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

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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.

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 (11.18-8.8)
- **FT3**: 12 pmol/L (5.1-7.4)

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 (CAG), 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.