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Investigating the genetic underpinning and associated audiological features of childhood hearing loss in Puerto Rico

Elinette Albino[1], Brenda Quiñones-Flores[2], Carmen Brewer[3], Rabia Faridi[2], Soami Santiago De Snyder[4], Thomas B. Friedman[2], Wanda M. Lugo Velez[4], Celinés Rodriguez-Acevedo[5], Carmen J. Buxo[6] and Isabelle Roux[2]

[1]School of Health Professions, Clinical Laboratory Sciences Program, Medical Sciences Campus, University of Puerto Rico, Rio Piedras, PR; [2]Laboratory of Molecular Genetics, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD; [3]Neurotology Branch, Division of Intramural Research, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD; [4]School of Health Professions, Doctor of Audiology Program, Medical Sciences Campus, University of Puerto Rico, Rio Piedras, PR; [5]School of Health Professions, Puerto Rico Genetics Laboratory, Medical Sciences Campus, University of Puerto Rico, Rio Piedras, PR and [6]School of Dental Medicine, Medical Sciences Campus, University of Puerto Rico, Rio Piedras, PR

OBJECTIVES/GOALS: Hearing loss (HL) can result from environmental and genetic factors. Some genetic variants may be more prevalent in populations living in geographic or cultural isolation. This study explores the genetic variants associated with HL in Puerto Rico and correlates these with auditory and balance disorders to uncover novel variants. METHODS/STUDY POPULATION: After obtaining individual informed consent and assent for a minor when applicable, we will collect clinical audiological data and biological samples (n = 600) from families across Puerto Rico with a history of severe to profound HL. Genomic DNA will be extracted, and exome and mitochondrial genome sequencing will be conducted to identify causal variants in genes associated with HL. The study will assess the prevalence of both novel and reported variants in genes associated with HL and investigate founder variants in the Puerto Rican population. Involvement of genes so far not associated with HL will also be considered when a genetic diagnosis cannot be established. Auditory phenotypes will be correlated with genetic findings, allowing for a comprehensive analysis of genetic contributions to HL in this population. RESULTS/ANTICIPATED RESULTS: This research will advance understanding of the genetic causes of HL in Puerto Rico, leading to more accurate diagnoses, personalized treatment options, and the discovery of novel genes associated with HL. It will also serve as an evidence-based reference to analyze the adequacy of current neonatal hearing screening protocols in PR. Recruitment and sample collection have begun, and we expect our findings to uncover population-specific variants. These results will provide a foundation for further genetic studies aiming at identifying the causes of HL in Puerto Ricans regardless of age of onset. DISCUSSION/SIGNIFICANCE OF IMPACT: This study will enhance our understanding of hereditary HL and serve as a basis for developing population-specific diagnostic tools and interventions, particularly in the Puerto Rican population. The research will support future genetic studies and address health disparities in HL in the island.

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Association of microbiome dysregulation with differential gene expression in a spontaneous equine model of osteoarthritis*

Zoë J. Williams[1,2], Lyndah Chow[1,2], Isabella Sabino[1,2], Renata Impastato[1,2], Luke Bass[1,2], Steven Dow[1,2] and Lynn Pezzanite[1,2]

[1]Department of Clinical Sciences, Colorado State University, Fort Collins, CO and [2]Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO

OBJECTIVES/GOALS: Osteoarthritis (OA) is a multifactorial disease where sustained gut inflammation is a continued source of inflammatory mediators driving degenerative processes in joints. The goal was to use spontaneous equine model to compare fecal and leukocyte microbiome and correlation to transcriptome in OA. METHODS/STUDY POPULATION: Seventy-six horses (31 OA, 45 controls) were enrolled by population-based sampling. Feces and peripheral blood mononuclear cells (PBMC) were collected. Horses were determined to have OA by clinical and radiographic evidence. Horses were excluded if they received medications or joint injections within two months. Fecal and circulating leukocyte bacterial microbial 16s-seq was performed. Bulk RNAseq of PBMC was performed by the Illumina platform. Gene expression data were mapped to the equine genome, and differential expression analysis was performed with DESeq2. Qiime2 was used for microbial analysis. Enrichment analysis was performed with a cluster profiler. Correlation analyses were performed between the datasets. RESULTS/ANTICIPATED RESULTS: Beta and alpha microbial diversity differed in feces and PBMC of OA vs. healthy horses. Horses with OA had an increased Firmicutes to Bacteroidetes ratio compared with controls. The fecal microbiome of OA horses had significantly higher amounts of Firmicutes *Oribacterium* (q DISCUSSION/SIGNIFICANCE OF IMPACT: These data suggest that altered microbiome and PBMC gene expression are associated with naturally occurring OA in the translational equine model. While *Oribacterium* has been detected in humans with rheumatoid arthritis, its role in OA warrants further proteomic and metabolomic profiling.

