

Clinical course in a girl with two hTPO mutations - homozygous c.1268G>A (p.Gly393Arg) and heterozygous c.208C>G (p.Ala70Pro): 27 years of follow up



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INTRODUCTION

Of the several genetic defects responsible for thyroid dysmorphogenesis, mutations in TPO gene are the most prevalent causes of inherited defects in congenital hypothyroidism (CH). Prevalent mutations are in exons 8-11 (catalytic site).

CLINICAL CASE

Girl, born at 16d after term, before the nationwide introduction of the neonatal screening, with asphyxia and BL 55 cm, BW 4 kg. Because of insufficient weight gain, feeding difficulties, prolonged jaundice she was referred to a pediatric endocrine clinic with high suspicion for CH. At d 42 all classical clinical signs of CH were fully present, the clinical diagnosis was confirmed by the hormonal constellation (Table 1) and a gland in situ was present as well (no data on the volume before L-T4 introduction).

Table 1: Hormonal constellation

Age	NTSH mU/l (Delfia)	TSH mU/l	T4 nmol/l	Tg ng/ml (Delfia)	ft4 pmol/l (Delfia)
42d	ND	>200	33	ND	-
11yrs	107	139	<20	22.6	<1.2

TREATMENT

L-thyroxin treatment was introduced, the dosages increased gradually up to 75 mcg/d. At 11 years the treatment was discontinued by the mother and permanent primary CH with an eutopic thyroid: normo-hypoechoic parenchyma, volume 9.6 ml were reconfirmed (Figure 1). The therapeutic strategy changed (gradual increment of L-T4, not until "toxic" dosages), a stable euthyroid situation was achieved, the adherence of the patient and the family improved.

