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Polygenic risk score analysis suggests that iron deficiency does not share genetic risk with Tourette syndrome.

Karla Claudio[1], Dongmei[2], Carol A. Mathews[3]
1.Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida. 2. Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetics Research, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston. 3. Department of Psychiatry, College of Medicine, University of Florida.

Research Category: Clinical Genetics/Pharmacogenetics

Abstract: Our group previously found that Tourette syndrome is genetically correlated with lower levels of ferritin (rg= -0.34; p <0.01), a protein involved in iron storage and homeostasis. Moreover, other investigators have found a significant association between iron deficiency and more severe tics, which were attenuated with iron supplementation. However, more evidence is needed in order to determine if iron homeostasis is etiologically related with Tourette syndrome. The present study aims to validate our previous findings using polygenic risk score (PRS) analysis. PRS is used to understand the genetic architecture of polygenic diseases by estimating the genetic load of one phenotype and using it as a predictor of another phenotype of interest, suggesting therefore that both traits have a common genetic etiology. For our study we obtained GWAS summary statistics for iron intake and iron deficiency from UK BioBank. In addition, we used genotyping information from a GWAS study performed in individuals diagnosed with Tourette syndrome and controls of European ancestry. These datasets were filtered to keep only single nucleotide polymorphisms (SNPs) with an imputation score > 80% and a minor allele frequency >1%. For our Tourette syndrome genotyping data, a filter to keep SNPs with a call rate >98% was also applied. These datasets were merged and polygenic risk scores were calculated using LDpred. A preliminary analysis showed that polygenic risk score from iron intake does not predict Tourette syndrome (Nagelkerke's R2= 0.084; p=0.31, s.e= 0.083). Our findings suggest that Tourette syndrome does not have a common genetic etiology with iron homeostasis. Nevertheless, further analyses using ferritin and/or iron saturation as a direct measure are warranted.
Presenting author email: KClaudio@cop.ufl.edu

1102
Geographically and socioeconomically disadvantaged patients use a higher proportion of drugs with potentially actionable pharmacogenetic interactions

Rachel Dalton, Joshua Brown, Julio Duarte
Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida.

Research Category: Pharmacogenomics

Purpose: "Pharmacogenetic (PGx) testing can aid in optimizing therapy of drugs with Clinical PGx Implementation Consortium (CPIC) guidelines. We hypothesized that drugs with CPIC guidelines are used at a higher rate in the underserved because many are off-patent and available at low cost. This study compared CPIC drug usage with health care access and socioeconomic indices in patients within the University of Florida Health System (UF-Health).
Methods: Electronic health record data (drug lists inputted in 2017, demographics, home zip code tabulation areas (ZCTAs)) were collected for adult UF-Health patients. Health care access scores (AS; range 1-100, 100 is greatest access) from ZCTA centroids to primary care providers were derived using the two-step floating catchment area method with 30-minute drive time areas. Data from the US Census Bureau were used to estimate ZCTA-level socioeconomic status. A negative binomial mixed-effects model was used to assess the relationship between the number of CPIC prescriptions and patient age, sex, race, ethnicity, total drug count, census data, and AS with ZCTA as a random effect.
Results: 58,428 patients were analyzed. Patients with lower AS had a greater number of CPIC prescriptions (p<0.001); every 10 unit decrease in AS was associated with a 2.1% increase in CPIC prescriptions. Patient age (p<0.001), total prescription count (p<0.001), African American race (p=0.01), and residence in ZCTAs with more households below the federal poverty level (p<0.001) were associated with increased CPIC prescriptions.
Conclusion: Underserved patients may further benefit from PGx testing to maximize the utility of prescriber encounters and ensure safe and efficacious use of CPIC drugs. Further research is needed to confirm the generalizability of these findings."
Presenting author email: racheldalton@cop.ufl.edu

1103
Transcriptomic approaches to enhance treatment in AML

Satyavardhan Rao Nittu, Jatinder Lamba, Abdelrahman Elsayed
Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida.

Research Category: Pharmacogenomics

Acute Myeloid Leukemia (AML) is a cancer of the myeloid precursor stem cells, characterized by excess production and accumulation of undifferentiated blast cells in the bone marrow. Despite an improvement in patient outcomes over the past two decades, disease relapse remains one of the major obstacles in AML treatment. Around 30% of patients relapse after achieving complete remission and those patients experience very poor outcomes after relapse. In this study, we aims to reveal differentially expressed genes at relapse compared to samples at diagnosis that can provide insights about important pathways implicated in disease relapse.
Reads Per Kilobase of transcript, per Million mapped reads (RPKM) normalized gene expression values of 58450 genes of 238 bone marrow samples at diagnosis and 43 bone marrow samples at relapse were downloaded from Therapeutically Applicable Research To Generate Effective Treatments (TARGET) database. 43221 genes with average RPKM expression values < 1 were excluded (15,229 genes were included in the next step of the analysis). Wilcoxon rank sum test was used to compare median expression value of each gene between diagnosis and relapse samples. 1843 genes was found differentially expressed between diagnosis and relapse samples with a Bonferonni corrected (p-value < 3.28E-06). Then, We ran a gene set enrichment analysis (GSEA) using MSigDB database for differentially expressed genes which revealed cell cycle, chromatin binding, RNA binding, DNA repair, P-53 signaling and WNT

signaling as the most enriched canonical pathways (FDR q-value < 0.05).
Acknowledgment: UF Cancer center and NIHR01CA132946
Presenting author email: nittus@cop.ufl.edu

1104
Impact of CYP2D6 inhibitors on opioid therapy in patients with pain

Noor Ahmed Nahid, EmilyJ Cicali, PharmD, BCPS, Julie A. Johnson, Pharm.D.
Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida.

