Supplemental tables

Table 1. Phenotypic characterization of male probands and family members harboring rare variants in *GNRHR*. ***complete loss of function; **partial loss of function; *predicted to be pathologic; no asterisk: predicted to be benign.

Patient (and reference)	Allele 1	Allele 2	Diagnosis	Testis (ml); phallus (cm) at presentation	Testosterone levels	Number of pulses; mean LH (Q10 min sampling x 12h for LH) at presentation	Treatments	Fertility
Complete Loss of GNRHR - Group 1 - cLOF/cLOF								
2	C279Y***	C279Y***	nIHH					
2b	C279Y***	C279Y***	nIHH					
Severe loss of GNRHR - Group 2 - cLOF/pLOF								
5	R139H***	T32I**	nIHH	2 ml; micropenis		0; <1.6		
Severe loss of GNRHR - Group 3 - pLOF/pLOF								
10	Q106R**, S217R**	Q106R**	nIHH/Fertile eunuch	12 ml				
7	Q106R**	P96S*	Fertile eunuch	12 ml		2; 3.9	T	
8 (42)	Q106R**	Q106R**	nIHH/Reversal	17 ml; 7 cm	71 ng/dl before treatment, then 271 ng/dl	1; 3.5	hCG	Yes, after 4 months of hCG.
12	R262Q**	L166P*	nIHH/Fertile eunuch	15 ml	58 ng/dl			
12b	R262Q**	L166P*	nIHH					
Moderate loss of GNRHR - Group 4 - cLOF/NL or pLOF/NL								
29	A171T***	NL	KS	3 ml; micropenis			T	
10b	Q106R**, S217R**	NL	CDP					
18	Q106R**	NL	adult onset IHH	20 ml; NL	41-107 ng/dl	0; 0.64	T, GnRH, hCG	Yes (1st w/pump, 2nd w/ hCG)
16	Q106R**	NL	nIHH	9 ml		2; 3.86		
19	Q106R**	NL	KS					
17	Q106R**	NL	nIHH	1 ml				
15	Q106R**	NL	nIHH					
24b	Q106R**	NL	nIHH					
22	Q106R**	NL	nIHH					
23	Q106R**	NL	nIHH				T	
12c	L166P*	NL	CDP					
30	R262Q**	NL	nIHH	1 ml; NL	25 ng/dl	1.5; 1.9	T, GnRH, Gonadotropin	

21	**R262Q****	**NL**	**KS**					
26	**L117P***	**NL**	**CDP**	**13 ml, 8-9 cm**	**363 ng/dl**		**No**	
28	**P146S***	**NL**	**KS**	**1 ml (cryptorchid); 5-6 cm**			**T, hCG**	
Normal GNRHR (not included in the four groups)								
34	**F216F**	**NL**	**nIHH**					
35	**F216F**	**NL**	**nIHH**					

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Table 2. Phenotypic characterization of female probands and family members harboring rare variants in *GNRHR*. ***complete loss of function; **partial loss of function; *predicted to be pathologic; no asterisk: predicted to be benign.

Patient (and reference)	Allele 1	Allele 2	Diagnosis	Spontaneous breasts; menarche	Number of pulses; mean LH (Q10 min sampling x 12h for LH)	Treatment	Ovutation / conception
Complete Loss of GNRHR - Group 1 - cLOF/cLOF							
1	Q11fsX23***	Q11fsX23***	nIHH				No ovulation w/ either GnRH or gnts
2c	C279Y***	C279Y***	nIHH				
Severe loss of GNRHR - Group 2 - cLOF/pLOF							
3	M1T***, , R139H***	Q106R**	nIHH	Tanner I; no menarche	0; 1.02	EP, GnRH pump	Ovulated on GnRH; conceived w/ gnts: healty baby
4 (35)	P320L***	N10K**, Q11K**	nIHH	Tanner III; no menarche	1; 1.78	EP, GnRH, Gonadotropin	No ovulation on GnRH; twins with gnts
6	L266R***	Q106R**	nIHH	Spontaneous breasts (?); nomenarche			
Severe loss of GNRHR - Group 3 - pLOF/pLOF							
10c	Q106R**, S217R**	Q106R**	nIHH				
11 (41)	Q106R**	R262Q**	nIHH	No breasts; no menarche	5; 2.03	EP, GnRH, Gonadotropin	Conceived 3 times with GnRH and 2 times with gnts; miscarriages at 7-11 weeks of gestation.
11b (41)	Q106R**	R262Q**	nIHH				Conceived with gntns: healthy babies
9	Q106R**	Q106R**	KS	Tanner IV; no menarche		EP	
13	R262Q**	R262Q**	nIHH				
Moderate loss of GNRHR - Group 4 - cLOF/NL or pLOF/NL							
14	Q106R**	L83V	nIHH	No breasts; no menarche		EP	
14b	Q106R**	L83V	nIHH				
25	Q106R**	S168A	HA	Breasts at 11-12; menarche at 16	5; 3.9		
20	Q106R**	NL	KS				
24	Q106R**	NL	nIHH				

