogen production from an adrenocortical carcinoma. *J Endocrinol Invest*. 1994; 17: 275-278.
33. George JT, Veldhuis JD, Tena-Sempere M, Millar RP, Anderson RA. Exploring the pathophysiology of hypogonadism in men with type 2 diabetes: kisspeptin-10 stimulates serum testosterone and LH secretion in men with type 2 diabetes and mild biochemical hypogonadism. *Clin Endocrinol (Oxf)*. 2013; 79: 100-104.
34. Wiehle R, Cunningham GR, Pitteloud N, Wike J, Hsu K, Fontenot GK, et al. Testosterone Restoration by Enclomiphene Citrate in Men with Secondary Hypogonadism: Pharmacodynamics and Pharmacokinetics. *BJU Int*. 2013.
35. Schwanzel-Fukuda M, Pfaff DW. Origin of luteinizing hormone-releasing hormone neurons. *Nature*. 1989; 338: 161-164.
36. Tsai PS, Gill JC. Mechanisms of disease: Insights into X-linked and autosomal-dominant Kallmann syndrome. *Nat Clin Pract Endocrinol Metab*. 2006; 2: 160-171.
37. Albuissou J, Pêcheux C, Carel JC, Lacombe D, Leheup B, Lapuzina P, et al. Kallmann syndrome: 14 novel mutations in KAL1 and FGFR1 (KAL2). *Hum Mutat*. 2005; 25: 98-99.
38. Hardelin JP, Levilliers J, Blanchard S, Carel JC, Leutenegger M, Pinard-Bertelletto JP, et al. Heterogeneity in the mutations responsible for X chromosome-linked Kallmann syndrome. *Hum Mol Genet*. 1993; 2: 373-377.
39. Salenave S, Chanson P, Bry H, Pugeat M, Cabrol S, Carel JC, et al. Kallmann's syndrome: a comparison of the reproductive phenotypes in men carrying KAL1 and FGFR1/KAL2 mutations. *J Clin Endocrinol Metab*. 2008; 93: 758-763.
40. Dode C, Levilliers J, Dupont JM, De Paepe A, Le Du N, Soussi-Yanicostas N, et al. Loss of function mutations in FGFR1 cause autosomal dominant Kallmann's syndrome. *Nat Genet*. 2003; 33: 463-465.
41. Falardeau J, Chung WC, Beenken A, Raivio T, Plummer L, Sidis Y, et al. Decreased FGF8 signaling causes deficiency of gonadotropin-releasing hormone in humans and mice. *J Clin Invest*. 2008; 118: 2822-2831.
42. Kim HG, Kurth I, Lan F, Melicani I, Wenzel W, Fom SH, et al. Mutations in CHD7, encoding a chromatin remodeling protein, causes idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. *Am J Hum Genet*. 2008; 83: 511-519.
43. Franco B, Guioli S, Pragliola A, Incern B, Bardoni B, Tonlorenzi R, 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.
44. Ogata T, Fujiwara I, Ogawa E, Sato N, Udaka T, Kosaki K. Kallmann syndrome phenotype in a female patient with CHARGE syndrome and CHD7 mutation. *Endocr J*. 2006; 53: 741-743.
45. Jongmans MC, van Ravenswaaij-Arts CM, Pitteloud N, Ogata T, Sato N, Claahsen-van der Grinten HL, et al. CHD7 mutations in patients initially diagnosed with Kallmann syndrome--the clinical overlap with CHARGE syndrome. *Clin Genet*. 2009; 75: 65-71.
46. Zenaty D, Bretones P, Lambe C, Guemas I, David M, Léger J, et al. Paediatric phenotype of Kallmann syndrome due to mutations of fibroblast growth factor receptor 1 (FGFR1). *Mol Cell Endocrinol*. 2006; 254-255: 78-83.
47. Bhagavath B, Layman LC. The genetics of hypogonadotropic hypogonadism. *Semin Reprod Med*. 2007; 25: 272-286.
48. Forni PE, Taylor-Burds C, Melvin VS, Williams T, Wray S. Neural crest and ectodermal cells intermix in the nasal placode to give rise to GnRH-1 neurons, sensory neurons, and olfactory ensheathing cells. *J Neurosci*. 2011; 31: 6915-6927.
