Idiopathic Hypogonadotropic Hypogonadism due to a *GNRH1* Mutation

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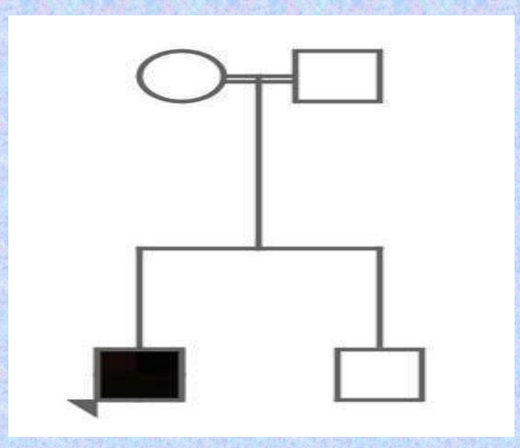
Background: Idiopathic hypogonadotropic hypogonadism may be normosmic (nIHH) or it may be associated with anosmia, which is known as Kallmann syndrome (KS). First mutation *GNRH1*was described in 2009 in patients with nIHH. Mutations of the human *GNRH1* gene are a very rare cause of nIHH, with only six mutations so far described.

Case: The proband is a 11.3-year-old boy who first presented at age 1 with micropenis and cryptorchidism. His past medical history is unremarkable except for a bilateral orchidopexy surgery at the age of two years. His parents are healthy cousins. The proband's height and weight are 149 cm (50th-75th percentile) and 84.5 kg (>95 percentile), respectively. His pubic and axillary hair are at Tanner stage 4 and 2, respectively. His testes are 1 mL bilaterally in the scrotum. His stretched penile length was 3.6 cm. Chromosome analysis revealed a 46,XY karyotype. Pelvic ultrasonography confirmed the absence of müllerian structures and the presence of both gonads with features of normal testes in the scrotum. His bone age is 11years.

Results: Genetic analysis of this patient identified a homozygous deletion (c.87delA) leading to a frameshift mutation (p.G29GfsX12) in *GNRH1*.



Whole exome sequencing data

1	#chr_name	chr_start	chr_end	ref_base	alt_base	hom_het	snp_qual	tot_depth	alt_depth	region	gene	change	annotation	dbSNP135_	SNP135_co	10No	11Oc	SCS	CLN	OMIM
40498	chr08	25246481	25246481	G	A	hom	17.8	2	2	intronic	DOCK5	.	.	rs2709602	rs2709602	0.883	0.90	.	.	.
40499	chr08	25247587	25247587	G	T	hom	23.5	4	4	intronic	DOCK5	.	.	rs1000798	rs1000798	0.498	0.53	.	.	.
40500	chr08	25257531	25257531	A	G	hom	222	41	41	intronic	DOCK5	.	.	rs3763520	rs3763520	0.517	0.52	.	.	.
40501	chr08	25267622	25267622	A	G	hom	222	73	73	exonic	DOCK5	synonymous_SNV	DOCK5:NM_024940:exon51:c.A5412G:p.P1804P,	rs2709618	rs2709618	0.510	0.54	.	.	.
40502	chr08	25280666	25280666	A	C	hom	148	36	36	intronic	GNRH1	.	.	rs2709608	rs2709608	0.960	0.97	.	.	.
40503	chr08	25280760	25280760	T	-	hom	214	49	49	exonic	GNRH1	frameshift_deletion	GNRH1:NM_001083111:exon2:c.87delA:p.G29fs,GNRH1:NM_000825:exon1:c.87delA:p.G29fs,	.	.	.	.	.	.	.
40504	chr08	25280800	25280800	C	G	hom	222	48	48	exonic	GNRH1	nonsynonymous_SNV	GNRH1:NM_001083111:exon2:c.G47C:p.W16S,GNRH1:NM_000825:exon1:c.G47C:p.W16S,	rs6185	rs6185	0.249	0.27	.	.	.
40505	chr08	25287556	25287556	A	G	hom	150	71	71	intronic	KCTD9	.	.	rs965130	rs965130	0.508	0.55	.	.	.
40506	chr08	25317691	25317691	A	T	hom	222	98	98	intronic	CDCA2	.	.	rs6987936	rs6987936	0.956	0.97	.	.	.
40507	chr08	25323777	25323777	T	C	hom	222	53	53	exonic	CDCA2	synonymous_SNV	CDCA2:NM_152562:exon5:c.T474C:p.N158N,	rs10108752	rs10108752	0.952	0.96	.	.	.
40508	chr08	25363864	25363864	G	A	hom	35.1	6	6	intronic	CDCA2	.	.	rs146273040	.	0.002	0.00	.	.	.

Conclusion: We here described a frameshift *GNRH1* mutation which is predicted to lead a total failure of GnRH synthesis. This mutation was previously reported by Chan et al. Comparison of phenotypes show no difference. *GNRH1* mutation in IHH are indeed very rare as we found only one mutation among 30 families with identified causative mutations. These rare patients offer a unique opportunity to study the effects of human GnRH deficiency.