10d	**Q106R****	**NL**	**HA**				**Conceived w/o treatments**
27	**P146S***	**NL**	**nIHH**		**5; 4.8**		**3 ovulations on pump, no pregnancy**
32	**R262Q****	**NL**	**HA**				
31	**R262Q****	**NL**	**KS**				
5b	**R139H***	**NL**	**Anosmia**				
21b	**Q106R****	**NL**	**cleft lip/palate**				
Normal GNRHR (not included in the four groups)							
33	**A50V**	**NL**	**CDP**				

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Table 3. Healthy family members harboring rare variants in *GN RHR*. ***complete loss of function; **partial loss of function; *predicted to be pathologic; no asterisk: predicted to be benign.

Subject	Gended	Heterozygous mutation
3c	M	M1T***, R139H***
3d	M	M1T***, R139H***
8c	M	Q106R**
8d	M	Q106R**
8e	M	Q106R**
11c	M	R262Q**
11f	M	R262Q**
11g	M	R262Q**
6c	M	Q106R**
12d	M	L166P*
3b	F	Q106R**
4b	F	N10K**, Q11K**
4c	F	P320L***
4d	F	N10K**, Q11K**
14c	F	L83V
14d	F	Q106R**
8b	F	Q106R**
24c	F	Q106R**
18b	F	Q106R**
11d	F	Q106R**
11e	F	Q106R**
6b	F	L266R***
12e	F	R262Q**
29b	F	A171T***
30b	F	R262Q**
32b	F	R262Q**

Table 4. SNPs used for SNP analysis of heterozygous subjects and their location within *GNRHR* gene.

SNP name	Location (relative to *GNRHR* transcriptional start site)	Location (relative to coordinate systems)
rs2627261	1-62	68302710
rs35400155	144	68302505
rs4986942	453	68302196
rs17082306	520-75	68293178
rs13130501	549	68293074
rs13149772	550	68293073
rs17088591	741+35	68292846
rs28933074	851	68288929
rs35845954	987+583	68288888
rs35610027	987+802	68289107
rs35683646	987+809	68289114
rs17635850	987+829	68289134
rs13150734	987+1260	68288703

Supplemental figure legends

Figure 1. Schematic of mutations in *GNRHR*.

Figure 2. Examples of pedigrees carrying *GNRHR* RSVs. A: family of proband #10; B: family of proband #12.

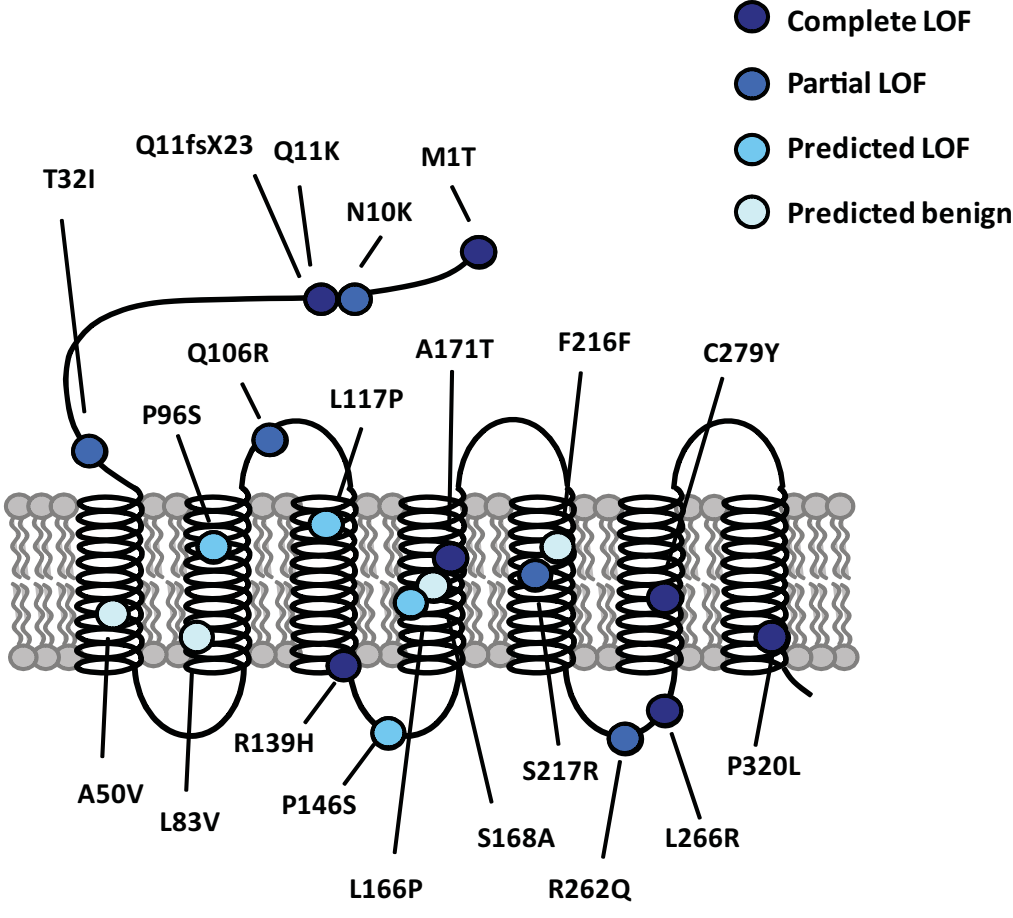
Complete LOF
Partial LOF
Predicted LOF
Predicted benign
T32I
Q11fsX23
Q11K
N10K
M1T
Q106R
P96S
L117P
A171T
F216F
C279Y
A50V
L83V
R139H
P146S
L166P
S168A
S217R
R262Q
L266R
P320L