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The role of peroxisome proliferator-activated receptor-alpha on blood pressure, glomerular filtration rate, and renal inflammation during high-salt hypertension*

Mark Hatcher[1], Blythe Shepard[2] and Dexter L Lee[1]

[1]Howard University and [2]Georgetown University

OBJECTIVES/GOALS: The study's goal is to investigate the role of PPAR-α on regulating blood pressure, glomerular filtration rate (GFR), renal inflammation, and renal sodium reabsorption in mice on a 4% high-salt diet. METHODS/STUDY POPULATION: GFR, systolic blood pressure (SBP), inflammatory biomarkers (KIM-1, TIMP2, NGAL, MCP-1, TNF-α, IL-6, IL-10, and IL-17), and renal sodium transporter expression (NKA, NHE3, NKCC2, NCC, ENaC, Aqp-2, and NHERF1) were measured in PPAR-α KO mice

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and wild-type controls treated with a 4% high-salt (HS) diet. Male C57BL6, B129S1, and PPAR-α KO mice (12 weeks old) will be treated with 4% HS diet for 28 days. Systolic blood pressure is measured by tail cuff. GFR is measured by transdermal FITC-Inulin radioactive fluorescence. Inflammatory biomarkers will be measured by cytokine array and western blot. Sodium transporter expression will be measured by western blot. RESULTS/ANTICIPATED RESULTS: Baseline SBP was 146 ± 31 mmHg (C57), 140 ± 24 mmHg (B129), and 153 ± 23 mmHg (KO). After 21 days of normal (control diet) or treatment (HS diet), control systolic pressures were 139 ± 18 mmHg (C57), 107 ± 23 mmHg (B129) and 147 ± 34 mmHg (KO), while HS systolic pressures were 166 ± 23 mmHg (C57) and 119 ± 34 mmHg (B129). We are collecting blood pressure for the KO HS group. Baseline GFR was 1194 ± 140 μL/min/g (C57), 1167 ± 279 μL/min/g (B129), and 1191 ± 157 μL/min/g (KO). DISCUSSION/SIGNIFICANCE OF IMPACT: We hypothesize significantly higher SBP, inflammatory marker expression, and renal sodium transporter expression in KO and B129 mice on a HS diet. We predict that PPAR-α expression in the kidney will be higher in C57 compared to B129. We predict that PPAR-α activity plays a vital role in reducing high-salt-induced hypertension and inflammatory markers.

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The effect of a novel inhibitor of Slc7a5 on remyelination in MS

