Haplo-insufficiency for *LHX4* alone does not result in hypopituitarism.

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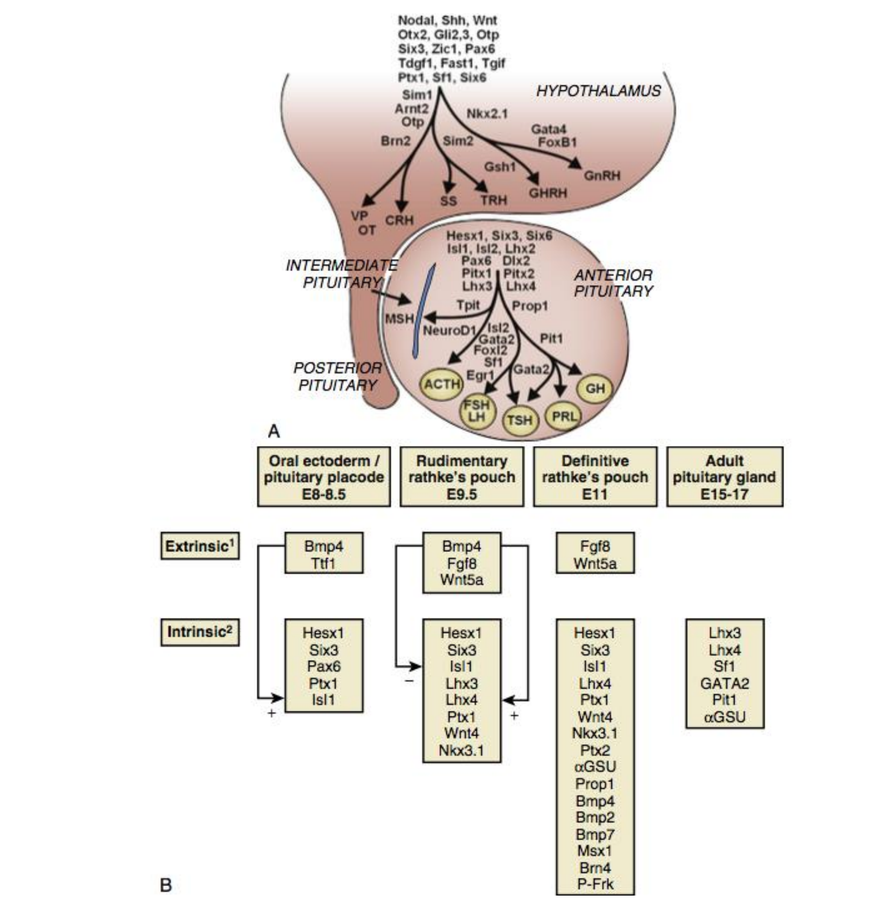
Background

Two LIM homeodomain transcription factors, Lhx3 and Lhx4, are critical in the development of the nervous system and pituitary gland in mice. *Lhx4* is expressed from E9.5 with peak expression between E10.5-E12.5, followed by a lower level until approximately E15.5. Recent work shows that *Lhx4* is necessary for efficient pituitary progenitor cell proliferation and restriction of p21 expression.[1] *Lhx4* null mice die shortly after birth and have pituitary hypoplasia. A homozygous *LHX4* mutation was found in a child with congenital hypopituitarism with ectopic posterior pituitary and neonatal death.[2] Heterozygous *LHX4* variants, but not deletions, have been described previously and are linked to hypopituitarism but have variable penetrance.



Index Case

- Baby girl, term, birth weight 3.1kg, no hypoglyc/jaundice
- Neonatal pneunomia, gastroesophageal reflux
- Severe feeding difficulties and food aversion
- Failure to gain weight
- NG feeding from 1.5 – 4.5 yrs of age
- Mild speech delay and mild developmental delay
- Mild constipation from 8-9 years of age
- Behavioural problems and night time incontinence

