

A familial case of congenital hypothyroidism (CH) due to a mutation in the thyroglobulin (TG) gene detected by Next Generation Sequencing (NGS)

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BACKGROUND

CH is a heterogeneous disorder. While the great majority of cases are considered sporadic, the use of NGS may bring significant advances in elucidating the underlying molecular mechanisms.

Mutations in the human TG gene have been reported and are associated with congenital goiter with hypothyroidism or euthyroidism. Usually TG gene defects are inherited in an autosomal recessive manner.

CASE PRESENTATION

We selected a family with three children affected by CH with gland in situ and diagnosed at neonatal screening: the index patient, his sister and his brother.

Data at diagnosis and follow-up are listed in the table below.

Patient	I Spot TSH (mcU/mL)	Serum TSH (mcU/mL)	Serum FT4 (ng/dl)	Thyroglobulin (ng/ml)	US	L-thyroxine (L-T4) therapy at diagnosis	Re-evaluation	TSH values without therapy (mcU/mL)
Index patient (2013)	10,01	16,9...11,07	1,2... 1,07	189 (0,2-55)	Normal	No	No	5,6-11,7
Sister (2005)	12,5	42,8	1,15	148 (0,2-55)	Normal	Yes	Stopped L-T4	7,32-14,71
Brother (2002)	10,7	19,51	1,1	34,8 (1-75)	Normal	Yes	Stopped L-T4	6,39-10,25

They present an **important familiarity for thyroid diseases**.

- The mother and her sister have a multinodular goiter in euthyroidism without anti-thyroid antibodies; the mother's TG level is 126 ng/mL (range 0-60 ng/ml).
- The maternal grandfather developed a multinodular goiter with a Plummer adenoma requiring thyroidectomy.

All family members have an adequate dietary iodine intake.

NGS analysis revealed a **heterozygous missense variant** (p.P118L) in the TG gene of the three siblings and of their mother.

MAF = 0,0087

The other analyzed genes (NKX2-1, PAX8, FOXE1, GLIS3, DUOX2, DUOXA2, SLC26A4, TPO, TSHR, JAG1) resulted wild-type.

CONCLUSIONS

According to the identification of the genetic variant in TG (although in heterozygous) with a strong positive family history for multinodular goiter, an adequate ultrasound follow-up and a tailored therapeutic strategy are needed. Indeed, these patients could benefit from hormone replacement therapy with levothyroxine, even in case of a mild increase in TSH concentrations, in order to avoid thyroid surgery in the future.

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