Research Category: Pharmacogenomics

Opioids are used to treat moderate to severe pain and oxycodone, hydrocodone, tramadol, and codeine comprise most opioid prescriptions written in the U.S. These drugs themselves have little to no analgesic effect and require the CYP2D6 enzyme to metabolize them into their active metabolites, which are responsible for the analgesic effect opioids provide. Thus, CYP2D6 enzyme activity is important to ensure efficacy for these select opioids. The FDA classifies certain drugs as moderate or strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, duloxetine, mirabegron etc.). These CYP2D6 inhibitors cause significant reduction in CYP2D6 enzyme activity and when given concomitantly with CYP2D6-mediated opioids, can decrease the efficacy of the opioid. Use of CYP2D6 inhibitors is highly prevalent, data indicates that approximately 20–30% of patients treated for pain are prescribed a CYP2D6 inhibitor. Further, pain is one of the most common reasons for seeking health care in U.S. and about 80% of all emergency department (ED) visits are related to pain related problems. We utilized the limited data set from University of Florida (UF) Health Informatics for Integrating Biology and the Bedside (I2B2) to define cases and controls. Patients with at least one ICD-9 or ICD-10 code for pain, taking a CYP2D6-mediated opioid, and taking a CYP2D6-inhibitor are defined as cases and patients with at least one ICD-9 or ICD-10 code for pain, taking a CYP2D6-mediated opioid, but not taking a CYP2D6-inhibitor are defined as controls. We hypothesized that the CYP2D6 enzyme inactivation caused by CYP2D6 inhibitors in case patients would result in more ED visits, indicating their opioid is not efficacious, as compared to control patients. The number of ER visits between cases and controls were compared and we observed 50% of the cases had an ER visit as compared to 40% of the controls (p-value <0.001). This supports our hypothesis that CYP2D6 inhibitors reduce the efficacy of CYP2D6-mediated opioids. Further investigations with patient-level data from the UF Health Integrated Data Repository (IDR) will help to confirm impacts of CYP2D6 inhibitors on CYP2D6-mediated opioids therapy in patients with pain.
Presenting author email: n.nahid@ufl.edu

1105
ACS vs. Non-ACS and MACE: Evaluating outcomes following CYP2C19-genotype guided antiplatelet therapy.

Cameron D. Thomas[1], Craig R. Lee[2], Dominick J. Angiolillo[3], Julio D. Duarte[1], Yiqing Chen, Francesco Franchi[3], Yan Gong[1], Caitrin W. McDonough[1], George A. Stouffer[4], Julia A. Johnson[1], Larisa H. Cavallari[1]
1. Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida. 2. Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC, and Center for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, Chapel Hill, NC 3. Division of Cardiology, College of Medicine-Jacksonville, University of Florida. 4. Division of Cardiology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

Research Category: Pharmacogenomics

Background: CYP2C19 loss-of-function (LOF) alleles impair clopidogrel (clop) effectiveness after percutaneous coronary intervention (PCI), but the impact of PCI indication on outcomes is unknown. A collaboration across four U.S. institutions examined outcomes after prospective implementation of CYP2C19 genotype-guided antiplatelet therapy (APT) in real-world settings.
Methods: Sites conducted CYP2C19 genotyping and recommended alternative APT in LOF allele carriers. Major atherothrombotic events (MACE, defined as death, MI, stroke, unstable angina, or stent thrombosis) within 12 months post PCI were ascertained by electronic health record abstraction (n=2023). Time to MACE was compared in LOF allele carriers receiving clop (LOF-clop) or alternative APT (LOF-alt) and non-LOF allele carriers separately in patients with acute coronary syndrome (ACS) and non-ACS PCI indications using Cox regression analyses.
Results: Mean age was 63±12 years, 73% were White, 612 (30.3%) had a LOF allele, and 69% underwent PCI due to ACS. In the ACS subset (n=1400), MACE risk was significantly higher in LOF-clop patients compared to LOF-alt (HR: 5.3; 95%CI, 2.8 to 10.2; p<0.001) and non-LOF (HR: 2.1; 95%CI, 1.4 to 3.0; p<0.001) patients. There was no evidence LOF-clop was associated with higher MACE risk in non-ACS patients (n=623) compared with LOF-alt (HR: 1.6; 95%CI, 0.6 to 4.6; p=0.361) and non-LOF (HR: 1.3; 95%CI, 0.6 to 2.8; p=0.456) allele carriers. Adjusting for clinical covariates did not affect results.
Conclusion: There was a higher risk for MACE in CYP2C19 LOF carriers prescribed clopidogrel vs. alternative APT in ACS, but not non-ACS, patients. Although sample size in non-ACS patients was limited, this suggests CYP2C19 genotype-guided APT may be most effective in high risk patients undergoing PCI."
Presenting author email: camerondthomas@cop.ufl.edu

1106
Clinical Pathology Bioinformatics Challenges and Opportunities for Effective Implementation of Genomic Medicine

Srikar Chamala[1], Kimberly Newsom[1], Matthew Farrer[2], Michael Clare-Salzler[3], Petr Starostik[3]
1. Dept. of Pathology, Immunology and Laboratory Medicine, College of Medicine, University of Florida. 2. Department of Neurology, College of Medicine, University of Florida. 3. University of Florida Health Pathology Laboratories- Department of Pathology, University of Florida

