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

Juliann M. Savatt, MS, CGC, Nicole M. Deckard, MS CGC, Gretchen Thone, MS, CGC, Whitney S. McDonald, PhD, Madiha M. Alvi, MD, FACP, FACE, Nicholas C. Purdy, DO FACS, Timothy L. Lindemann, MD, FACS, FAAOA, Amy C. Sturm, MS, CGC, Adam H. Buchanan, MS, MPH, CGC.
Geisinger, Danville, PA, USA.

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