A novel mutation in the Thyroglobulin gene resulting in Neonatal Goiter and Congenital Hypothyroidism in an Eritrean infant

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Background

- Congenital hypothyroidism (CH) has a reported incidence between 1/2000 – 1/4000 live births
- 85% of cases are sporadic and secondary to a structural abnormality of the thyroid gland (dysgenesis) including thyroid agenesis or an ectopic or sublingual thyroid gland
- 15% of cases are hereditary and secondary to an inborn error of thyroid hormone synthesis
- These conditions are usually transmitted in an autosomal recessive fashion, and can cause varying severity of hypothyroidism, with or without other clinical features (Table 1)

Gene	Gene Symbol	Chromosomal location	Process affected	Clinical features
Sodium iodide symporter	SLC5A5 (NIS)	19p13	Iodide trapping	Reduced thyroidal iodide or pertechnetate uptake
Pendrin	SLC26A4 (PDS)	7q31	Iodide efflux into follicular lumen	Sensorineural deafness enlarged vestibular aqueduct PIOD and goiter
Thyroglobulin	**TG**	**8q24**	**Matrix protein for hormone synthesis**	**Hypothyroidism, goiter, absent or very low serum TG level**
Thyroid peroxidase	TPO	2p25	Iodide organification/coupling reaction	TIOD or PIOD
Dual oxidase 2	DUOX2 (THOX2)	15q15.3	H_2O_2 generation (co-substrate for TPO)	Permanent or transient CH PIOD
DUOX maturation factor 2	DUOXA2	15q15.3	H_2O_2 generation (co-substrate for TPO)	Mild CH PIOD
Iodotyrosine deiodinase	IYD (DEHAL1)		Intrathyroidal iodide recycling	Negative CH screen, goiter, hypothyroidism (after neonatal period)

Table 1: Genetic causes of Congenital Hypothyroidism

Case report

- 35 year old woman of Eritrean origin, referred due to the finding of a neck mass on fetal ultrasound at term
- A large mass visualized in the neck and upper chest consisting of 2 lobes consistent with an enlarged thyroid (Figure 1)
- Following delivery initial examination was notable for a large diffuse neck swelling (Figure 2)
- Following results of Thyroid Function Tests treatment with Levothyroxine was commenced on day 2 of life

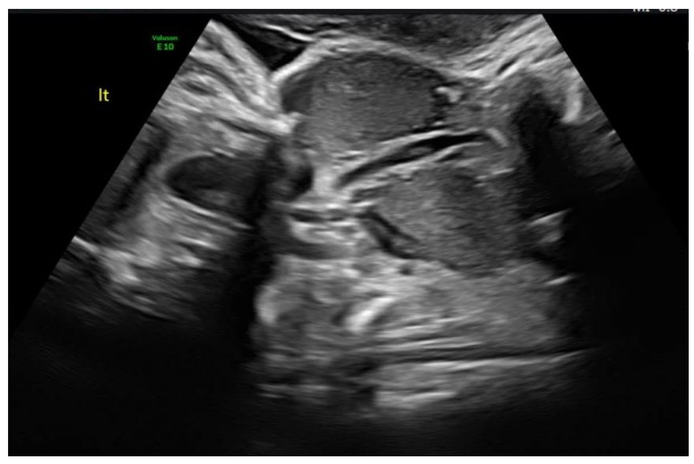


Figure 1: Goiter on antenatal US

Thyroid function

	TSH (mIU/l) (0.4-20)	FT4 (pmol/l) (0-30)	FT3 (pmol/l) (2.46-9.8)
Day 1	272.39	6.3	5.5
Day 4	47.64	9.9	12.8
Day 7	12.72	12.7	7.9

Laboratory investigations

- **<u>Thyroglobulin 0.7 picg/l (0-55)</u>**
- Thyroglobulin antibody <20U/ml
- Thyroid Stimulating Antibodies 575% (0-150)
- Thyroid blocking antibodies undetectable

