Supplementary Figure Legends:

Supplementary Figure 1

Pedigree of the family with *THRA* mutation, showing their thyroid function tests and genotype.

Supplementary Figure 2

Amplicons encompassing the mutant codon (A263V) in TRα1 or α2 cDNAs, synthesized from PBMC RNA in the patient (P1) or control subject, were generated using a common forward (α-FOR) and specific (α1-REV, α2-REV) reverse primers (upper panel). The location of Cac8I restriction sites (vertical line) together with expected size of DNA products following such enzymatic digestion of either WT or A263V mutant TRα1 or α2 cDNAs is shown in the middle panel. Gel electrophoresis indicates three fragments (223bp, 174bp, 102bp) from Cac8I digestion of WT TRα1 cDNA (Control), whereas loss of one Cac8I site in the A263V mutant cDNA from the patient (P1), yields a novel band (276bp) together with lower intensity fragments (174, 102bp) bands, with the 223bp band (asterisked) common to both cDNA species being unchanged. Likewise RFLP analysis of α2 cDNAs yields 174 and 102bp bands derived from WT alleles in the control subject, whereas a high intensity 276bp band

in P1 reflects loss of a Cac8I site derived from the mutant allele. Additional bands (asterisked 153bp, 122bp) present in both subjects, confirm that the digested cDNAs are α2-derived. Electropherograms (lower panel) show sequencing of α1 and α2 cDNAs and heterozygosity for the single nucleotide substitution (T/C) in P1 or homozygosity for the wild type nucleotide (C) in the control subject.

Supplementary Figure 3

Radiolabelled T3 binding to in vitro translated WT TRα1, A263V mutant TRα1, WT TRβ1 and A317V mutant TRβ1 proteins, in the absence (open bars) or presence (black bars) of excess (100nM) unlabelled hormone, is shown. The inset shows comparable parallel translation of ^{35}S-methionine labelled wild type and mutant proteins.

Supplementary Figure 4

Protein-protein interaction assays in JEG-3 cells cotransfected with a reporter gene (UASTKLUC), vectors expressing GAL4-coactivator (TRAP220) or GAL4-corepressor (NCoR) fusion proteins and constructs expressing a heterologous activation domain linked to TRs (VP16-WT, VP16-A263V). Western blotting (inset) confirmed comparable VP16-receptor fusion expression.

Supplementary Table

Thyroid function tests, reverse T3 and thyroglobulin levels, together with *THRB* genotype, in family with A317V TRβ mutation. Abbreviation: ND: not done.

Supplementary Figure 5

JEG-3 cells were transfected with empty, WT or A317V TRβ expression vectors together with a thyroid hormone responsive reporter gene, assaying T3-dependent activation.

Supplementary Figure 6

Dominant negative inhibition by A317V mutant TRβ was tested in JEG-3 cells cotransfected with reporter gene and equal combinations of expression vectors as indicated. **p<0·01.

Supplementary Figure 7

Crystallographic modelling of the TRβ1 ligand binding domain (LBD) bound to T3 (blue), highlighting the normal amino acid (alanine 317, green), with substitution of the larger valine residue (red) predicting steric hindrance to T3 binding.

Supplementary Figure 8

Clinical photographs of skin tags from other patients with *THRA* mutations. Affected father (panel A) and proband (panel B) with F397fs406X mutation and child (panel C) with E403X mutation in TRα1.

Supplementary Figure 9

Dominant negative inhibition of WT TRβ1 by A263V mutant TRα1 was tested in cells cotransfected with reporter gene and equal combinations of expression vectors as indicated. * $p<0{\cdot}05$; *** $p<0{\cdot}001$,