Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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IBS as EUR (N=30) and YRI as AFR (N=30). We simulated 6 different patterns of admixture (NAT%/EUR%/AFR%: 70/30/0, 50/50/0, 95/5/0, 5/95/0, 15/60/25, 33/33/34) considering a single event of admixture 9 generations ago. This results in realistic simulated truth datasets with known phase and LA which can be used for method benchmarking. We then called LA on this truth dataset using RFMix_v1 under three different NAT reference panel combinations: 1) Well matched but low sample size (remaining samples from NAT-HGDP); 2) Low sample size and Admixed reference panel (PEL-1KG); 3) Large sample size but not well matched (PEL-1KG + EAS-1KG). We tested the accuracy of haplotypes with small NAT proportions (5% NAT, 95% EUR) and the impact of using a 3-way reference for 2-way admixed cohorts. Finally, we quantified the LAI true positive calls of the test to assess their respective performance and to identify the location and direction of error of wrong calls.

We find that for all 6 simulated demographic models the NAT calls performed worse (true positive rate - TPR = \sim 93%) and with larger standard deviations when compared to EUR (TPR \geq 98%) and AFR calls (TPR \geq 99%). We also observed a prominent decrease in TPR when the ancestry proportion is lower than 5%. There was no major impact of using a 3-way reference panel for 2-way admixed LatAm cohorts. The direction of wrong calls was in systematically overcalling AFR ancestry over EUR or NAT (3-way ancestry), and EUR over NAT (2-way admixture). Our results will help guide researchers as to how to best study underrepresented LatAm cohorts. This in turn will allow for their more appropriate inclusion in mixed psychiatric collections, such as in population genetic efforts examining demography or ancestry-specific association studies such as with Tractor. This work informs on best practices for LA analysis in admixed cohorts using existing reference resources, as well as the optimal reference panel choices more broadly across admixed populations.

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YOUR ILLNESS ON DRUGS: THE GENETICS OF SUBSTANCE USE INFORMS OUR RESPONSE TO SOMATIC DISEASES

Chair: Howard Edenberg 1, Co-chair: Alexander Hatoum 1, Discussant: Arpna Agrawal 1

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Overall Abstract: SUDs are among the top contributors to all cause mortality. This session highlights cross-cutting genetic and genomic analyses that illuminate the relationships between substance use disorders (SUDs) and aspects of health and disease beyond the known relationships with other psychiatric disorders. This is a topic that has gotten very little attention in the past. It is timely, given multiple global health crises, as it addresses the role of SUDs in respiratory and cardiometabolic illness, COVID-19 and HIV/AIDS - each among the leading contributors to mortality. The first talk will showcase findings from a phenome-wide analysis (PheWAS) of alcohol and cannabis involvement, using medical center data. It demonstrates that genetic liability for substance use has a profound effect on multiple bodily systems. For example, genetic liability for cannabis use predicted respiratory illness while that for alcohol use predicted heart disease. Individuals with SUDs are at higher risk to develop severe cases of COVID-19. The second talk examines genetic correlations between COVID-19 severity phenotypes and 1014 heritable traits, and reveals that the largest genetic causality proportions were for alcohol use frequency, smoking and cannabis use. Third, we pivot from the current pandemic to the ongoing HIV epidemic to discuss the impact of cocaine abuse among HIV+ individuals. The findings showed cocaine use increased viral load, worsened progression, accelerated mortality, and increase the latent viral reservoir. Specific DNA methylation and gene expression differences that appear to be biological mediators of these relationships were uncovered. The last talk addresses the mediating role of behavioral disinhibition, which is genetically correlated with SUD, using a multivariate GWAS approach to creating a broad genetic measure of externalizing behavior (EXT). Pooling data from \sim 1.5 million people, more than 500 genetic loci were discovered. A PheWAS showed that EXT-PRS was associated with 255 of the 1335 disease phenotypes tested (FDR < 0.05). Individuals with higher EXT-PRS showed poorer health in nearly every bodily system. To conclude, the panel will discuss the importance of considering the genetics of SUDs more broadly, to better understand both psychiatric and somatic disorders and the enormous health burden arising from them.

Disclosure: Nothing to disclose.

