

R E V I E W

Syndromic infertility

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Summary. Infertility due to genetic mutations that cause other defects, besides infertility, is defined as syndromic. Here we describe three of these disorders for which we perform genetic tests. 1) Hypopituitarism is an endocrine syndrome characterized by reduced or absent secretion of one or more anterior pituitary hormones with consequent dysfunction of the corresponding peripheral glands. Deficiencies in all the hormones is defined as pan-hypopituitarism, lack of two or more hormones is called partial hypopituitarism, whereas absence of a single hormone is defined as selective hypopituitarism. Pan-hypopituitarism is the rarest condition, whereas the other two are more frequent. Several forms exist: congenital, acquired, organic and functional. 2) The correct functioning of the hypothalamic-pituitary-gonadal axis is fundamental for sexual differentiation and development during fetal life and puberty and for normal gonad function. Alteration of the hypothalamic-pituitary system can determine a condition called hypogonadotropic hypogonadism, characterized by normal/low serum levels of the hormones FSH and LH. 3) Primary ciliary dyskinesia is frequently associated with infertility in males because it impairs sperm motility (asthenozoospermia). Primary ciliary dyskinesia is a group of genetically and phenotypically heterogeneous disorders that show morphostructural alterations of the cilia. Adult women with primary ciliary dyskinesia can be subfertile and have an increased probability of extra-uterine pregnancies. This is due to delayed transport of the oocyte through the uterine tubes. (www.actabiomedica.it)

Key words: hypopituitarism, primary ciliary dyskinesia, hypogonadotropic hypogonadism

Genetics of hypopituitarism

Hypopituitarism is an endocrine syndrome characterized by reduced or absent secretion of one or more anterior pituitary hormones with consequent dysfunction of the corresponding peripheral glands. Deficiencies in all the hormones is defined as pan-hypopituitarism, the lack of two or more hormones is called partial hypopituitarism, whereas the absence of a single hormone is defined as selective hypopituitarism. Pan-hypopituitarism is the rarest of the three. Several forms exist: congenital, acquired, organic and functional (1).

Combined pituitary hormone deficiency (CPHD) is characterized by impaired production of several pituitary hormones, such as growth hormone, thyroid-stimulating hormone, prolactin, adrenocorticotrophic hormone and gonadotropic hormone, and is caused by mutations in transcription factors involved in pituitary ontogenesis. Congenital hypopituitarism has a low incidence with respect to secondary hypopituitarism due to pituitary adenomas, trans-sphenoidal surgery, or radiotherapy. The incidence of congenital hypopituitarism in the population is 1:3000-4000 (2). Genetic mutations associated with congenital hypopituitarism

mainly affect eight genes encoding transcription factors: *PRO1* (thyroid-stimulating, follicle-stimulating, growth, luteinizing and adrenocorticotrophic hormones and prolactin are low or absent), *POU1F1* (growth and thyroid-stimulating hormones and prolactin are low or absent), *HESX1* (thyrotropin, follicle-stimulating, growth, luteinizing and adrenocorticotrophic hormones are low or absent), *LHX3* (thyroid-stimulating, follicle-stimulating, growth, luteinizing and adrenocorticotrophic hormones and prolactin are low or absent), and *LHX4* (thyroid-stimulating, growth, luteinizing, follicle-stimulating and adrenocorticotrophic hormones are low or absent) (2).

The clinical phenotype depends on the affected hormone, the severity of pituitary impairment and age of onset. In childhood, congenital idiopathic forms are the most frequent, and are associated with developmental retardation, delay of puberty and absence of adrenarche. In adulthood, acquired forms are more frequent (3).

Loss-of-function mutations in *PRO1* are the most common cause of sporadic and familial cases of CPHD. This gene is mutated in 11% of cases. The mutation rate, however, varies considerably in relation to geographical area. The prevalence of the mutation is less than 1% in western European, American, Australian and Japanese populations, and higher in Russian and eastern European populations. Patients with mutations in *PRO1* show growth hormone (GH), prolactin (PL), and thyroid-stimulating hormone (TSH) deficiency and variable defects in the secretion of luteinizing (LH), follicle-stimulating (FSH) and adrenocorticotrophic (ACTH) hormones (4).

