Maternally inherited resistance to thyroid hormones with discordant postnatal phenotypes in two infant brothers

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Introduction

Resistance to thyroid hormone (RTH) is an uncommon disease that can present with a wide variety of clinical signs. Here, we describe 2 siblings who both inherited a known maternal THRB mutation but presented in 2 very different ways; sibling 2 was later found to have a 22q11.2 deletion.

Resistance to thyroid hormone

Thyroid hormone resistance is an uncommon disease with a prevalence estimated at 1:40,000 individuals. Mutations in *THRB* on chromosome 3 are the most commonly described molecular defects. The inheritance is generally dominant but 15 to 20% of cases appear *de novo*.

Abnormal THRBs have minimal or reduced T3 binding and fail to mediate T3-regulated transcription. The defective THRB interferes with the normal THRB, producing an inactive homodimer (a dominant negative effect).

Patients usually present with increased levels of T4 and T3 with an "inappropriately" normal or high TSH.

Clinical manifestations are widely variable and can include symptoms of both hyperthyroidism and hypothyroidism. While some patients are asymptomatic and simply diagnosed based on abnormal TFTs, others can present with goiter, tachycardia, failure to thrive, delayed bone maturation, hyperactivity or developmental delay.

Even within families, there can be variability in the clinical presentation.

22q11.2 Deletion Syndrome

22q11.2 deletion is found in 1 in 4,000 individuals.

Most commonly, patients present with congenital heart disease (usually conotruncal defects), cleft palate, learning difficulties, immune deficiency secondary to thymic hypoplasia, and can present with hypocalcemia secondary to hypoparathyroidism. A significant proportion of patients also present with genitourinary tract abnormalities, such as renal agenesis, hydronephrosis, multicystic/dysplastic kidneys, duplicated kidney, horseshoe kidney, absent uterus, hypospadias, inguinal hernia, and cryptorchidism.

Feeding difficulties, laryngomalacia/stridor and ear abnormalities are also frequent findings.

Mother

Our patients' mother was the first in her family to be diagnosed with thyroid hormone resistance.

She had previously been known for migraines only. In 2006, thyroid function tests were done in the context of fatigue and revealed a normal TSH with an elevated free T4, however no action was taken.

They were repeated in 2009 and showed at TSH of 2.8 mU/L , free T4 of 31 pmol/L and a free T3 of 11.8 pmol/L.

Referral was made to Endocrinology to further assess these unusual results. Upon review of the family history, her father was also noted to have a similar pattern (see Pedigree). A diagnosis of probable thyroid hormone resistance was made.

She was referred to Genetics in 2010 to confirm the diagnosis with a molecular test, however at the time no genetic testing was offered.

In 2014, molecular testing became available and a c.728G>A, p.R243Q mutation in *THRB* was found, confirming the clinical diagnosis.

She has been followed by Endocrinology since but has remained asymptomatic and has not needed treatment.

