right adrenalectomy. Post-op plasma M, NM and ACTH were <0.20nmol/L, 0.36nmol/L and <5pg/mL.
DISCUSSION
Within the past 6 months, we have seen 2 cases of ACTH-secreting pheochromocytoma with different clinical symptoms and pre-op courses. Ectopic ACTH secretion may not cause classic Cushingoid features as in patient 1. Failure to recognize ectopic ACTH pre-op can lead to post-op complications such as AI. Patient 2 demonstrates that treatment of the hypercortisolemia may be necessary in order to adequately control BP and glucose levels prior to surgery.

Adipose Tissue, Appetite, and Obesity

MECHANISMS AND TREATMENT OF OBESITY IN HUMANS

Potential Role of Mutations in TBX3 in Human Weight Regulation

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Introduction: *Tbx3* has been shown to play a role in the terminal specification of hypothalamic melanocortin neurons during neonatal development & in maintaining the plasticity of their peptidergic role in adulthood in animal experiments (1). The absence of humans with biallelic mutations in *TBX3* & the conservation of the critical domains across species emphasizes its essential role in life. Heterozygous mutations in humans have been associated with ulnar mammary syndrome (UMS) with a spectrum of phenotype including obesity. Based on these observations, we hypothesized that heterozygous mutations in the conserved regions of *TBX3* may play an important role in the weight regulation pathway in humans.

Methods: The Genetics of Early Childhood Obesity (GECO) study enrolls children with severe (BMI > 120% of 95th %tile of CDC reference) early onset (< 6 years) obesity. Whole exome sequencing (WES) was performed in a subset of proband-parent trios. Peripheral mononuclear cells (PBMCs) from selected families were collected to generate induced pluripotent stem cells using non-integrating Sendai virus. Differentiation into disease-relevant hypothalamic neurons was performed using the published protocol (2). Loss-of-function models & isogenic controls were created using CRISPR/Cas9 & their cellular/molecular phenotypes were obtained at several time points during the course of differentiation.

Results: We have identified a family with heterozygous mutation in *TBX3* (p.His205Tyr, c.613 C>T, g.115118728 G>A). The proband is an 11-year old boy with morbid obesity (BMI 43.9 kg/m^2, BMIz + 3.25), advanced bone age, precocious puberty & type 2 diabetes. Trio analysis ruled out recessive & compound heterozygote causative variants, & none of the identified *de novo* variants were considered pathogenic. His mother suffers from severe obesity (BMI 38 kg/m^2 post-bariatric surgery) supporting an autosomal dominant inheritance of the phenotype. The putative causal variant in *TBX3* segregates in the proband, mother & maternal grandmother. Located in the DNA binding domain of T-box, the variant is predicted to be deleterious by 4 *in silico* algorithms & rare in population-based databases (mean allele frequency 0.006% in gNOMAD, absent in ClinVar). Consistent with the variable penetrance of the phenotype in UMS, neither mother nor child have the classic features, but, the mother has uterine anomalies causing 6 spontaneous abortions & was unable to breast feed due to inverted nipples. Ongoing functional studies in human hypothalamic neurons suggest that a decrease in melanocortin signaling possibly explaining the phenotype in this family.

Conclusions: Mutations in *TBX3* in humans may have a role as a monogenic cause of obesity and disease-relevant hypothalamic stem cells can serve as models to study them.

Ref: 1) Quarta et al. Nat Metab 2019, 1(2), 222-35; 2) Wang et al. JCI, 125(2): 796-808

Diabetes Mellitus and Glucose Metabolism

TYPE 2 DIABETES MELLITUS

Effect of Night Shifts on Glycemic Variability in Patients with Type 2 Diabetes

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Effect of night shifts on glycemic variability in patients with type 2 diabetes

The analysis of indicators of carbohydrate metabolism and variability of glycemia in patients with type 2 diabetes mellitus working in night shifts was carried out. As model patients with impaired circadian rhythm, the study included 34 patients, railway transport drivers, with shift mode and the presence of night shifts, with work experience of more than 5 years, the duration of type 2 diabetes mellitus (DM2) from 1 to 7 years, who are on oral therapy with hypoglycemic drugs. Simulation of different working conditions (day-night) was carried out in the simulator "driver's cabin". All patients underwent a study of the main indicators of carbohydrate metabolism (fasting glycemia, postprandial glycemia, glycated hemoglobin (HbA1c)), as well as continuous daily glucose monitoring (CGMS) using Medtronic MiniMed iPro2 system (from 3 to 7 days).

Target glycemic levels were not achieved: fasting glycemia was 6.98±1.41 mmol/l; postprandial glycemia was 9.57±1.65 mmol/l; HbA1c was 7.23±1.62%.

The analysis of CGMS revealed high variability of glycemic index MAGE-4.88±0.59 mmol/l. also calculated indicators SD - 1.52±0.63 mmol/l; Conga - 3.17±0.54 mmol/l; MODD - 2.27±0.12 mmol/l.

The period of hyperglycemia (glucose value above 7.8 mmol/l) according to the results of CGMS was 43.5% (min 19-max 56). The duration of hypoglycemic States in