49. Su Z, He C. Olfactory ensheathing cells: biology in neural development and regeneration. *Prog Neurobiol*. 2010; 92: 517-532.
50. Legouis R, Hardelin JP, Levilliers J, Clavier JM, Compain S, Wunderle V, et al. The candidate gene for the X-linked Kallmann syndrome encodes a protein related to adhesion molecules. *Cell*. 1991; 67: 423-435.
51. Pitteloud N, Acierno Jr JS, Meysing A, Eliseenkova AV, Ma J, Ibrahim OA, et al. Mutations in fibroblast growth factor receptor 1 causes both Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism. *Proc Natl Acad Sci USA*. 2006; 103: 6281-6286.
52. Dodé C, Teixeira L, Levilliers J, Fouveaut C, Bouchard P, Kottler ML, et al. Kallmann syndrome: mutations in the genes encoding prokineticin-2 and prokineticin receptor-2. *PLoS Genet*. 2006; 2: e175.
53. Pitteloud N, Zhang C, Pognatelli D, LiJD, Raivio T, Cole LW, 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.
54. Cole LW, Sidis Y, Zhang C, Quinton R, Plummer L, Pignatelli D, 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.
55. Leroy C, Fouveaut C, Leclercq S, Jacquemont S, Boullay HD, Lespinasse J, et al. Biallelic mutations in the prokineticin-2 gene in two sporadic cases of Kallmann syndrome. *Eur J Hum Genet*. 2008; 16: 865-868.
56. Abreu AP, Trarbach EB, de Castro M, Frade Costa EM, Versiani B, Matias Baptista MT, et al. 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.
57. Sarfati J, Guiochon-Mantel A, Rondard P, Arnulf I, Garcia-Piñero A, Wolczynski S, et al. A comparative phenotypic study of kallmann syndrome patients carrying monoallelic and biallelic mutations in the prokineticin 2 or prokineticin receptor 2 genes. *J Clin Endocrinol Metab*. 2010; 95: 659-669.
58. Kochar Kaur K, Allahbadia GN, Singh M. An update on the role of prokineticins in human reproduction-potential therapeutic applications. *O J Gen*. 2013; 3: 201-215.
59. Kim HG, Ahn JW, Kurth I, Ullmann R, Kim HT, Kulharya A, Ha KS. WDR1, a WD protein that interacts with transcription factor EMX, is mutated in idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. *Am J Hum Genet*. 2010; 87: 465-479.
60. Hanchate NK, Giacobini P, Lhuillier P, Parkash J, Espy C, Fouveaut C, Leroy C. SEMA3A, a gene involved in axonal pathfinding, is mutated in patients with Kallmann syndrome. *PLoS Genet*. 2012; 8: e1002896.
61. Young J, Metay C, Bouligand J, Tou B, Francou B, Maione L, Tosca L. 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.
62. de Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the KISS1-derived peptide receptor GPR54. *Proc Natl Acad Sci U S A*. 2003; 100: 10972-10976.
63. Pallais JC, Bo-Abbas Y, Pitteloud N, Crowley WF Jr, Seminara SB. Neuroendocrine, gonadal, placental, and obstetric phenotypes in patients with IHH and mutations in the G-protein coupled receptor, GPR54. *Mol Cell Endocrinol*. 2006; 254-255: 70-7.
64. Topaloglu AK, Tello JA, Kotan LD, Ozbek MN, Yilmaz MB, Erdogan S, Gurbuz F. Inactivating KISS1 mutation and hypogonadotropic hypogonadism. *N Engl J Med*. 2012; 366: 629-635.
65. Topaloglu AK, Reimann F, Guclu M, Yalin AS, Kotani LD, Porter KM, 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.
66. Kaur KK, Allahbadia G, Singh M. Kisspeptins in human reproduction-future therapeutic potential. *J Assist Reprod Genet*. 2012; 29: 999-1011.
67. 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.
