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Early diagnosis and treatment of a newborn with a *POU1F1* mutation

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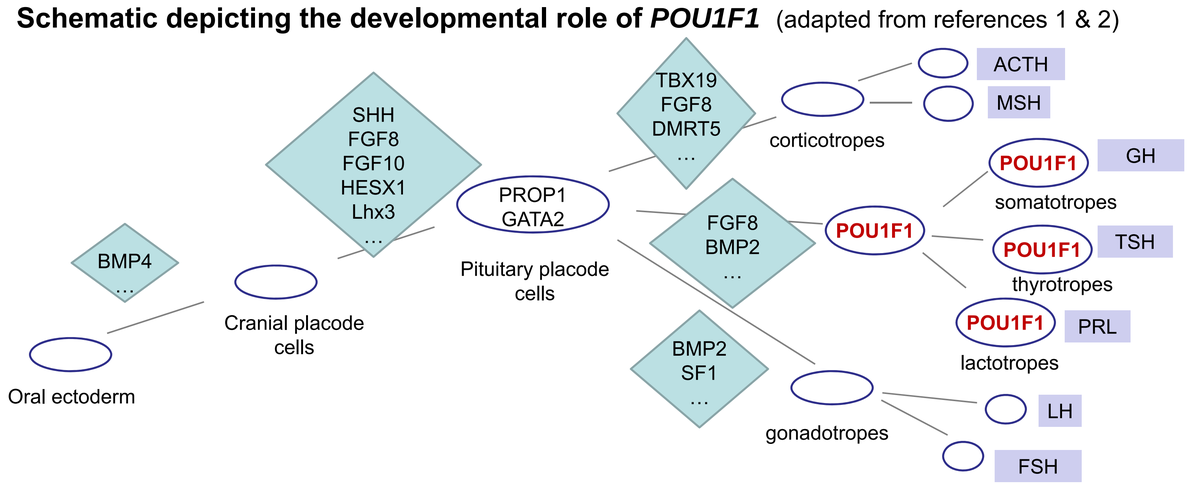
Introduction

POU1F1 (PIT-1) encodes a pituitary-specific homeodomain transcription factor that is crucial for the development and differentiation of anterior pituitary cell types.

Mutations in *POU1F1* result in combined pituitary hormone deficiency (CPHD). Specifically, *POU1F1* mutations cause growth hormone (GH), thyrotropin (TSH) and prolactin (PRL) deficiency.

The R271W mutation exhibits a dominant-negative effect leading to mutant polypeptides that disrupt the activity of the wild-type gene when overexpressed.

Schematic depicting the developmental role of *POU1F1* (adapted from references 1 & 2)



Abbreviations

BMP :	*bone morphogenic protein*
FGF:	*fibroblast growth factor*
Lhx:	*LIM homeodomain protein*
SHH :	*sonic hedgehog*
PROP1:	*prophet of Pit1*
TBX:	*T-box (TPIT)*
DMRT5 :	Doublesex and mab-3–related transcription factor 5
SF1 :	Steroidogenic factor 1
ACTH:	adrenocorticotrophic hormone
MSH :	melanocyte-stimulating hormone
GH :	growth hormone
TSH:	thyroid-stimulating hormone
PRL:	prolactin
LH:	luteinizing hormone
FSH:	follicle-stimulating hormone

Case report

Presentation & family history

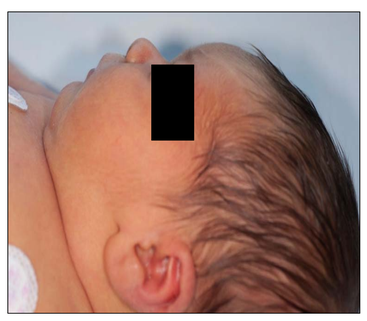
Full-term infant born following spontaneous, uneventful pregnancy.

Mother's history is notable for CPHD (GH / TSH / PRL). She was diagnosed & treated at 12 months of age and harbors *POU1F1* R271W mutation.

