Supplementary Material

Figure S1. ExAC Non-Finnish European individuals show marginal mutation prevalence in CHH genes. Histograms showing CHH genes mutational estimated prevalence in ExAC non-Finnish European (n=33,370). Each bar contains the frequency of nonsynonymous (i.e., missense and inframe InDels, in black), splicing (in white) and nonsense (i.e., frameshift and stop gained variants, in grey) variants accounting for each gene prevalence. Estimation of prevalence was calculated from the number of heterozygous and homozygous variants found in each gene.

Figure S2. Familial and sporadic cases display different burden of rare variants in CHH genes. Frequencies of familial (A) and sporadic (B) CHH, KS and nCHH probands with no mutations (white) and with at least one mutation in CHH genes (grey).

Figure S3. Different strategies in variants filtering. Mutation prevalence of known CHH genes in CHH (A), CDGP (B), CoLaus (C) and ExAC NFE (D) individuals using three different filtering strategies: (1) MAF<1% in ExAC NFE and at least one deleterious prediction in SIFT and/or PolyPhen-2 for missense variants (blue bars); (2) MAF<1% in ExAC NFE and two deleterious predictions in SIFT and PolyPhen-2 for missense variants (yellow bars); (3) MAF<0.1% in ExAC NFE and at least one deleterious prediction in SIFT and/or PolyPhen-2 for missense variants (red bars).

Figure S4. CHH patients are enriched with PTVs in PTV-intolerant genes. Frequency of PTVs occurring in PTV-intolerant (pLi≥0.9, black) and in PTV-tolerant genes (pLi≤0.1, white) in CHH and ExAC NFE individuals. Intermediate pLi scores (>0.1 and <0.9) are shown in grey.

Table S1. Mutation prevalence of CHH genes in screened cohorts. Prevalence of putative mutations in cases and controls. ExAC NFE prevalence was estimated by dividing the sum of heterozygous and homozygous mutations in each gene to the total population (n=33,370).

Table S2. Putative mutations identified in the CHH cohort. Abbreviations as follows: KS, Kallmann syndrome; nCHH, normosmic congenital hypogonadotropic hypogonadism; Zyg, zygosity; Het, heterozygous; Hom, homozygous; Hem, hemizygous; D, deleterious; T, tolerated; PPH2, PolyPhen-2. PolyPhen-2 “possibly damaging” and “probably damaging” predictions were considered both as “deleterious”, while “benign” were defined as “tolerated” for consistency; LOF, loss-of-function, with experimental data supporting the affected protein functionality with this variant.

Table S3. Number of screened individuals harboring mutated CHH genes. Number and frequency of cases and controls having no rare variants in CHH genes, one gene mutated or at least two genes mutated (oligogenicity). Differences between CHH, KS, and nCHH vs. CDGP probands and controls were analyzed via a two-sided Fisher’s exact test.

Supplementary References


