SAT-069

**Background:** Hereditary hypophosphatemic rickets (HHR) is a group of inherited disorders characterized by hypophosphatemia due to renal-phosphate wasting and impairment of vitamin D metabolism, rickets and disproportioned short stature. Different genetic defects are known to cause HHR, but similar clinical and biochemical features were reported. Dominant- X-linked HR (XLHR) is the most frequent form, with an incidence of 1 in 20,000, although dominant and recessive autosomal forms are also described. XLHR is caused by inactivating mutations in the PHEX gene (located at Xp22.1), encoding an endopeptidase which regulates the phosphaturic secretion. Affected individuals present with a broad phenotypic spectrum, ranging from isolated hypophosphatemia up to severe symptoms of rickets. Therefore NGS studies represent an useful tool for molecular diagnosis characterization.

**Aim:** to develop a reliable NGS diagnostic tool for HHR and related disorders.

**Patients and Methods:** we develop a NGS panel including 13 genes related with HHR or other hypophosphatemic disorders, using Illumina TruSeq Custom Amplicon technology.

We analyzed 12 patients which have been sent to our laboratory for molecular genetic testing under suspicion of HHR based on clinical phenotype and laboratory studies but with no proven mutation in PHEX gene by Sanger sequencing or MLPA analysis or other hypophosphatemic disorder.

**Results:** A previously reported pathogenic variant (p.Arg153Gln) was found in SLC9A3R1 gene encoding NHERF1 cotransporter, which interact with phosphate and sodium renal transporter NaPi2a in a 13 months old girl. There are only 5 reported cases with alterations in this gene and all of them were adult patients with nephrocalcinosis. The patient was referred to our hospital due to hypercalcemia. She had poor weight gain and laboratory findings showed high serum calcium (16.6 mg/dl), mild serum phosphate (3.9 mg/dl), very low parathyroid hormone (PTH) (< 3 ng/ml), normal 25OHvit D (40 ng/ml) levels, and elevated urinary calcium/creatinine rate (2), and low phosphate tubular reabsorption (85%). Ultrasound showed nephrocalcinosis. Since she had hypophosphatemia and renal phosphate wasting with symptomatic severe PTH independent hypercalcemia probably secondary to excessive calcitriol production with hypercalciuria, a molecular alteration of CYP24A1 or SLC34A1 genes was suspected.

**Conclusion:** NGS allowed to report for the first time the identification of a mutation in the SLC9A3R1 gene in a pediatric patient. An early diagnosis might improve long term outcome starting the right therapy to avoid progression of nephrocalcinosis and chronic renal failure.

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**Diabetes Mellitus and Glucose Metabolism**

**TYPE 2 DIABETES MELLITUS**

**Breast Cancer Treatment Causes Diabetes**

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Polymorphisms in the gene that encodes the glucocorticoid receptor (GR), an essential regulator of the hypothalamic-pituitary-adrenal axis, have been linked to some psychiatric disorders. Considering that psychiatric manifestations are present in nearly all patients with hypercortisolism, we hypothesized a possible correlation of polymorphisms in the GR gene and clinical and psychiatric manifestations, in CD. To investigate the frequency and clinical implications of the GR gene polymorphism Bcl-1 in patients with CD, we conducted a cross-sectional, case-controlled study. Fifty-three Brazilian patients with CD aged between 12 and 75 years and one hundred healthy controls aged between 42 and 67 years, of both genders, who provided written informed consent, were enrolled. Blood samples were collected from patients for DNA extraction and sequencing for analysis of the GR gene polymorphism Bcl-1. Clinical data (obesity, skin lesions, muscle weakness, hypertension, diabetes, hypokalemia, and sex-related disorders) were obtained through retrospective analysis of medical records, appointment with endocrinologist and with psychiatrist. Mini International Neuropsychiatric Interview, scales self-applicable of anxiety and depression were used to address psychiatric conditions. From the 53 patients studied, 48 were women (90.56%), and 16 patients had macroadenoma (2 of them had tumors larger than 4 cm). Overall frequencies of the Minor Allele for Bcl-1 polymorphism, which corresponds to the risk allele for psychiatric illness in the normal population, did not significantly differ between CD patients (67.92%) and controls (74.00%). Similarly, differences in Minor Allele Frequencies among subgroups of patients presenting with psychiatric and clinical manifestations of CD were not statistically significant. Although data from the literature strongly suggests a correlation between Bcl-1 polymorphism with psychiatric disorders (especially depression) in the normal population, this association was not observed in our cohort of patients with CD. More studies are needed to better clarify a possible role for GR gene polymorphisms as modifiers of the spectrum of psychiatric and clinical manifestations of CD.