Fig. 1

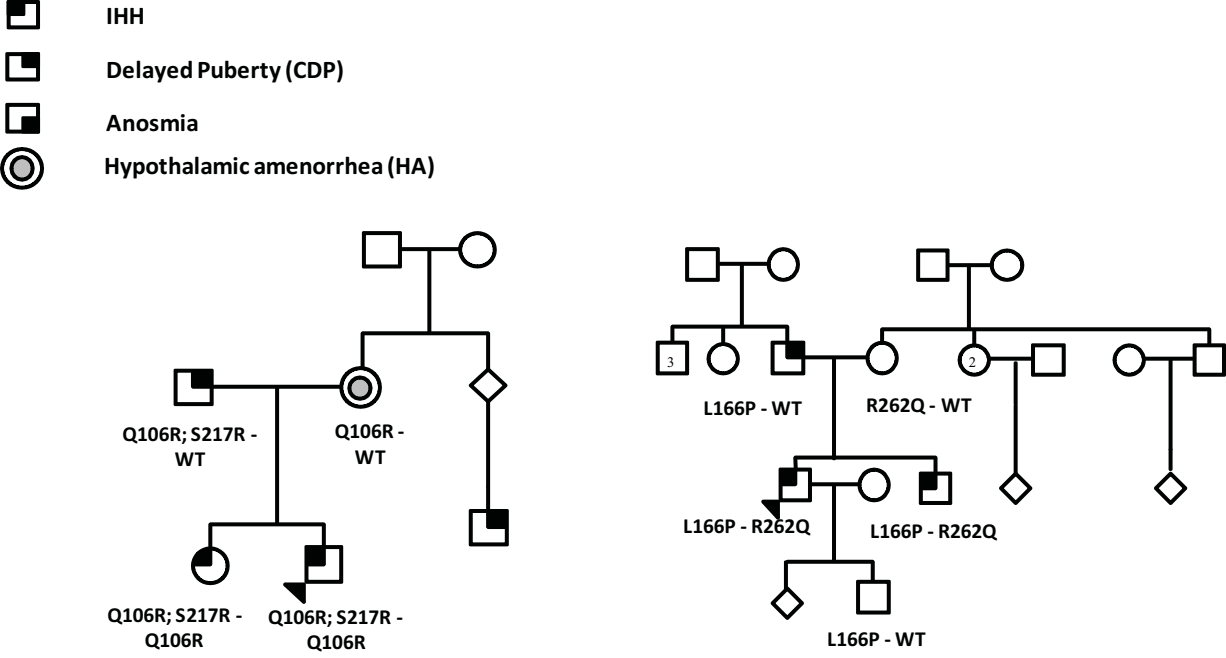
IHH
Delayed Puberty (CDP)
Anosmia
Hypothalamic amenorrhea (HA)
Q106R; S217R - WT
Q106R - WT
Q106R; S217R - Q106R
Q106R; S217R - Q106R
3
2
L166P - WT
R262Q - WT
L166P - R262Q
L166P - R262Q
L166P - WT

Fig. 2