Genetic diagnosis of congenital growth hormone deficiency by massive parallel sequencing using a target gene panel

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* Nothing to disclose

Background

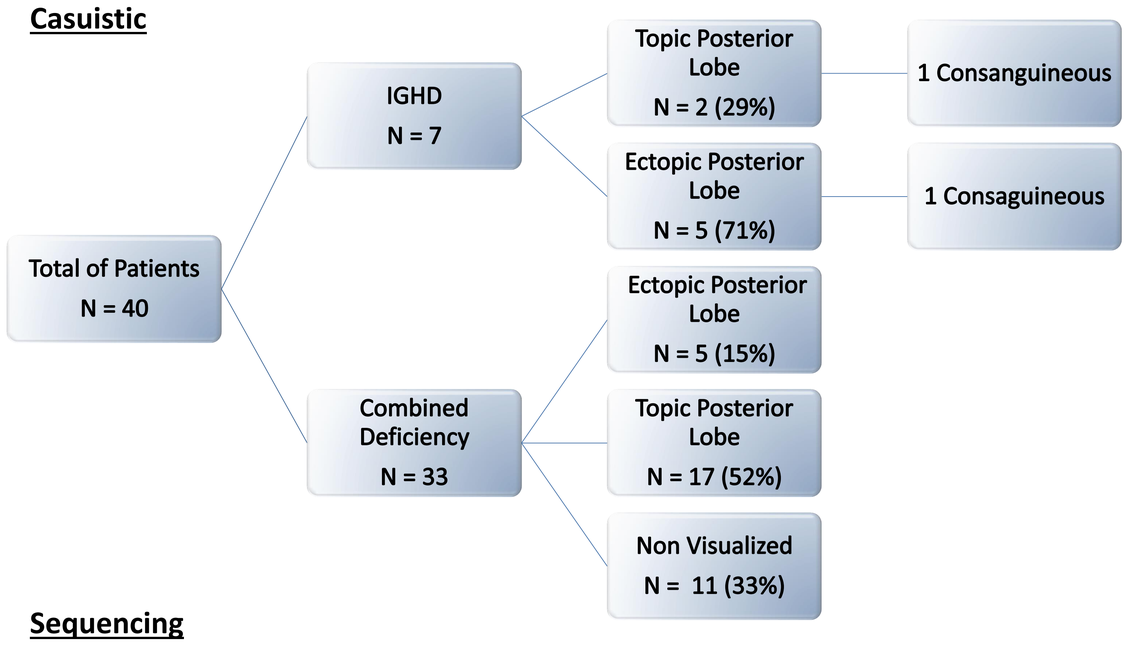
Congenital GH deficiency (GHD) can be isolated (IGHD) or combined with other pituitary hormone deficiencies (CPHD). The identification of mutations has clinical implications for the management of patients and genetic counseling.

Objective

To prospectively conduct a molecular-genetic analysis in selected target genes in patients with congenital IGHD or CPHD.

Methods

Casuistic



Sequencing

Target regions

- **Design technology:** Agilent Sure Design
- **Genes included:** 27 gene associated with GHD + 57 genes associated with growth disorders without GHD

Sequencing

- **Fragmentation technology:** Covaries
- **Capture:** Agilent Sure Select Kit
- **Sequencing:** Ilumina NextSeq
- **Confirmation:** Sanger sequencing