Mutations in *POU1F1* are the second most frequent cause of pituitary hormone deficiency. The phenotype associated with *POU1F1* mutations can be inherited by dominant or recessive transmission. The major mutation is the heterozygous p.Arg271Trp, found in ~30% of patients with *POU1F1* mutations. In sporadic cases, mutations in this gene are only found in 1.6% of cases. *POU1F1* is a member of the POU family of transcription factors and is expressed in the anterior lobe of the pituitary gland. The phenotype associated with *POU1F1* mutations has severely low levels of GH and PRL, variable levels of TSH, short stature, facial dysmorphism, and dysphagia during infancy (5).

Another gene with occasional mutations is *HESX1*. Mutations in this gene occur in 0.45% of sporadic cases. Single heterozygous mutations causes a less severe disorder with incomplete penetrance, whereas homozygous mutations cause a severe and completely penetrant disorder (6).

Biallelic mutations in *LHX3* cause deficiencies in GH, PRL, TSH, LH, FSH and ACTH. Mutations in *LHX3* are found in 0.3% of sporadic cases and 11.1% of familial cases (7).

The pathological phenotype associated with heterozygous mutations in *LHX4* is inherited as an autosomal dominant trait with variable penetrance. Patients with CPHD have variable reductions in serum levels of GH, TSH, ACTH and gonadotropin. Cranial magnetic resonance imaging shows pituitary gland hypoplasia in most cases. However, there is a wide phenotypic variability within and between families.

Finally, mutations in the *GLI2* gene have been reported in patients with combined pituitary hormone deficiency and ectopic posterior pituitary lobe. For instance, several individuals with truncating mutations in *GLI2* show pituitary anomalies, polydactyly and subtly dysmorphic facial features. The inheritance pattern is dominant with incomplete penetrance and variable phenotype. There are mutations in *GLI2* in 1.5% of CPHD cases.

The genes associated with combined pituitary hormone deficiency are: *PRO1*, *SOX3*, *POU1F1*, *HESX1*, *LHX4*, *LHX3*, *OTX2* and *GLI2* (Table 1). Pathogenic variants may be missense, nonsense, splicing or small indels. MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the genes listed in the table. Our NGS test has an analytical sensitivity (proportion of true positives) and analytical specificity (proportion of true negatives) of $\geq 99\%$ (coverage depth $\geq 10x$).

Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a genetically and phenotypically heterogeneous group of inherited disorders due to morphological and structural alterations of the cilia. It is characterized by chronic bronchorrhea with bronchiectasis and chronic sinusitis and

Table 1. Genes associated with combined pituitary hormone deficiency

Gene	Inheritance	OMIM gene	OMIM phenotype	OMIM phenotype ID	Gene function
<i>PROP1</i>	AR	601538	CPHD2	262600	Paired-like homeodomain transcription factor required for pituitary development
<i>POU1F1</i>	AD, AR	173110	CPHD1	613038	Regulation of expression of genes involved in pituitary development and hormone expression
<i>HESX1</i>	AD, AR	601802	CPHD5	182230	Transcriptional repressor expressed in developing forebrain and pituitary gland
<i>LHX3</i>	AR	600577	CPHD3	221750	LIM-containing domain transcription factor required for pituitary development and motor neuron specification
<i>LHX4</i>	AD	602146	CPHD4	262700	LIM-containing domain transcription factor required for pituitary development
<i>SOX3</i>	XLR	313430	PHPX	312000	Transcription factor required for pituitary function and development of CNS midline structures
<i>OTX2</i>	AD	600037	CPHD6	613986	Homeodomain-containing transcription factor required for brain, craniofacial and sensory organ development
<i>GLI2</i>	AD	165230	CJS	615849	Zinc finger transcription factor required for embryogenesis

CJS = Culler-Jones syndrome; CNS = central nervous system; CPHD = combined pituitary hormone deficiency; PHPX = panhypopituitarism, X-linked; AR = autosomal recessive; AD = autosomal dominant; XLR = X-linked recessive.

is the second most common congenital disease of the respiratory system after cystic fibrosis. The prevalence is estimated at around 1:20000 (8).