68. Layman LC, Cohen DP, Jin M, Xie J, Li Z, Reindollar RH, Bolbolan S. Mutations in gonadotropin-releasing hormone receptor gene cause hypogonadotropic hypogonadism. *Nat Genet*. 1998; 18: 14-15.
69. Bouligand J, Ghervan C, Tello JA, Brailly-Tabard S, Salenave S, Chanson P, Lombès M. Isolated familial hypogonadotropic hypogonadism and a GNRH1 mutation. *N Engl J Med*. 2009; 360: 2742-2748.
70. Chan YM, de Guillebon A, Lang-Muritano M, Plummer L, Cerrato F, Tsiaras S, Gaspert A. GNRH1 mutations in patients with idiopathic hypogonadotropic hypogonadism. *Proc Natl Acad Sci U S A*. 2009; 106: 11703-11708.
71. Tello JA, Newton CL, Bouligand J, Guiochon-Mantel A, Millar RP, Young J. Congenital hypogonadotropic hypogonadism due to GnRH receptor mutations in three brothers reveal sires affecting conformation and coupling. *PLoS One*. 2012; 7: e38456.
72. Maione L, Albarel F, Bouchard P, Gallant M, Flanagan CA, Bobe R, et al. R31C GNRH 1 mutation and congenital hypogonadotropic hypogonadism. *PLoS One*. 2013; 25: 8: e69616.
73. Lewkowicz-Shupntoff HM, Hughes VA, Plummer L, Au MG, Doty RL, Seminara SB, et al. Olfactory Phenotypic spectrums in idiopathic hypogonadotropic hypogonadism: Pathophysiological and genetic implications. *J Clin Endocrinol Metab*. 2012; 97: E136-E144.
74. Moya-Plana A, Villanueva C, Laccourreye O, Bonfils P, de Roux N. PROKR2 and PROK2 mutations cause isolated congenital anosmia without gonadotropic deficiency. *Eur J Endocrinol*. 2012; 168: 31-37.
75. Chung WC, Moyle SS, Tsai PS. Fibroblast growth factor 8 signaling through fibroblast growth factor receptor 1 is required for the emergence of gonadotropin-releasing hormone neurons. *Endocrinology*. 2008; 149: 4997-5003.
76. Ladher RK, Wright TJ, Moon AM, Mansour SL, Schoenwolf GC. FGF8 initiates inner ear induction in chick and mouse. *Genes Dev*. 2005; 19: 603-613.
77. Martinez-Morales JR, Del Bene F, Nica G, Hammerschmidt M, Bovolenta P, Willbrodt J. Differentiation of the vertebrate retina is coordinated by an FGF signaling center. *Dev Cell*. 2005; 8: 565-574.
78. Perantoni AO, Timofeeva O, Naillat F, Richman C, Pajni-Underwood S, Wilson C, et al. Inactivation of FGF8 in early mesoderm reveals an essential role in kidney development. *Development*. 2005; 132: 3859-3871.
79. Lewandoski M, Sun X, Martin GR. Fgf8 signalling from the AER is essential for normal limb development. *Nat Genet*. 2000; 26: 460-463.
80. Miraoui H, Dwyer A, Pitteloud N. Role of fibroblast growth factor (FGF) signaling in the neuroendocrine control of human reproduction. *Mol Cell Endocrinol*. 2011; 346: 37-43.
81. Tornberg J, Sykiotis GP, Keefe K, Plummer L, Hoang X, Hall JE, et al. Heparan sulfate 6-O-sulfotransferase, a gene involved in extracellular sugar modifications, is mutated in patients with idiopathic hypogonadotropic hypogonadism. *Proc Natl Acad Sci U S A*. 2011; 108: 11524-11529.
82. Miraoui H, Dwyer AA, Sykiotis GP, Plummer L, Chung W, Feng B, Beenken A, 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.
83. Costa-Barbosa FA, Balasubramaniam R, Keefe KW, Shaw ND, Al-Tassan N, Plummer L, et al. Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. *J Clin Endocrinol Metab*. 2013; 98: E943-953.
84. Dodé C, Hardelin JP. Clinical genetics of Kallmann syndrome. *Ann Endocrinol (Paris)*. 2010; 71: 149-157.
85. Fideleff HL, Boquete HR, Suárez MG, Azaretsky M. Prolactinoma in

- children and adolescents. *Horm Res.* 2009; 72: 197-205.