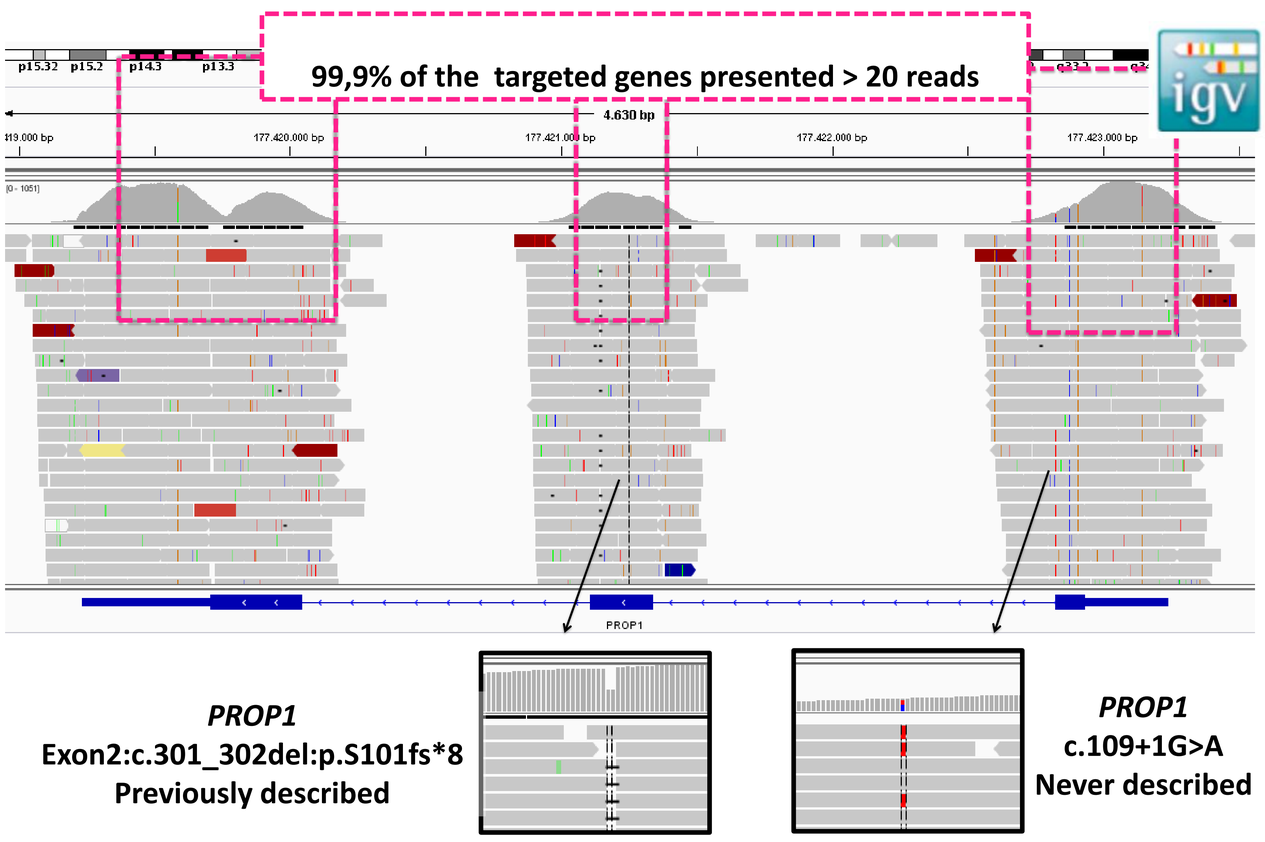
Data analysis

- **Minor allele frequence:** < 1%
- **Data basis:** ExAC, 1000G, ESP6500
- **Location**: Exonic or splice site
- ***In silico*:** Polyphen, Mutation Taster, SIFT, GERP
- **Evaluation of gains or losses:** copy number analysis for targeted resequencing method

Final variant classification (ACMG Nomenclature)

1. Pathogenic 2. Likely pathogenic 3. Benign 4. Likely benign 5. Uncertain significance

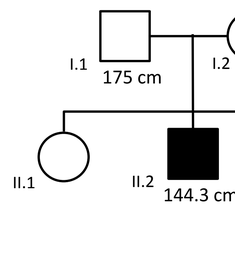
Results



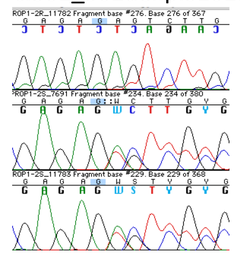
PROP1
Exon2:c.301_302del:p.S101fs*8
Previously described