Research Category: Clinical implementation of genomics

Patient care is rapidly evolving towards an increasing inclusion of genomic or precision medicine in which genomic tests are used by clinicians for disease predisposition, prognosis, diagnosis and therapeutic decision-making. However, unlike other clinical pathology laboratory tests, development, deployment, and delivery of genomic tests and results is an intricate process. Genomic technologies are diverse, fast evolving, and generate massive data. Implementation of these technologies in a CLIA certified and CAP accredited pathology laboratory often require custom clinical-grade computational data analysis and management workflows. Additionally, accurate classification and reporting of clinically-actionable genetic mutation requires well curated disease/application specific knowledgebases and expertise. Furthermore, lack of 'out of the box' technical features in Electronic Health Record (EHR) systems necessitate custom solutions for communicating genetic information to clinicians and patients. Genomic data generated as part of clinical care easily adds great value for translational research. However, this requires developing centralized genomic data and integrating it with patient health data warehouses that in turn make it extremely valuable and useful for translational research. In this presentation we discuss current and future innovative clinical bioinformatics solutions and workflows developed at UF Health for effective implementation of genomic medicine across molecular pathology, patient care, and translational genomic research.
Presenting author email: schamala@ufl.edu

1107
Single Nucleotide Polymorphism in Genes of Prognostic Significance in AML

Akhila Dadwai, Abdelrehman Elsayed, Jatinder Lamba
Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida.

Research Category: Pharmacogenomics

Drug resistance and relapse remain two major obstacles in Acute myeloid Leukemia (AML) treatment, whereas coexistence and persistence of leukemic stem cells (LSCs) are considered a primary cause of relapse. Our lab has recently used Lasso regression analysis to develop a six gene leukemic stem cell signature (pLSC6) using gene expression levels of leukemic cells. The LSC6 signature included DNMT3B, GPR56, SPINK2, SOCS2, CD34 and FAM30A that was significantly associated with risk-groups and outcomes in pediatric AML (Elsayed, et al. Leukemia (2019)). The standard chemotherapeutic regimen used for the treatment of AML includes cytarabine, daunorubicin, and etoposide (ADE). Using a similar approach we recently developed a five gene ADE drug response score (ADE-RS5) that includes ABCC1, DCTD, TOP2A, CBR1 and MPO a significant predictor of treatment outcome in multiple AML cohorts. Interpatient variability in gene expression levels can be due to SNPs in regulatory regions or due to epigenetic differences. In this study, we aim to identify SNPs that can explain part of the intra-patient variability of the expression levels of these genes (LSC6 and ADE-RS5). Using the Genotype-Tissue Expression (GTEx) database, we compiled a list of 74 unique SNPs that were found significantly associated with either lower or higher expression of genes of interest in whole blood and has a minor allele frequency (MAF) > 0.05. An example includes the GPR56 rs1965226 SNP located in a transcription factor binding site in the promoter region of GPR56 gene. This SNP was found significantly associated with lower expression of GPR56 in whole blood (GTEx; N=670, P=0.000006). Moving forward, the final SNP list will be genotyped using AML patient samples and evaluated for association with treatment outcomes.
Presenting author email: akhila.dadwai@ufl.edu

1108
Comparison of pharmacogenomic testing results by race/ethnicity in the RIGHT Protocol Study

Nicholas B. Larson[1], Debra J Jacobson[1], Michaela E. McGree[1], Suzette J. Bielinski[2], Jennifer L. St. Sauver[3], Janet E. Olson[2], John L. Black III[4], Ann M. Moyer[4], Steve E. Scherer[5], Liewei Wang[6], Richard M. Weinshilboum[6]
1. Division of Biomedical Statistics and Informatics, Mayo Clinic. 2. Department of Health Sciences Research, Mayo Clinic. 3. Department of Health Sciences Research, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic. 4. Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota. 5. Human Genome Sequencing Center, Baylor College of Medicine. 6. Department of Molecular Pharmacology & Experimental Therapeutics, Mayo Clinic

Research Category: Pharmacogenomics

Introduction: The Right Drug, Right Dose, Right Time Using Genomic Data to Individualize Treatment Protocol (RIGHT Protocol) study is a pre-emptive pharmacogenomics (PGx) testing initiative at Mayo Clinic designed to deliver point-of-care clinical decision support and study the effects of integrating preemptive PGx into applied clinical practice. A current limitation is that the majority of PGx studies to date have been conducted in populations of European ancestry. Consequently, the distribution of PGx metabolizer phenotypes and occurrence of novel pharmacogene alleles among diverse populations are less understood.
Methods: PGx testing for RIGHT participants (N = 10,077) was performed by the Baylor Human Genome Sequencing Center Clinical Laboratory using the PGRN-Seq v.3 next-generation sequencing assay. The Mayo Clinic Personalized Genomics Laboratory provided allelic interpretation and predicted phenotypes for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DPYD, SLCO1B1, TPMT, and UGT1A1 for deposit in patient electronic health records. Reported phenotypes across RIGHT for each gene were tabulated, while genotypes were reviewed for mention of novel star alleles. We investigated potential differences in prevalence of interpreted PGx phenotypes and instances of novel alleles by self-reported race and ethnicity using chi-square tests.
Results: A total of 9475 (94%) RIGHT participants were white and 112 (1.1%) were of Hispanic ethnicity. Individual interpreted gene phenotype distributions varied significantly by race (P<0.005) for 4/10 genes and by Hispanic ethnicity for 0/10 genes. A total of 435 white participants (4.5%) carried at least one novel PGx gene allele, compared to 40 (7.6%) non-white participants (P<0.001). Prevalence of novel alleles for individual genes differed significantly for SLCO1B1 by race and DPYD by ethnicity, with minority populations carrying higher rates of novel alleles.
Conclusions: We observed a higher rate of novel alleles among minority populations relative to whites in a large population-based PGx sequencing cohort. Minority-focused PGx sequencing

studies may advance characterization of population-specific alleles and improve personalized medicine.
Presenting author email: larson.nicholas@mayo.edu

