PHENOTYPE AND GENOTYPE OF FOUR PATIENTS WITH THYROID HORMONE RESISTANCE SYNDROME DUE TO MUTATIONS IN THE *THRB* GENE

Meropi Toumba[1,2], Vassos Neocleous[2], Pavlos Fanis[2], Nicos Skordis[3,4,2], Leonidas A Phylactou[2,5], George A Tanteles[6], Marinella Kyriakidou-Himonas[7], Michalis Picolos[8]

[1]Pediatric Endocrine Clinic, IASIS Hospital, Paphos, Cyprus; [2]Department of Molecular Genetics, Function & Therapy, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus; [3]Division of Pediatric Endocrinology, Paedi Center for specialized Pediatrics, Nicosia, Cyprus; [4]St George's, University of London Medical School at the University of Nicosia, Cyprus; [5]Cyprus School of Molecular Medicine, Nicosia, Cyprus; [6]Department of Clinical Genetics, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus; [7]Larnaca Endocrinology Center, Larnaca, Cyprus; [8]Alithias Endocrinology Center, Nicosia, Cyprus

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BACKGROUND

Resistance to thyroid hormone (RTH) is a dominantly inherited rare disorder (1:40000) mainly due to mutations in the *THRB* gene that lead to a decreased end-organ responsiveness to thyroid hormone. Clinical and molecular characteristics of four patients with RTH are described.

PATIENTS

Four patients; two boys (8.3 and 9.2 years) and 2 adults (35 year old male and 27 year old female).

METHODS

Direct sequencing analysis of the *THRB* gene.

RESULTS

TABLE: Four patients from three non-related families.

Patient	Age (years)	Gender	Clinical signs at presentation	FT4 pmol/L	FT3 pmol/L	TSH mU/L	TSH receptor abs	Mutation
1	9.2	Male	Goiter, ADHD, obesity	54.9	15.2	2.55	Negative	p.Pro453Thr
2	8.3	Male	Goiter, R.tcachycardia	26.8	10.25	1.89	Negative	p.Arg438Cys
3	27	Female	Goiter, R.tachycardia, tx PTU	24.2	7.42	3.49	Negative	p.Arg438Cys
4	35	Male	Goiter, AF, tx MT	30.2	11.19	2.89	Negative	p.His435Leu

FIGURE 1. Genetic analysis of the THRB:p.Arg438Cys mutation. (A) Pedigree of the family of patient 3. Squares and circles indicate males and females, respectively. Black shading indicates the presence of the p.Arg438Cys mutation. (B) Sequence electropherograms of the p.Arg438Cys mutation.