86. Jagannathan J, Dumont AS, Jane JA Jr. Diagnosis and management of pediatric sellar lesions. *Front Horm Res.* 2006; 34: 83-104.
87. Young J. [Endocrine consequences of hemochromatosis]. *Presse Med.* 2007; 36: 1319-1325.
88. Özgör B, Selimoğlu MA. Coeliac disease and reproductive disorders. *Scand J Gastroenterol.* 2010; 45: 395-402.
89. Farooqi IS, Wangenstein T, Collins S, Kimber W, Matarese G, Keogh JM, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N Engl J Med.* 2007; 356: 237-247.
90. Lin L, Gu WX, Ozisik G, To WS, Owen CJ, Jameson JL, et al. Analysis of DAX1 (NR0B1) and steroidogenic factor-1 (NR5A1) in children and adults with primary adrenal failure: ten years' experience. *J Clin Endocrinol Metab.* 2006; 91: 3048-3054.
91. Netchine I, Sobrier ML, Krude H, Schnabel D, Maghnie M, Marcos E, et al. Mutations in LHX3 result in a new syndrome revealed by combined pituitary hormone deficiency. *Nat Genet.* 2000; 25: 182-186.
92. Pinto G, Abadie V, Mesnage R, Blustajn J, Cabrol S, Amiel J, et al. CHARGE syndrome includes hypogonadotropic hypogonadism and abnormal olfactory bulb development. *J Clin Endocrinol Metab.* 2005; 90: 5621-5626.
93. Rottembourg D, Linglart A, Adamsbaum C, Lahlou N, Teinturier C, Bougnères P, et al. Gonadotrophic status in adolescents with pituitary stalk interruption syndrome. *Clin Endocrinol (Oxf).* 2008; 69: 105-111.
94. Reynaud R, Gueydan M, Saveanu A, Vallette-Kasic S, Enjalbert A, Brue T, et al. Genetic screening of combined pituitary hormone deficiency: experience in 195 patients. *J Clin Endocrinol Metab.* 2006; 91: 3329-3336.
95. Sedlmeyer IL, Palmert MR. Delayed puberty: analysis of a large case series from an academic center. *J Clin Endocrinol Metab.* 2002; 87: 1613-1620.
96. Coutant R, Biette-Demeneix E, Bouvattier C, Bouhours-Nouet N, Gatelais F, Dufresne S, et al. Baseline inhibin B and anti-Müllerian hormone measurements for diagnosis of hypogonadotropic hypogonadism (HH) in boys with delayed puberty. *J Clin Endocrinol Metab.* 2010; 95: 5225-5232.
97. Pitteloud N, Hayes FJ, Boeole PA, DeCruz S, Seminara SB, McLaughlin DT, et al. The role of prior pubertal development, biochemical markers of testicular maturation and genetics in elucidating the phenotypic heterogeneity of idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab.* 2002; 87: 152-160.
98. De Luca F, Argente J, Cavallo L, Ceowne E, Delemarre-Vande Waal HA, De Sanctis C, et al. Management of puberty in constitutional delay of growth and puberty. International workshop on management of puberty for optimum auxological results. *J Pediatr.* 2001; 14: 953-957.
99. Young J. Approach to the male patient with congenital hypogonadotropic hypogonadism. *J Clin Endocrinol Metab.* 2012; 97: 707-718.
100. Chew S, Balasubramanian R, Chan WM, Kang PB, Andrews C, et al. A novel syndrome caused by the E410K amino acid substitution in the neuronal  $\beta$ -tubulin isotype 3. *Brain.* 2013; 136: 522-535.
101. Teixeira L, Guimiot F, Dodé C, Fallet-Bianco C, Millar RP, Delezoide AL, et al. Defective migration of neuroendocrine GnRH cells in human arrhinencephalic conditions. *J Clin Invest.* 2010; 120: 3668-3672.
