47

Cross-ancestry GWAS meta-analysis of keloids discovers novel susceptibility loci in diverse populations*

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OBJECTIVES/GOALS: We aimed to conduct an updated genome-wide meta-analysis of keloids in expanded populations, including those most afflicted by keloids. Our overall objective was to improve understanding of keloid development though the identification and further characterization of keloid-associated genes with genetically predicted gene expression (GPGE). METHODS/STUDY POPULATION: We used publicly available summary statistics from several large-scale DNA biobanks, including the UK Biobank, FinnGen, and Biobank Japan. We also leveraged data from the Million Veterans Program and performed genome-wide association studies of keloids in BioVU and eMERGE. For each of these datasets, cases were determined from ICD-9/ICD-10 codes and phecodes. With these data we conducted fixed effects meta-analysis, both across ancestries and stratified by broad ancestry groups. This approach allowed us to consider cumulative evidence for genetic risk factors for keloids and explore potential ancestry-specific components of risk. We used FUMA for functional annotation of results and LDSC to estimate ancestry-specific heritability. We performed GPGE analysis using S-PrediXcan with GTEx v8 tissues. RESULTS/ANTICIPATED RESULTS: We detected 30 (23 novel) genomic risk loci in the cross-ancestry analysis. Major risk loci were broadly consistent between ancestries, with variable effects. Keloid heritability estimates from LDSC were 6%, 21%, and 34% for European, East Asian, and African ancestry, respectively. The top hit (P = 1.7e-77) in the cross-ancestry analysis was at a replicated variant (rs10863683) located downstream of LINC01705. GPGE analysis identified an association between decreased risk of keloids and increased expression of LINC01705 in fibroblasts (P = 3.6e10-20), which are important in wound healing. The top hit in the African-ancestry analysis (P = 5.5e-31) was a novel variant (rs34647667) in a conserved region downstream of ITGA11. ITGA11 encodes a collagen receptor and was previously associated with uterine fibroids. DISCUSSION/SIGNIFICANCE: This work significantly increases the yield of discoveries from keloid genetic association studies, describing both common and ancestry-specific effects. Stark differences in heritability support a potential adaptive origin for keloid disparities. Further work will continue to examine keloids in the broader context of other fibrotic diseases.

48

Analyzing Changing Trends in Hepatocellular Carcinoma

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OBJECTIVES/GOALS: To quantify changing trends in hepatocellular carcinoma (HCC) etiologies, mainly hepatitis C related HCC (HCV-HCC), nonalcoholic fatty liver disease related HCC (NAFLD-HCC), and alcoholic liver disease related HCC (ALD-HCC), at a single center as well as compared to large national databases. METHODS/STUDY POPULATION: This is a retrospective longitudinal study using a single-center database of patients presenting with HCC from January 1995 to September 2023. Etiologies were confirmed through patient history, clinical exam, and viral serologies. Trends in rate of etiology were analyzed using linear regression. Further investigation will include survival analysis. To improve generalizability, the single-center data were supplemented with national cross-sectional data from the NHANES database on liver disease prevalence from March 1999 to August 2023. Data were provided through questionnaire, clinical exam, and viral serologies. Trends in rates will be analyzed using linear regression. RESULTS/ANTICIPATED RESULTS: Among the single center cohort, NAFLD-HCC increased at an average rate of 1.3% per year (95% Confidence Interval (CI) = 1.1% to 1.4%) and HCV-HCC decreased at an average rate of -0.56% per year (95% CI = -0.83% to -0.29%). Projecting the linear models for the past ten years forward, HCV-HCC is predicted to take up a lower proportion than NASH-HCC by 2026 and lower proportion than ALD-HCC by 2028. Future results will include analysis of the changing proportions of etiologies for liver transplant and survival analysis for HCC by etiology from the single center cohort. Additionally, national trends in HCC etiologies will be provided from the NHANES database. The trends from liver transplant etiology and NHANES are expected to parallel the preliminary results. DISCUSSION/SIGNIFICANCE: As the prevalence of NAFLD increases in the general population, more cases of NAFLD-HCC will be seen in the future. Understanding the changing trends can guide surveillance recommendations, shape treatment algorithms, and frame research priorities.

49

The Effect of Pesticide Exposure on Immunological Responses in Children against SARS-CoV-2

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OBJECTIVES/GOALS: The objective is to assess the effect of pesticide exposure (individually and pesticide mixtures) on the immune response to COVID-19 in children. The goal is to improve scientific knowledge on factors affecting COVID-19 and identify a potentially modifiable factor to reduce disparities in COVID-19 morbidity. METHODS/STUDY POPULATION: Blood samples will be obtained from 50 children with asthma two time points; baseline and 12 months later. SARS-CoV-2 infection or vaccination will be determined with blood exposome RNA analyses.. Immunological response will be measured using neutralizing, phagocytizing, and NK-activating anti-body responses biomarkers. Pesticide exposure will be measured via urinary pesticide metabolites (UPMs). For individual metabolites multivariable analyses for each pesticide will be conducted using generalized estimating equation (GEE) models with compound symmetry correlation to account for the repeated measures design. To assess the pesticide mixture, weighted quantile sum regression (WQS) will be used. RESULTS/ANTICIPATED RESULTS: The main hypothesis is that increased pesticide exposure results in a reduction in the immunological response to SARS-CoV-2 infection and the COVID-19 vaccine. Therefore, we anticipate that increasing concentrations of individual UPMs as well as the increasing index will result in reductions in markers of the immune response to SARS-CoV-2 infection and the COVID-19 vaccine. DISCUSSION/SIGNIFICANCE: Exposure to pesticides is a