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GPM Journal Bytes

A quarterly online publication of journal summaries brought to you by the American Heart Association's **Council on Genomic and Precision Medicine**.

The opinions of the summary authors in this publication are their own and not necessarily those of the American Heart Association.

Happy New Year to all of you!! I hope that you will find this issue of Journal Bytes a great way to start off 2022! In this issue we welcome a wonderful guest contributor, Dr. Julio Duarte, and highlight several important and provocative papers. As always, our goal is to summarize important and relevant papers from multiple journal sources in the realm of genomic and precision medicine from the past several months and help you save time while staying well informed.

We welcome any suggestions you may have to help us make Journal Bytes serve you better. If you have any suggestions, or questions, please do not hesitate to contact us. And please do not forget to follow the GPM Council on twitter @GenPrecisionMed.

Best wishes for a happy and healthy 2022,
Sharon Cresci MD, FAHA, FACC, FASE
Chair, GPM Professional/Public Education & Publications Committee

A Novel Use of Deep Learning and Retinal Vasculature to Predict Cardiometabolic Risk

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Zekavat SM, Raghu VK, Trinder M, Ye Y, Koyama S, Honigberg MC, Yu Z, Pampana A, Urbut S, Haidermota S, O'Regan DP, Zhao H, Ellinor PT, Segrè AV, Elze T, Wiggs JL, Martone J, Adelman RA, Zebardast N, Del Priore L, Wang JC, Natarajan P. Deep *Learning of the Retina Enables Phenome- and Genome-Wide Analyses of the Microvasculature*. Circulation. 2022 Jan 11;145(2):134-150. doi: 10.1161/CIRCULATIONAHA.121.057709. Epub 2021 Nov 8. PMID: 34743558; PMCID: PMC8746912.
https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.057709

The authors leveraged deep learning techniques to analyze 97,895 retinal fundus images from 54,813 UK Biobank participants to assess vascular density and vascular branching complexity. They then performed four different PheWAS analyses (phenotype at enrollment; phenotype developed after enrollment; quantitative biomarkers; quantitative ocular traits) with 1866 International Classification of Disease-based conditions and also performed GWAS analyses. The authors found that lower vascular density and lower vascular branching complexity were associated with higher risk of prevalent and incident cardiometabolic phenotypes, including hypertension, diabetes, and BMI, and a higher risk of incident mortality. GWAS identified 13 novel loci associated with vascular density and 7 novel loci associated with vascular branching in genes enriched for pathways involved in angiogenesis and inflammation. These results demonstrate how deep learning techniques applied to the analysis of images can provide physiologically relevant information, and when combined with biomarker and genetic data, can be used to predict risk of a range of cardiometabolic diseases.

How Can We Better Personalize Blood Pressure Control Strategies?

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Berry JD, Nambi V, Ambrosius WT, Chen H, Killeen AA, Taylor A, Toto RD, Soliman EZ, McEvoy JW, Pandey A, Joshi PH, Blankenberg S, Kitzman DW, Ballantyne CM, de Lemos JA. *Associations of High-Sensitivity Troponin and Natriuretic Peptide Levels With Outcomes After Intensive Blood Pressure Lowering: Findings From the SPRINT Randomized Clinical Trial.* JAMA Cardiol. 2021 Dec 1;6(12):1397-1405. doi: 10.1001/jamacardio.2021.3187. PMID: 34468696; PMCID: PMC8411355.
https://pubmed.ncbi.nlm.nih.gov/34468696/

While others have previously shown that high-sensitivity cardiac troponin T (hscTnT) and N-terminal pro brain natriuretic peptide (NT-proBNP) are biomarkers for increased risk of mortality, whether risk associated with these biomarkers can be reduced is still unclear. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that intensive blood pressure treatment (to a goal SBP < 120 mmHg) significantly reduced the risk of mortality and HF development in high-risk hypertensive patients. Berry, et al. conducted a post hoc analysis of SPRINT, comparing the effect of intensive BP lowering on clinical outcome risk in patients with elevated hscTnT and/or NT-proBNP, compared to those without elevated levels. The investigators found considerably greater 4-year absolute risk reductions in intensively treated patients with either biomarker elevated, which were even greater in patients with both biomarkers elevated. These effects were most apparent with risk of all-cause mortality and incident HF, with substantially lower numbers needed to treat (NNT) to prevent one death with intensive BP lowering (14 for patients with both biomarkers elevated vs. 103 for patients with neither elevated). These findings suggest that hscTnT and/or NT-proBNP may be able to identify a high-risk patient population who would especially benefit from intensive BP lowering.

