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THYROID FUNCTION

NEW MUTATION IN HUMAN TRα PROTEINS

A new human mutation in *THRA,* the gene that encodes thyroid hormone receptor (TR) α proteins has been identified by Krishna Chatterjee and colleagues. This missense mutation affects the two proteins encoded by the gene, TRα1 and TRα2, which are generated by alternative splicing.

Many mutations in the gene that encodes TRβ (*THRB*) are known in humans, but very few carriers of *THRA* mutations have been identified. TRα1 binds to thyroid hormones and to DNA, whereas TRα2 binds to DNA only and has no known function. Chatterjee and colleagues previously reported a premature stop mutation in *THRA* that only affects TRα1. In their new study, they analysed the clinical, biochemical and genetic features of the new mutation in three patients from the same family.

"The patients' clinical and biochemical phenotype resembles that of previous cases with a defect restricted to TRα1, with no extra features," comments Chatterjee. However, "whilst missense mutant TRα1 function is impaired at low thyroid hormone levels, the mutant receptor function is restored at high T_3 concentrations and is comparable to that of its normal counterpart." This observation contrasts with previous findings in patients with other TRα1 mutations, in whom the defect has more severe consequences. The three patients in the study had in fact been treated with thyroxine from an early age, which might explain why their clinical phenotype was comparatively mild.

"*THRA* mutations may occur more commonly than previously thought, with absence of overtly abnormal thyroid function limiting ascertainment of cases," says coauthor Carla Moran. The researchers plan to define a phenotypic and biochemical signature for TRα-related disorders to facilitate their earlier recognition and treatment. Chatterjee also thinks that increasing knowledge about the differences between TRβ and TRα in mediating thyroid hormone action might provide a rational basis for development of receptor-subtype-specific thyroid hormone analogues.

Joana Osório

Original article Moran, C. *et al.* Resistance to thyroid hormone caused by a mutation in thyroid hormone receptor (TR)α1 and TRα2: clinical, biochemical, and genetic analyses of three related patients. *Lancet Diabetes Endocrinol.* doi:10.1016/S2213-8587(14)70111-1

Further reading Bochukova, E. *et al.* A dominant negative mutation in the thyroid hormone receptor α gene. *N. Engl. J. Med.* **366**, 243–249 (2012)