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

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Background:

GnRH receptor gene mutations are responsible for development to normosmic idiopathic hypogonadotropic hypogonadism (iHH) and known to be the most frequent cause of this condition1. Nevertheless, the reported frequency of GnRH receptor mutations in iHH patients estimated to be as low as 3-6%2,3.

Objective:

To evaluate the frequency of GnRH receptor 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 panel and PGM semiconductor sequencer (Ion Torrent). The panel included genes: CHD7, DNM3L, DUSP6, FGFR1, FGFR8, FGFR1, FLK73, GNRH1, GNRH2, HS6ST1, IL17RD, INS3, KAL1, KISS1, KISS1R, LHB, NELF, POLR3B, PROKR2, RBM28, SEMA3A, SPRY4, TACR3, WDR11, GREAT, TAC3, KAL4, NROB1, POLR3A, MKN3. 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 GnRH receptor 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 GnRH receptor were detected as part of digenic defects in 2 cases: with a hemizygous mutation p.E156Gfs*5X in KAL1; with heterozygous mutation p.V248M in FGFR1.

One patient was hyposmic with a digenic defect in GnRH receptor and KAL1.

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KS = Kallmann syndrome, nHH = normosomic 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 GnRH receptor was detected in the heterogeneous group of patients (normosomic 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 GnRH receptor and KAL1, hypogonadism can be due to changes in each of these defects. The defects in GnRH receptor and FGFR1 genes probably potentiate each other.

References:


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