Ultrastructural defects of the 9+2 axoneme of cilia and flagella may be: partial or complete loss of internal dynein arms, central microtubule anomalies, and radial spoke defects. These defects cause recurrent sinusitis, bronchiectasis due to immotile cilia in the upper and lower airways, and infertility due to altered cilia in the oviduct as well as altered sperm flagella (9).

Fifty percent of patients show *situs inversus*. The association of *situs inversus*, sinusitis and bronchiectasis is the classical triad known as Kartagener syndrome. It is noteworthy that this syndrome is a subgroup of primary ciliary dyskinesia (10). In fact, we know that *situs inversus* is caused by motility failure of nodal cilia that allow lateralization of organs during early embryogenesis (11).

In some subjects, primary ciliary dyskinesia is associated with other disorders like polycystic kidney, retinitis pigmentosa, Barder-Biedl syndrome and Usher syndrome, the pathogenesis of which is linked to structural defects of the primary cilia (12). Respiratory disorders can appear at birth (neonatal respiratory distress), during infancy and rarely in adulthood, and may include chronic infections of the upper and lower respiratory tract. Bronchiectasis is not present at birth but may be a secondary effect of a chronic lung disease (8).

Severity and progression of the disease are variable among patients and depend on what ciliary substructures are altered. About 50% of male patients with PCD are infertile due to lack of sperm motility (9,13). Adult women with PCD may be subfertile and at risk of extra-uterine pregnancies due to delayed oocyte transport through the uterine tubes (10). The most fre-

quent ultrastructural defects of PCD in spermatozoa are (14,15):

- reduction and/or absence of the outer dynein arm: ~38.5% of all PCD cases;
- reduction and/or absence of both dynein arms (outer and inner): ~10.5% of all PCD cases;
- microtubule (axoneme) disorganization due to absence of the inner dynein arm and defects in the central apparatus: ~14% of all PCD cases;
- absence or interruption of central apparatus (i.e. the pair of central microtubules and/or radial spokes): ~7% of all PCD cases;
- reduction and/or absence of the inner dynein arm (rare);
- oligocilia with or without normal ultrastructure (rare).

Most cases of primary ciliary dyskinesia or Kartagener syndrome have autosomal recessive inheritance, although some cases with X-linked recessive inheritance have been reported. Currently, 39 genes are known to be involved in PCD (Table 2). The most frequent mutations are in: *DNAH5*, *DNAH11*, *CCDC39*, *DNAI1*, *CCDC40*, *CCDC103*, *SPAG1*, *ZMYND10*, *ARMC4*, *CCDC151*, *DNAI2*, *RSPH1*, *CCDC114*, *RSPH4A*, *DNAAF1*, *DNAAF2* and *LRR6*. Table 2 shows the frequencies of biallelic pathogenic variants in affected unrelated subjects. Pathogenic variants may be missense, nonsense, splicing and small indels. MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the genes listed in Table 2.

Hypogonadotropic hypogonadism

Correct functioning of the hypothalamo-pituitary-gonadal axis is fundamental for differentiation and sexual development during the fetal period and puberty (16). Hypogonadotropic hypogonadism (HH) is caused by alterations in this axis. Such alterations cause low serum levels of sex hormones associated with normal or low levels of FSH and LH. The prevalence of HH is 1/8000 newborns (17).

Clinically, patients with HH show little or no sexual development, primary amenorrhea (women)

and oligozoospermia (men). Other possible features may be: cleft palate, tooth agenesis, visual impairment, intellectual disability (and other neurological abnormalities), and renal agenesis (18).

Hypogonadotropic hypogonadism may be considered isolated when only the gonads are impaired. There are two forms of the isolated HH: Kallmann syndrome (HH associated with anosmia) is caused by defects in embryonic migration of neurons secreting gonadotropin releasing hormone (GnRH); normosmic HH, in which HH is the only symptom and is due to altered signaling, regulation and secretion of GnRH (19).

The HH may have autosomal dominant, autosomal recessive or X-linked inheritance.

The first gene variation discovered in cases of HH was in *ANOS1* (or *KAL1*). *ANOS1* encodes an adhesion molecule (anosmin), probably involved in migration of olfactory and GnRH-secreting neurons toward the hypothalamus during embryo development. Hypogonadotropic hypogonadism associated with *ANOS1* mutations has X-linked recessive inheritance, so only males are affected. Besides HH and anosmia, patients with mutations in *ANOS1* show renal agenesis and neurological disorders such as intellectual disability, sensorineural deafness and synkinesis (20).