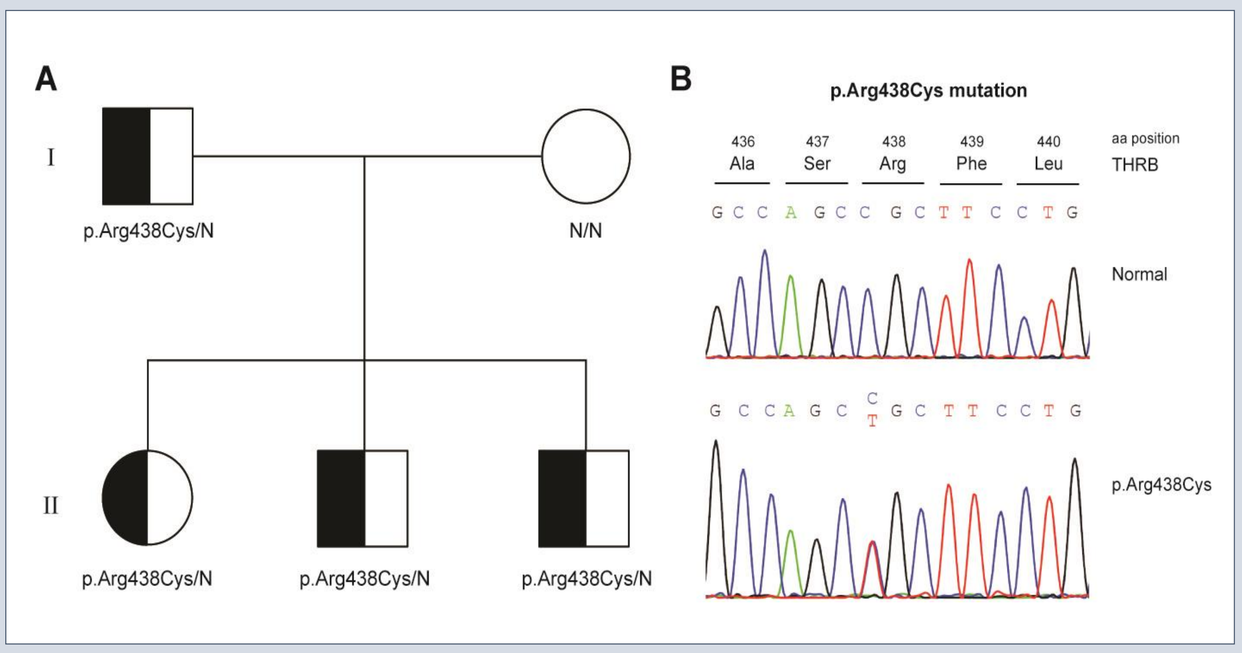
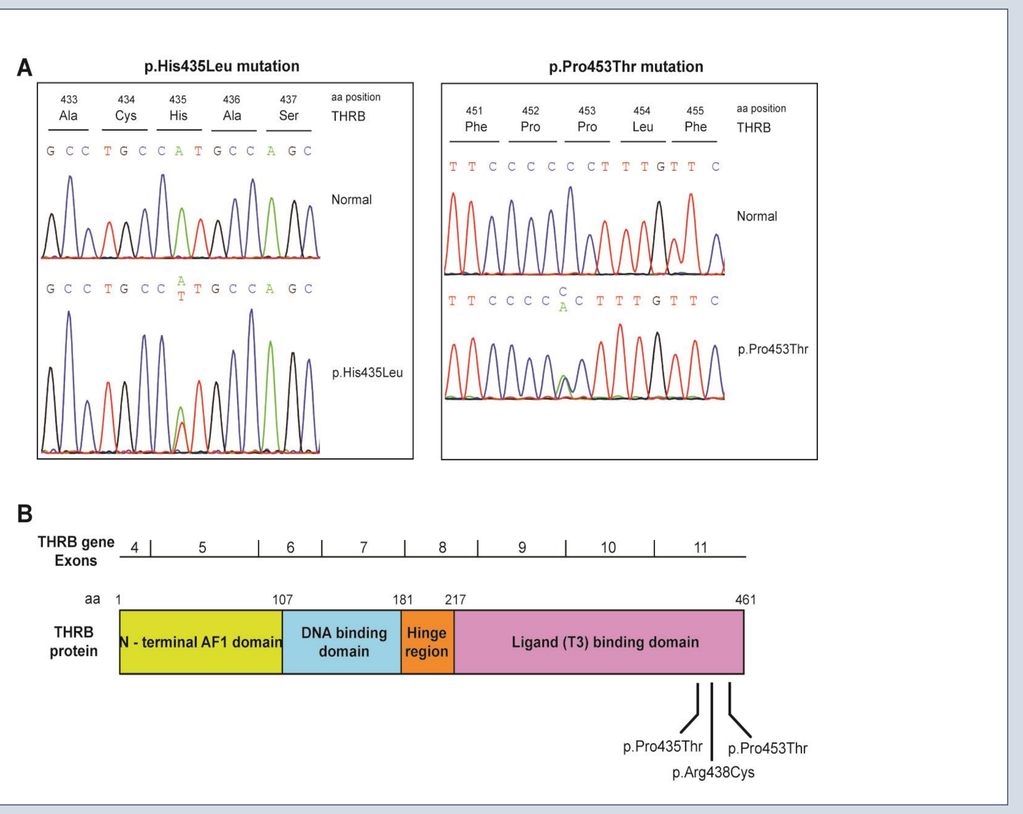


FIGURE 2. Identification of the THRB mutations. (A) Sequence electropherograms of the identified p.His435Leu and p.Pro453Thr mutations. (B) Schematic domain-structure diagram of THRB protein. The upper tier shows the exons corresponding to the *THRB* gene and the lower tier shows the structures of the THRB protein. The positions of the identified mutations are indicated.



CONCLUSIONS

- Common mutations in the *THRB* gene are characterized by various phenotypes; clinically asymptomatic, thyroid hormone deprivation suggestive symptoms or thyroid hormone excess symptoms.
- RTH can be suspected in both children and adults with elevated thyroid hormones and not suppressed TSH.
- Prompt molecular diagnosis and genetic counseling could prevent unnecessary tests and inappropriate treatments.

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