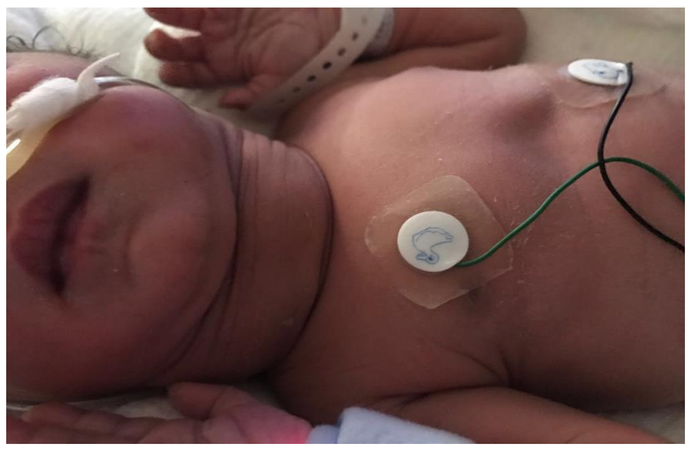


Figure 2: Neonatal Goiter

Genetics

- Sanger sequencing of the thyroglobulin gene (TG, ENST00000220616.8) revealed a homozygous donor splice site mutation at the exon 30-intron 30-31 boundary; c.5686+1delG (figure 5)
- This mutation has not previously been reported in the literature, and its functional effects have not been definitively evaluated. However, point mutations resulting in single nucleotide substitutions at the same site (c.5686+1G>A, T or C) have been reported in association with CH
- These observations, and the clinical context, suggest that TG c.5686+1delG is highly likely to be the cause of CH in this patient

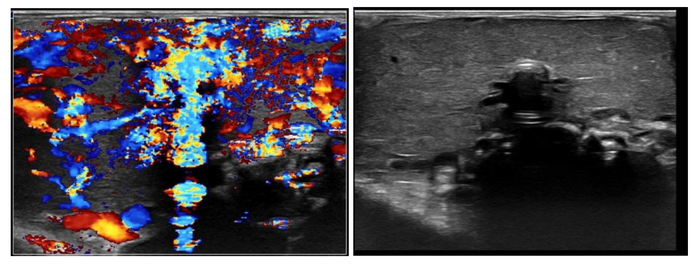


Figure 3: Thyroid gland as visualized on post-natal ultrasound and with doppler

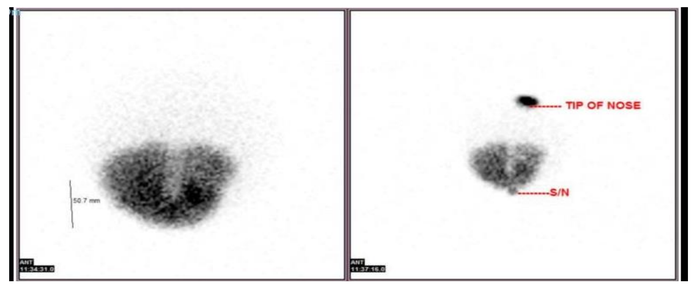
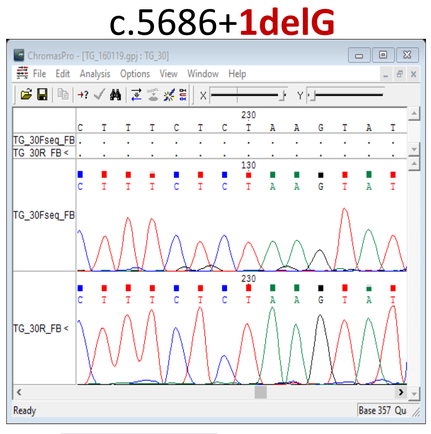


Figure 4: Diffusely enlarged thyroid with increased uptake on technetium scan

c.5686+**1delG**



Exon 30 **G**taag

5' splice site Donor site

Figure 5: Mutation in TG gene on Sanger sequencing

Discussion

- Thyroglobulin (TG) is crucial for thyroid hormone biosynthesis and storage in the thyroid follicular lumen
- TG mutations are a common cause of dyshormonogenesis with an estimated frequency of at least 1:100,000 births
- Affected individuals exhibit a spectrum of thyroid dysfunction which can range from severe CH to euthyroid goitre. Foetal goitre has also been reported
- The biochemical hallmark of CH due to TG mutations comprises an inappropriately low serum thyroglobulin level despite elevated TSH concentrations
- This case highlights the usefulness of genetic testing as the parents can be counselled re risk to future children and further pregnancies can be monitored for foetal goiter

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