Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Hypophosphatemia Gene Panel Sponsored Program: A High Yield Of Molecular Diagnoses from Clinically Confirmed XLH and Suspected XLH/ Genetic Hypophosphatemia

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X-linked hypophosphatemia (XLH), an X-linked dominant disorder caused by a pathogenic change (variant) in the *PHEX* gene, affects males and females of all ages. Rickets and osteomalacia may be present along with short stature, lower limb deformity, muscle pain and/or weakness/fatigue, bone pain, joint pain/stiffness, hearing difficulty, enthesopathy, osteoarthritis and dental abscesses. Patients with XLH have below-normal serum phosphate and elevated serum FGF23. XLH is one of multiple etiologies of hypophosphatemia; depending on genetic cause, management may differ. The program provides a no-cost test to confirm a clinical XLH diagnosis or to aid diagnosis of suspected XLH or other genetic hypophosphatemia.

Methods Program eligibility criteria: >/=1y old and either clinical XLH diagnosis (*confirmatory*) or suspicion of XLH/ genetic hypophosphatemia (*suspected*) as evidenced by 2 or more clinical signs/ symptoms. The next generation sequencing gene panel includes 13 genes: *ALPL, CLCN5, CYP2R1, CYP27B1, DMP1, ENPP1, FAH, FAM20C, FGF23, FGFR1, PHEX, SLC34A3* and *VDR*. Copy number variant (CNV) detection was performed.

Results 317 unrelated probands have been tested as of October 2, 2019. Of 158 XLH confirmatory samples received, 143 (90.5%) had a *PHEX* variant: 14 (9.8%) were variants of uncertain significance (VUS) and 129 (90.2%) were either pathogenic or likely pathogenic (P/LP) XLH molecular diagnoses. Of the 15 patients (9.5%) where no *PHEX* variant was found, one had a P variant in *FGF23* (autosomal dominant hypophosphatemic rickets molecular diagnosis) and another had P and LP variants in *ENPP1* (autosomal recessive hypophosphatemic rickets Type 2 molecular diagnosis). Of 159 suspected samples, 101 (63.5%) had a *PHEX* variant: 14 (13.9%) were variants of uncertain significance (VUS) and 87 (86.1%) were P/LP (XLH molecular diagnoses). No *PHEX* variant was found for 58 (36.5%) of suspected samples; however, 5 of these had other findings: a dominant-negative heterozygous P variant for *ALPL* was detected in 3 samples (3 hypophosphatasia, HPP, molecular diagnoses); a fourth carried two P variants in *ALPL*; a fifth had a LP variant and a VUS in *ENPP1* (autosomal recessive hypophosphatemic rickets Type 2). Of 121 unique P/LP *PHEX* variants detected, 59 were deletions duplications or insertions. A complex rearrangement and an Alu-mediated insertion were detected in the full cohort. To date, additional family member testing was performed for 10 probands with original VUS: in 4 cases the VUS was reclassified to P/LP; 2 were reclassified to P/LP due to more clinical info, highlighting the value of family testing and clinical info to resolve VUS. RNA analyses to resolve VUS and unidentified variants may further improve molecular diagnoses of genetic hypophosphatemia. Program results demonstrate a high diagnostic yield for confirmatory and suspected XLH/ genetic hypophosphatemia.

Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

Impact of Race and Obstructive Sleep Apnea on Glucose and Insulin Regulation in Women with PCOS

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The prevalence of prediabetes and diabetes is substantially higher in PCOS women with obstructive sleep apnea (OSA) compared to PCOS women without OSA[1,2,3]. Prior studies, however, did not examine the complex interaction between race and OSA on metabolic function in PCOS. We sought to determine if the impact of OSA on glucose and insulin metabolism is affected by race. We studied non-Hispanic white (NHW) (n=53) and African-American (AA) (n=48) women with PCOS. Following an overnight polysomnogram (PSG), PCOS women (NHW without OSA n=40; NHW with OSA n=13; AA without OSA n=36; AA with OSA n=12) had a 2-h 75-g oral glucose tolerance test (OGTT) with blood sampling every 30 minutes for measurement of glucose, insulin, and C-peptide concentrations. OSA severity was measured by the Apnea-Hypopnea Index (AHI). Only women without OSA (AHI < 5) or with moderate-to-severe OSA (AHI > 15) were included in these analyses; women with mild OSA were excluded. Insulin secretion rates (ISR) during the OGTT were derived by deconvolution of C-peptide levels [4]. Area under the curve (AUC) response to the glucose challenge was calculated using the trapezoidal method. BMI and age did not differ between races in PCOS women without OSA (BMI [kg/m^2]: 36.3±1.2 vs. 37.2±1.1, p=0.58; Age [yr]: 27.7±0.8 vs. 27.2±0.8, p=0.65; for NHW and AA respectively), or in PCOS women with OSA (BMI [kg/m^2]: 42.8±1.7 vs. 44.7±2.0, p=0.50; Age [yr]: 31.4±1.6 vs. 28.6±1.6, p=0.18; for NHW and AA respectively). OSA severity was similar in NHW and AA PCOS women without OSA (AHI: 1.5±0.2 vs 2.1±0.2, p=0.076), and PCOS women with OSA (AHI: 32.0±4.9 vs. 28.3±4.4, p=0.26). Higher glucose responses during the OGTT were observed in NHW PCOS women with OSA compared to both NHW (AUC: 18,965±648 vs. 15,797±371, p=0.0004) and AA (AUC: 18,965±648 vs. 15,801±497, p=0.0005) PCOS women without OSA. Glucose responses did not differ significantly between AA PCOS women with OSA and AA PCOS women without OSA (AUC: 17,104±965 vs. 15,801±497, p=0.15). Similarly, ISR was higher in NHW PCOS women with OSA compared to both NHW (AUC: 5,648±488