1109
A Systematic Approach to Designing Pharmacogenetic Clinical Decision Support for Medication Classes Affected by Multiple Genes

Kelsey J. Cook[1], Emily J. Cicali[1], Ben Staley[2], Rhonda Cooper-DeHoff[1], Kristin Wiisanen[1]
1. Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida. 2. Department of Pharmaceutical Outcomes & Policy, College of Pharmacy, University of Florida

Research Category: Pharmacogenomics

Background: Clinical decision support (CDS) can help facilitate clinical implementation of pharmacogenetics. To date, pharmacogenetic CDS development efforts have focused primarily on single gene–drug pairs (e.g., CYP2C19–clopidogrel). However, as preemptive, multi-gene pharmacogenetic tests become more widely accepted, there is a growing need for efficient and sustainable strategies to develop CDS for medication classes affected by variability in multiple genes (e.g., thiopurines–TPMT/NUDT15; selective serotonin reuptake inhibitors [SSRIs]-CYP2C19/CYP2D6).
Methods: We used SSRIs and CYP2C19/CYP2D6 to pilot a systematic approach to build CDS logic and Best Practice Advisory (BPA) language for drug classes affected by multiple genes. This approach was based on established single gene-drug pharmacogenetic CDS already employed within UF Health. From the existing CDS, we identified the foundational elements of BPAs as the pharmacogenetic test result, problem statement, and clinical recommendation with therapeutic alternatives. For SSRIs, we identified all actionable gene-drug pairs warranting a BPA (according to Clinical Pharmacogenetics Implementation Consortium [CPIC] guidelines) and any potential genotype-drug combinations that could be encountered clinically. We then mapped all potential combinations to the foundational alert elements to create problem statements and clinical recommendations for all potential SSRI and single- or multi-gene scenarios.
Results: We identified a total of 36 potential actionable genotype-drug clinical scenarios to recommend a therapeutic alternative. Once these were mapped to the foundational alert elements, a total of 8 distinct problem statements with 12 different evidence-based recommendations for 16 unique BPAs were developed.
Conclusions: CDS development and build strategies for drug classes influenced by multiple genes needs to be expanded and optimized as multi-gene pharmacogenetic panels become available. This systematic approach allowed us to create SSRI BPAs that incorporate both the CYP2C19 and CYP2D6 genotype. Our approach simplified the CDS build and can be applied to other drug classes affected by multiple genes.
Presenting author email: kelsey.cook@cop.ufl.edu

1110
Modeling the Value of Systematic Pharmacogenetic Testing in an Integrated Healthcare Delivery System

Alison L.H. Quinn[1], Thomas M. Delate[1], Susan M. Gouchoe[2]
1. Kaiser Permanente, Colorado. 2. Kaiser Permanente, California

Research Category: Pharmacogenomics

Objective: The objective of this study was the assess the value of systematic, preemptive pharmacogenomic (PGx) testing for four gene/drug pairs that are commonly prescribed.
Methods: An economic modeling formula was created in Microsoft Excel to determine one-year costs. Preemptive PGx testing was compared to no PGx testing for all adult patients identified as incident users of allopurinol, carbamazepine, azathioprine, and/or clopidogrel between January 2011 and July 2017 in an integrated healthcare delivery system. Membership was approximately 85% White, 8% African American, and 4% Asian out of 480,000 members. Inputs included industry-standard genotyping costs, prescribed and alternate medication wholesale accusation costs, and the probability of adverse outcomes and their costs from the literature.
Results: For allopurinol: 2,624 patients were identified as eligible for preemptive testing of HLA-B*58:01, which would be cost-incurring by $1.39M or $502, $453, and $352 per Asian, African American, and White patient, respectively. For carbamazepine: 1,518 patients were identified as eligible for preemptive testing of HLA-B*15:02, which would be cost-incurring by $1.72M or $246, $324, $324 per Asian, African American, and White patient, respectively. For azathioprine: 823 patients were identified as eligible for preemptive testing of TPMT, which would be cost-avoidant of $0.34M or $40, $582 and $414 per Asian, African American and White patient, respectively. For clopidogrel: 2,364 patients were identified as eligible for preemptive testing of CYP219, which would be cost-avoidant of $0.55M or $706, $334, and $217 per Asian, African American, and White patient, respectively.
Conclusions: Using a real-world population of patients receiving commonly prescribed medications, modeling of preemptive PGx testing for all patients prior to receiving azathioprine or clopidogrel suggests that testing would be cost-avoidant while preemptive testing for allopurinol and carbamazepine would incur costs from the perspective of an integrated healthcare delivery system. Incorporating PGx testing of cost-avoidant gene/drug pairs into prescribing practices may have a beneficial impact on the total cost of care for integrated healthcare delivery systems. Delivery systems with more diverse race memberships could have different cost outcomes.
Presenting author email: alison.l.quinn@kp.org

1111
Effectiveness of an Advanced Pharmacogenomics Independent-Study and Experiential Rotation in Building Medical Genetic and Pharmacogenomics Expertise in Doctor of Pharmacy Students