102. Raivio T, Avbeli M, McCabe MJ, Romero DJ, Swyer AA, Tommiska J, et al. Genetic overlap in Kallmann syndrome, combined pituitary hormone deficiency, and septo optic dysplasia. *J Clin Endocrinol Metab.* 2012; 97: E694-699.
103. McCabe MJ, Gaston-Massuet C, Gregory LC, Alatzoglou KS, Tziaferi V, Sbai O, et al. Variations in PROKR2, but not PROK2, are associated with hypopituitarism and septo-optic dysplasia. *J Clin Endocrinol Metab.* 2013; 98: E547-557.
104. McCabe MJ, Alatzoglou KS, Dattani MT. Septo-optic dysplasia and other midline defects: the role of transcription factors: HESX1 and beyond. *Best Pract Res Clin Endocrinol Metab.* 2011; 25: 115-124.
105. Cohen MM Jr. Holoprosencephaly: clinical, anatomic, and molecular dimensions. *Birth Defects Res A Clin Mol Teratol.* 2006; 76: 658-673.
106. Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. Holoprosencephaly. *Orphanet J Rare Dis.* 2007; 2: 8.
107. Vaaralahti K, Raivio T, Koivu R, Valanne L, Laitinen EM, Tommiska J. Genetic Overlap between Holoprosencephaly and Kallmann Syndrome. *Mol Syndromol.* 2012; 3: 1-5.
108. Trabados S, Maione L, Salenave S, Baron S, Gallarnd F, Bry-Gauillard H, et al. Estradiol levels in men with congenital hypogonadotropic hypogonadism and the effects of different modalities OF different treatment. *Fert Steril.* 2011; 95: 2324-2329.
109. Bouvattier C, Tauber M, Jouret B, Chaussain JL, Rochiccioli P. Gonadotropin treatment of hypogonadotropic hypogonadal adolescents. *J Pediatr Endocrinol Metab.* 1999; 12 Suppl 1: 339-344.
110. Quinton R, Cheow HK, Tymms DJ, Bouloux PM, Wu FC, Jacobs HS, et al. Kallmann's syndrome: is it always for life? *Clin Endocrinol (Oxf).* 1999; 50: 481-485.
111. Raivio T, Falardeau J, Dwyer A, Quinton R, Hayes FJ, Hughes VA, et al. Reversal of idiopathic hypogonadotropic hypogonadism. *N Engl J Med.* 2007; 357: 863-873.
112. Hoffman AR, Crowley WF Jr. Induction of puberty in men by long-term pulsatile administration of low-dose gonadotropin-releasing hormone. *N Engl J Med.* 1982; 307: 1237-1241.
113. Pitteloud N, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley WF Jr, et al. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab.* 2002; 87: 4128-4136.
114. Sykiotis GP, Hoang XH, Avberg M, Hayes FJ, Thambundit A, Dwyer A, et al. Congenital idiopathic hypogonadotropic hypogonadism: Evidence and defects of the Hypothalamus, pituitary, and testis. *J Clin Endocrinol Metab.* 2010; 95: 3019-3027.
115. Sinisi AA, Asci R, Bellastella G, Maione L, Esposito D, Elefante A, et al. Homozygous mutation in the prokineticin-receptor2 gene (Val274Asp) presenting as reversible Kallmann syndrome and persistent oligozoospermia: case report. *Hum Reprod.* 2008; 23: 2380-2384.
116. Dwyer AA, Sykiotis GP, Hayes FJ, Boepple PA, Lee H, Loughlin KR, et al. Trial of recombinant Follicle-Stimulating hormone pretreatment in patients with congenital hypogonadotropic hypogonadism. *J Clin Endocrinol Metab.* 2013; 98: E1790-1795.
117. Piteloud N, Thambundit A, Dwyer AA, Falardeau JL, Plummer L, Caronia LM, et al. Role of seminiferous tubular development in determining the FSH vs LH Responsiveness to GnRH in early sexual maturation. *Neuroendocrinology.* 2009; 90: 260-268.
118. Bouvattier C, Maione L, Bouligand J, Dodé C, Guiochon-Mantel A, Young J. Neonatal gonadotropin therapy in male congenital hypogonadotropic hypogonadism. *Nat Rev Endocrinol.* 2011; 8: 172-182.