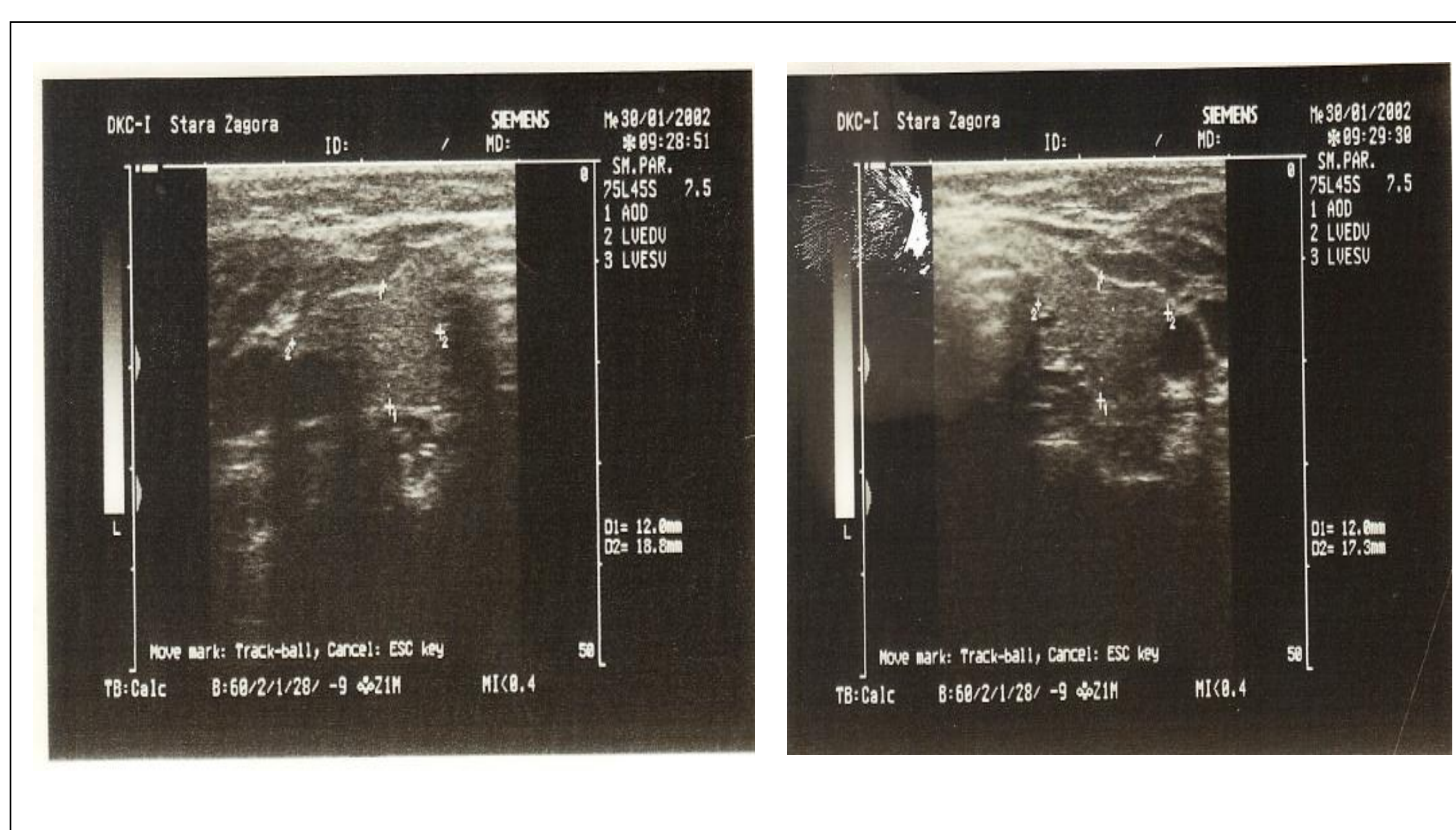


Figure 1a: Ultrasound of thyroid gland at age 11

MONITORING AND FOLLOW-UP

Normal growth (Fig 2) and development, very good school and academic results were evident during the complex follow up until 18 yrs and the entire transition period. The patient present a suitable candidate for the hTPO study based on permanent severe CH, eutopic thyroid: normo-hypoechoic parenchyma with linear hyperechoic lines, volume 8.7 ml (Fig 1b), measurable Tg.