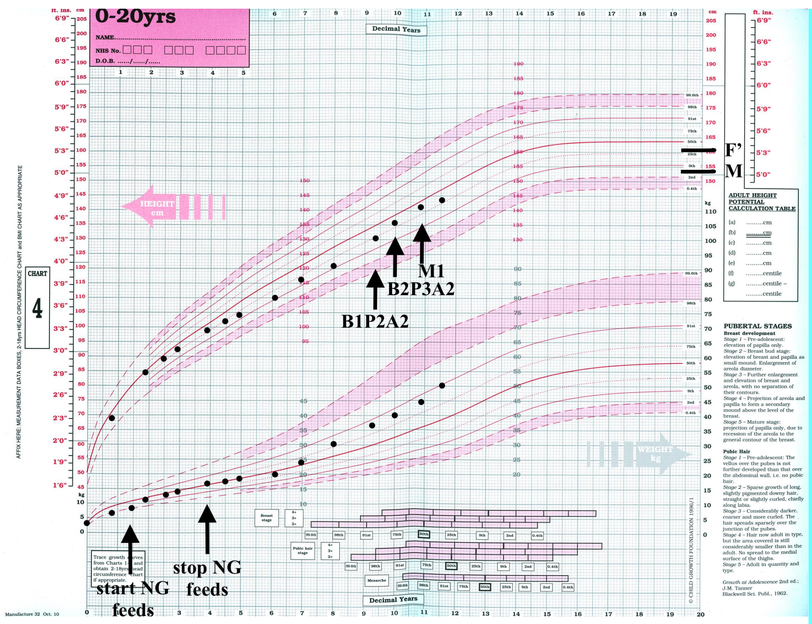
Genetic analysis with CGH (age 9 yrs)

- Microdeletion in chromosome 1 including *LHX4*
- 1q25.2q25.3 (179,329,152-181,516,624)x1 (2.2MB)

Family history

- Asian Mother healthy, no miscrriages. Normal chromosome 1.
- Asian Father: Type 2 DM since age 30. No genetic test result.
- Not consanguineous. Brother and sister healthy
- 2 cousins: syndromic, abnormal kidneys, one cousin died at 8 months

Physical examination and Growth



- Not dysmorphic
- Obese
- Mild ac. Nigricans
- Mild hypertrichosis

Growth chart

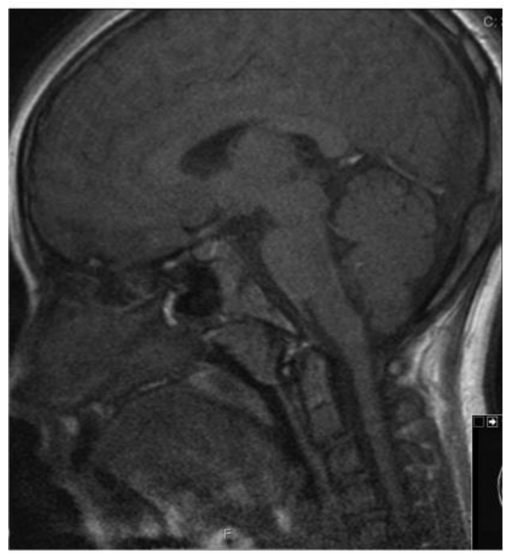
- Initial poor weight gain needing NG
- Reduced height velocity after stopping NG feeds
- Fast progression through puberty

Endocrine investigations (age 10.1)

FT4 11.2 pmol/L (9-19)
TSH 1.34 mU/L (0.5-6)
Cortisol random 163 nmol/L
FSH 4.3, LH 2.3 U/L
Prolactin 167 nmol/L
IGF1 613 ng/mL (62-504)
Plasma osmol 288

MRI brain

Normal pituitary, brain structures and vertebrae



Discussion

- The index case is hemizygous for *LHX4*
- It is currently not known whether this is a de novo deletion
- She had a fast progression through puberty and may have a small final height, but does not curently have hypopituitarism
- Redundancy or rescue by other transcription factors may be responsible for the absence of a pituitary phenotype in *LHX4* dosage reduction.
- Heterozygous *LHX4* mutations previously described in hypopituitarism may be part of a digenic or oligogenic cause of disease or act in a dominant negative fashion.

References

1Grucins P et al, ***Molecular Endocrinology* 29: 597–612, 2015**
2Gregory LC et al, J Clin Endo and Metab 2015;100:2158-64

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