- mild developmental delay
- spontaneous puberty (menarche 12 yo)
- adult Height: 157cm (-1.1 SDS)

Physical examination

- weight: 3300 g (-0.5 SDS)
- length: 47 cm. (-1.6 SDS)
- head circumference: 37.5 cm (+2.7 SDS)
- APGAR: 09/10/10
- hypotonia
- icterus
- marked nasal bridge
- large fontanelles
  anterior:4x3.5 cm
  posterior: 2x1 cm)
- micropenis : 2.4 x 0.7cm
- otherwise normal examination



Treatment

- L-thyroxine substitution initiated on day 2 of life.
- GH (0.025mg/kg/day) on day 4 of life. This effectively prevented further hypoglycemic events as evidenced by continuous glucose monitoring.

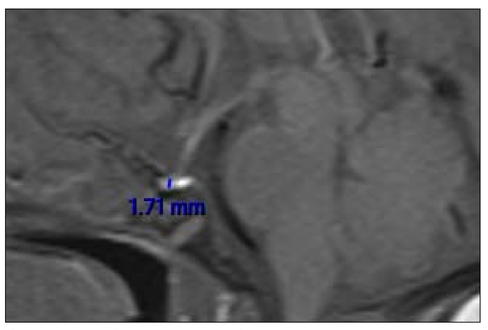
Results

Laboratory results

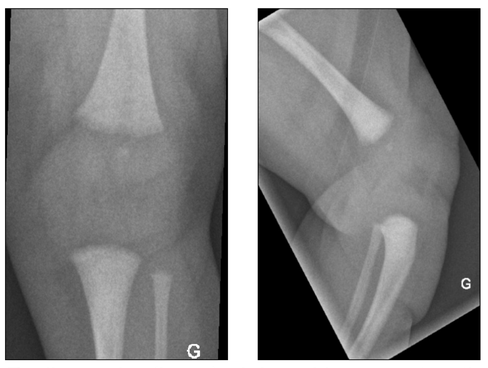
	Unit	normal range	cord blood	day 2 hypoglycemia	2 months minipuberty
TSH	mU/l	3.1-6.8	0.695	1.71	
fT4	pmol/l	12-22	9	4.7	18
PRL	µg/l	4-16	2	0.4	
glycemia	mmol/l	2.1-4.9		**1.7**	
cortisol	nmol/l	>500		619	
insulin	mU/l			<1	
GH	nmol/l		0.06	<0.05	
IGF1	µg/l	48-313		<35	<35
IGFBP3	ng/l	0.5-1.4		<0,5	1.2
LH	UI/l	0-13	0.5		2.7
FSH	UI/l	0-28	0.3		1
testosterone	nmol/l	4-14	3.4		7.2
AMH	ng/ml				>210
Inhibin B	pg/ml				790

CPHD confirmed → central hypothyroidism, GHD, PRL deficiency

Imaging studies



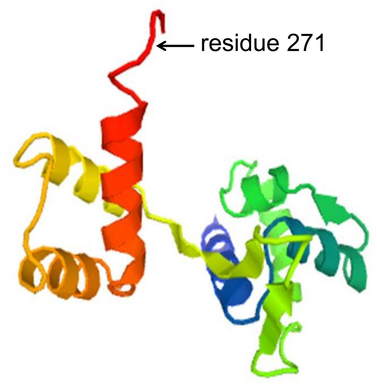
Cranial MRI: hypoplastic adenohypophysis



Radiographs (knee): delayed bone maturation

Genetic testing

- Blood was sent to the laboratory of Dr. Roland Pfaeffle of the University of Leipzig (Germany) for genetic analysis.
- Sequencing of *POU1F1* revealed the same p.R271W mutation as the mother.
- The residue maps to the C-terminal end of the POU-homeodomain (see right) http://www.uniprot.org/uniprot/P28069



Discussion

Diagnostic challenges

CPHD in neonates:

→ symptoms are non-specific

→ neonatal screening (TSH & T4) is needed to detect central hypothyroidism

Possible consequences :

→ inverse relationship between age at hypothyroidism diagnosis/treatment and intelligence quotient[3]

→ risk of brain injury due to severe, repeated hypoglycemia[4]

Treatment challenges

GH substitution:

→ few cases with GH substitution beginning during neonatal period : (starting dose = 0.021-0.033mg/kg/day)[5]

→ favorable outcomes when GH treatment initiated before 1 year of age[6]

Treatment during pregnancy:

→ thyroid substitution needs to be adapted during pregnancy

→ to our knowledge, there is currently no recommendation for the growth hormone substitution during pregnancy

References

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Growth

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