GNRHR was the first gene found to have variations in cases of normosmic HH, a disorder with autosomal recessive inheritance. The gene encodes the GnRH receptor, a protein expressed in the pituitary gland. The associated phenotype is highly variable, ranging from very severe (total absence of puberty) to partial or delayed pubertal development (21).

Since involvement of *ANOS1* and *GNRHR* in hypogonadotropic hypogonadism was discovered, 28 other associated-genes have emerged (Table 3). More than 2% of cases have mutations in *ANOS1*, *CHD7*, *FGFR1*, *GNRHR*, *IL17RD*, *PROKR2*, *SOX10* or *TACR3*. The other genes have only been found in a few families (18).

Pathogenic variants may be missense, nonsense, splicing or small indels. MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes (Table 3).

Table 2. Genes associated with primary ciliary dyskinesia

Gene	Inheritance	OMIM gene	OMIM phenotype	OMIM or HGMD phenotype ID	Frequency of biallelic variants in affected unrelated subjects (22)
<i>DNAI1</i>	AR	604366	CILD1	244400	2%-10%
<i>DNAAF3</i>	AR	614566	CILD2	606763	<1%
<i>DNAH5</i>	AR	603335	CILD3	608644	15%-29%
<i>HYDIN</i>	AR	610812	CILD5	608647	<1%
<i>NME8</i>	AR	607421	CILD6	610852	<1%
<i>DNAH11</i>	AR	603339	CILD7	611884	6%-9%
<i>DNAI2</i>	AR	605483	CILD9	612444	2%
<i>DNAAF2</i>	AR	612517	CILD10	612518	<1%-2%
<i>RSPH4A</i>	AR	612647	CILD11	612649	1%-2%
<i>RSPH9</i>	AR	612648	CILD12	612650	<1%
<i>DNAAF1</i>	AR	613190	CILD13	613193	1%-2%
<i>CCDC39</i>	AR	613798	CILD14	613807	4%-9%
<i>CCDC40</i>	AR	613799	CILD15	613808	3%-4%
<i>DNAL1</i>	AR	610062	CILD16	614017	<1%
<i>CCDC103</i>	AR	614677	CILD17	614679	<4%
<i>DNAAF5</i>	AR	614864	CILD18	614874	<1%
<i>LRRC6</i>	AR	614930	CILD19	614935	1%
<i>CCDC114</i>	AR	615038	CILD20	615067	<2%
<i>DRC1</i>	AR	615288	CILD21	615294	<1%
<i>ZMYND10</i>	AR	607070	CILD22	615444	2%-4%
<i>ARMC4</i>	AR	615408	CILD23	615451	<3%
<i>RSPH1</i>	AR	609314	CILD24	615481	2%
<i>C21ORF59</i>	AR	615494	CILD26	615500	<1%
<i>CCDC65</i>	AR	611088	CILD27	615504	<1%
<i>SPAG1</i>	AR	603395	CILD28	615505	<4%
<i>CCNO</i>	AR	607752	CILD29	615872	<1%
<i>CCDC151</i>	AR	615956	CILD30	616037	<3%
<i>CENPF</i>	AR	600236	STROMS	243605	<1%
<i>RSPH3</i>	AR	615876	CILD32	616481	<1%
<i>GAS8</i>	AR	605178	CILD33	616726	/
<i>DNAJB13</i>	AR	610263	CILD34	617091	/
<i>TTC25</i>	AR	617095	CILD35	617092	/
<i>PIH1D3</i>	XLR	300933	CILD36	300991	9.5%
<i>DNAH1</i>	AR	603332	CILD37	617577	<1%
<i>STK36</i>	AR	607652	CILD	1147369503	/

CILD = ciliary dyskinesia, primary; STROMS = Stromme syndrome; AR = autosomal recessive; XLR = X-linked recessive; HGMD = Human Gene Mutation Database (<https://portal.biobase-international.com/hgmd/pro/>)

