TITLE

FGFR1 loss-of-function mutations of in three Japanese patients with isolated hypogonadotropic hypogonadism and split hand/foot malformation

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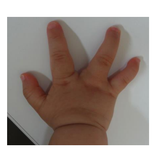
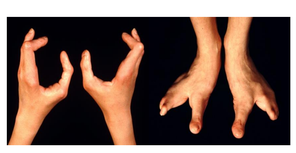
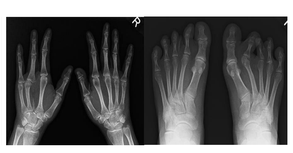
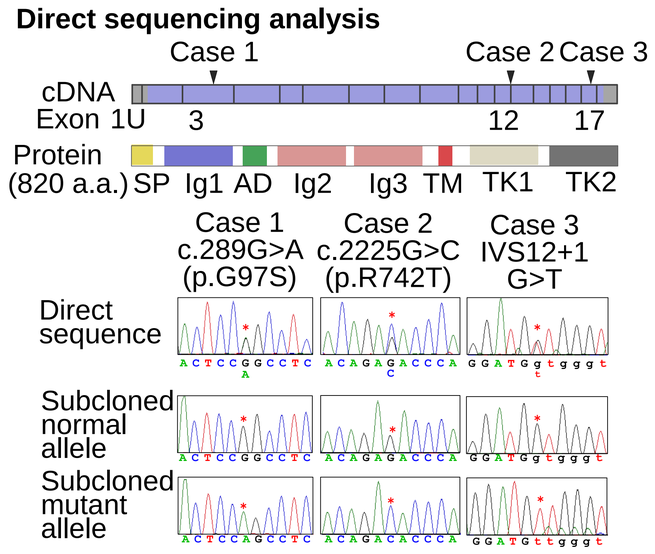
OBJECTIVES

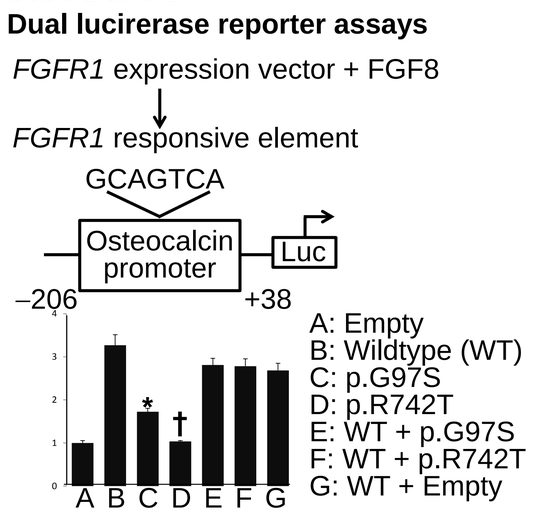
Background: Heterozygous loss-of-function mutations of *FGFR1* are known to cause Kallmann syndrome (KS) and isolated hypogonadotropic hypogonadism (IHH). Furthermore, recent studies have also indicated that heterozygous loss-of-function mutations lead to IHH and split hand/foot malformation (SHFM).
Objective and hypotheses: The objective of this study was to examine *FGFR1* in three Japanese patients with IHH and SHFM.

