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RESEARCH NOTE

Novel mutation of type-1 insulin-like growth factor receptor (IGF-1R) gene in a severe short stature pedigree identified by targeted next-generation sequencing

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Abstract. Insulin-like growth factor receptor (IGF-1R) deficiency is a rare form of short stature, and is difficult to clinically diagnose. Targeted next-generation sequencing (NGS) allows for the rapid and inexpensive assessment of short stature. We identified mutations in the pedigree of a Chinese boy with severe short stature using targeted NGS; we then assessed the clinical characteristics and evaluated the efficacy of growth hormone therapy. NGS analysis revealed a novel heterozygous missense mutation in exon3 (c.926C>T, p.S309L) of the type-I IGF-1R gene in the proband, which was inherited from the mother. The proband, mother and grandfather suffered from severe growth failure. After recombinant human growth hormone therapy, the patient's growth rate increased. The novel missense mutation in *IGF-1R* (c.926C > T, p.S309L) is associated with severe short stature in Chinese individuals. Targeted NGS may enable efficient diagnosis and genetic consultation of children with short stature.

Keywords. short stature; IGF1R mutation; targeted NGS.

Introduction

Short stature is one of the most common symptoms encountered by pediatric endocrinologists. Defects in a wide variety of genes can cause severe growth disorders. However, these defects are hard to detect. Targeted next-generation sequencing (NGS) is an advanced and inexpensive method for rapid genetic assessment of short stature.

We identified a novel heterozygous type-I insulin-like growth factor receptor (IGF-1R) gene mutation in a severely short Chinese boy using targeted NGS. Our findings provide essential information about IGF-1R mutations in the Chinese population.

Material and methods

Case presentation

The patient first presented at the age of 5 years and 11 months to our centre for short stature. He presented with a height of 97.3 cm (−4.74 standard deviation score (SDS)), weight of 13 kg (−3.7 SDS) and body mass index of 13.82 kg/m^2 (< −2SD). He was born at 36 weeks of gestation with a birth weight of 2.15 kg (−2.85 SDS), birth height of 50 cm, and head circumference of 47 cm (−2.0 SDS). His mother's height was 145 cm (−3.05 SDS). The other family members of the patient also displayed short stature (figure 1). The patient's bone age was 2.5 years, and was delayed by 3 years. Laboratory tests including growth hormone (GH) stimulation test, serum IGF-1 levels, IGF-binding protein (IGFBP)-3, serum luteinizing hormone, follicle-stimulating hormone, oestradiol, and testosterone were normal. Magnetic resonance imaging revealed a relatively small pituitary gland.

NGS targeting 277 short stature-associated genes and 19 related copy number variation regions was performed according to the manufacturer's protocol (MyGenostics, Baltimore, USA) (table 1). A novel heterozygous mutation of exon 3 (c.926C>T, p.S309L) in the *IGF1R* gene was identified in the proband and his mother (figure 1a). However, the mutation was not detected in the coding region of

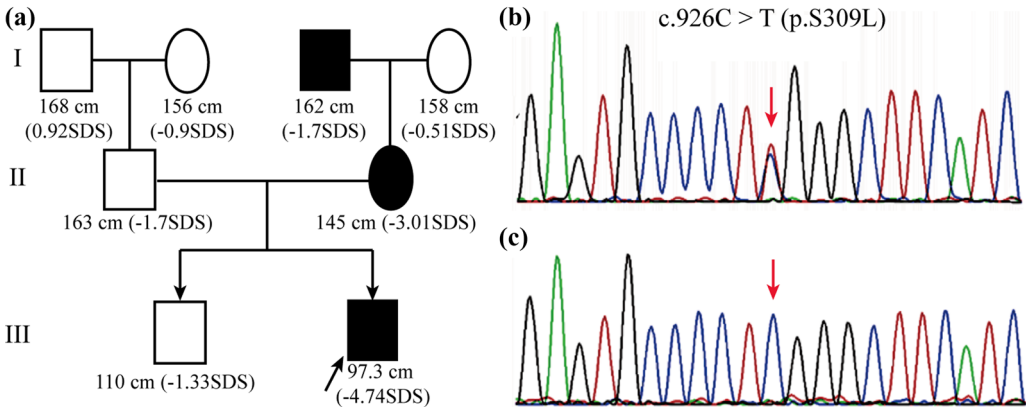

Figure 1. The pedigree and sequencing results of IGF-1R mutation. (a) The family history of patients with IGF-1R mutations, proband gene mutation from his mother and grandfather. (b) Proband IGF-1R gene c.926C>T (p. S309L); (c) normal control. An arrow represents the point of variation.

the IGF-1R gene in his father and 100 unrelated healthy individuals (figure 1, b&c). This mutation has not been previously reported in the single-nucleotide polymorphism (SNP) database (http://www.ncbi.nlm.nih.gov/SNP/), and it was predicted to be deleterious by Align-GVGD software.