Shannon Kinney[1], Shannon Bailey[1], Elizabeth Klejna, Susan Capasso[2]
1. Department of Pharmaceutical & Administrative Sciences, College of Pharmacy and Health Sciences, Western New England University. 2. Bay Path University

Research Category: Genomics Education

Pharmacists can play a critical role in the clinical implementation of pharmacogenomics (PGx). Thus, Doctor of Pharmacy (PharmD) programs are identifying best practices for educating future pharmacists in PGx concepts and therapeutic use. Our college's PharmD curriculum includes a required 2 credit medical genetics and PGx course in the first year. We designed an additional advanced PGx independent study and a similar Advanced Pharmacy Professional Experience (APPE) rotation that require students to interpret personal raw genetic data (23andMe) and to develop and complete molecular genetic tests in the laboratory to further enhance understanding of these topics. In addition, the 6 week APPE rotation includes interactions with a licensed genetic counselor and PGx case reviews with oncology and psychology pharmacists.

We utilized pre-post examinations and surveys to objectively assess the effect of these courses on basic and applied PGx knowledge, as well as students' perceptions of their PGx skills and use of PGx clinically. The exams were proctored and students were able to utilize Pharmgkb.org and ncbi.nlm.nih.gov resources. We piloted our approach and collected responses from one student per course. When comparing the pre/post-exams for both students (pre-exam grades 67.1% and 61.1%, post-exam grades 94.2% and 94.6%), areas of growth included foundational knowledge of medical genetic diagnosing and prescribing, skills utilizing PharmGKB and NCBI resources, such as determining metabolizer phenotype from a raw genotype, and clinical application of PGx, including mechanisms for payment of genetic tests. The survey results for both participants demonstrated increased confidence in their abilities to analyze genetic data and make therapeutic recommendations based on the results, as well as increased understanding of clinical and ethical implications of genetic testing.

Our results suggest that these unique course formats, which incorporate personal genetics and molecular laboratory experience, allow PharmD students to develop expertise in understanding and implementing PGx, gaining skills that go beyond an introductory course. The addition of interaction with a genetic counselor and practicing pharmacists also allowed the APPE student to appreciate the different roles that exist in the use of genetics clinically. These results may be helpful for other pharmacy programs that are incorporating PGx education into their curricula as required by ACPE.

Presenting author email: shannon.kinney@wne.edu

1112
LASSO Regression Analysis Identifies DNA-Damage Gene Expression Signature Predictive of Clinical Outcomes in Patients Using Gemtuzumab Ozogamicin

Mohammed O. Gbadamos[1], Abdelrahman H. Elsayed[1], Rhonda E. Ries[2], Soheil Meshinchi[2], Jatinder K. Lamba[1]
1. Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida.2. Fred Hutchinson Cancer Research Center

Research Category: Cancer genomics

In 2017, the FDA announced reapproval of gemtuzumab ozogamicin (GO), a CD33-directed antibody-drug conjugate, for treatment of AML. While the future of GO in AML is bright, studies have shown that there is interpatient variability in GO response. Hitherto, efforts to understand this interpatient variation in regard to calicheamicin, the DNA-damaging cytoxin linked to the antibody portion of GO, have been limited. Herein, our group has used the least absolute shrinkage and selection operator (LASSO) regression analysis algorithm to identify genes predictive of clinical outcomes in response to GO.

This study included 218 pediatric AML patients treated with GO enrolled in the AAML03P1 and AAML0531 clinical trials with Illumina Hi-Seq 2000 RNA-seq gene expression data for 18 genes relevant to calicheamicin pharmacodynamics and clinical data available. A penalized LASSO regression algorithm was used to fit a Cox regression model on the expression levels of the selected genes. A thousand iterations of LASSO regression were performed with a model inclusion cutoff of 85% for genes to be included in the final model. A gene expression signature, designated as DNA-Damage Response Score (DDRS), was generated using the expression of the 7 genes included in the final model: AKT1, ATR, BAD, BCL2L1, CASP9, PRKDC, XRCC4 multiplied by the average coefficients from the LASSO models. Patients were classified into high or low DDRS groups by recursive partitioning and the groups were then evaluated for their association with clinical outcomes.

Patients in the DDRS High group had significantly worse event-free survival (EFS; HR = 2.80, P < 1*106) and worse overall survival (HR = 2.15, P < 0.01). Consistent results were seen within standard-risk group patients where patients in the DDRS High group had significantly worse EFS (HR = 2.49, P < 0.01). In multivariate analysis, DDRS remained a significant predictor of EFS amongst age, risk group, FLT3 status, and WBC (HR = 1.96, P < 0.01). DDRS also was found to be specific for GO response as DDRS was not associated with the outcome of patients treated on the same treatment protocol excluding the administration of GO (P = 0.3). Similar results were observed in a validation cohort of 128 pediatric AML patients treated on the same treatment protocol. These results hold promise as a predictive tool for guiding clinical decisions regarding GO and efforts are ongoing to expand this investigation to bigger and more diverse AML cohorts.

Presenting author email: mgbadamosi@ufl.edu

1113
TPMT-NUDT15

Amanda L. Elchynski, Meghan J. Arwood, Emily Cicali, Amanda Elsey, Benjamin Staley, Khoa Nguyen, Kristin Wiisanen
Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida.