Cardiovascular Endocrinology

PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

Estrogen Synergistically Interacts with Optic Atrophy Protein 1 to Promote Thrombosis
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SUN-572
Thrombosis is a major concern in: premenopausal females on oral contraceptives, menopausal women undergoing hormone replacement therapy, postmenopausal women and transgender individuals receiving estrogen supplementation. The mechanisms linking estrogen exposure with increased thrombosis risk is incompletely understood. Analysis of platelet transcripts in the Framingham cohort identified Optic atrophy 1 (OPA1) expression as being highly predictive of female sex and correlating with increased risk of diabetes and cardiovascular disease. OPA1 regulates mitochondrial fusion, electron transport chain (ETC), complex assembly, cristae morphology and apoptosis. Thus, to determine the functional relationship between platelet OPA1 expression and platelet function in relation to sex steroids we generated mice with platelet specific deletion of OPA-1 protein (pOPA1KO). Male pOPA1KO exhibited structurally and functionally compromised mitochondria with a 50% reduction in mitochondrial DNA and respiration. Male pOPA1KO mice exhibited a prothrombotic phenotype they had: increased agonist-induced activation, shortened time to stable occlusion of the carotid artery as assessed in vivo by (rose Bengal) photochemical injury (~25 min knockout vs ~35 min control), and were more prone to develop a thrombus (14/15 knockouts vs. 4/8 controls) following permanent ligation of the inferior vena cava. In contrast, female pOPA1KO mice had normal mitochondrial structure, function and DNA. Both agonist-induced platelet activation and thrombus formation was unchanged in pOPA1KO females. Paradoxically, pOPA-1 KO female mice had increased time to stable occlusion of the carotid artery as assessed by photochemical injury (~75 min Knockout vs ~35 min control). Notably, when platelets from pOPA-1 KO or control males were transferred into females following deple- tion of endogenous platelets, the reconstituted male platelets acquired the phenotype of female pOPA-1 KO mice. Thus, the time to stable occlusion of the carotid artery following photochemical injury was increased. Similarly, reconstitution of male mice with female pOPA1KO platelets were no longer prothrombotic. Gonadectomized pOPA1KO males had an increased time to stable occlusion and gonadectomized female pOPA1KO no longer exhibited increased time to stable carotid artery occlusion. Eugonadal pOPA1KO male mice treated with estrogen exhibited the pOPA1KO female thrombotic phenotype, with increased time to stable occlusion relative to control males. Additionally, OPA-1 levels were positively correlated with increased platelet aggregation and increased estrogen levels in third trimester pregnant human females. Together, these findings reveal a synergistic interaction between platelet OPA1 levels and estrogen to promote thrombosis.

Genetics and Development (including Gene Regulation)

ENDOCRINE DISRUPTING CHEMICALS

Comparative Histopathology of Endocrine Glands in Phthalate Exposed Male Wistar Rats Unveil the Vulnerability of Adrenal Gland and Augmented by Molecular Docking
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SAT-710
Limited research has been conducted on adrenal gland as a target of endocrine-disrupting chemicals (EDCs). Moreover,