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TWO NOVEL MUTATIONS IN GLI2 GENE IN TWO UNRELATED ARGENTINEAN PREPUBERAL PATIENTS, ONE WITH ISOLATED GROWTH HORMONE DEFICIENCY AND ANOTHER WITH MULTIPLE PITUITARY HORMONE DEFICIENCY, BOTH WITH DEVELOPMENTAL DEFECTS IN POSTERIOR PITUITARY GLAND

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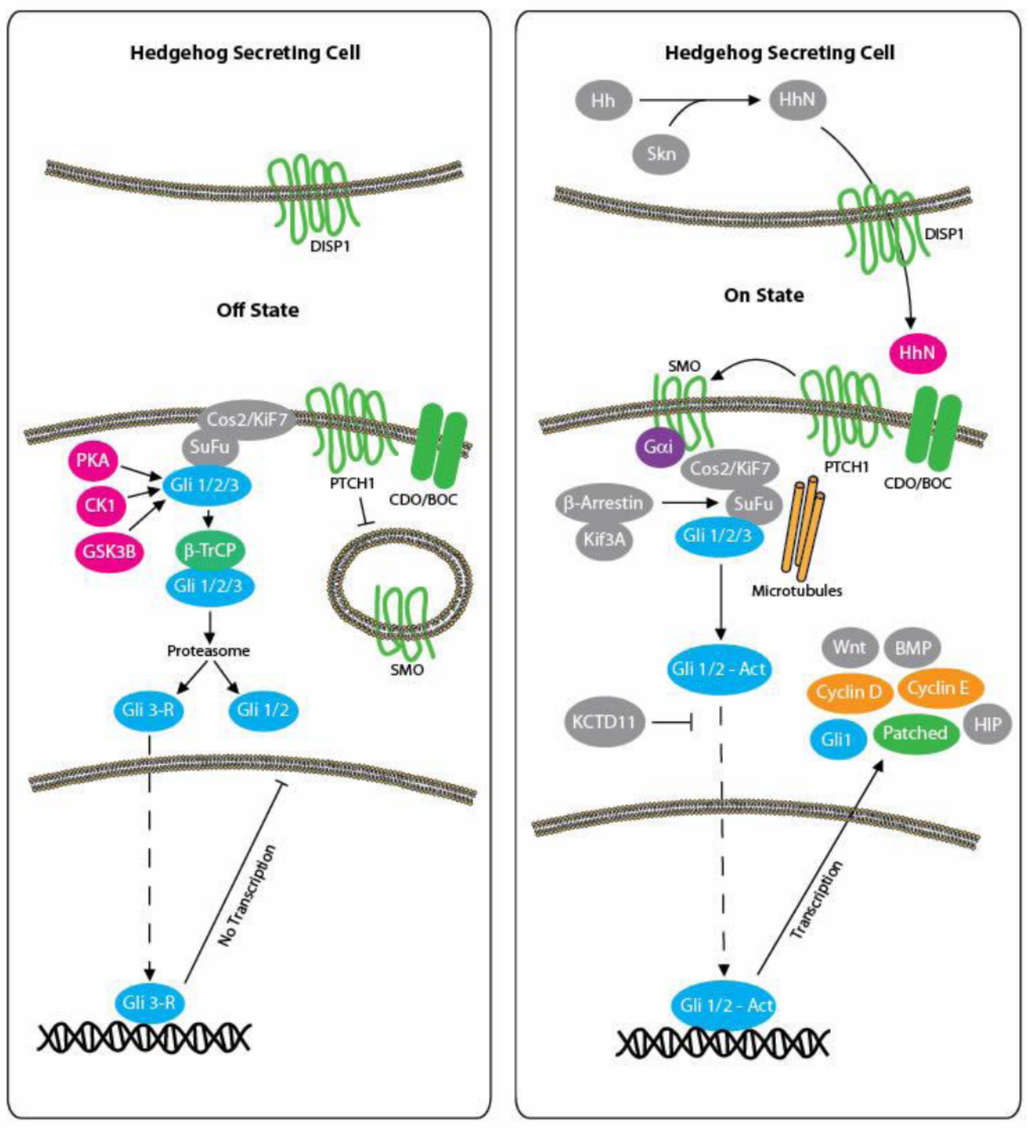
INTRODUCTION

- Congenital growth hormone deficiency (CGHD) may be isolated (IGHD) or multiple pituitary hormone deficiency (MPHD).
- The Sonic Hedgehog signaling (SHH) pathway has an important role in the pituitary development and growth, acting early in ventral forebrain. The SHH signaling mediates its effects through three zinc fingers proteins (Gli1, Gli2 and Gli3), which lead to activation or repression of target genes.
- In the last years, several reports showed variants in *GLI2* as a frequent cause of CGHD, especially in patients with ectopic posterior lobe *(Bear KA et al 2014)*.
- Mutations in *GLI2* have been described associated with a diverse range of phenotypes, including holoprosencephaly and polydactyly.



