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Background

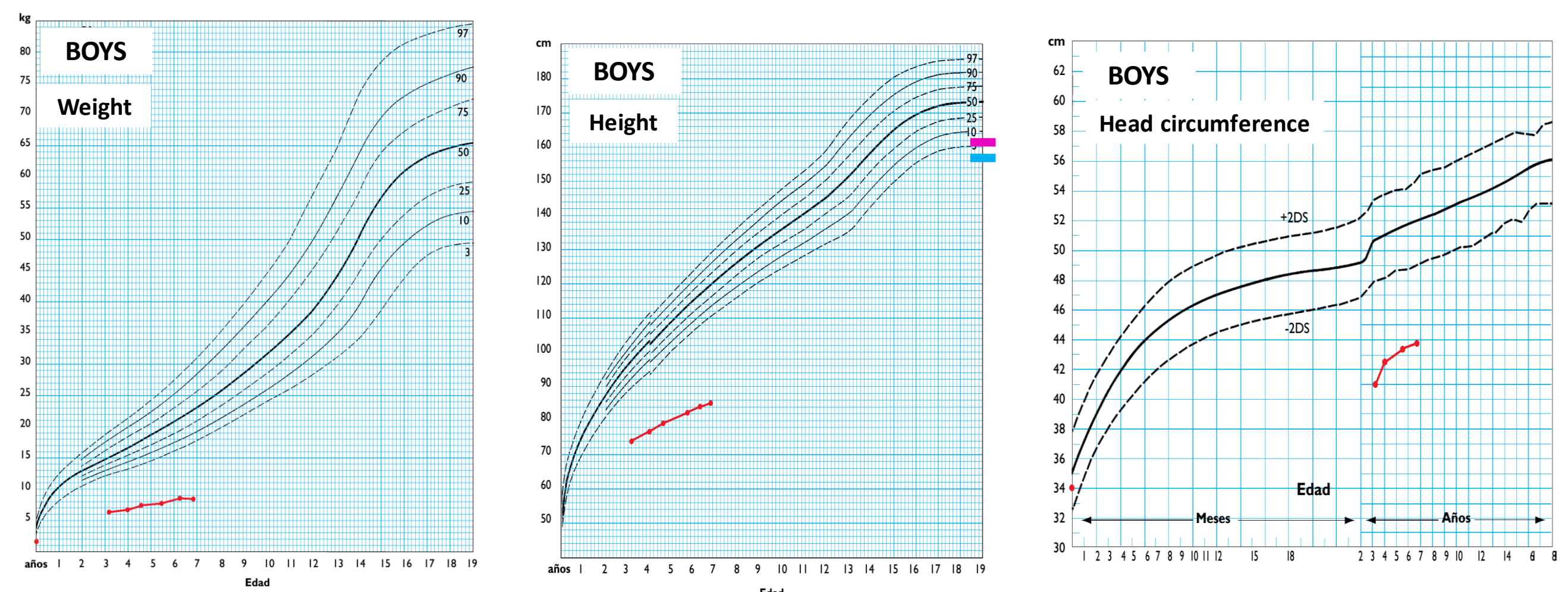
Human *IGF1* gene defects are characterized by intrauterine and postnatal growth retardation, sensorineural deafness, microcephaly and intellectual disability. Few cases have been reported so far, and the underlying pathophysiology has been characterized in only three of them.

