High prevalence of GnRH receptor mutations in Russian patients with idiopathic hypogonadotropic hypogonadism

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Background:

GNRHR gene mutations are responsible for development to normosmic idiopathic hypogonadotropic hypogonadism (iHH) and known to be the most frequent cause of this condition[1]. Nevertheless, the reported frequency of *GNRHR* mutations in iHH patients estimated to be as low as 3-6%[2,3].

Objective:

To evaluate the frequency of *GNRHR* gene defects in a heterogeneous group of Russian patients with iHH and described the phenotype of patients with identified defects.

Methods:

144 patients with iHH (119 boys, 25 girls) were included in the study, 51 of them had olfactory impairment. 'Hypogonadotropic hypogonadism panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). The panel included genes: *CHD7, DNMT3L, DUSP6, FGF17, FGF8, FGFR1, FLRT3, GNRH1, GNRHR, HS6ST1, IL17RD, INSL3, KAL1, KISS1, KISS1R, LHB, NELF, POLR3B, PROKR2, RBM28, SEMA3A, SPRY4, TACR3, WDR11, GREAT, TAC3, KAL4, NR0B1, POLR3A, MKRN3*. Interpretation of the sequencing results and assessment of the pathogenicity of sequence variants were performed according to the ACMG guidelines (2015).

Results:

4 sequence variants in GNRHR were detected in 15 patients (11%), 4 girls and 11 boys. The most frequent mutations in our group were p.R139H (n=13), p.M1T (n=6) and p.R262Q (n=3). Mutations in *GNRHR* were detected as part of digenic defects in 2 cases: with a hemizygous mutation p.E156Gfs5X in *KAL1*; with heterozygous mutation p.V248M in *FGFR1*.

One patient was hyposmic with a digenic defect in *GNRHR* and *KAL1*.

№	sex	phenotype	gene	exon	c.	p.	position	D/ND
1	M	nHH	*GNRHR*	1	G416A	R139H	homo	D
2	M	nHH	*GNRHR*	1	G416A	R139H	homo	D
3	F	nHH	*GNRHR*	1	G416A	R139H	hetero	D
				3	G785A	R262Q	hetero	D
4	M	KS	*GNRHR*	1	G417A	R139H	hetero	D
				1	T2C	M1T	hetero	D
			KAL1	4	467delA	E156Gfs5X	hemi	
5	M	nHH	*GNRHR*	1	G416A	R139H	hetero	D
				3	G785A	R262Q	hetero	D
6	M	nHH	*GNRHR*	1	G416A	R139H	homo	D
				1	T2C	M1T	hetero	D
7	M	nHH	*GNRHR*	3	G785A	R262Q	homo	D
			FGFR1	5	G742A	V248M	hetero	ND
8	M	nHH	*GNRHR*	1	G417A	R139H	homo	D
				1	T2C	M1T	homo	D
			GNRHR	1	G417A	R139H	homo	D
9	F	nHH	*GNRHR*	1	T2C	M1T	homo	D
			GNRHR	1	G417A	R139H	hetero	D
10	M	nHH	*GNRHR*	1	T2C	M1T	hetero	D
			GNRHR	1	G417A	R139H	homo	D
11	M	nHH	*GNRHR*	1	T227C	M76T	hetero	ND
12	M	nHH	*GNRHR*	1	G417A	R139H	homo	D
13	F	nHH	*GNRHR*	1	A317G	Q106R	hetero	D
14	M	nHH	*GNRHR*	1	G417A	R139H	hetero	D
			GNRHR	1	T2C	M1T	hetero	D
15	M	nHH	*GNRHR*	1	G417A	R139H	hetero	D
				1	G785A	R262Q	hetero	D

KS – Kallmann syndrome, nHH – normosmic HH, homo – homozygous, hetero – heterozygous, hemi – hemizygous, D – previously described, ND – not previously described

Conclusions: A high percentage (10%) of iHH due to mutations in *GNRHR* gene was detected in the heterogeneous group of patients (normosmic iHH and KS). 13 cases of hypogonadism were completely explained by the identified changes in GnRH receptor gene. In a patient with the digenic defect in *GNRHR* and *KAL1* genes, hypogonadism can be due to changes in each of these genes. The defects in *GNRHR* and *FGFR1* genes probably potentiate each other.

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