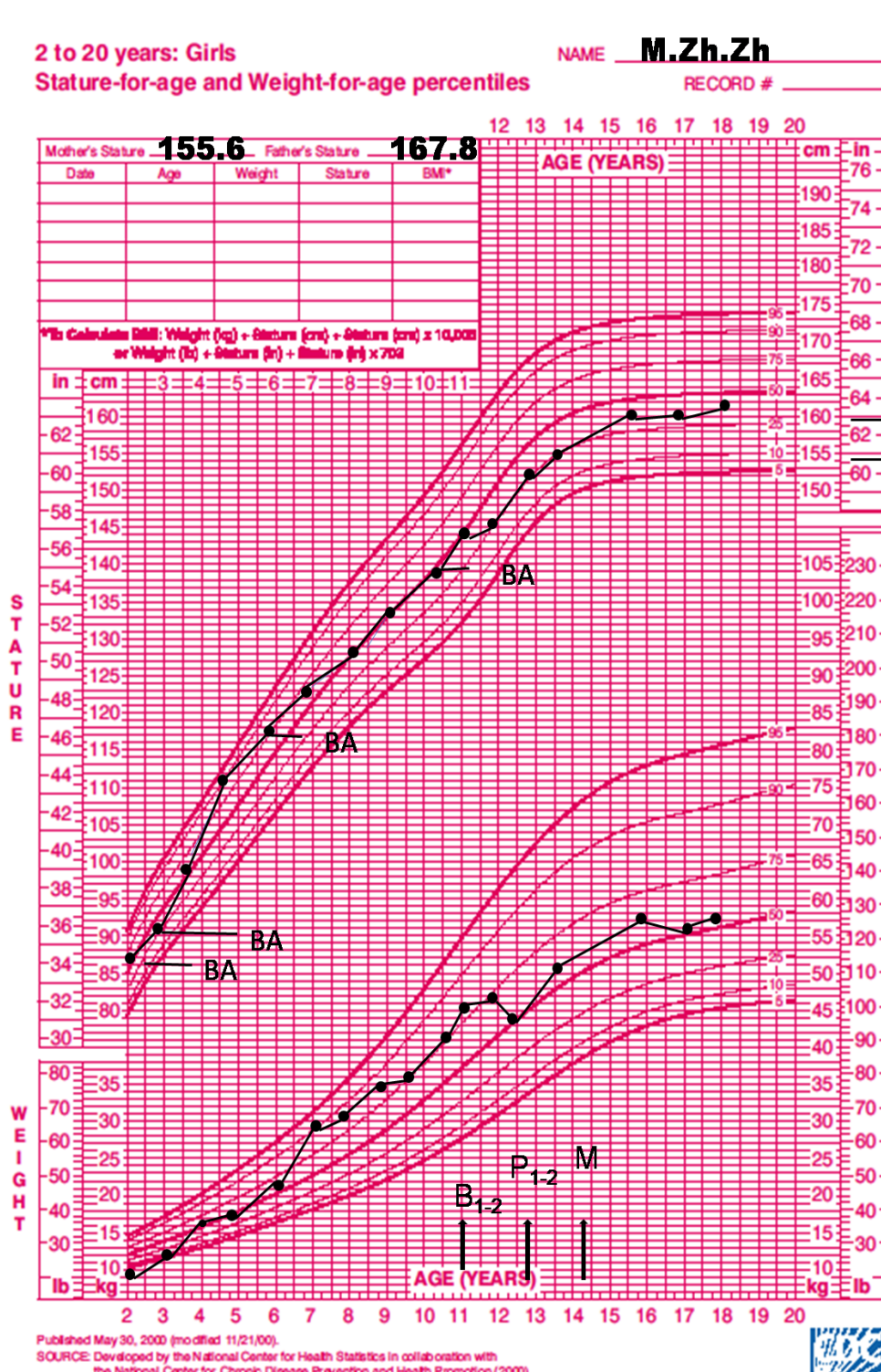


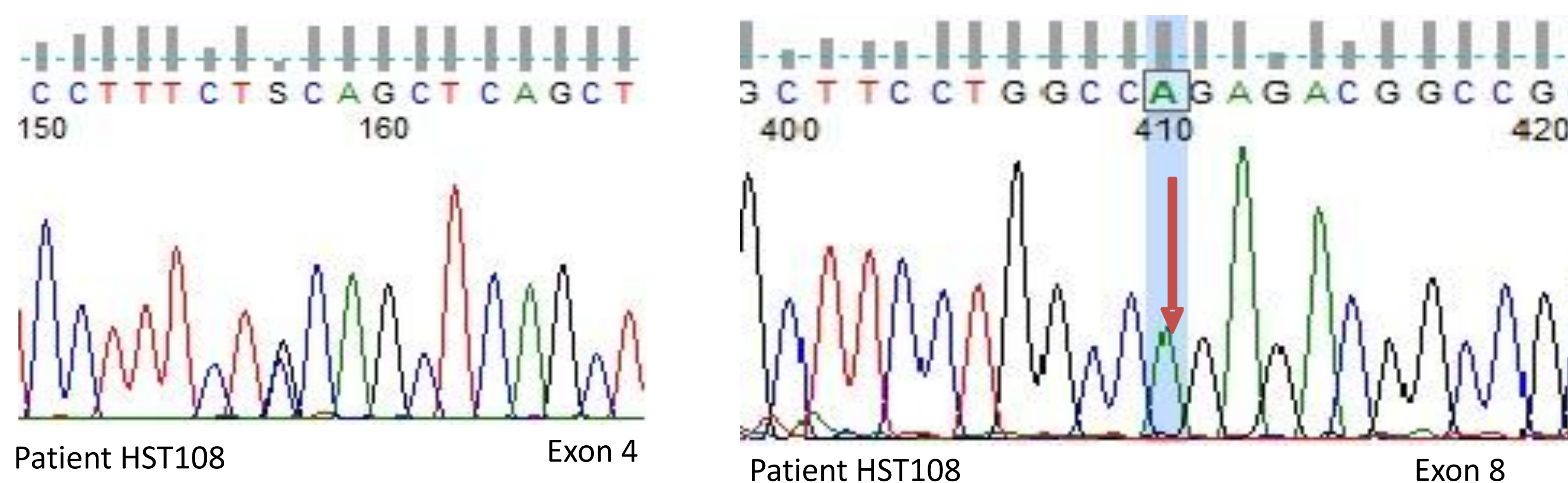
Figure 2 Growth curve



Figure 1b: Ultrasound of thyroid gland at age 27

MOLECULAR DIAGNOSIS

A homozygous mutation c.1268G>A (p.Gly393Arg) and a heterozygous missense c.208C>G (p.Ala70Pro) were found by Sanger sequencing. The homozygous mutation is new, undescribed in the databases. A stop-gain mutation, with the functional consequence of a protein lacking the catalytic site and therefore inability of effective thyroid hormone synthesis (p.Gly393*Ter), on the same position has been described. The missense heterozygote c.208C>G (p.Ala70Pro) in exon 4 is a rare variant (Exac MAF=0.007) with unknown clinical significance and may also contribute to the phenotype as it is predicted as possibly damaging and deleterious by Polyphen and SIFT prediction programs.



CONCLUSIONS

Early molecular genetic studies are important for patients with primary CH and eutopic thyroid glands because of refining the treatment and follow up strategy - the increased risk for thyroid cancer should be kept in mind.

Genetic consultation and possibilities for having healthy offsprings in patients diagnosed before screening introduction is nowadays part of the complex personalized care (2).

The case contributes to the genotype-phenotype data in congenital hypothyroidism due to hTPO mutations (normal Tg without l-T4, several mutations inside and outside the hTPO catalytic center).

REFERENCES

1. Leger, J., A. Olivieri, M. Donaldson et al.- European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism.-J Clin Endocrinol Metab 2014, 99, 363-384.

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