Hitting two birds with one stone: missense variant in B4GALT1 influences multiple cardiovascular disease pathways

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Montasser ME, Van Hout CV, Miloscio L, Howard AD, Rosenberg A, Callaway M et al. *Genetic and functional evidence links a missense variant in B4GALT1 to lower LDL and fibrinogen.* Science 2021; Dec 3; 374 (6572): 1221-1227. PMID: **34855475** https://pubmed.ncbi.nlm.nih.gov/34855475/

Elevated low-density lipoprotein cholesterol (LDL-C) and fibrinogen both independently increase the risk of cardiovascular disease by affecting atherosclerosis and thrombosis, respectively. A whole-exome sequencing (WES) analysis was performed in a founder population of the Old Order Amish (n=6,890) to identify variants associated with LDL-C. A missense variant (rs551564683, p.Asn352Ser) in B4GALT1, a member of the beta-1,4-galactosyltransferase gene family, was associated with 13.9 mg/dl lower LDL-C, lower levels of fibrinogen and higher AST levels. The B4GALT1 Ser homozygotes showed decreased galactosylation and sialyation in plasma glycoproteins, fibrinogen and ApoB100 consistent with decreased enzymatic activity of B4GALT1. The minor allele frequency of rs551564683 in the Amish population was 6%, however it is very rare in the general population. Therefore, as replication, burden testing of rare variants in B4GALT1 was performed in two large Biobanks (Geisinger's DiscovEHR and UK Biobank) which recapitulated the associations with lower LDL-C and higher AST and found an association of decreased risk of

coronary artery disease. This study provides evidence for the pleiotropic role of B4GALT1 in the regulation of lipid metabolism and fibrinogen levels and may represent a new target for cardioprotection.

Functional Pharmacogenomics Identifies a Novel Genetic Variant and New Therapeutic Options for Pediatric Anthracycline Induced Cardiomyopathy

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Tarek Magdy, Mariam Jouni, Hui-Hsuan Kuo, Carly J. Weddle, Davi Lyra-Leite, Hananeh Fonoudi, Marisol Romero-Tejeda, Mennat Gharib, Hoor Javed, Giovanni Fajardo, Colin J.D. Ross, Bruce C. Carleton, Daniel Bernstein, and Paul W. Burridge. *Identification of Drug Transporter Genomic Variants and Inhibitors That Protect Against Doxorubicin-Induced Cardiotoxicity.* Circulation. 2021, https://doi.org/10.1161/CIRCULATIONAHA.121.055801

Variation in the genetic locus *SLC28A3*, a drug transporter gene, is associated with a lower risk for anthracycline induced cardiomyopathy (AIC) in pediatric patients by genetic association studies. Human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM) from patients who were carriers of the variant rs7853758 in this gene and did not develop AIC after treatment with doxorubicin were compared to controls who did not have this protective variant. The protective effect of this variant was functionally validated in-vitro in this cell system by demonstrating reduced apoptosis and increased cell viability in the presence of doxorubicin. Reduced doxorubicin uptake in the cells was demonstrated by a flow cytometry-based assay in the hiPSC-CM from patients harboring this protective variant. The protective effect of this genetic variant likely results from reduced SLC28A3 transporter function as demonstrated by *SLC28A3* knock-out and overexpression in hiPSC-CM. Haplotype analysis with subsequent base editing in hiPSC-CM identified a novel variant rs11140490 in the *SLC28A3* locus to be cardioprotective by regulating a long non-cording RNA *SLC28A3-AS1*, increased expression of which results in decreased expression of *SLC28A3* and thus is cardioprotective. Finally using a drug library screening approach desipramine was found to be cardioprotective in-vitro hiPSC-CM and in-vivo mice AIC models. The authors propose that desipramine and the long non-cording RNA *SLC28A3-AS1* could be potential new therapy to prevent AIC.

Association of Genetic Variants With Outcomes in Patients With Nonischemic Dilated Cardiomyopathy

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Escobar-Lopez L, Ochoa JP, Mirelis JG, Espinosa MÁ, Navarro M, Gallego-Delgado M, et.al. *Association of Genetic Variants With Outcomes in Patients With Nonischemic Dilated Cardiomyopathy. J Am Coll Cardiol*. 2021 Oct 26;78(17):1682-1699. doi: 10.1016/j.jacc.2021.08.039. PMID: 34674813. https://pubmed.ncbi.nlm.nih.gov/34674813/

A retrospective analysis was performed of 1,005 consecutive dilated cardiomyopathy (DCM) patients aged >15 years with left ventricular ejection fraction (LVEF) <50% at 20 inherited cardiac disease and heart failure clinics in Spain. All patients underwent genetic testing for variants in >50 genes associated with cardiomyopathies, and 372 (37.0%) had a pathogenic or likely pathogenic (P/LP) variant. Of the 363 patients with a single P/LP variant, *TTN* accounted for 38.7%, *LMNA* and *DSP* both 8.5%, *BAG3* 6.6%, *FLNC* 5.8%, *RBM20* 5.5%, and *MYH7* 4.7%. During a median follow-up period of 4 years, major adverse cardiovascular events (MACEs), defined as end-stage heart failure, major ventricular arrhythmias, or stroke, occurred at a higher rate in those with P/LP variants (31.7%) compared with those without P/LP variants (19.7%), with a hazard rate of 1.51. The worst outcomes were observed in the LP/P-positive group with an LVEF <35% and variants in the nuclear envelope gene group, including *LMNA*. Thus, DCM patients with P/LP genetic variants have a worse prognosis than those without an identified variant, and prognosis further varies depending on the underlying gene.

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