The following abstracts from The Journal of Clinical Endocrinology & Metabolism have been selected by the editors of Endocrinology as being particularly relevant to readers interested in translational science.

**New Insights into Thyroglobulin Pathophysiology Revealed by the Study of a Family with Congenital Goiter**

*(J Clin Endocrinol Metab, published April 21, 2010, 10.1210/jc.2009-2109)*

**ABSTRACT**

**Context:** Thyroglobulin (TG) gene mutations cause congenital hypothyroidism (CH) with goiter. A founder effect has been proposed for some frequent mutations. Mutated proteins have a defect in intracellular transport causing intracellular retention with ultrastructural changes that resemble an endoplasmic reticulum storage disease.

**Objective:** To reveal new aspects of thyroglobulin pathophysiology through clinical, cellular, molecular, and genetic studies in a family presenting with CH due to TG mutations from Galicia, an iodine-deficient area of Spain.

**Design:** The included clinical evaluation of family members, DNA sequencing for TG gene mutation and haplotyping analysis, ultrastructural analysis of thyroid tissue specimens from affected subjects, analysis of effects of mutations found on TG gene transcription, and in vitro studies of cellular production and secretion of mutated proteins.

**Setting:** Locations included primary care and university hospitals.

**Results:** Family members with CH, mental retardation, and goiter were compound heterozygous for c.886C>T (p.R277X) and g.IVS35/H11001delG. For c.886C>T, a founder effect cannot be excluded, and its transcription was hardly detectable. g.IVS35/H11001delG caused an in-frame deletion in exon 35 and produced a protein that, although synthesized, could not be secreted. Ultrastructural analyses showed morphological changes consistent with an endoplasmic reticulum storage disease.

**Conclusion:** The shorter thyroglobulin resulting from the novel g.IVS35/H11001delG was retained within the endoplasmic reticulum of thyrocytes, and together with p.R227X caused severe hypothyroidism with goiter. p.R277X, the most commonly described TG mutation, is caused by a TG exon-7 highly mutation-prone region, and the possibility that some cases were introduced to South America from Galicia cannot be excluded.

**Missense Mutations in the Melanocortin 2 Receptor Accessory Protein That Lead to Late Onset Familial Glucocorticoid Deficiency Type 2**

*(J Clin Endocrinol Metab, published April 28, 2010, 10.1210/jc.2009-2731)*

**ABSTRACT**

**Background:** Familial glucocorticoid deficiency (FGD) is an autosomal recessive disorder characterized by isolated glucocorticoid deficiency. Mutations in the ACTH receptor [melanocortin 2 receptor (MC2R)] or the MC2R accessory protein (MRAP) cause FGD types 1 and 2, respectively. Typically, type 2 patients present early (median age, 0.1 yr), and no patient reported to date has presented after 1.6 yr.

**Aim:** The aim of this study was to investigate the cause of disease in two families with late-onset FGD.

**Patients:** The proband in family 1 was diagnosed at age 4 yr. Family review revealed two older siblings with undiagnosed FGD. One sibling was well, whereas the second had cerebral palsy secondary to hypoglycemic seizures. The proband in family 2 was diagnosed at age 18 yr with symptoms of fatigue, weight loss, and depression.

**Methods:** The coding exons of MC2R and MRAP were sequenced. ACTH dose-response curves were generated for MC2R when transfected with wild-type or mutant MRAP constructs using HEK293 cells. MC2R trafficking with both mutant MRAPs was investigated using immunocytochemistry.

**Results:** MRAP gene analysis identified two novel homozygous missense mutations, c.175T>G (p.Y59D) in family 1 and c.76T>C (p.V26A) in family 2.
In vitro analysis showed that the Y59D mutant had significant impairment of cAMP generation, and both mutants caused a shift in the dose-response curve to the right when compared to wild type. Immunocytochemistry showed normal trafficking of MC2R when transfected with both mutant MRAPs, indicating a probable signaling defect.

Conclusion: These results indicate that missense MRAP mutations present with a variable phenotype of ACTH resistance and can present late in life.

Nonsense Mutations in FGF8 Gene Causing Different Degrees of Human Gonadotropin-Releasing Deficiency

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ABSTRACT

Context: FGFR1 mutations cause isolated hypogonadotropic hypogonadism (IHH) with or without olfactory abnormalities, Kallmann syndrome, and normosmic IHH respectively. Recently, missense mutations in FGF8, a key ligand for fibroblast growth factor (FGF) receptor 1 in the ontogenesis of GnRH, were identified in IHH patients, thus establishing FGF8 as a novel locus for human GnRH deficiency.

Objective: Our objective was to analyze the clinical, hormonal, and molecular findings of two familial IHH patients due to FGF8 gene mutations.

Methods and Patients: The entire coding region of the FGF8 gene was amplified and sequenced in two well-phenotyped IHH probands and their relatives.

Results: Two unique heterozygous nonsense mutations in FGF8 (p.R127X and p.R129X) were identified in two unrelated IHH probands, which were absent in 150 control individuals. These two mutations, mapped to the core domain of FGF8, impact all four human FGF8 isoforms, and lead to the deletion of a large portion of the protein, generating nonfunctional FGF8 ligands. The p.R127X mutation was identified in an 18-yr-old Kallmann syndrome female. Her four affected siblings with normosmic IHH or delayed puberty also carried the p.R127X mutation. Additional developmental anomalies, including cleft lip and palate and neurosensory deafness, were also present in this family. The p.R129X mutation was identified in a 30-yr-old man with familial normosmic IHH and severe GnRH deficiency.

Conclusions: We identified the first nonsense mutations in the FGF8 gene in familial IHH with variable degrees of GnRH deficiency and olfactory phenotypes, confirming that loss-of-function mutations in FGF8 cause human GnRH deficiency.

Serum 25-Hydroxyvitamin D and Depressive Symptoms in Older Women and Men

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ABSTRACT

Context: Hypovitaminosis D and depressive symptoms are common conditions in older adults.

Objective: We examined the relationship between 25-hydroxyvitamin D (25(OH)D) and depressive symptoms over a 6-yr follow-up in a sample of older adults.

Design and Setting: We conducted a population-based cohort study (InCHIANTI Study) in Tuscany, Italy.

Participants: A total of 531 women and 423 men aged 65 yr and older participated.

Main Outcome Measure: Serum 25(OH)D was measured at baseline. Depressive symptoms were assessed at baseline and at 3- and 6-yr follow-ups using the Center for Epidemiological Studies-Depression Scale (CES-D). Depressed mood was defined as CES-D of 16 or higher. Analyses were stratified by sex and adjusted for relevant biomarkers and variables related to sociodemographics, somatic health, and functional status.

Results: Women with 25(OH)D less than 50 nmol/liter compared with those with higher levels experienced increases in CES-D scores of 2.1 (P = 0.02) and 2.2 (P = 0.04) points higher at, respectively, 3- and 6-yr follow-up. Women with low vitamin D (Vit-D) had also significantly higher risk of developing depressive mood over the follow-up (hazard ratio = 2.0; 95% confidence interval =