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.

Family history
- 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

Index Case
- Baby girl, term, birth weight 3.1kg, no hypoglycaemia
- Neonatal pneumonia, 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 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)

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 currently 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
2Gregory LC et al, J Clin Endo and Metab 2015;100:2158-64