FOXL2 gene and combined pituitary hormone deficiency: a possible link

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Background

Mutations in candidate genes are rarely identified in congenital hypopituitarism. Extrapituitary symptoms can point towards new genes of interest.

Blepharophimosis Ptosis Epicanthus Syndrome (BPES) is a rare affection that combined congenital alteration of eyelids with ovarian dysgenesis in some families. Genetic lesions are often heterozygous mutations of the *FOXL2* gene[1].
We have previously observed the association of BPES with hypopituitarism in some rare non-related cases[2].

FOXL2 is a transcription factor from the Forkhead family, involved in embryonic development. This gene is essential for the development of female gonads and ovarian function and has recently been implicated in ovarian granula cell tumor.
FOXL2 is expressed early in the pituitary gland, essentially in gonadotropic cells, but also in thyrotropic cells[3]. FOXL2 knock-out mice are smaller and have low IGF1 levels.

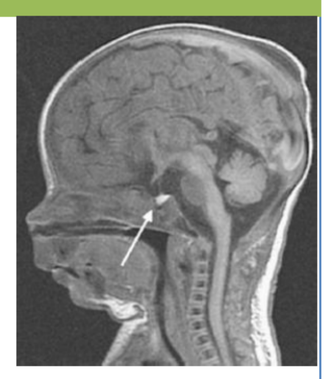
Objective

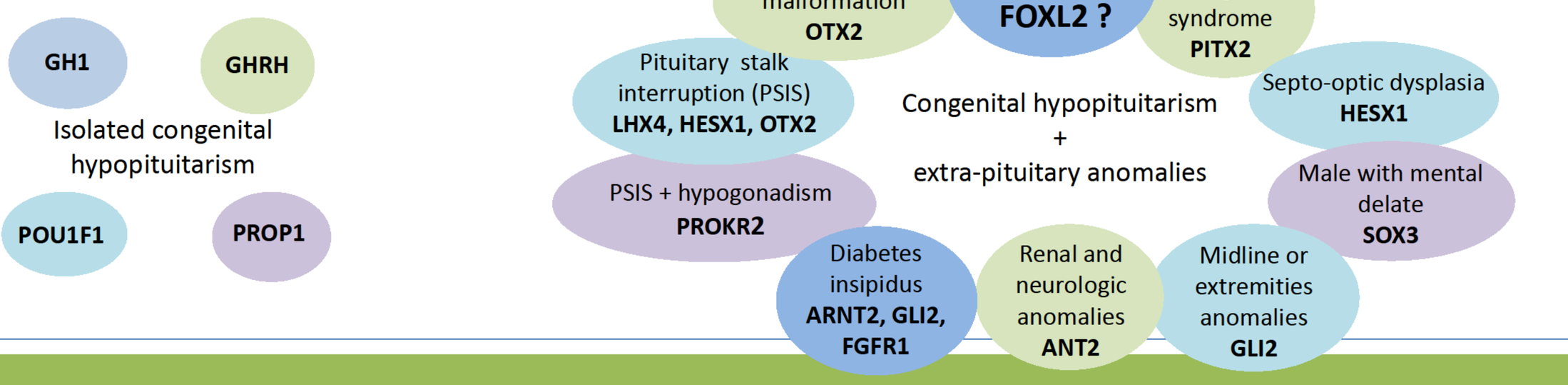
Better define the possible molecular association between ocular anomalies and hypopituitarism.

Method

Cohort of 22 patients with hypopituitarism and ocular anomalies (eyelid / eyeball / optic nerve)

Screening of
- FOXL2 in patients with eyelid anomalies
- OTX2 and HESX1 in all patients
- selected candidate genes based on clinical and radiological signs



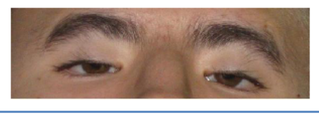


Results

FOXL2 2 mutations in patients with BPES

Patient 1
- 1092-1108dup
- BPES, strabism, astigmatism, dysmorphia
- CPHD (GH, TSH, ACTH)
- MRI showed hypoplasia of antehypophysis, malformation of Chiari 1, syringomyelia C5-C7

Patient 2
- c675_1008del
- BPES and isolated GHD
- MRI showed PSIS



OTX2 1 mutation

- c.426delC
- Patient presenting with septo-optic dysplasia, bilateral microphtalmia, mental retardation, autism
- Isolated GHD
- MRI showed normal antehypophysis, no postypophysis, and hypoplasia of optic chiasma.

Other genes no mutation identified

Conclusion

This study indicates a possible role of FOXL2 in hypothalamus and pituitary development. FOXL2 mutation is indeed the most frequent molecular anomaly within our cohort of patients with hypopituitarism and ocular anomalies.
Further studies are necessary to determine if FOXL2 should be sequenced in CPHD patients presenting eyelid anomalies distinct from those observed in BPES.

References

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