Frequent TSH receptor genetic alterations with variable signaling impairment in a large series of children with nonautoimmune isolated hyperthyrotropinemia.

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Context: Heterozygous mutations in the TSH receptor gene (*TSHR*) are associated with partial TSH resistance, characterized by isolated nonautoimmune hyperthyrotropinemia (NAHT). The prevalence and management of this condition is controversial.

Objective: Our objective was to investigate the prevalence and clinical impact of *TSHR* alterations in a large series of pediatric patients with NAHT and to dissect their mechanism of action.

Design and Setting: For this prospective multicenter study, clinical data and samples were collected in the clinical units and conveyed to a centralized laboratory for analysis.

Patients: Subjects included 153 unrelated patients with NAHT aged <18 yr. Exclusion criteria included thyroid dysgenesis or major associated congenital defects.

Main Outcome Measures: Parameters of thyroid function, *TSHR* gene analysis, and TSHR functional assays were evaluated.

Results: The frequency of heterozygous nonpolymorphic *TSHR* variations was 11.8%.We identified seven previously unknown variations: a frameshift (p.Q33PfsX46), one intronic (g.IVS4+2A→G), and five novel missense (p.P162L, p.Y466C, p.I583T, p.I607T, and p.R609Q) variations. The missense variations variably affected TSHR membrane expression and G_s and/or $G_{q/11}$ signaling. Several variations cosegregated with NAHT in the affected families. Parameters of thyroid function were similar between affected and unaffected family members.

Conclusions: Nonpolymorphic alterations in the *TSHR* gene are commonly associated with isolated NAHT in young patients, thus configuring partial TSH resistance as the most frequent inheritable cause of isolated NAHT. The identification of *TSHR* defects may thus be helpful for a tailored management of subclinical hypothyroidism. We provide further evidence that besides the wellknown defects in G_s signaling, *TSHR* genetic alternations found in NAHT may frequently impair the $G_{q/11}$ pathway.