increase resulting in androgen excess in both salt-wasting (SW) or simple virilizing (SV) forms. As androgens play a role in the human psychosexual development favoring male psychosexuality, this study was designed to evaluate the impact of androgen exposure on the psychosexuality of individuals with CAH due 21-hydroxylase deficiency. **Methods:** This retrospective cohort includes 46,XX individuals (115 female-assigned; 8 male-assigned) with a molecular diagnosis of CAH due to *CYP21A2* pathogenic variants in homozygous or compounds heterozygous state. External genitalia virilization was scored using Prader scale. Phenotype, time at diagnosis, sex assignment, and gender change were assessed. The gender role at childhood was assessed through the playmates and toys profile at childhood. Gender identity was assessed by a projective psychological test (HTP). Sexual orientation was assessed by self-report sexual identity. Compliance of glucocorticoid replacement was assessed by adequate testosterone and androstenedione serum levels for age. **Results:** CAH was diagnosed at the neonatal time in 73% (n=78). Fifth-nine (51%) had the SW form and 49% (n=56) had the SV form. While all cases of SW were diagnosed at the neonatal time (0.12 ± 0.14 months), the mean age at diagnosis among SV was 6.03 ± 8.45 years (p=<.001). The median of Prader score was 3 in both forms. Male sex assignment was associated with more virilized external genitalia (p=.002). Gender change occurred in 6 cases (female to male), all with SV form. The prader score was higher among those who changed gender (p=.01). All of those who changed their gender had poor treatment compliance. A total of 13% (n=15) of all groups defined themselves as homosexual. There was a strong association between male toys and preference for male playmates in childhood with homosexuality and male gender identity in adulthood with both gender change from female to male and homosexuality. **Conclusion:** Prenatal androgen exposure favors male psychosexuality in 46,XX CAH individuals as observed by the association between highest Prader scores and all assessed psychosexual outcomes. This influence is also substantiated by post-natal androgen exposure as observed by compliance issues and late diagnosis among those who changed from female to male gender.

Genetics and Development (including Gene Regulation)

FROM BENCH TO BEDSIDE: GENETICS, DEVELOPMENT AND CELL SIGNALING IN ENDOCRINOLOGY

Electronic Health Record-Based Genome-Wide Meta-Analysis Identifies New Susceptibility Loci for Non-Alcoholic Fatty Liver Disease

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Background: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent form of liver disease. Observational studies documented associations of NAFLD with several chronic and infectious diseases but whether these associations underlie causal effects is unknown. The molecular mechanisms and genetic architecture of NAFLD are poorly understood. Our objectives were to identify genetic loci associated with NAFLD and determine whether the presence of NAFLD was causally associated with human diseases.

Methods: We created a NAFLD genetic instrument through the identification of independent single-nucleotide polymorphisms (SNPs) associated with NAFLD in a meta-analysis of genome-wide association study (GWAS) (6715 cases and 682,748 controls). Using inverse-variance weighted Mendelian Randomization (MR), we investigated the impact of NAFLD on human disease-related phenotypes in the UK Biobank and FinnGen cohorts as well as in the COVID-19 host genetics initiative. **Results:** We first performed a GWAS meta-analysis of four cohorts and found variants significantly associated with NAFLD (p<5.0E-8) at six genetic loci (*MTARC1*, *GCKR*, *TRIB1*, *LMO3*, *SUGP1* [*TM6SF2*] and *PNPLA3*). Using a risk factor informed Bayesian approach (bGWAS), we identify variants at three additional loci (*LPL*, *FTO*, and *APOE*). To determine if the association between NAFLD and human diseases shows evidence of causality, we performed MR across the human disease-related phenome (>800 diseases) using a genetic instrument for NAFLD. Results of these analyses suggest that NAFLD was not causally associated with diseases outside the spectrum of liver diseases. We also found no causal association between genetically predicted NAFLD and COVID-19-related outcomes.

Conclusions: This study identified several new genetic loci associated with NAFLD. NAFLD was not causally associated with diseases outside those of the spectrum of liver diseases. This finding suggests that the resolution of NAFLD might not prevent other diseases previously associated with NAFLD.

Genetics and Development (including Gene Regulation)

FROM BENCH TO BEDSIDE: GENETICS, DEVELOPMENT AND CELL SIGNALING IN ENDOCRINOLOGY

Evaluation of Mayer-Rokitansky-Kuster-Hauser (MRKH) Patient Families by Whole Genome Sequencing

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Introduction: MRKH is a characterized by the congenital absence of the uterus and vagina in 46,XX individuals.

A subset of these patients also has associated renal, skeletal, cardiac and/or auditory defects. Familial cases suggest a genetic component, but to date only pathogenic variants in *WNT4* and *HNF1B* have been confirmed. We hypothesize that *de novo* heterozygous variants in candidate genes will be present in some patients with MRKH.