Research Category: Clinical implementation of genomics

Background: Thiopurines (e.g., azathioprine, mercaptopurine) are used to treat malignant and nonmalignant conditions. In 2014, UF Health Precision Medicine Program (PMP) implemented clinical pharmacist-supported TPMT genotyping in malignant and nonmalignant patient populations with clinical decision support (CDS) in the electronic health record. New CPIC guidelines were published in 2018 that incorporated NUDT15 into genotype-guided thiopurine dosing recommendations. The level of supporting evidence and clinical uptake of NUDT15 genotyping for thiopurines varies widely among different indications and patient populations. As a result, strategies to implement combined TPMT/NUDTI5 genotyping should be individualized based on provider and institutional needs.

Objective: Describe the process and outcomes to revise clinical pharmacist and CDS strategies for TPMT genotype-guided thiopurine dosing to incorporate NUDT15 in a tertiary academic medical center with a primarily nonmalignant patient population.
Methods: In 2019, UF Health PMP reviewed updated CPIC recommendations, published literature and guidelines for genotype-guided thiopurine dosing, FDA-approved drug labeling in the context of known thiopurine drug usage, and TPMT genotyping patterns within UF Health. We identified areas where clinical pharmacist and CDS strategies should be individualized for implementation of combined TPMT/NUDT15 testing in this primarily outpatient adult gastroenterology and rheumatology patient population.
Results: CPIC recommendations for adjusting genotype-guided thiopurine doses incorporate weight-based thresholds. Because lower thiopurine doses are indicated in nonmalignant versus malignant conditions, in some cases, the same TPMT/NUDT15 genotype result may lead to different clinical recommendations in different patient populations within UF Health. Evidence supporting the role of NUDT15 and provider use of NUDT15 genotype to guide thiopurine therapy is less prevalent in nonmalignant populations as compared with its use in malignancy. Within UF Health, hematology/oncology providers are using and have requested clinical support for NUDT15 genotyping, whereas it is not used routinely in nonmalignant patient populations. Because of these and other factors, we developed separate CDS rules, language, alert trigger criteria, and provider educational strategies for genotype-guided thiopurine dosing in nonmalignant versus malignant conditions within UF Health. This is in contrast to previous TPMT-only decision support, which required only one CDS build and minimal provider education within our institution. As with our previous TPMT implementation, alerts for providers to order NUDT15 genotype with thiopurines will be limited to pediatric hematology/oncology patients.
Conclusion: Developing and operationalizing pharmacist and CDS strategies to integrate NUDT15 and TPMT genotype-guided dosing of thiopurines is feasible in a diverse patient population. However, clinicians should be aware that provider education needs, CDS strategies, and clinical recommendations may need to be individualized.
Presenting author email: aelchynski@cop.ufl.edu

1114
Development of an algorithm to calculate clinical CYP2D6 phenoconversion in practice

Emily J. Cicali, Kelsey Cook, D. Max Smith, Amanda Elchynski, Julie Johnson, Larisa H. Cavallari, Kristin Wiisanen
Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida

Research Category: Pharmacogenomics

Introduction: CYP2D6 genetic variability and concomitant CYP2D6 inhibitors can affect activity of the CYP2D6 enzyme, which is involved in metabolizing ~25% of common medications. CYP2D6 genotype-guided dosing recommendations and instructions for calculating the impact of drug-drug interactions are available, but the process to integrate these two factors is not well known or easily accessible to many clinicians.
Research Question or Hypothesis: Can an algorithm be developed to efficiently calculate effects of medication-induced clinical CYP2D6 phenoconversion in practice?
Study Design: Systematic process review
Methods: The phenoconversion calculation was based on Clinical Pharmacogenetics Implementation Consortium guidelines. Steps include: 1) Calculate genotype-based activity score; 2) Identify CYP2D6 inhibitors; 3) Adjust genotype-based activity score by a factor of 0, 0.5, or 0.5, with strong, moderate, or weak inhibitors, respectively; and 4) Translate adjusted activity score to clinical phenotype. This process was applied to a range of CYP2D6 genotype-CYP2D6 inhibitor combinations to identify common principles to inform a phenoconversion algorithm.
Results: The following commonalities emerged: In the presence of a strong CYP2D6 inhibitor, all patients will have a CYP2D6 poor metabolizer clinical phenotype (i.e., activity score = 0). In patients with a genotype-based activity score of 0, 0.5, 2.0, or >4.5 adding a moderate CYP2D6 inhibitor does not change clinical phenotype. In patients with an activity score of 1.0, 1.5, or 3.0-4.0, clinical phenotype changes by one level with a moderate CYP2D6 inhibitor (e.g., CYP2D6 ultrarapid metabolizer is phenoconverted to CYP2D6 normal metabolizer). These principles were used to develop and test an algorithm that is being adapted to build a freely available online CYP2D6 phenoconversion calculator.
Conclusion: Iterative application of a process to calculate clinical CYP2D6 phenoconversion with use of various CYP2D6 genotype-inhibitor combinations identified commonalities that were used to create a phenoconversion algorithm. Availability of this algorithm in an accessible, automated online platform may benefit clinicians using CYP2D6 genotype to guide medication use.
Presenting author email: emily.cicali@cop.ufl.edu

1115
Association of SLC5A2 Polymorphisms with Cardiovascular Outcomes in Heart Failure Patients

Zohara T. Gruen
Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL

Research Category: Pharmacogenomics

In the United States alone, there are over 5.5 million individuals diagnosed with heart failure (HF). In the EMPA-REG trial, patients with HF treated with empagliflozin had significantly reduced rates of mortality, as compared to their placebo counterparts. While it has been shown that empagliflozin, an SGLT2 inhibitor, reduces the incidence of death from cardiovascular causes, the mechanistic rationale underlying this outcome is still unknown. The aim of this project was to determine if single nucleotide polymorphisms (SNPs) in SLC5A2, the gene encoding SGLT2, are associated with cardiovascular outcomes in HF patients.