PROP1
c.109+1G>A
Never described

PROP1

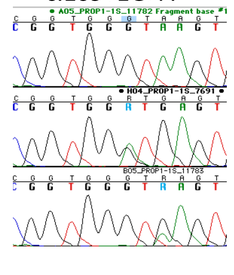


c.301_302del:p.S101fs*8



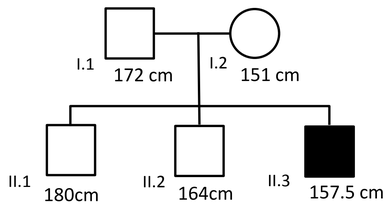
II.1
Index (II.2)
II.3

c.109+1G>A

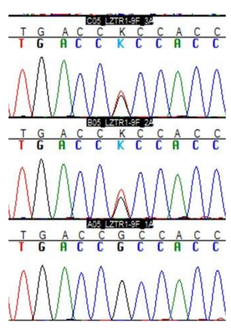


- Diagnosed at 7 years, non-measurable IGF-I. Patient was not treated with rhGH.
- Hormone deficiency: GH, LH, FSH, TSH, PRL, ACTHp.
- MRI: partial empty sella, topic posterior lobe, normal stalk

LZTR1



881G>T: p.R294L

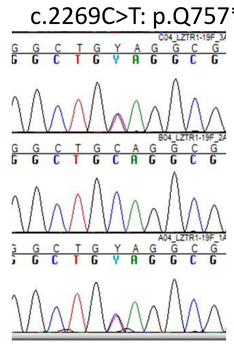


INDEX (II.3)

I.2, II.1, II.2

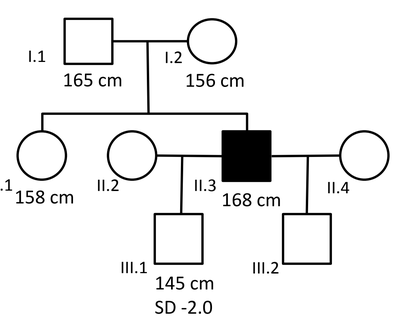
I.1

c.2269C>T: p.Q757*

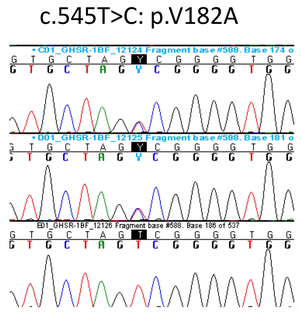


- Noonan Syndrome: typical facial features and cardiopathy (great vessel transposition, pulmonary stenosis, interatrial and interventricular communication)
- IGF-I non-measurable, ITT: GH peak 2.0 µg/L. Isolated growth hormone deficiency. GH replacement from 12 to 20 years. RMI: topic posterior lobe, stalk thickening

GHSR



c.545T>C: p.V182A



Index (II.3), III.1

I.1, II.1

- Appropriate for gestational age, vaginal delivery, weight 3570g, length 50 cm
- IGF-I 55 ng/ml, clonidine: GH peak: < 0.1 µg/L. Hormone deficiency: GH, TSH, LH/FSH. RMI: hypoplastic anterior pituitary, topic posterior lobe

Gene	Allelic variant	ExAC	In silico		Family analysis	Classification
			SIFT	Poly Phen-2		
PROP1	c.301_302del:p.S101fs*8	0.0001	-	-	Brother w/ normal phenotype	Pathogenic
	c.109+1G>A	0	-	-	Upsent	Pathogenic
LZTR1	c.G881T:p.R294L	0	T	D	Mother w/ normal phenotype	Pathogenic
	c.C2269T:p.Q757X	0.00001657	T	0	Mother w/ normal phenotype	Pathogenic
GHSR	c.545T>C: p.V182A	NA	D	D	2 members w/ normal phenotype	Likely pathogenic
TGIF	c.A260T:p.Q87L	0.0003	T	P	3 members w/ normal phenotype	Benign
LHX3	c.C8T:p.A3V	0.0009	T	D	Mother w/ normal phenotype	Likely Benign
SHH	c.C368T:p.P123L	0.0006	D	B	Mother w/ normal phenotype	Likely Benign
GLI2	c.T1504C:p.F502L	0.0003	T	B	Mother w/ normal phenotype	Benign
KAL1	c.C716G:p.T239R	0	D	D	No random inactivation of the X chromosome	Benign

Summary and Conclusions

The panel provided good coverage of the known genes previously associated to GHD and exclusion of mutations in many patients. The panel established the diagnosis of 3 patients. Low rate of diagnoses could be due to incomplete penetrance, digenic or environmental conditions or mutations in genes not previously associated with GHD.

The patients with negative results are candidates for whole exome sequencing.

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