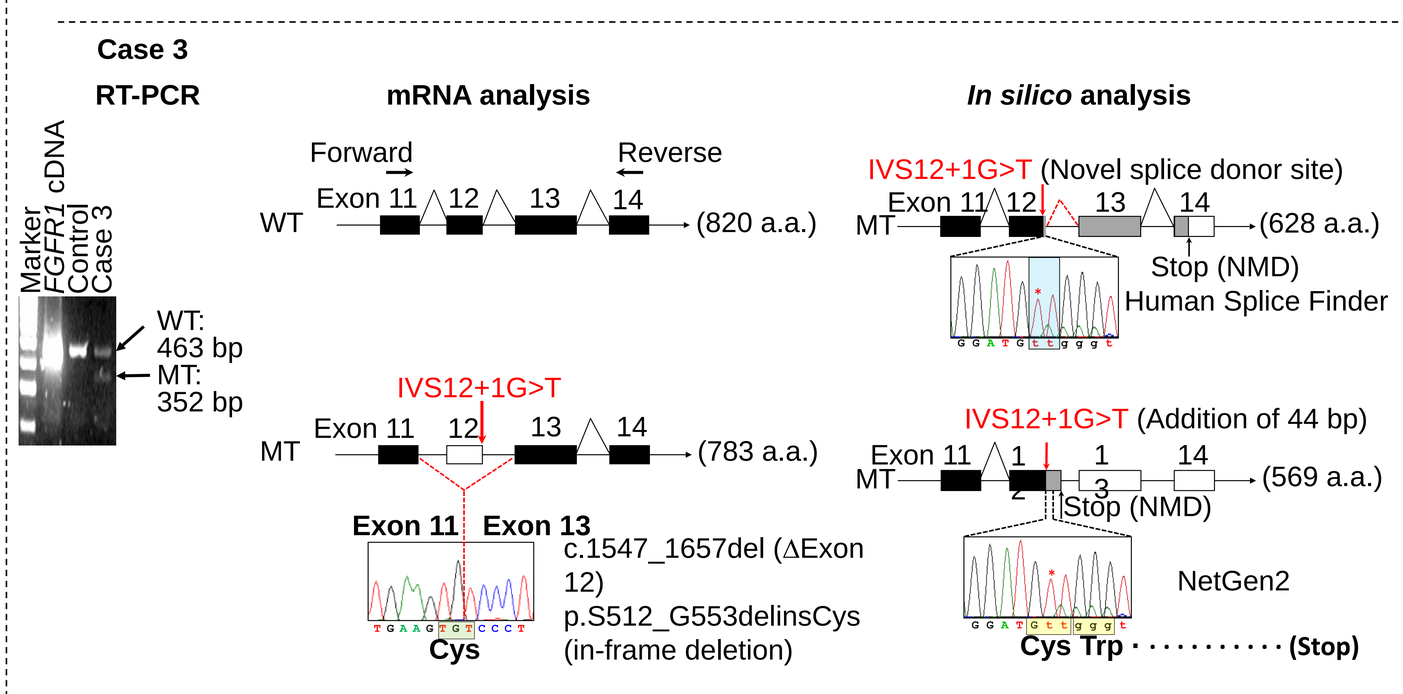
METHODS

Method: This study consisted three Japanese patients (cases 1–3) with IHH and SHFM. Case 1 was a 3-month-old boy with micropenis, low serum LH (<0.1 mIU/mL) and testosterone (<0.03 ng/mL) at mini-puberty, and right split hand. Case 2 was a 17-year-old boy with no pubertal development, low serum LH (<0.1 mIU/mL) and testosterone (<0.03 ng/mL), and bilateral split hands and feet. Case 3 was a 34-year-old female with primary amenorrhea, low serum LH (0.4 mIU/mL) and E2 (<10 pg/mL), and left split hand. We performed direct sequencing for *FGFR1* coding regions and their flanking splice sites, luciferase analysis for missense mutations, and RT-PCR based sequence analysis and *in silico* analysis for a splice donor site mutation.

	Case 1	Case 2	Case 3
Age at examination	3 months	17.5 years	34 years
Sex	Male	Male	Female
<Genital findings>			
Tanner stage	G1, PH1	G1, PH1	G1, PH2
Penile length (cm)	0.9	3	・・・
Testis size (mL)	<1	2	・・・
Testis position	Inguinal	Inguinal	・・・
Scrotum	Hypoplastic	Hypoplastic	・・・
Uterus	・・・	・・・	Hypoplastic on MRI
<Serum hormone values>			
LH (IU/L)	<0.10 → 0.68	<0.5 → <0.5	0.4 → 3.4
FSH (IU/L)	0.29 → 5.04	<0.5 → <0.5	2.1 → 6.6
Teststerone (nmol/L)	<0.3	<0.3	・・・
Estradiol (nmol/L)	・・・	・・・	<30
Oher hormones	Normal	Normal	Normal
<Olfactory function>			
Sense of smell		Normal	Normal
Olfactory bulbs	Normal on MRI	Not examined	Not examined
Olfactory sulcus	Normal on MRI	Not examined	Not examined
<Other features>	Cheilognatho-palatoschisis		Cleft lip Cleft palate VSD
Father	Normal	Normal	Normal
Mother	Normal	Normal	Normal
Extremities			







RESULTS

Direct sequencing identified two heterozygous missense mutations (a previously reported p.G97S in case 1 and a novel p.R744T in case 2) and a novel heterozygous splice donor site mutation (IVS12+1G>T in case 3). The two missense mutations had drastically reduced luciferase activities, without a dominant negative effect. The splice donor site mutation was found to have yielded a small amount of mRNA skipping exon 12 (p.Ser512_Gly553delinsCys), and was predicted to have produced two aberrant mRNAs that satisfy the condition for nonsense-mediated mRNA decay, by using an alternative splice donor site (p.G553fsX628) and by escaping splicing at the IVS12 exon-intron junction (p.G553fsX569).

CONCLUSIONS

The results provide further support for the notion that heterozygous loss-of-function mutations of *FGFR1* cause IHH with SHFM.

References

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55ESPE 728--P1
Pituitary and Neuroendocrinology
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DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS 10-12 SEPTEMBER
PosterSessionOnline.com