PITUITARY RESISTANCE TO *EXOGENOUS* LEVO-THYROXINE IN HUMANS

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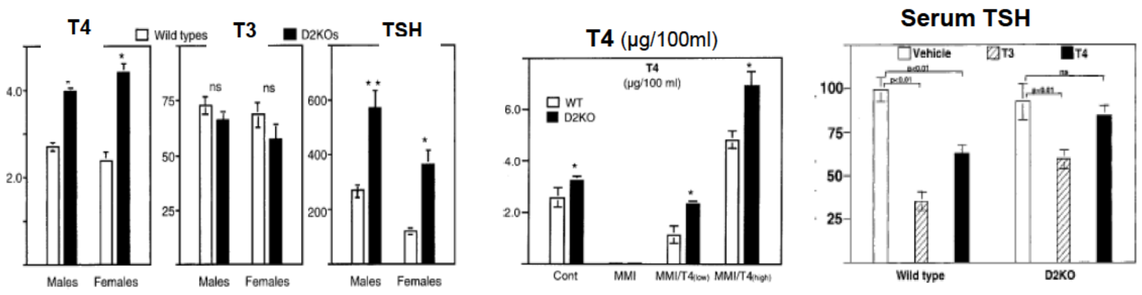
INTRODUCTION

• The pituitary set-point for TSH synthesis and secretion is known to be an individual characteristic with a strong genetic influence.

•Type II iodothyronine deiodinase is a pituitary enzyme involved in local deiodination of T4 to T3 and therefore in the negative feed-back loop for TSH secretion.

•Defects in *DIO2* gene have not been reported in humans; however, Dio2 knockout mouse has pituitary resistance to (exogenous) T4 with elevated TSH, T4 and TSH/T4 ratio, and normal T3, when challenging the thyroid gland with anti-thyroid drugs (shown below).



OBJECTIVE

To identify human thyroid hormone phenotypes consistent with type 2 deiodinase defects.

PATIENTS & METHODS

From a pediatric cohort of 26 patients with suspected pituitary TH resistance, 12 had THRB mutations (12/26 patients, 46%), and the 14 were subjected to the following **inclusion criteria** for DIO2 screening:

1. Elevated TSH (>5 mU/ml), FT4 (>1.7 ng/dl) and TSH/FT4 ratio (> 0.15)[1] with normal FT3 (3.5-6.5).
2. Be treated with high dose levo-thyroxine, which was unable to normalize TSH or (alternatively) do it at the expense of clinical/biochemical hyperthyroidism.

Complete clinical history and serum thyroid hormone profiling (TSH, FT4 and FT3) and calculation of TSH/FT4 and FT4/FT3 ratios.

PCR and Sanger sequencing of the coding region of *DIO2* and *TSHR* genes.

RESULTS

From an initial cohort of 14 patients, 6 patients (43 %) were identified fulfilling our two inclusion criteria (TABLE 1).

Remarkably, all patients presented with the characteristic hormonal phenotype only after the occurrence of a thyroid disease leading to absence of functional thyroid tissue.

- 4/6 (3 males) had severe thyroid hypoplasia on ultrasound and/or scintigraphy, detected at neonatal screening
- 1 girl had euplastic hypothyroidism detected at 8 months of age.
- 1 girl had destructive thyroiditis at 13 years old.

No mutations in DIO2 coding region including the SECIS element in 3'-UTR were identified (Figure 2).

Table 1. Hormonal and clinical findings.

	TSH mU/L N: 0.5-4.5	FT4 pmol/L N: 10-19.8	FT3 pmol/L N: 3.5-6.5	TSH/FT4 N: 0.03-0.13[1]	SNP (rs225014)	Thyroid disease
1	12,1	24,8	5,9	0,49	AA	hypoplasia
2	20,8	25,1	5,4	0,83	AG	hypoplasia
3	9,8	21,5	6	0,46	GG	hypoplasia
4	8,3	22,1		0,37	AG	euplastic
5	9,2	23,9	2,2	0,38	AG	hypoplasia
6	9,17	24,8	4,9	0,37	AA	thyroiditis
	11.6 4.7	**23.7 1.5**	**4.9 1.5** (5/6)	**0.48 0.18**	**MAF 0.42**	

No mutations in DIO2 coding region including the SECIS element in 3'-UTR were identified. Furthermore, 3/6 were heterozygous and 1 homozygous for the frequent DIO2 polymorphism (rs225014, Thr92Ala). This SNP has been associated with a lower enzyme stability, but its presence in some but not all patients indicated is not the major driving factor causing this novel human phenotype.

[1]Bay Bjorn et al J Clin Endocrinol Metab, July 2009, 94(7); 2478-2481

CONCLUSIONS

• In a case-finding study we identified a homogeneous group of patients characterized by persistently elevated/difficult to normalize TSH despite exogenous L-T4 treatment. This hormonal pattern fully overlaps that described in *Dio2* KO mice.

• Defects in TSH feed-back regulation may not be infrequent, buy they may remain silent/compensated until the loss of thyroid tissue co-occurs.

• The phenotype is recognizable by high TSH/FT4 ratio and represents an aberrant set-point for TSH secretion and feedback whose genetic determinants need to be investigated (SECIS element at non-coding DIO2, DIO2 deubiquitinases).

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