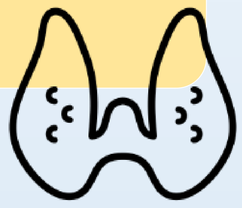
An incidental finding of thyroid hormone resistance due to a *de novo* mutation in the *THRB* gene

Noa Shefer Averbuch[1,2,3], Monica França[4], Liora Lazar[1,2], Ariel Tenenbaum[1,2], Moshe Phillip[1,2], Liat de Vries[1,2]
[1]The Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Raphael Recanati Genetics Institute, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel
[4]Endocrinology Laboratory, The University of Chicago, South Maryland Avenue, Chicago, IL

Background:

Thyroid hormone resistance (THR) is a rare genetic disorder, mainly caused by an inherited mutation in the TH receptor beta (*THRB*) gene. Other causes include thyroid hormone (TH) cell transporter defects or metabolism defects.

Reduced responsiveness of target tissues to TH → Elevated TH + Normal/ elevated TSH level



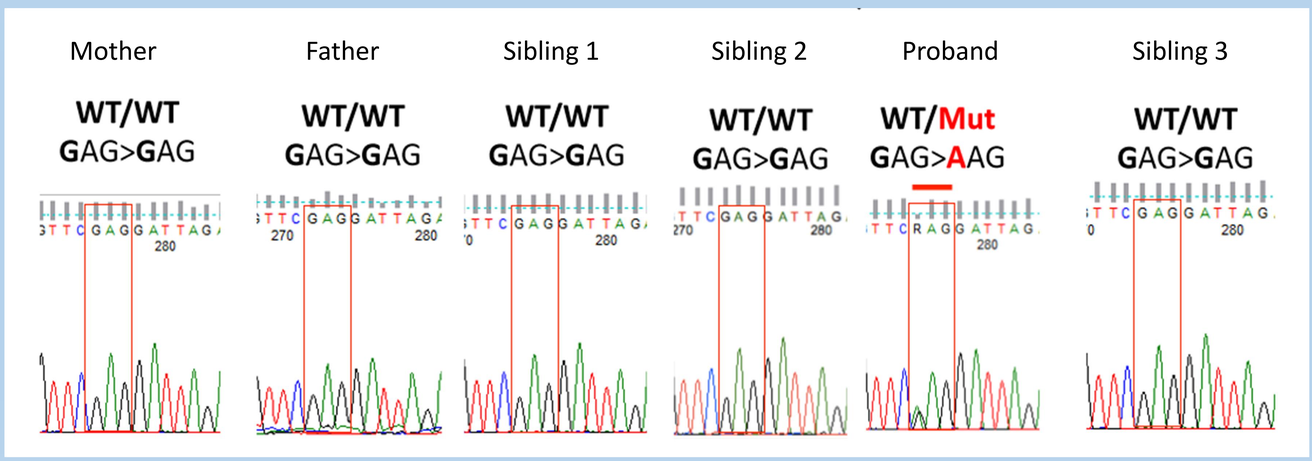
Patient:

A previously healthy 5 year-old boy,

normal growth, mild developmental delay

Clinical data	
Pulse	90
Blood pressure	102/60
Bone age	No advancement
Height SDS	+1.1
Weight SDS	+1.3

Laboratory tests	
TSH	1.1 mIU/L (0.64-6.27)
fT4	38.8 pmol/L (11-18.8)
fT3	12 pmol/L (5.1-7.4)
Repeated tests with different assays ruled out suspected Biotin excess	
Thyroglobulin antibodies	4.2 IU/ml (0-150)
Anti-thyroid peroxid	1.2 IU/ml (0-75)
Anti TSH receptor antibodies	2.1 IU/L (0-2.5)

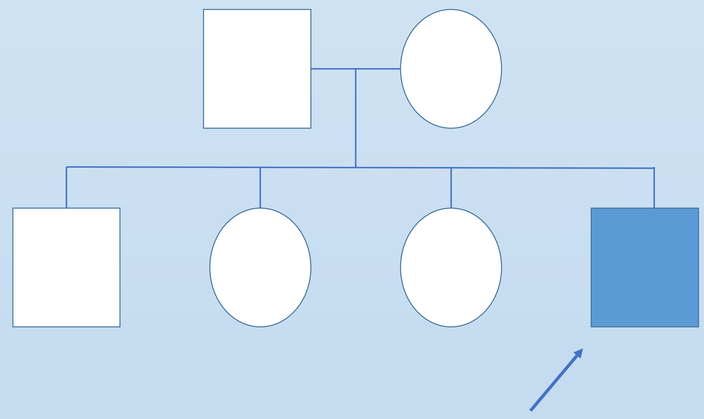


Methods:

Thyroid function tests were performed for all 6 family members.

Sanger sequencing of the *THRB* gene was performed for all 6 family members.

Sequencing was executed at the endocrinology laboratory at The University of Chicago (NIH support).



Results:

Parents and 3 siblings were all found to have normal thyroid functions.

The proband was found to have a ***de novo* mutation** in one allele of the *THRB* gene, c.1663G>A;p.Glu460Lys. This missense mutation, in a CpG dinucleotide hot spot (C GAG), results in replacement of glutamine with lysine (E460K). This mutation, previously described in 10 families, reduces the binding affinity for T3 to 25% that of the normal receptor.

Conclusions:

✓A fast genetic diagnosis can avoid an unnecessary, costly and invasive work-up.

✓Although *THRB* mutations inheritance is autosomal dominant, de novo mutation should be considered.

✓Accurate diagnosis is crucial for appropriate follow-up and genetic counseling.