**Supplemental data 2**

***Proband # 1 (p.Y99C).*** The male nIHH proband (UPSIT score 31/40, 7$^{th}$ percentile) exhibited partial puberty (testicular volume 11 mL) with reversal of his hypogonadotropic hypogonadism following pulsatile GnRH treatment at age 24. He has been previously reported (47) (Table 1A). The proband's brother has delayed puberty (UPSIT score 36/40, 35$^{th}$ percentile), and his father has no apparent reproductive phenotype (UPSIT score 34/40, 33$^{rd}$ percentile), yet all three harbor the same *FGFR1* mutation (p.Y99C) (Fig. 4). In contrast to the mild and variable phenotypes of this pedigree, *in vitro* studies revealed severe loss-of-function (Fig. 3A & B, Table 1B). No other gene defects were found.

***Proband #2 (p.N117S).*** The female proband carrying the p.N117S mutation presented with primary amenorrhea and absent breast development (Table 1A). The proband's sister and brother also have nIHH, two other sisters had delayed puberty, and both parents appeared asymptomatic (Fig. 4). All family members have a normal sense of smell by history. While the two sisters with delayed puberty carry the heterozygous *FGFR1* mutation, the proband's sister with nIHH does not, and the affected brother declined study participation. The discrepancy between the severe clinical phenotype of the proband, the mild *in vitro* defects (Fig. 3A & B, Table 1B), and the lack of segregation within the family suggests additional gene defects and/or environmental cues might be contributing to the phenotype. Consistent with this hypothesis, we identified a compound heterozygous *GNRHR* mutation [p.L83V + p. Q106R] in the proband and her affected sister, while the two sisters with delayed puberty carry only one mutant *GNRHR* allele (Fig. 4). The Q106R mutant has been shown previously to be a partial loss-of-function (11) and herein our data show that L83V mutant allele is a complete loss-of-function (Fig. 3D).

***Proband # 3: (p.Y228D).*** The sporadic female proband carrying a heterozygous p.Y228D *FGFR1* mutation has severe nIHH (UPSIT score 35/40, 25$^{th}$ percentile) with no spontaneous menarche or breast development, undetectable gonadotropins, and low serum $E_2$ levels (Table 1A). Additionally, she has osteoporosis and Raynaud's disease (Fig. 4). She conceived on gonadotropin therapy and her son, although prepubertal, appears unaffected. In this case, the phenotype correlates well with the severe loss-of-function of the mutant Y228D (Table 1B). No other gene defects were found.

***Proband # 4: (p.I239T).*** The female proband was diagnosed at age 19 with severe nIHH (UPSIT score 34/40, 25$^{th}$ percentile) with no breast development and primary amenorrhea (Table 1A). She conceived twice on gonadotropin therapy, one daughter and a set of dizygotic female twins (Fig. 4). Annually, she discontinued hormonal replacement therapy for three months, yet remained amenorrheic. At age 42, she experienced a reoccurrence of menses off treatment (7-9 periods a year) and sustained this cyclicity over the subsequent decade. At age 52, her serum FSH was 4.4 IU/L, LH was 3.1 IU/L, $E_2$ was 134 pg/mL, and progesterone was 1.38 nmol/L, consistent with mid-follicular phase hormone levels. Her oldest daughter was diagnosed with partial nIHH (UPSIT score 35/40, 16$^{th}$ percentile) at age 16 with Tanner IV breast development and primary amenorrhea. She was treated with oral contraceptive pills (OCP) and at age 21 remained amenorrheic after discontinuing therapy. The dizygotic twin daughters were started on estrogen therapy at age14 yr for delayed puberty. They had Tanner II and Tanner III breast development and primary amenorrhea. After age 18, they both discontinued hormonal therapy and remained amenorrheic. A maternal niece also presented at age 18 with primary amenorrhea, some spontaneous breast development, and was diagnosed with nIHH. The proband, her eldest

affected daughter, and one of the twin daughters carry the heterozygous p.I239T *FGFR1* mutation. The activity of the I239T mutant is severely compromised (Fig. 3A & B), which is not consistent with the proband's mild phenotype (reversal of HH) (Table 1B). Additional screening revealed a heterozygous *PROKR2* mutation (p.S202G) only in the proband.

***Proband # 5 (p.R250Q) and #6 (p.R470L).*** Detailed descriptions of these two nIHH probands with absent puberty have been previously reported (10, 12) (Table 1A). While the p.R470L mutant has been reported to be loss-of-function (12), we performed herein the *in vitro* studies of the p.R250Q mutant (Fig. 3A & B). Further, these two probands have been previously described to carry additional mutations, a heterozygous *FGF8* mutation (p.K100E) and a compound heterozygous *GNRHR* mutation [p.Q106R + p.R262Q], respectively (10, 12).

***Proband # 7 (p.A671P).*** The sporadic male nIHH proband (UPSIT score 33/40, 14$^{th}$ percentile) presented at age 22 with incomplete virilization, partial puberty (testicular volume = 5 mL), clinodactily, osteopenia, and a history of wrist fracture resulting from minimal trauma (Table 1A, Fig. 4). A detailed neuroendocrine evaluation revealed undetectable gonadotropin levels consistent with absent endogenous GnRH secretion. In line with his clinical presentation, the mutant A671P exhibits a marked decrease in the tyrosine kinase activity (Fig. 3C). No other gene defects were identified.

***Proband # 8 (p.K618N).*** The sporadic male proband exhibited prominent frontal bossing, wide angle chest, Tanner II-III gynecomastia, and absent puberty (Table 1A, Fig. 4). A detailed neuroendocrine evaluation revealed undetectable gonadotropins and hypogonadal T. The severity of the reproductive phenotype in this case does not correlate with the moderate defects observed in the mutants *in vitro* (Fig. 3A-C). We identified an additional heterozygous loss-of-function GNRHR mutation (p.R262Q) in the proband (11).

***Proband # 9 (p.Q680X).*** The severe reproductive phenotype of the male nIHH proband (UPSIT score 36/40, 31$^{th}$ percentile) with cleft lip/palate has been previously reported in relation to the variable disease expressivity among other family members carrying the mutation (22) (Table 1A, Fig. 4). We performed herein the *in vitro* studies of the p.Q680X mutant (Fig. 3A & B). The severe clinical picture of the proband is consistent with the markedly impaired expression of the mutant and absent activity in the transcriptional assay *in vitro*. No other gene defects were detected in the proband.