Treatment with rhGH (0.2 U/kg/d) (Simon *et al.* 2008) commenced at 5 years and 11 months of age. Changes in height, body weight, and bone age were evaluated every 3 months. IGF-1 and IGFBP3 levels were also regularly monitored. The rhGH was well tolerated. After one year, height SDS had increased by 0.763. The 8 cm per year growth rate was significantly higher compared to the rate before treatment (table 2).

Signed parental informed consent was obtained for the publication of this case report.

Results and discussion

Components of the IGF system are ubiquitously expressed throughout foetal and postnatal life, and regulate the development of multiple tissues and organs (Klammt *et al.* 2011). The mitogenic and metabolic effects of IGF-1 are mediated through the IGF-1R cell-surface tyrosine kinase receptor.

Several IGF-1R mutations have been recently described as the cause of prenatal and postnatal growth retardation in humans because of IGF-1 insensitivity (Juanes *et al.* 2015). Our previous studies on 1327 samples revealed the association of an SNP of IGF-1R with genetic susceptibility to idiopathic short stature (Yang *et al.* 2013).

Defects in IGF-1R have been associated with intrauterine and postnatal growth retardation in over 20 families. However, the correlation between genotype and phenotype has remained unclear. The variability in specific clinical and biochemical features in individuals with different IGF-1R mutations may be related to the specific functions of the mutated IGF-1R regions or variations in genetic background.

Overall, these studies indicate that IGF-1R plays a pivotal role in development and that its mutations should be evaluated to identify the specific functional change and clinical symptoms. Nevertheless, the clinical diagnostic criteria of molecular screening for IGF-1R mutations are unclear and data from more clinical cases would be helpful to complement the characteristics of the phenotypic spectrum.

The present report describes the case of a Chinese boy with small for gestational age, short stature, microcephaly, and delayed body age. We identified a c.926C>T (p. S309L) missense mutation in *IGF1R* using targeted NGS. The mutation was predicted to be deleterious using the Align-GVGD web portal (http://agvgd.iarc.fr/). The proband's mother and grandfather harboured the same mutation; the SD of their height was −3.1 (short stature) −1.7 (mild short), respectively, indicating a critical family history in this case. Therefore, we believe that this mutation is the most likely cause of short stature observed in this pedigree. We looked into the effect of the mutation on the protein three-dimensional structure and interaction with IGF, but did not find any supporting evidence through computer docking studies. Further functional analysis is needed to confirm the possible effects of the mutation.

The majority of IGF-1R mutations are heterozygous and most are missense mutations (Essakow *et al.* 2016). These might cause IGF-1R deficiency and impair ligand binding and signal transduction, eventually resulting in growth retardation (Kawashima *et al.* 2014; Ocaranza *et al.* 2017). Most IGF-1R deficient patients of short stature are diagnosed as microcephaly after birth (Fujimoto *et al.* 2015; Juanes *et al.* 2015). The symptoms of the patients analysed in the present study are consistent with the reported clinical features of IGF-1R mutations.

Several patients with IGF-1R abnormalities have received GH treatment (Muller *et al.* 2012; Mahmoud

Table 1. List of 277 short stature-related genes and 19 short stature-associated copy number variation regions.