Aim

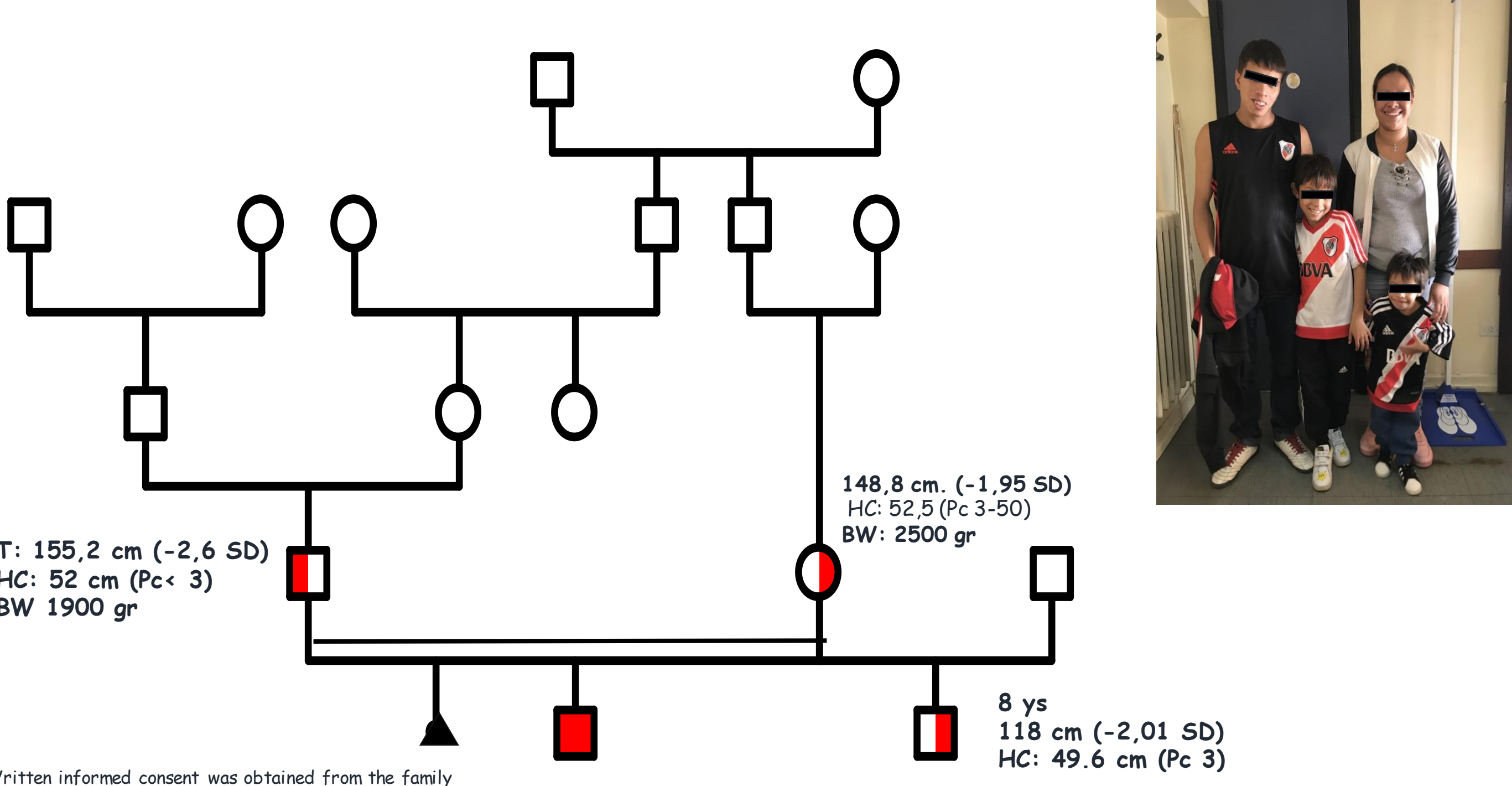
To describe a patient with severe short stature presenting a novel homozygous *IGF1* gene mutation and its underlying pathogenic mechanism.

Case Report

Patient born from consanguineous parents at 40 weeks of gestational age with IUGR. Birth weight: 1910 g (-3.06 SD), length: 38 cm (-6.3 SD), and head circumference: 34 cm (-0.4 SD). At 3.2 years of age, the patient's height was 74 cm (-6.15 SD), weight 6.1 kg (-5.1 SD), head circumference 41 cm (-6.05 SD). Physical examination revealed proportionate short stature, microcephaly, and facial dysmorphism (frontal bossing, triangular face, bulbous nose, full lips, retrognathia). He also presented bilateral sensorineural deafness, mild global developmental delay, and hyperactivity behavior.