In a cohort of heart failure patients recruited from the University of Illinois at Chicago, we identified 13 SNPs within 5 kb of SLC5A2 after filtering by linkage disequilibrium and minor allele frequency. The primary outcome was a composite of cardiovascular hospitalizations and all-cause mortality. Associations were tested using a Cox proportional hazard regression model adjusted for age, sex, race, smoking history, diabetes history, NYHA, beta-blocker dosage, and ACE Inhibitor/ARB use. P-values ≤ 0.05 after adjustment using false discovery rate were considered significant.

Of the 13 SNPs analyzed, 4 were significantly associated with the primary outcome. All of them, (the variant alleles) were associated with a reduced risk (HR = 0.65; Adj p-value = 0.013), rs3813008 (HR = 0.63; Adj. p-value = 0.033), rs9924771 (HR = 0.73; Adj. p-value = 0.047), and rs9927250 (HR = 0.71; Adj. p-value = 0.047). In summary, our results suggest that SNPs in SLC5A2 are associated with cardiovascular outcomes in HF patients. Future studies are needed to determine the mechanism by which these SNPs affect SLC5A2 function.

Presenting author email: zoharagruen@ufl.edu

1116

A 5-gene Ara-C, Daunorubicin and Etoposide (ADE) Drug Response Score as a Prognostic Tool to Predict AML treatment Outcome

Abdelrahman H. Elsayed[1], Xueyuan Cao[2], Susana Raimondi[3], James Downing[3], Raul Ribeiro[4], Tanja Gruber[4], Rhonda Ries[5], Soheil Meshinchi[5], Jeffrey E. Rubnitz[4], Stanley Pounds[6], Jatinder K. Lamba[1]

1. Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL. 2. Department of Nursing, University of Tennessee. 3. Department of Pathology, St. Jude Children's Research Hospital. 4. Department of Oncology, St. Jude Graduate School of Biomedical Sciences. 5. Fred Hutchinson Cancer Research Center. 6. Biostatistics Department St. Jude Graduate School of Biomedical Sciences

Research Category: Cancer genomics

Cytarabine, daunorubicin and etoposide (ADE) are commonly used for remission and intensification of pediatric acute myeloid leukemia (AML). However, development of drug resistance is a major cause of treatment failure.

This study included 163 cases with AML enrolled in the multi-center AML02 clinical trial with Affymetrix U133A microarray gene expression and clinical data available. We used a penalized LASSO regression algorithm (glmnet R-package) to fit a 1000 cox regression iterations on diagnostic gene expression levels of 66 genes of pharmacological significance (PK/PD) to ADE. Five genes represented in at least 95% of the models were included to build an ADE-Response Score (ADE-RS) equation. After computing a score for each patient based on average 1000 regression models coefficient multiplied by expression level of each gene, patients were classified into low or high ADE-RS score groups using recursive portioning implemented in Rpart-R package.

Patients in the high ADE-RS group had significantly worse event free survival (EFS; HR=4.07, P<0.0001) and overall survival (OS; HR= 4.54, P<0.0001) and higher proportion of minimal residual disease (MRD1) positive patients (P=0.014). These results were validated in an independent cohort of 603 pediatric AML patients enrolled in COG AAML0531 and AAML03P1 clinical trials. In addition, we recently developed a six-gene leukemic stem cell score (pLSC6; Elsayed, et al. Leukemia (2019)). We further integrated pLSC6 and ADE-RS score groups and observed significantly better prediction of treatment outcomes in AML02, COG and TCGA cohorts. In all study cohorts, patients in low/low pLSC6/ADE-RS group demonstrated better outcomes compared to the low/high and the high/high score groups. In a multivariable cox-regression models that included pLSC6-ADE response score groups, MRD1 status, risk groups, WBC at diagnosis and age in AML02 cohort, high pLSC6-ADE score group was found significantly associated with poor EFS (HR=6.02, P<0.00001) and was the only significant predictor of poor OS (HR=8.3, P<0.00001) In conclusion, in this study, we defined a pharmacological response score focused on key genes of PK/PD significance to ADE. In addition, integrated pLSC6 and ADE-RS has a potential to predict treatment outcomes using diagnostic gene expression levels and accordingly might help after proper validation to develop tailored treatment strategies to improve treatment outcomes of AML patients.

Presenting author email: aelsayed@ufl.edu

1117

Validation of SGCD (rs2116737) Genotype-Discrimination Interaction as a Determinant of Blood Pressure Variation in the Jackson Heart Study

Leanne Dumeny[1], Chu J. Hsiao[2], Adam P. Bress[3], Larisa H. Cavallari[4], Dayna A. Johnson[5], Connie J. Mulligan[6], Daichi Shimbo[7]

1. Department of Biochemistry & Molecular Biology, University of Florida. 2. Jacob School Medicine and Biomedicinal Science, University at Buffalo. 3. Department of Population Health Sciences, University of Utah School of Medicine 4. Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL. 5. Rollins School of Public Health, Emory University. 6. Department of Anthropology, University of Florida. 7. Columbia University Irving Medical Center

Research Category: Pharmacogenomics

Previous anthropological studies have demonstrated the utility of integrating genetic and psychosocial data, such as discrimination, to understand complex phenotypes such as blood pressure (BP). In these studies, including both single nucleotide polymorphisms (SNP) and psychosocial measures in the model only revealed significant SNPs after accounting for gene by social environment interactions.