ACAN	ADAMTS10	ADAMTS2	ADAMTSL2	AGPS	ALDH18A1	ALDH3A2
ALMS1	ANKRD11	AP4B1	AP4E1	AP4S1	ARID1A	ARSB
ARSE	ATP8B1	ATR	ATRX	AUTS2	B3GALT6	BCOR
BLM	BMP2	BMPR1B	BRAF	BRCA2	BTK	C5orf42
CANT1	CASR	CCDC8	CDAN1	CDC6	CDT1	CENPE
CENPJ	CEP152	CEP63	CHD7	CHMP1A	CHST3	CLCN5
COL10A1	COL11A1	COL11A2	COL1A1	COL1A2	COL2A1	COL6A2
COL9A1	COL9A2	COL9A3	COMP	CREBBP	CRIPT	CRTAP
CTCF	CUL7	CYP27B1	CYP2R1	DKC1	DLL3	DNA2
DVL1	DYM	ECEL1	EIF2AK3	ENPP1	EP300	ERCC2
ERCC3	ERCC4	ERCC5	ERCC6	ERCC8	EVC2	EXOSC3
FAM111A	FANCA	FANCC	FANCE	FBN1	FGD1	FGF23
FGF8	FGFR1	FGFR2	FGFR3	FLNB	FOXG1	FOXI1
FUCA1	GALNS	GDF5	GH1	GHR	GHRHR	GLB1
GLI2	GLI3	GNPAT	GNPTAB	GNPTG	GNS	GRM1
GUSB	HBA1	HBB	HCCS	HDAC8	HES7	HESX1
HGSNAT	HMGA2	HMGB3	HRAS	HSPG2	HYAL1	IDS
IDUA	IFITM5	IGF1	IGF1R	IGF2	IGFALS	IGSF1
IHH	IKBKB	IKBKG	IL2RG	IMPAD1	INPPL1	ITCH
JAG1	KCNJ1	KCNJ10	KDM6A	KIAA1033	KIF22	KLF1
KMT2D	KRAS	LAMTOR2	LARP7	LBR	LHX3	LHX4
LIFR	LMBR1	LMNA	LRBA	LTBP2	LTBP3	MATN3
MCM4	MCM9	MCPH1	MECP2	MESP2	MGAT2	MMP13
MMP2	MPLKIP	MYCN	MYH3	NAGLU	NBN	NEK1
NF1	NIN	NIPBL	NKX3-2	NME1	NOG	NPR2
NRAS	NSUN2	OBSL1	OFD1	ORC1	ORC4	ORC6
OTX2	PALB2	PAPSS2	PAX8	PCNA	PCNT	PDE4D
PEX7	PHC1	PHEX	PIEZO2	PIK3R1	PITX2	PLEC
PLK4	POC1A	PORCN	POU1F1	PRKAR1A	PROKR2	PROP1
PTH1R	PTHLH	PTPN11	RAB18	RAB33B	RAB3GAP1	RAB3GAP2
RAD21	RAD51C	RAF1	RAPSN	RARA	RBBP8	RECQL4
RIT1	ROR2	RPS19	RPS6KA3	RTEL1	RTTN	SEMA3E
SEPN1	SERPINF1	SGSH	SHOX	SLC19A2	SLC26A2	SLC26A4
SLC2A2	SLC34A3	SLC35D1	SLC39A13	SLC39A4	SLX4	SMAD4
SMARCA2	SMARCA4	SMARCAL1	SMARCB1	SMC1A	SMC3	SOS1
SOX11	SOX2	SOX3	SOX9	SPINK5	SPR	SRCAP
STAT3	STAT5B	STIL	STRA6	TBCE	TBX15	TBX6
TCTN3	TERT	THRA	TINF2	TNNI2	TNNT3	TPM2
TRAPPC2	TRIM37	TRIP11	TRPS1	TRPV4	TSHR	TTI2
TUBGCP6	UBR1	USB1	VDR	VPS33B	VPS53	WDR35
WISP3	WNT5A	XRCC4	ZMPSTE24	1q21.1del	2p16p22dup	4p16.3del
4q21del	5p15.2terdel	5q35.2q35.3dup	7q11.23del	8q21.11q24.13del	11p13del	12q14del
13q14del	14q22.1q22.3del	14q32.2-qter	17p11.2del	17p13.3del	18p11del	18q22.3q23del
22q11.2del						

Table 2. Clinical and biochemical characteristics of the proband after rhGH treatment.

GH treatment	Age (y)	Height (cm)	HtSDS	BW (kg)	BWSDS	BA	IGF-1 (52–316 ng mL^{-1})	IGFBP-3 (1.3–6.1 μg mL^{-1})
Pretreatment	5 y 11 m	97.3	−4.74	13	−3.7	2.5	204	4.31
1 m	6 y	98.5	NA	13.5	NA	NA	235	4.5
3 m	6 y 2 m	99.6	NA	15	NA	N/A	186	3.77
6 m	6 y 5 m	102	−4.16	14.5	−3.23	2.7	249	4.74
9 m	6 y 8 m	103	NA	15.5	NA	NA	212.1	5.47
1 y	6 y 11 m	105.3	−3.98	17	−2.53	3	341	N/A

HtSDS, height in SDS; BW, body weight; BWSDS, body weight SDS; BA, bone age. NA, not available.

et al. 2017), which has produced effective height gain in all cases without side effects. In the present study, rhGH treatment was effective. The patient responded well to the treatment. However, due to the limited number of cases and treatment period, no definite conclusion can be drawn, and further functional research is needed. These results

provide important and novel insights into short stature disorders.

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