AIM

- To analyze the presence of *GLI2* gene alterations in two patients, one with IGHD and another with MPHD, both with developmental defects in posterior pituitary gland.

METHODS

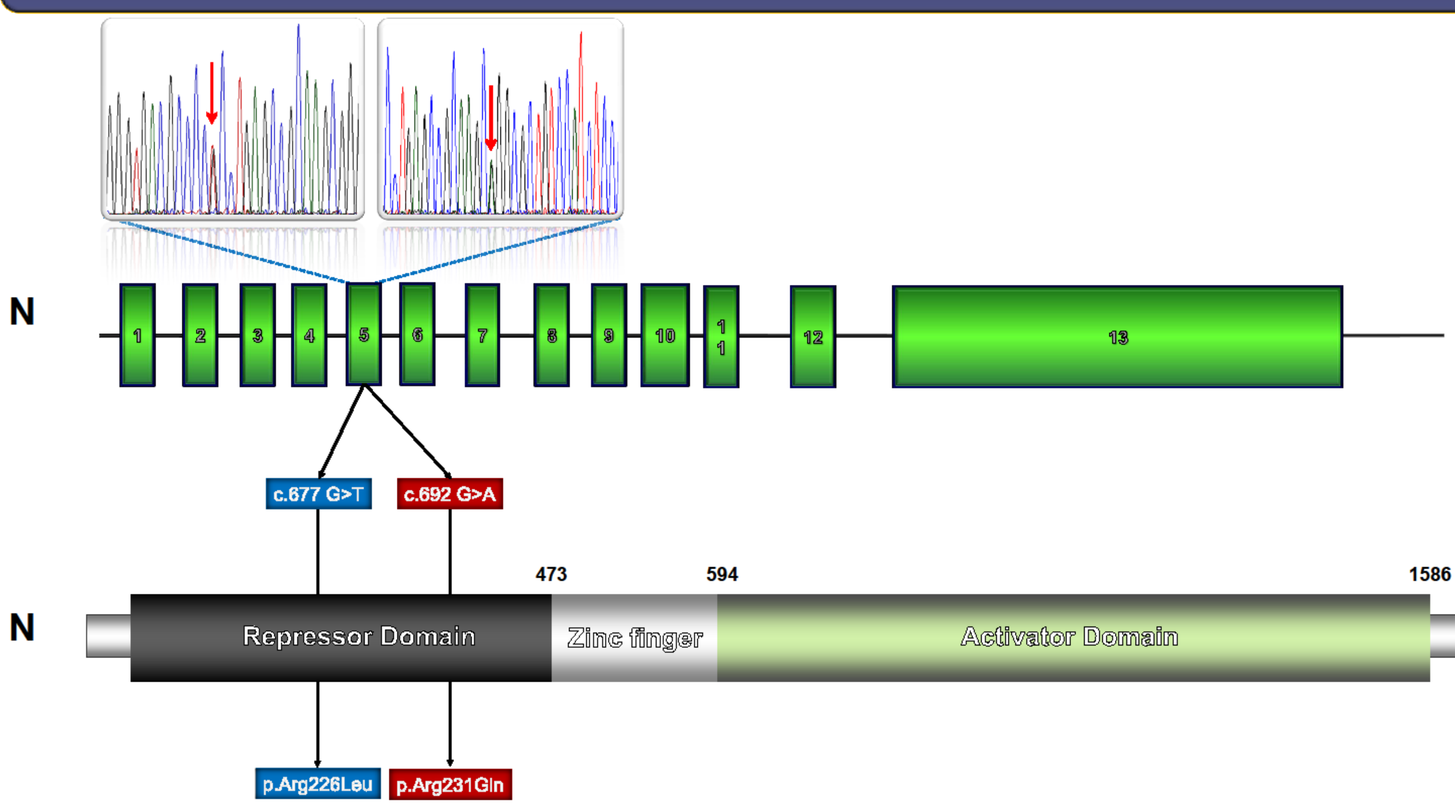
- Molecular Analysis: Genomic DNA was isolated from mononuclear cells of the affected subjects and relatives according to standard procedures. The coding sequence (exon 1-13) and flanking intronic regions of GLI2 gene were PCR amplified from genomic DNA, using specific primers *(Marcela M. Franca et al 2010).*
- Each purified product was automated sequenced using BigDye Terminator version 3.1 cycle sequencing kit (Applied Biosystems, Buenos Aires, Argentina) and 3130 Genetic Analyzer capillary DNA sequencer (Applied Biosystems). The nucleotide sequences obtained were compared with those from GenBank accession number: NG_009030.1.
- *In silico* assays: online tools such as SIFT, PolyPhen2 and Mutation Taster were applied to identify the potential functional impact of newly found variants.

