## 482 Translational gene editing strategies for understanding and treating CHCHD10-associated amyotrophic lateral sclerosis (ALS)

Adriana Morales Gomez<sup>1</sup>, Nathan P. Staff<sup>2</sup> and Stephen C. Ekker<sup>3,2</sup> <sup>1</sup>Mayo Clinic Department of Neurology; <sup>2</sup>Mayo Clinic, Rochester, MN, USA Department of Pediatrics and Center for Rare Disease, Dell Medical School and <sup>3</sup>The University of Texas at Austin, Austin, Texas, USA

OBJECTIVES/GOALS: This study aims to explore transcriptional adaptation, where mutations in one gene trigger compensatory changes in related genes, and how this affects the variability in clinical manifestations of ALS. Our findings will provide insights for therapeutic strategies, while we also use gene editing to investigate correcting variants in ALS patients. METHODS/STUDY POPULATION: The presence of a premature termination codon triggers transcriptional activation. Therefore, we utilized CRISPR-Cas9 tool to generate a premature termination codon in CHCHD10 gene in multiple types of cells, including induced pluripotent stem cells derived from patient samples with known CHCHD10 mutations causative for Amyotrophic lateral sclerosis. CRISPR-Cas9 tool was delivered via ribonucleoprotein electroporation and transfected cell's DNA was sequenced to validate gene editing. To confirm transcriptional adaption, changes in levels of protein and gene expression will be measured via immunoblot and quantification of CHCHD10 and CHCHCD2 from whole cell lysates of the edited cells. RESULTS/ANTICIPATED RESULTS: Utilizing CRISPR-Cas9 tools, we anticipate that CHCHD2 gene can functionally compensate for the loss of function in the CHCHD10 locus through transcriptional adaptation. Additionally, employing single-stranded oligodeoxynucleotides (ssODNs) we aim to accurately correct the genetic aberrations in ALS patient cells, and study the pathomechanisms of aberrant CHCHD10. DISCUSSION/ SIGNIFICANCE OF IMPACT: The significance of this research lies in its potential to uncover transcriptional adaptation in humans, which could explain why patients with the same genetic variant experience different symptoms. By understanding this mechanism, we could pave the way for novel therapies, especially for CHCHD10associated ALS.

## Human leukocyte antigen (HLA) alleles associated with severe COVID-19 outcomes in the All of Us cohort\*

483

Grace Kim, Grace J. Kim<sup>1,2</sup>, Nayane Brito<sup>3</sup>, San Chu<sup>4</sup>, Ronald Horswell<sup>4</sup>, Nicolas Vince<sup>3</sup> and Lucio Miele<sup>1</sup>

<sup>1</sup>Department of Genetics, Louisiana State University Health Sciences Center, New Orleans, LA, United States; <sup>2</sup>School of Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, United States; <sup>3</sup>Cente for Research in Transplantation and Translational Immunology, Nantes Université, Nantes, Cedex, France and <sup>4</sup>Department of Population and Public Health, Pennington Biomedical Research Center, Baton Rouge, LA, United States First author

OBJECTIVES/GOALS: The primary objective of this study is to investigate the relationship between human leukocyte antigen (HLA) alleles to COVID-19 clinical severity, specifically: hospitalization, mortality, pneumonia by COVID-19, post-acute sequelae of SARS-CoV-2 infection (PASC), and clinical lab values. METHODS/STUDY POPULATION: We are conducting a retrospective cohort study utilizing the All of Us controlled tier dataset. The base population was defined as any patients with a COVID-19 diagnosis code (ICD-10: U07.1 or SNOMED: 840539006) and genomic sequencing data. PASC definitions were developed by the N3C consortium and refined in house. A total of 15,252 patients (64.5% female; 50.4% self-reported European ancestry; 18.8% selfreported African ancestry; 34.5% > 65 years old) are included in this study. HLA Class I and Class II alleles will be imputed from a global diversity reference panel utilizing the HIBAG "R" package. RESULTS/ANTICIPATED RESULTS: Controlling for age, sex, race, and COVID-19 vaccination status, we anticipate determining the HLA alleles associated with severe clinical outcomes, such as Pneumonia by COVID (n = 1,436) and PASC (ICD-10:U09.9 or SNOMED:119303003 or OMOP:OMOP5160861 [n = 498]). We will assess which HLA alleles are associated with markedly different IgM and IgG COVID-19 serum antibody levels (n = 1,024). Coexisting conditions, i.e., type 2 diabetes, chronic obstructive pulmonary disease, and hypertension, will be controlled for with the Charlson comorbidity index. The accuracy of HLA allelic imputation will be validated in patients with long-read whole genome sequences. DISCUSSION/SIGNIFICANCE OF IMPACT: Our findings can help identify patients who may be at risk of severe COVID-19 infection, particularly those undergoing bone marrow or organ transplantation. We hope this study will accelerate personalized care of COVID-19 in vulnerable populations.

## 484

## MAPping impulsivity: Cortical architecture as a biosignature for relapse vulnerability in substance use disorders

Holly ChapmanJonathan D. Hommel, Kathryn A. Cunningham, Gracie Vargas and Noelle C. Anastasio The University of Texas Medical Branch

OBJECTIVES/GOALS: One in 14 individuals have a substance use disorder (SUD). We suggest that a trait of poor impulse control, or high impulsivity, may predict relapse risk. We explore how changes in brain structure linked to decision-making and reward might drive high impulsivity, helping create a "biosignature" to identify those most at risk and guide treatment choices. METHODS/ STUDY POPULATION: Male rats were phenotyped as high impulsive (HI) or low impulsive (LI) based on premature responses on the one-choice serial reaction time (1-CSRT) task. Rats then received an intracranial infusion of a retrograde virus (AAVr2) in the nucleus accumbens (NAc) to trace corticoaccumbens neurons back to the medial prefrontal cortex (mPFC). After impulsivity phenotyping (ITI8), another cohort of animals performed cocaine self-administration followed by 30 days of abstinence. Cue reactivity, a measure of relapse-like behaviors, was performed on abstinence day 30. Analyses of microtubule-associated protein 2 (MAP2), a cytoskeletal marker of dendrites, spines, and somas was performed with western blotting and fluorescent images of brain slices after phenotyping and cocaine abstinence. RESULTS/ANTICIPATED RESULTS: HI rats made greater premature responses, a marker of impulsive action vs. LI rats at baseline (p DISCUSSION/SIGNIFICANCE OF IMPACT: Poor inherent impulse control and drug cues heighten relapse risk. We found high impulsivity linked to brain structure differences and lower protein markers of synaptic (units supporting signaling) strengthening. Future investigations into brain-behavior links with impulsivity may further identify a SUD relapse vulnerability biosignature.