119. Raivio T, Wikström AM, Dunkel L. Treatment of gonadotropin-deficient boys with recombinant human FSH: long-term observation

- and outcome. *Eur J Endocrinol.* 2007; 156: 105-111.
120. Main KM, Schmidt IM, Toppari J, Skakkebaek NE. Early postnatal treatment of hypogonadotropic hypogonadism with recombinant human FSH and LH. *Eur J Endocrinol.* 2002; 146: 75-79.
  121. Main KM, Schmidt IM, Skakkebaek NE. A possible role for reproductive hormones in newborn boys: progressive hypogonadism without the postnatal testosterone peak. *J Clin Endocrinol Metab.* 2000; 85: 4905-4907.
  122. Bouoneres P, Francois M, Pantalone L, Rodrique D, Bouvattier C, Demesteere E, et al. Effects of an early postnatal treatment of hypogonadotropic hypogonadism with a continuous subcutaneous infusion of recombinant follicle stimulating hormone and luteinizing hormone. *J Clin Endocrinol Metab.* 2008; 93: 2202-2205.
  123. Gennari L, Nuti R, Bilezikian JP. Aromatase activity and bone homeostasis in men. *J Clin Endocrinol Metab.* 2004; 89: 5898-5907.
  124. Khosla S, Amin S, Orwoll E. Osteoporosis in men. *Endocr Rev.* 2008; 29: 441-464.
  125. Khosla S. Update in male osteoporosis. *J Clin Endocrinol Metab.* 2010; 95: 3-10.
  126. Rochira V, Zirilli L, Maffei L, Premrou V, Aranda C, Baldi M, et al. Tall stature without growth hormone: four male patients with aromatase deficiency. *J Clin Endocrinol Metab.* 2010; 95: 1626-1633.
  127. Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, et al. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypothalamic effects: evidence from tandem study of normal and gonadotropin-releasing hormone deficient men. *J Clin Endocrinol Metab.* 2008; 93: 784-791.
  128. George JT, Veldhuis JD, Roseweir AK, Newton CL, Faccenda E, Millar RP, et al. Kisspeptin-10 is a potent stimulator of LH and increases pulse frequency in men. *J Clin Endocrinol Metab.* 2011; 96: E1228-1236.
  129. Jayasena CN, Comninou AN, De Silva A, Abbara A, Veldhuis JD, Nijher GM, et al. Effects of neurokinin B administration on reproductive hormone secretion in healthy men and women. *J Clin Endocrinol Metab.* 2014; 99: E19-27.
  130. Millar RP, Newton CL. Current and future applications of GnRH, kisspeptin and neurokinin B analogues. *Nat Rev Endocrinol.* 2013; 9: 451-466.
  131. Martin C, Balasubramanian R, Dwyer AA, Au MG, Sidis Y, Kaiser UB, et al. 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.
  132. Dodé C, Rondard P. PROKR2/PROKR2 Signaling and Kallmann Syndrome. *Front Endocrinol (Lausanne).* 2013; 4: 19.
  133. Sykiotis GP, Plummer L, Hughes VA, Au M, Durrani S, Nayak-Young S, et al. Oligogenic basis of isolated gonadotropin-releasing hormone deficiency. *Proc Natl Acad Sci U S A.* 2010; 107: 15140-15144.
  134. Sarfati J, Fouveaut C, Leroy C, Jeanpierre M, Hardelin JP, Dodé C. Greater prevalence of PROKR2 mutations in Kallmann syndrome patients from the Maghreb than in European patients. *Eur J Endocrinol.* 2013; 169: 805-809.
  135. Pingault V, Bodereau V, Baral V, Marcos S, Watanabe Y, Chaoui A, et al. Loss-of-function mutations in SOX10 cause Kallmann syndrome with deafness. *Am J Hum Genet.* 2013; 92: 707-724.

#### Cite this article

Kaur KK, Allahbadia GN, Singh M (2014) Male Hypogonadism-A review of Secondary Hypogonadism with Special Emphasis on Hypogonadotropic Hypogonadism. *J Endocrinol Diabetes Obes* 2(2): 1023.