PATIENTS

AT BIRTH	P1	P2
Sex	Female	Male
GESTATIONAL AGE (weeks)	40	38
WEIGHT Kg (SDS)	3.180 (-0.1)	3.420 (0.5)
FIRST EXAMINATION		
CRONOLOGICAL AGE (years)	2	0.64
BONE AGE (years)	1.3	
Length / Height cm (SDS)	74.4 (-3.5)	64.8 (-1.96)
WEIGHT Kg (SDS)	9.15 (-2.14)	7.53 (-1.17)
HEAD CIRCUMFERENCE cm (SDS)	44.5 (-2.5)	42.5 (-2)
NEUROLOGICAL DEVELOPMENT	Mild neurodevelopmental delay at the language area	Neurodevelopmental delay (probably associated with seizures)
ADITIONAL FINDINGS	Right cleft lip and palate with a nasal tooth. Low nasal bridge. Left eye strabismus	Neonatal Hypoglycemia Micropenis.
POSTERIOR LOBE	Ectopic	Absent
ANTERIOR PITUITARY	Hypoplastic anterior pituitary and absent pituitary stalk.	Hypoplastic anterior pituitary and absent pituitary stalk.
GH DEFICIENCY	IGHD	MPHD
BIOCHEMICAL MEASUREMENTS		
BASAL GH ng/ml	0.28	0.55
GH PEAK ng/ml	2.57	0.75
IGF1 ng/ml (SDS)	10.8 (-3.94)	
TSH (mUI/ml)/T4(mcg/dl)/T4L(ng/dl)/T3(ng/ml)	3.98/8/1.14/1.39	3.84/4.6/0.36/1.88
ACTH(pg/ml)/cortisol(mcg/dl)	16.3/10.8	-/3.4
KARYOTYPE	46,XX	46,XY
MOLECULAR ANALYSIS	p.[Arg231Gln];[=]	p.[Arg226Leu;Met1444Ile;Leu1445Phe];[Met1444Ile;Leu1445Phe]*

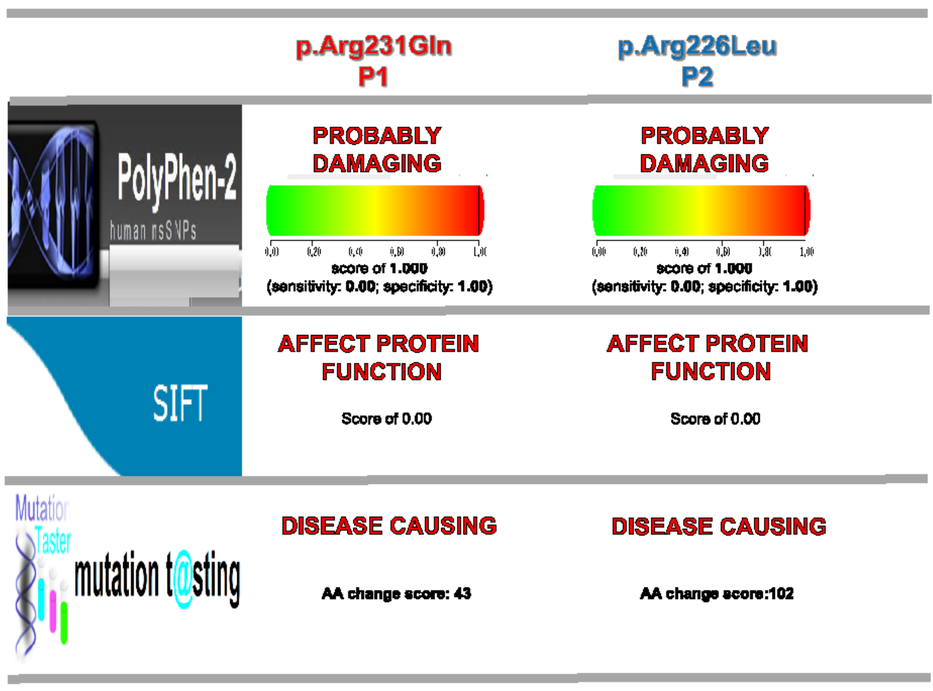
*Met1444Ile;Leu1445Phe Rs146467786;rs146207623 SNP

MOLECULAR ANALYSIS



These variations were not found in the databases of NCBI, ensembl genome browser and Exac browser beta.

***In Silico* tools**



CONCLUSION

- We report two novel heterozygous missense mutations in the *GLI2* gene that affect the repressor domain of the protein and two homozygous missense mutations in the activator domain of the protein in two affected non related patients with different clinical phenotype. Our study suggests that GLI2 gene would be one of the candidate genes to analyze when developmental defects in posterior pituitary gland are present. The highly variable phenotype found suggests the presence of additional unknown factors that could contribute to the phenotypic variation observed in these patients.

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