Table 3. Genes associated with hypogonadotropic hypogonadism

Gene	Inheritance	OMIM gene	OMIM phenotype	OMIM or HGMD phenotype ID	Gene function
<i>KISS1</i>	AR	603286	HH13	614842	Stimulation of GnRH-induced gonadotropin secretion, activation of GnRH neurons
<i>HS6ST1</i>	AD	604846	HH15	614880	Neuron development, neuron branching
<i>IL17RD</i>	AD, AR	606807	HH18	615267	Fate-specification of GnRH-secreting neurons
<i>PROK2</i>	AD	607002	HH4	610628	Chemoattractant for neuronal precursor cells in olfactory bulb
<i>GNRHR</i>	AR	138850	HH7	146110	Receptor for GnRH. Stimulation of LH and FSH secretion
<i>TACR3</i>	AR	162332	HH11	614840	Receptor for neurokinin B. Expressed in hippocampus, hypothalamus, substantia nigra
<i>SPRY4</i>	AD	607984	HH17	615266	Regulation of neurite outgrowth in hippocampal neurons
<i>SEMA3A</i>	AD	603961	HH16	614897	Inhibition of axonal outgrowth, stimulation of apical dendrite growth
<i>FEZF1</i>	AR	613301	HH22	616030	Embryonic migration of GnRH-releasing neurons into brain
<i>FGF17</i>	AD	603725	HH20	615270	Induction and patterning of embryonic brain
<i>GNRH1</i>	AR	152760	HH12	614841	Stimulation of LH and FSH secretion
<i>FGFR1</i>	AD	136350	HH2	147950	Mesoderm patterning, correct axial organization during embryo development, skeletogenesis, development of GnRH neuronal system
<i>CHD7</i>	AD	608892	HH5	612370	Formation of neural crest
<i>NSMF</i>	AD	608137	HH9	614838	Guidance of olfactory axon projections, migration of LHRH neurons
<i>FGF8</i>	AD	600483	HH6	612702	Regulation of embryo development, cell proliferation, differentiation, migration. Brain, eye, ear, limb, GnRH neuronal system, hippocampal neuron development
<i>WDR11</i>	AD	606417	HH14	614858	Regulation of GnRH production
<i>FSHB</i>	AR	136530	HH24	229070	Beta subunit of FSH. Induction of egg and sperm production
<i>TAC3</i>	AR	162330	HH10	614839	Central regulator of gonad function
<i>DUSP6</i>	AD	602748	HH19	615269	Expression regulated by GnRH
<i>KISS1R</i>	AR	604161	HH8	614837	Neuroendocrine control of gonadotropin axis
<i>LHB</i>	AR	152780	HH23	228300	Promotion of spermatogenesis and ovulation by stimulating gonads to synthesize steroids

(continued on the next page)

Table 3 (continued). Genes associated with hypogonadotropic hypogonadism

Gene	Inheritance	OMIM gene	OMIM phenotype	OMIM or HGMD phenotype ID	Gene function
<i>PROKR2</i>	AD	607123	HH3	244200	Induction of tangential and radial migration of olfactory bulb interneurons
<i>FLRT3</i>	AD	604808	HH21	615271	Spatial organization of brain neurons.
<i>ANOS1</i>	XLR	300836	HH1 (KS)	308700	Neural cell adhesion, axonal migration, patterning of mitral and tufted cell collaterals to olfactory cortex
<i>SOX10</i>	AD	602229	WS2E	611584	Development of neural crest, peripheral nervous system, glia
<i>AXL</i>	AD	109135	HH	1734393901	GnRH neuron survival and migration
<i>CCDC141</i>	AR	616031	KS	817012261	Neural radial migration
<i>SEMA3E</i>	AD	608166	KS	817012261	Ensuring synapse formation specificity
<i>SRA1</i>	AR	603819	HH	1734393901	Mediation of transcriptional co-activation of steroid receptors

GnRH = gonadotropin-releasing hormone; HH = hypogonadotropic hypogonadism; KS = Kallmann syndrome; WS = Waardenburg syndrome; AD = autosomal dominant; AR = autosomal recessive; XLR = X-linked recessive; HGMD = Human Gene Mutation Database (<https://portal.biobase-international.com/hgmd/pro/>)

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with infertility. When a suspect of syndromic infertility is present we perform the analysis of all the genes present in this short article. In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of $\geq 99\%$ (coverage depth $\geq 10x$).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