Sibling 1

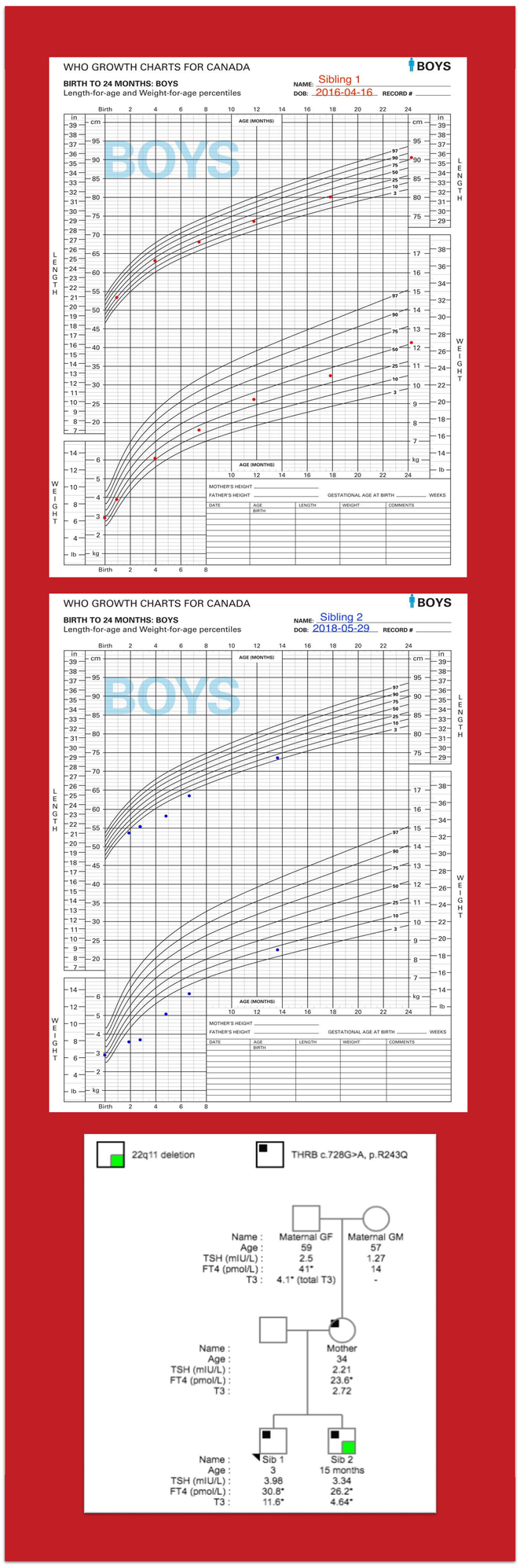
Sibling 1 was born at 37 weeks gestation. The pregnancy had been followed closely by obstetrics. Serial ultrasounds were performed, to monitor growth.

Thyroid volume was assessed on one of the ultrasounds and was noted to be "normal".

Delivery was uncomplicated. Birth weight was 2.92 kg and mother and baby were discharged home on day of life 2. The baby was exclusively breastfed in infancy.

At 2 days of life, whole blood TSH at routine newborn screening was 1.4 mU/L and serum TSH was 3.28 and free T4 39.6 pmol/L. Similar results were obtained at 3 months (TSH 3.98; fT4 30.8). Growth was unremarkable (Figure) and there was no other medical problem.

Molecular testing confirmed that he a had inherited the known c.728G>A, p.R243Q mutation in *THRB* from his mother.



Sibling 2

Sibling 2 was also born after an uncomplicated pregnancy, at 37 weeks. Birth weight was 2.92 kg. Antenatal ultrasounds had showed a small cystic right kidney. Thyroid volume assessed on ultrasound at 25 weeks gestation was noted to be "small".

At 2 days of life, whole blood TSH at routine newborn screening was 5.2 mU/L and serum TSH was 4.26 and free T4 53.37 pmol/L. Similar results were obtained at 3 months (TSH 1.8; fT4 31.7)

In addition, he had a preauricular tag. He was discharged at day of life 2; however, he was readmitted on day of life 5 for stridor.

After investigations, he received a diagnosis of laryngomalacia; on day of life 10, a CT angiogram was performed and did not show any malformations of the heart or vessels; the aortic arch was normally angulated.

On subsequent follow-up, he was noted to have failure to thrive (weight -3 SD) but did not exhibit any other sign of hyperthyroidism.

In the context of the multiple anomalies and failure to thrive, an aCGH was performed and revealed a 22q11.2 deletion. This deletion was absent in the parents.

Feeding with enriched formula led to adequate catch up growth (Figure).

At 7 months, he presented to the emergency room with febrile seizures. Serum calcium was 2.56 mmol/L.

Conclusion

Our 2 siblings had similarly normal antenatal course and normal birth weights, presumably protected from thyrotoxicosis secondary to elevated maternal FT4 levels by their own mutation, as has been described by Anselmo *et al*. In addition, their very similar biochemistry suggest a similar degree of severity and therefore would not account for the different post-natal course.

To our knowledge, sibling # 2 is the first reported case of simultaneous RTH and 22q11 deletion. Given the estimated prevalence of both syndromes, the likelihood of this occurring by chance would be 1:160 million.

While there is no obvious biological link between the two conditions, it is the contrast with the postnatal evolution of sibling # 1 that led us to broaden the diagnostic investigations in sibling # 2.

References:

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Thyroid

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