Meghan Bullard, Brent Harris and Jeffrey Huang
Georgetown University

OBJECTIVES/GOALS: This study aims to first understand the expression of the L-type amino acid transporter, Slc7a5, in demyelinated plaques in postmortem multiple sclerosis (MS) CNS tissue. It also seeks to understand the effect of a novel inhibitor of Slc7a5 on remyelination in mice with experimental autoimmune encephalomyelitis. METHODS/STUDY POPULATION: Using single-cell RNA sequencing (scRNA-seq), we will examine the expression of Slc7a5 in demyelinated plaques in postmortem CNS tissue of patients with MS compared to non-lesioned regions (n = 3/group). Using visually evoked potential (VEP) on mice with experimental autoimmune encephalomyelitis (EAE), we will determine the ability of the Slc7a5 allosteric inhibitor OKY-034 to promote remyelination compared to EAE-only controls (n = 10/group). Lastly, we will use spatial transcriptomics with scRNA-seq to map transcriptional activity within different populations of cells to determine how OKY-034 changes gene expression in specific cell types compared to EAE-only controls (n = 3/group). RESULTS/ANTICIPATED RESULTS: A conditional knockout of Slc7a5 showed that microglial activation and oligodendrocyte differentiation were affected in demyelinated lesions. This suggests that it plays a role in numerous cell types in active demyelinated plaques, which is what we expect to find from our scRNA-seq data in post-mortem CNS tissue of patients with MS. Measuring VEP is a noninvasive way to measure remyelination in both clinical and research settings. OKY-034 increases oligodendrocyte differentiation suggesting remyelination, so we expect that administration of OKY-034 in mice with EAE will lead to restored VEP compared to control and EAE-only mice. Lastly, because OKY-034 reduces inflammation, we expect to see a decrease in gene expression for genes involved in an immune response. DISCUSSION/SIGNIFICANCE OF IMPACT: Completion of this study will lead to understanding what the effect the allosteric Slc7a5 inhibitor OKY-034 has on remyelination and whether it may serve as a novel therapeutic drug that can be administered orally for the treatment of MS. This could lead to its further development as a treatment for progressive MS.

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Novel inflammatory gene expression changes occur within the occluded vasculature of large vessel ischemic stroke

Destiny Hooper[1], Miranda Marion[2], Xiang Zhang[3], Charles Prestigiacomo[3], Peyman Shirani[3], Aaron Grossman[3], Matthew Smith[3], Carlos Cruchaga[1], Jin-Moo Lee[1], Carl Langefeld[2] and Daniel Woo[3]
[1]Washington University; [2]Wake Forest University and [3]University of Cincinnati

OBJECTIVES/GOALS: We hypothesized that the bulk transcriptomic profiling of blood collected from within the ischemic vasculature during an acute ischemic stroke with large vessel occlusion (LVO) will contain unique biomarkers that are different from the peripheral circulation and may provide much-needed insight into the underlying pathogenesis of LVO in humans. METHODS/STUDY POPULATION: The transcriptomic biomarkers of Inflammation in Large Vessel Ischemic Stroke pilot study prospectively enrolled patients ≥ 18 years of age with an anterior circulation LVO, treated with endovascular thrombectomy (EVT). Two periprocedural arterial blood samples were obtained (DNA/RNA Shield™ tubes, Zymo Research); 1) proximal to the thrombus, from the internal carotid artery and 2) immediately downstream from the thrombus, by puncturing through the thrombus with the microcatheter. Bulk RNA sequencing was performed and differential gene expression was identified using the Wilcoxon signed rank test for paired data, adjusting for age, sex, use of thrombolytics, last known well to EVT, and thrombolysis in cerebral infarction score. Bioinformatic pathway analyses were computed using MCODE and reactome. RESULTS/ANTICIPATED RESULTS: From May to October 2022, 20 patients were screened and 13 were enrolled (median age 68 [SD 10.1], 47% male, 100% white). A total of 608 differentially expressed genes were found to be significant (p-value) DISCUSSION/SIGNIFICANCE OF IMPACT: These results provide evidence of significant gene expression changes occurring within the ischemic vasculature of the brain during LVO, which may correlate with larger ischemic infarct volumes and worse functional outcomes at 90 days. Future studies with larger sample sizes are supported by this work.

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Evaluating fibroblast growth factor receptor (FGFR) pathway mRNA expression and protein activation in cholangiocarcinoma tumors

Leah Stein[1], Julie W. Reeser[2], Michele R. Wing[2], Eric Samorodnitsky[2], Anoosha Paruchuri[2], Amy Smith[2], Thuy Dao[2], Zachary Risch[2], Emanuel F. PetricoinIII[3] and Sameek Roychowdhury[2]
[1]The Ohio State University; [2]The Ohio State University Wexner Medical Center and James Cancer Hospital and [3]Center for Applied Proteomics and Molecular Medicine, George Mason University

OBJECTIVES/GOALS: Personalized cancer therapy based on genomic testing is advancing patient care. Genomic alterations in fibroblast growth factor receptor (FGFR) predict response to FGFR inhibitors; however, the role of RNA expression and protein activation is not known. We propose to examine the

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