Methods: DNAs from 30 quads (an MRKH proband and three relatives) were subjected to whole genome sequencing (WGS), and heterozygous variants in coding regions with < 0.02 frequency were filtered by two different methods. In the first approach, variants were filtered by 1) top consequence variant (splice site, stop-gain, frameshift, and missense, respectively); 2) impact score; 3) mapping quality; 4) cytobands; 5) intolerance; 6) *de novo* variants; and 7) plausibility based on familial genotype. The second approach considered only heterozygous variants found in the proband and absent in all other family members, which were then filtered by top consequence (splice donor and acceptor sites, stop-gain, frameshift).

Results: Five pedigrees were excluded for inadequate sequence in one or more individuals. 55,033 variants in coding regions with < 2% frequency were identified in the 25 remaining quads for analysis. Using the first approach, 42 candidate gene variants in 32 genes were identified - 12 splice variants, 10 stop-gains, 15 frameshift variants and 5 missense variants. Of these, *MUC22* contained 2 missense variants from different families. Additionally, *DICER1* had multiple splice variants and is essential for mouse urogenital tract development. In the second approach, 39 candidate genes were identified—6 splice variants in 6 genes, 18 stop-gains in 17 genes, and 17 frameshift variants in 16 genes. Zinc finger genes (*ZNF418, ZNF646, ZNF135,* and *ZNF772*) comprised the most frequent class of the 39 genes. Two genes (*MIR4436A* and *ZNF418*) contained attractive variants in two different families.

Conclusion: WGS has been shown to improve detection of gene variants in coding regions, more so than whole exome sequencing (WES). We previously performed WES on 111 MRKH probands without family members and analyzed variants in candidate genes suggested by mouse and preliminary human studies. Interestingly, in this study, only three genes overlapped with previously suspected candidate genes. Here, we identified new candidates based upon potential deleteriousness. These candidate genes will be studied further in our families to determine their role in Mullerian development.

Genetics and Development (including Gene Regulation)

FROM BENCH TO BEDSIDE: GENETICS, DEVELOPMENT AND CELL SIGNALING IN ENDOCRINOLOGY

Experience Completing Population Screening for Variants Associated With Endocrine Tumor Syndromes in a Large, Healthcare-Based Cohort

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Hereditary endocrine tumor syndromes (ETS) including Multiple Endocrine Neoplasia Types 1 and 2 (MEN1 and MEN2), von Hippel-Lindau (VHL), and Hereditary Paraganglioma and Pheochromocytoma syndromes (PGL/PCC) have a collective prevalence of 1 in 8500. In current practice, patients' personal and family histories are used to determine whether genetic testing for ETS is warranted. Population genetic screening for other actionable conditions implies that current practice can be enhanced to identify individuals with genetic variants and that identification of such individuals can lead to improvements in risk management and early-onset diagnoses. It is unknown whether such benefits occur when screening for ETS risk. We report on the rate of syndrome-related features and post-disclosure risk management in patients informed of a pathogenic/likely pathogenic (P/LP) variant in a gene associated with an ETS through the MyCode Community Health Initiative (MyCode). MyCode is a biobank of individuals from a health system who consent to health-related research and return of clinically actionable results. Exome sequences are analyzed for P/LP variants in actionable genes, confirmed by a clinical laboratory, and disclosed to participants and their providers. All participants are offered follow-up with a genetics provider post-disclosure. Here, we focus on participants that received a P/LP variant in *MEN1, RET*, *VHL*, or an *SDHx* gene from June 2016-October 2019. From May-July 2020 we performed dual, manual review of participants' electronic health records to assess personal and family histories, risk management behaviors, and post-disclosure diagnoses of endocrine neoplasms.

Of 87,493 participants with available exome data, P/LP variants in genes of interest were identified in and disclosed to 80 participants (65% female, 99% self-reported White race, 99% self-reported non-Hispanic ethnicity, median age 57 years at results disclosure, median time since disclosure 2 years). Eighty-one percent of participants (n=65) did not have a prior diagnosis of an ETS and were included in additional analyses. Five participants (8%) had a personal history of syndrome-related features; 16 (25%) had a positive family history. Only seven (11%) met existing clinical testing criteria pre-disclosure. Post-disclosure, 37 (57%) completed at least one recommended risk management behavior; 11 of these (17%) were diagnosed with a syndrome-related neoplasm (e.g., medullary thyroid cancer).

Results of population screening in a healthcare cohort suggest genetic variants associated with ETS risk are more common than previously reported (1 in 1094). Though additional studies on clinical utility are needed, these results suggest that screening healthcare populations for genetic risk can enable detection of individuals at risk for ETS, lead to uptake of risk management, and facilitate relevant clinical diagnoses.

Genetics and Development (including Gene Regulation)

FROM BENCH TO BEDSIDE: GENETICS, DEVELOPMENT AND CELL SIGNALING IN ENDOCRINOLOGY

Favorable Prognostics of Post-Exercise Irisine Released as Prophylaxis of Serious Covid-19 in Obese Elderly