Identification of a THRA mutation in a 2yr old child with clinical features of hypothyroidism and multisystem involvement

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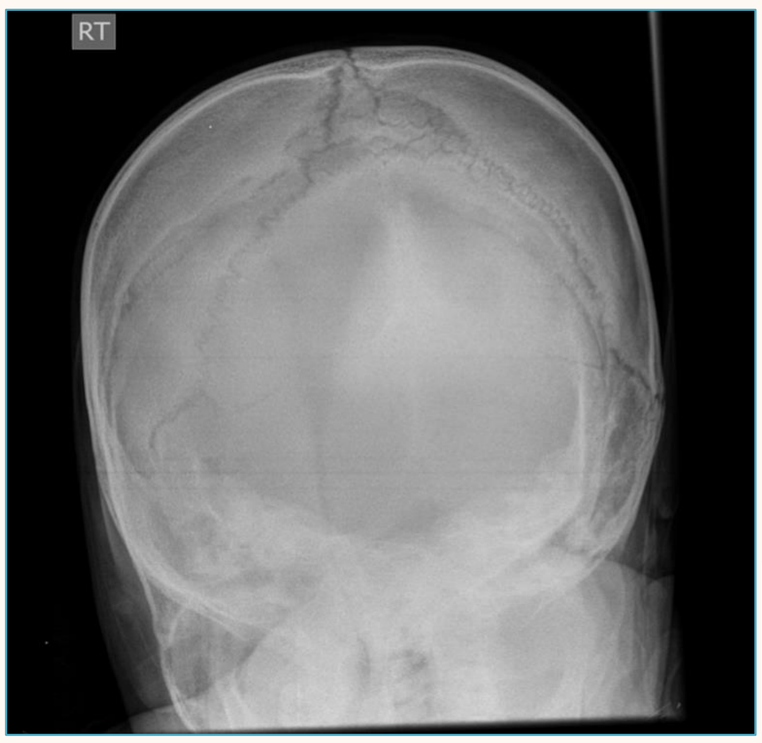
Background: Thyroid hormones act via receptors (TRα; TRβ) encoded by separate genes (*THRA,THRB*). Mutations in *THRA* are a recently recognised cause of resistance to thyroid hormone alpha (RTHα), a disorder with tissue specific hypothyroidism but near normal thyroid function tests.

Aim: We describe the youngest recorded case of RTHα, in a 2yr old boy with disproportionate short stature, global developmental delay, constipation and a heterozygous missense mutation (p.G291S) in *THRA*.

Case Report:
A 16-month old male was referred to endocrine clinic with short stature and deranged thyroid functions. He had disproportionate stature with reduced subischial leg length (Table 1). He is in foster care due to maternal antenatal history of substance abuse (exposure to methadone, heroine and alcohol in utero). He had global developmental delay, mild dysmorphism and constipation, all attributed to chromosome 16p13.11 microduplication.
Examination revealed coarse facial appearance, depressed nasal bridge, long philtrum and central hypotonia. He was noted to have small kidneys and gastroesophageal reflux. He also had delay in speech, motor milestones and visual maturation delay with hypermetropia. Laboratory investigations revealed normocytic anaemia, elevated creatine kinase levels, low-normal T4 and elevated T3 levels leading to altered T4:T3 ratio, with normal TSH levels. *THRA* sequencing identified a heterozygous missense (p.G291S) mutation, which is homologous to a known pathogenic mutation in *THRB* (G345S), causing RTHα. Correlation of genotype with phenotype and assessment of response to thyroxine therapy (25mcg/day) is being undertaken.



Radiograph of skull showing multiple wormian bones

Table 1
Clinical and biochemical characteristics

Variables	2019
Age (years)	2.34
Weight (Kg)	13.35 (-0.21SDS)
Height (cm)	81.0 (-1.9 SDS)
Sitting Height (cm)	36.5 (-3.27 SDS)
Subischial leg length (cm)	34.5
BMI (kg/m^2)	20.35 (2.79 SDS)
Thyroxine dose	None
TSH (mU/L), (rr 0.7-6.0)	2.63
Free T4, (rr 12- 22 pmol/L)	10.8
Free T3, (rr 3.5-8.5 pmol/L)	10.7
TPO (<15 iu/L)	Negative
CK μ/L, (rr 40-320 U/l)	388
RBC mass (Oct 2018), (4.6– 6.2x 10^{12}/L)	3.68
IGF1 nmol/L, (2-20nmol/L)	6.8
Peak Cortisol nmol/L, (rr >550nmol/L) Short synacthen test	740

References:
1. Resistance to Thyroid Hormone alpha – emerging definition of a disorder of thyroid hormone action. Moran C and Chatterjee K , J Clin Endoc Metab, July 2016, 101(7):2636–2639.
2. Resistance to thyroid hormone due to defective thyroid receptor alpha, Carla Moran, et al, Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 647-657

Conclusion:
We suggest that *THRA* sequencing should be considered in patients with clinical features of hypothyroidism, raised CK, anaemia and near-normal thyroid function tests but altered T4:T3 ratio. This case broadens the phenotypic spectrum of RTHα.