addition to novel disease gene discovery. **Methods:** WES was performed for 13 unrelated patients with congenital hypopituitarism born from consanguineous parents. The variants were filtered assuming autosomal recessive inheritance, rare variants in population databases, *in silico* analysis predicted as deleterious and pituitary and/or hypothalamus gene expression. To determine whether variants in *CDH2* that were predicted to be deleterious were functionally significant, L1 fibroblast lines that have no endogenous CDH2 protein were stably transfected with either human wild type or variant *CDH2*, the transfected cells were labelled with lipophilic dyes, and cell adhesion properties were assessed. **Results:** Homozygous pathogenic or likely pathogenic allelic variants were found in 2 of the 13 patients. First, a female patient with GH, TSH, ACTH and LH/ FSH deficiencies presenting ectopic posterior pituitary lobe, non-visualized stalk, and hypoplastic anterior pituitary lobe had two homozygous rare variants predicted as deleterious: *PLA2G4A* p.Asn703Lys and *CDH2* c.865G>A (p.Val289Ile). Only *CDH2* is known to be expressed in the pituitary, and *Pla2g4a* null mice have a pleiotropic phenotype without obvious hypopituitarism. The *CDH2* variant is rare and classified as deleterious. Sanger sequencing of *CDH2* in four family members of the affected proband revealed that the unaffected parents and two unaffected siblings were heterozygous carriers. The effect of the *CDH2* variant on cell aggregation was assessed in cell culture. Large cell aggregates formed in cells transfected with wild type *CDH2*, but cell aggregates were small or absent in cells that were either non-transfected or transfected with the *CDH2* variant. Second, a patient with isolated GHD and no MRI abnormalities was identified with a rare, likely deleterious, homozygous *GH1* c.171delT (p. Phe 57Leufs*43) variant. He had a sister who died at the age of 5 and had features of GHD. **Conclusion:** In a cohort of congenital hypopituitarism from consanguineous parents we had 15% molecular diagnosis using WES. We identified a variant in a known gene, *GH1* c.171delT and a variant in a novel gene, *CDH2* p.Val289I.

Cardiovascular Endocrinology

VASCULAR DISEASE AND PATHOPHYSIOLOGY

MiRNA-99a and mTOR2 Mediate Enhanced Endothelial Mineralocorticoid Receptor Signaling-Induced Activation of Sodium Channel and Endothelium Stiffness

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SAT-LB97

In diet induced obesity enhanced endothelial cell (EC) mineralocorticoid receptor (MR) (ECMR) and downstream sodium channel (EnNaC) activity increases oxidative stress and inflammation, thereby promoting vascular stiffness and associated impaired endothelial mediated relaxation. For example, consumption of a Western diet (WD) containing excess fat (46%) and fructose (17.5%) for 16 weeks elevated plasma aldosterone levels and increased vascular MR expression in conjunction with increased endothelial and vascular stiffness in female mice. EC specific deletion of either the ECMR or EnNaC significantly attenuated this diet induced endothelial/vascular stiffness. Emerging information suggests that abnormal expression of miR-99a may be involved in these processes. To this point, we recently observed that aldosterone (10^{-7} mol/L) causes a reduction in miR-99a that was prevented by the MR antagonist, spironolactone (10μM) in in vitro ECs. By using RNA sequencing, we also demonstrated that ECMR activation reduced arterial miR-99a expression in diet induced obesity. Since the *mammalian target of rapamycin* (*mTOR2*)/SGK1 signaling pathway is involved in aldosterone activation of ENaC we then explored the effects of miR-99a on mTOR2 expression. Indeed, miR-99a reduced mTOR2. We further observed that inhibition of mTOR2 with PP242 inhibited EnNaC activity as determined by patch clamping of ECs. Collectively these data suggest that consumption of a WD induced ECMR activation and increased EnNaC activity and endothelial stiffness, in part, by reducing the tonic inhibitory effects exerted by miR-99a on mTOR2 mediated EnNaC activation.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Analysis of Clinical Characteristics and Gene Mutation in Four Cases of Gitelman Syndrome

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SUN-LB133

Analysis of Clinical Characteristics and Gene Mutation in four Cases of Gitelman Syndrome

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Abstract: Gitelman syndrome is an autosomal recessive renal tubular disorder characterized by renal salt wasting with secondary hyperreninemia and hyperaldosteronism, chronic hypokalemia with renal K wasting and metabolic alkalosis, and hypomagnesemia, and hypocalciuria. GS was found to be caused by mutations in SLC12A3 encoding the thiazide-sensitive sodium chloride cotransporter (NCCT) on the apical membrane of distal convoluted tubule. The prevalence worldwide is estimated at approximately 1:40,000, making it one of the most frequent inherited renal tubular disorders. To date, over 400 mutations scattered throughout SLC12A3 have been identified in GS patients. The majority of patients are compound heterozygous for SLC12A3 mutations, but a significant number of GS patients are found to carry only a single SLC12A3 mutation. The type of the SLC12A3 mutation may be a determinant factor in the severity of GS. The purpose of this