Pedigree



Auxological evolution

CA (ys)		3 1/6	4	4 7/12	5 1/2	6 1/4	6 5/6
Weight	kg	6.100	6.650	7.100	7.900	8.500	8.200
	Z score (SD)	-5.10	-4.90	-4.84	-5.6	-4.86	-5.19
Height	cm	74	76.5	79.9	82	84.3	85.8
	Z score (SD)	-6.15	-6.40	-6.13	-6.52	-6.56	-6.70
SH	Cm	42	-	-	46.8	49.5	-
HC	cm	41	42.5	42.8	43.4	42.8	43.8
HV	cm/y	-	3.9	5.8	2.3	3	2.5
BA	Ys	-	-	-	-	-	4

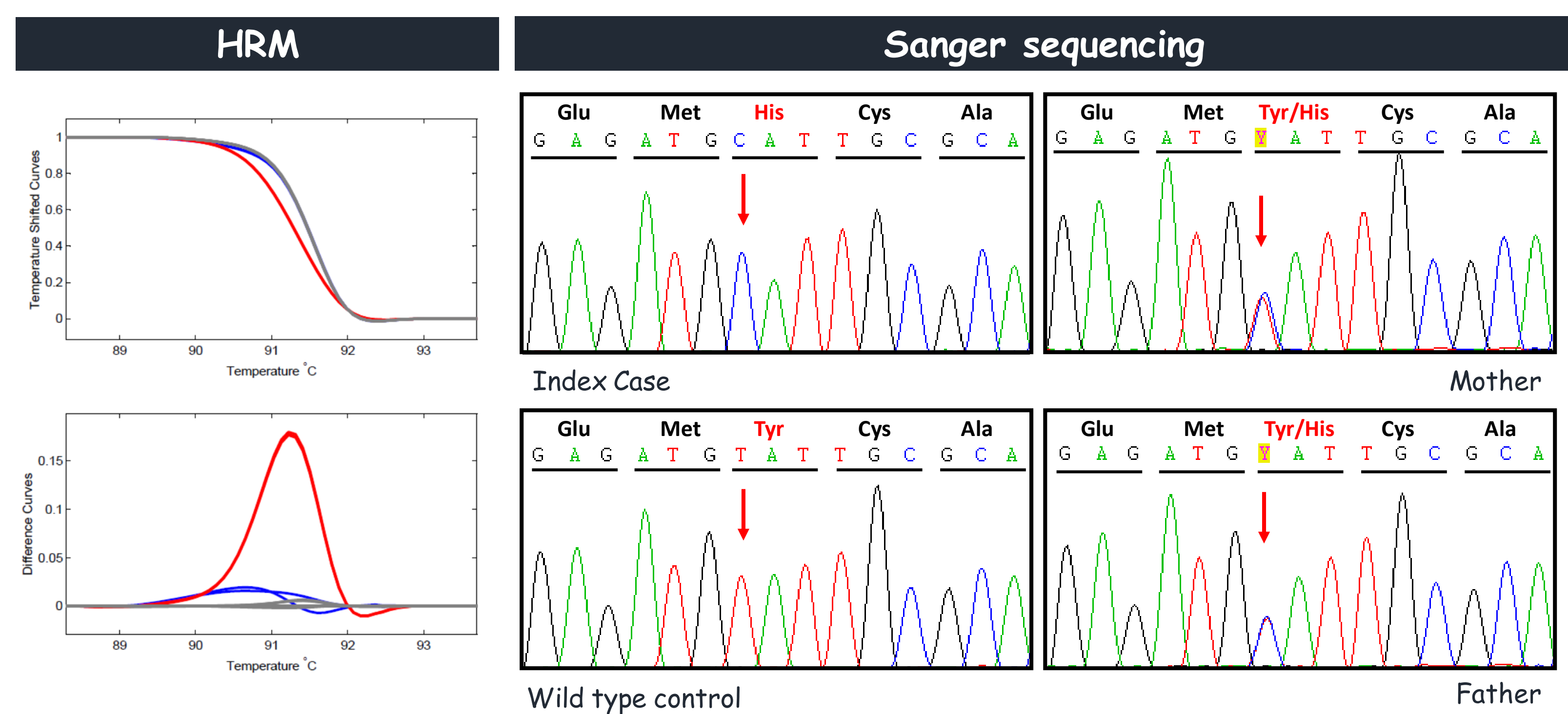
Results

	3 4/12	3 7/12	4 0/12	5 9/12	6 5/12	6 10/12	References
TSH (μUI/ml)	4.30	-	-	1.53	2.59	5.3	0.5- 6.5
FT4 (ng/dL)	1.46	-	-	1.23	1.46	1.38	0.8- 2.2
TG Ab/ TPO Ab (U/ml)	Negative	-	-	-	Negative	-	-
LH (mUI/ml)	0.34	-	0.12	<0.1	-	<0.1	0.1- 0.3
FSH (mUI/ml)	1.09	-	0.69	0.65	-	0.94	0.6- 4.6
To (ng/dL)	<10	-	-	<10	-	<10	<10
AMH (pmol/L)	593	-	426	597	-	584	300- 1800
Cortisol (μg/dL)	10.4	-	-	10.4	17.8	-	6- 21
Prolactin (ng/ml)	↑ 49.6	-	-	6.7	9.6	-	2- 15
GH, basal (ng/ml)	9	29.10	1.57	2.97	-	0.48	-
IGF-1 (ng/ml) (SD)	89	108	47	75	206	164	-
(CLIA)	(+0.31)	(+0.75)	(-1.15)	(-0.71)	(+2.95)	(+2.12)	-
IGF-BP3 (μg/ml)/(SD)	3.86	4.12	2.66	2.3	5.3	4.5	-
(+1.22)	(+1.55)	(-0.32)	(-1.58)	(+2.31)	(+1.27)	-	-
Insulin (μUI/l)	-	-	2.6	-	5.4	-	1.8-12

Molecular Techniques:

- **SNP-Array** (850K, Illumina) identified multiple loss of heterozygosity regions, including 12q23.2, where *IGF1*, a potential candidate gene for the patient's phenotype, maps.
- **High Resolution Melting (HRM)** for *IGF1* gene exonic and known regulatory regions was performed.
- **Sanger sequencing** of *IGF1* fragments with altered mobility detected by HRM identified a **homozygous c.322T>C** variant, predicted to result in p.Tyr108His change in the protein.

NM_00111283.2: c.322T>C (p.Tyr108His)