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PHENOME-WIDE GENETIC CORRELATION AND CAUSALITY OF COVID-19 SEVERITY HIGHLIGHTS OVERLAP WITH SUBSTANCE-USE TRAITS

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Abstract: The recent emergence of the SARS-Cov-2 virus has quickly escalated into a pandemic causing Coronavirus virus disease 2019 (COVID-19) and infecting more than 25 million people in the US. Several population categories have been identified to be at high risk to develop COVID-19 severe symptoms. Among them, there are individuals affected by substance use disorders (SUD). More than 80 million individuals in the US suffer from at least one SUD. The physiological deterioration from addictive substances leads to impaired pulmonary, cardiovascular, and metabolic function, increasing the risk of experiencing severe outcomes from COVID-19. To understand the impact of lifestyle and health factors on COVID-19 susceptibility, we investigated three COVID-19 phenotype definitions (i.e., critically ill, hospitalization, and reported COVID-19 diagnosis) from \sim1 million individuals using COVID-19 Host Genetics Ini-
tiative (HGI) genome-wide data. We analyzed pairwise genetic correlation between COVID-19 phenotypes and 1014 heritable health disorders and lifestyle traits from the UK Biobank (N>450,000). More than 120 trait-pairs survived a 5% false discovery rate multiple-testing correction and were further investigated for genetic causality proportion via linear latent variable analysis. The largest causal effects were observed with respect to the impact of alcohol use frequency (gcp-hospitalization =78.5%; gcp-critical illness =76.8%), smoking (gcp-hospitalization=58.5%), tobacco (gcp-hospitalization=60.1%; gcp-critical illness=6.8%), and cannabis use (gcp-critical illness=9.5%) on the risk of being COVID-19 susceptible(p<10-5). These findings align with epidemiological observations that patients with SUD and COVID-19 experience higher vulnerability to adverse consequences from COVID-19.

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USING OMICS TO UNDERSTAND THE ADVERSE EFFECTS OF COCAINE USE ON HIV OUTCOMES

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Abstract: With the success of combination antiretroviral therapy (cART) and public health strategies to reduce HIV incidence, much of the HIV burden in developed countries is now as a chronic disease, including among drug users. Managing HIV progression and searching for an HIV cure are paramount. Higher pretreatment viral load is associated with HIV progression and with a larger HIV latent reservoir (HLR). A cure is dependent on eliminating the HLR. Cocaine is one of the most frequently abused illicit drugs among HIV+ individuals. However, we and others have shown that it increases viral load, worsens progression, slows decline of viral production after cART, and accelerates mortality. The association between cocaine abuse and these HIV outcomes appears to be partially mediated by cocaine’s effects on DNA methylation. In a new study using the Women’s Interagency HIV Study (WIHS) cohort, we: (1) demonstrate, for the first time, that HLR in CD4 T-cells is robustly elevated among those abusing cocaine (p=0.0001); and (2) in the first transcriptome-wide study of cocaine abuse in peripheral tissue (N=257), we discovered 124 differentially expressed genes by cocaine abuse status in CD4 T-cells (FDR <0.1), several with prior associations to cocaine (e.g., HOMER1, p=1.49E-05), HIV virion packaging (e.g., RN7SL1, p=9.07E-07), and HIV latency (e.g., POLR1B, p=3.28E-05). Here, we present adverse effects of cocaine abuse across these HIV outcomes and the roles of specific DNA methylation and gene expression differences as biological mediators of these relationships.

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SELF-REGULATION AS A GENETIC FACTOR LINKING SUBSTANCE USE AND BIOMEDICAL OUTCOMES

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Abstract: Several substance use and psychiatric disorders, and associated behavioral challenges, are related to self-regulation, including substance use disorders, childhood behavior problems, and risky sexual behavior. These disorders have profound individual and societal costs. Previous twin-family studies have indicated that there is a strong heritable component shared across behaviors and disorders characterized by behavioral undercontrol. We applied multivariate genomic structural equation modeling to study the underlying genetic liability that influences this spectrum of externalizing disorders, identifying 579 independent loci. To evaluate medical outcomes associated with genetic liability to externalizing, we conducted a phenome-wide association study (PheWAS) in 66,915 genotyped individuals of European-ancestry in the BioVU biorepository, a U.S.-based biobank of electronic health records from the Vanderbilt University Medical Center, spanning 1990 to 2017. A logistic regression was fit to 1,335 case/control disease phenotypes. Of these, 255 disease phenotypes were associated with the externalizing polygenic score at a false discovery rate less than 0.05. The most abundant associations were with mental and behavioral disorders, such as substance use, mood disorders, suicidal ideation, and attempted suicide. But importantly, individuals with higher polygenic scores also showed worse health in nearly every bodily system. They were more likely to suffer, for example, from ischemic heart disease, viral hepatitis C and HIV infection, type 2 diabetes and obesity, cirrhosis of liver, sepsis, and lung cancer. Behaviors related to self-regulation, e.g., smoking, drinking, drug use, condomless sex, and overeating, contribute to many of these medical outcomes. These analyses demonstrate the wide-reaching effects of a genetic liability for behavioral undercontrol, influencing substance use and psychiatric conditions, as well as other biomedical disorders.

Disclosure: Nothing to disclose.

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PUSHING THE ENVELOPE WITH POLYGENIC RISK SCORES IN PSYCHIATRIC GENETICS: WHETHER, WHEN, AND HOW TO IMPLEMENT

Chair: Alex Ramsey, Co-chair: Laura Bierut, Discussant: Laura Bierut

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