- Chung TT, Koch CA, Monson JP. Hypopituitarism. Endotext. South Dartmouth (MA): MDText.com, Inc., 2018
- Pfäffle R, Klammt J. Pituitary transcription factors in the aetiology of combined pituitary hormone deficiency. Best Pract Res Clin Endocrinol Metab 2011; 25: 43-60.
- Brämswig J, Dübbers A. Disorders of pubertal development. Dtsch Arztebl Int 2009; 106: 295-303.
- Turton JP, Mehta A, Raza J, et al. Mutations within the transcription factor PROP1 are rare in a cohort of patients with sporadic combined pituitary hormone deficiency (CPHD). Clin Endocrinol (Oxf) 2005; 63: 10-8.
- Turton JP, Reynaud R, Mehta A, et al. Novel mutations within the POU1F1 gene associated with variable combined pituitary hormone deficiency. J Clin Endocrinol Metab 2005; 90: 4762-70.
- Thomas PQ, Dattani MT, Brickman JM, et al. Heterozygous HESX1 mutations associated with isolated congenital pituitary hypoplasia and septo-optic dysplasia. Hum Mol Genet 2001; 10: 39-45.
- Netchine I, Sobrier ML, Krude H, et al. Mutations in LHX3 result in a new syndrome revealed by combined pituitary hormone deficiency. Nat Genet 2000; 25: 182-6.
- Mirra V, Werner C, Santamaria F. Primary ciliary dyskinesia: an update on clinical aspects, genetics, diagnosis, and future treatment strategies. Front Pediatr 2017; 5: 135.
- Imtiaz F, Allam R, Ramzan K, Al-Sayed M. Variation in DNAH1 may contribute to primary ciliary dyskinesia. BMC Med Genet 2015; 16: 14.
- Leigh MW, Pittman JE, Carson JL, et al. Clinical and genetic aspects of primary ciliary dyskinesia/Kartagener syndrome. Genet Med 2009; 11: 473-87.
- Nonaka S, Tanaka Y, Okada Y, et al. Randomization of left-right asymmetry due to loss of nodal cilia generating left-

- ward flow of extraembryonic fluid in mice lacking KIF3B motor protein. *Cell* 1998; 95: 829-37.
12. Afzelius BA. Cilia-related diseases. *J Pathol* 2004; 204: 470-7.
 13. Ben Khelifa M, Coutton C, Zouari R, et al. Mutations in DNAH1, which encodes an inner arm heavy chain dynein, lead to male infertility from multiple morphological abnormalities of the sperm flagella. *Am J Hum Genet* 2014; 94: 95-104.
 14. Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. *Am J Respir Crit Care Med* 2013; 188: 913-22.
 15. Davis SD, Ferkol TW, Rosenfeld M, et al. Clinical features of childhood primary ciliary dyskinesia by genotype and ultrastructural phenotype. *Am J Respir Crit Care Med* 2015; 191: 316-24.
 16. Plant TM. 60 years of neuroendocrinology: the hypothalamo-pituitary-gonadal axis. *J Endocrinol* 2015; 226: T41-54.
 17. Kim SH. Congenital hypogonadotropic hypogonadism and Kallmann syndrome: past, present, and future. *Endocrinol Metab (Seoul)* 2015; 30: 456-66.
 18. Balasubramanian R, Crowley WF. Isolated gonadotropin-releasing hormone (GnRH) deficiency. *GeneReviews*. Seattle (WA): University of Washington, Seattle, 2017.
 19. Forni PE, Wray S. GnRH, anosmia and hypogonadotropic hypogonadism - where are we? *Front Neuroendocrinol* 2015; 36: 165-77.
 20. Topaloglu AK. Update on the genetics of idiopathic hypogonadotropic hypogonadism. *J Clin Res Pediatr Endocrinol* 2017; 9: 113-22.
 21. 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 sites affecting conformation and coupling. *PLoS One* 2012; 7: e38456.
 22. Zariwala MA, Knowles MR, Leigh MW. Primary ciliary dyskinesia. *GeneReviews*. Seattle (WA): University of Washington, Seattle, 2015.
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- Received: 5 August 2019
Accepted: 5 September 2019
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