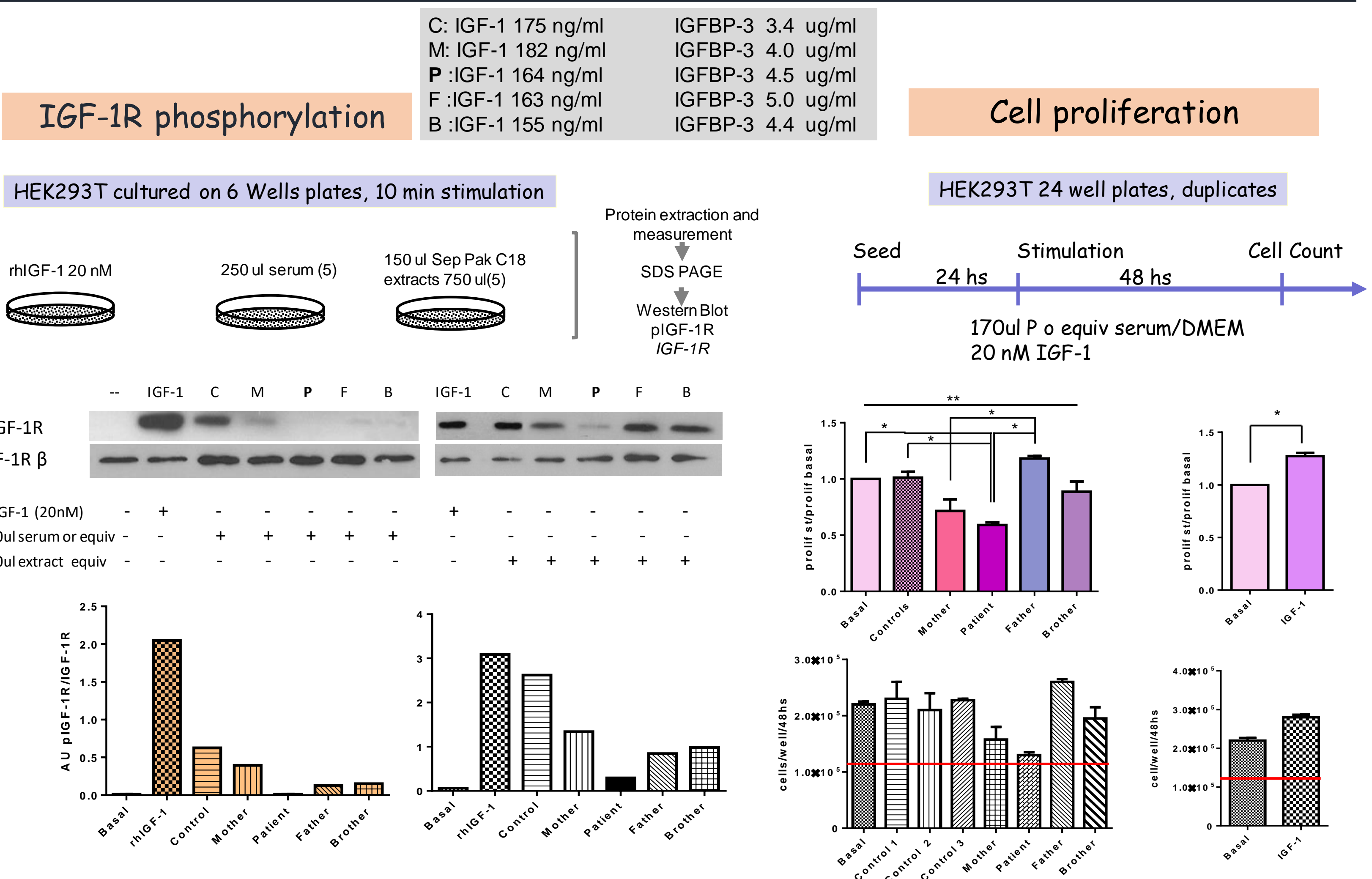


In silico studies

- ✓ p.Tyr108His variant, which has not been previously described, changes a highly conserved Tyr residue (Tyr60 according to the mature IGF-1 peptide aminoacid numbering), in the insulin domain.
- ✓ Although it is classified as Variant of Unknown Significance (VUS) according to ACMG guidelines, it is consistently predicted as pathogenic by multiple bioinformatic tools.
- ✓ Tyr108 (Tyr60) is located in the A domain of IGF-I and has already been described to be critical for IGF-I interaction with its receptor (IGF1-receptor).

CADD	DANN	MetaR	POLYPHEN	MUTATION TASTER	SIFT	GERP	gnomAD Exomes (ExAC)	gnomAD Genomes	1000G
27.4	0.9983	Damaging	Probably damaging (0.999)	Disease causing (1)	Damaging (0)	5,8499	Absent	Absent	Absent

In vitro studies



Conclusion

We described a patient with severe short stature harboring a novel *IGF1* mutation involving a change of a conserved amino acid. This change may cause a diminished affinity of IGF-I for its receptor, resulting in a decreased activation of IGF-1R and therefore of its biological activity.