We sought to externally validate SNPs associated with BP in African Americans (AAs) identified in a study by Quinlan et al. in 2016 that incorporated novel measures of unfair treatment/discrimination and revealed new genes and biological pathways relevant to BP variation. Our validation was done using a larger cohort study of AAs, the Jackson Heart Study (JHS). Systolic and diastolic BP were measured twice in the same visit using a random-zero mercury sphygmomanometer and averaged. During this visit, perceived discrimination was assessed as lifetime occurrence of unfair treatment in nine social domains using the JHS discrimination instrument. Using available GWAS data, 28 significant SNPs were imputed from 1000 Genomes Project Phase 1 (version 3). Our analysis was conducted separately on participants who reported use of BP medications (n= 1532) and those who did not (n=1407). We similarly tested for associations of SNPs with BP using 3 linear regression models adjusting for global ancestry, sex, age, education, BMI, and relatedness. Model 1 tested only the SNPs, model 2 tested the SNPs and discrimination, and model 3 tested an interaction between SNPs and discrimination.

JHS participants were 62% female, with a mean age of 55 years. Participants on average experienced unfair treatment in three domains in their lifetime. In participants not on BP medications, we found that rs2116737, in the gene SGCD, achieved

Bonferroni-corrected significance ($p < 0.004$) with systolic BP in a recessive genotype model ($\beta = 11.92$; $p = 2.00 \times 10\text{-}4$) and was only identified through model 3, the gene-discrimination interaction model. No significant findings were seen in patients using BP medications. rs2116737 is an intronic variant in SGCD, a gene that is highly expressed in arterial tissue, suggesting vascular regulation as a possible mechanism behind the interaction.
In conclusion, the findings suggest accounting for a gene by social environment interaction can identify new SNPs that deserve further investigation in understanding BP variation.
Presenting author email: ldumeny@ufl.edu

1118

Diabetes and Major Cardiovascular Events in CYP2C19-Guided Clopidogrel Recipients

Margarita I. Gonzalez, Cameron D. Thomas, Mohamef H. Shahin, Lukas G. Kovar, D. Max Smith, Amanda R. Elsey, Kristin W. Weitzel, R. David Anderson, Rhonda M. Cooper-DeHoff, David R. Nelson, Julie A. Johnson, Larisa H. Cavallari
Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida.

Research Category: Pharmacogenomics

Clopidogrel is the most widely used P2Y12 inhibitor in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) despite high patient-specific pharmacodynamic variability. Comorbid diabetes mellitus (DM) has been shown to result in impaired antiplatelet effects due to enhanced platelet reactivity and reduced plasma levels of the active clopidogrel metabolite. The objective of this study was to examine the influence of DM on post-PCI cardiovascular outcomes following CYP2C19 genotype-guided use of clopidogrel. The primary outcome was the incidence of a major adverse cardiovascular event (MACE), defined as the first occurrence of death, myocardial infarction, unstable angina, stent thrombosis, or stroke within 12 months following the PCI. This study included data for 241 patients identified as CYP2C19 normal or rapid/ultra-rapid metabolizers prescribed clopidogrel after PCI. Of these patients 122 (50.6%) had DM and were more likely to have a medical history of hypertension, dyslipidemia, and prior revascularization at baseline than non-DM patients ($p < 0.05$). The occurrence of a MACE was documented in 31 DM patients and 15 non-DM patients (25.4% vs 12.6%; $p = 0.09$). Among normal metabolizers ($n = 139$), the incidence of unstable angina is significantly higher in patients with DM than in patients without DM (25% vs 2.1%; $p = 0.02$) With the exception of unstable angina, the incidence of MACE components was comparable between normal metabolizers with and without DM. These results demonstrate that CYP2C19 genotype-guided use of clopidogrel in normal metabolizers with DM is associated with an increased risk of unstable angina following PCI when compared to those without DM.
Presenting author email: margonzalez@ufl.edu

1119

Precision Medicine under the Big Sky: Pharmacogenetic Implementation in Rural Settings

Tianna Leitch[1], Shayna Killam[1], Kirk Katseanes[1], Susan Trinidad[2], LeeAnna Muzquiz[3], Kate Krebsbach, Corbin Schwanke[4], Abdallah Elias[4], Erica Woodahl[1]
1. Department of Biomedical and Pharmaceutical Sciences, University of Montana. 2. Department of Bioethics and Humanities, University of Washington. 3. University of Washington Medical School. 4. Sodair Children's Hosiptal

Research Category: Pharmacogenomics

Recent scholarship has generated much optimism about the potential of precision medicine to transform healthcare. Yet, implementation strategies have been limited to major academic medical centers serving metropolitan communities and large health systems. By contrast, rural, community-based health systems have been slow to implement precision medicine advances, threatening to exacerbate existing health care disparities for rural populations. In Montana—where two-thirds of the population live in rural areas—we have established partnerships with early adopter sites who are eager to implement pharmacogenetics. Our partners serve high-risk rural populations including American Indian, pediatric, and low-income patients across the state. Our goal is to gather perspectives from key stakeholders to ensure that our implementation approach is feasible and accepted by clinical partners. We conducted 31 semi-structured interviews with healthcare personnel, including physicians, pharmacists, informatics specialists, electronic health record coordinators, and administrators. Interviews were transcribed and imported into Atlas.ti to identify and organize themes generated from interview questions. Two team members independently reviewed transcripts and created a codebook based on major themes. The codebook was then extensively revised through consensus by the analytic team. We identified major themes involving provider-perceived benefits to patients such as individualized treatments, reduced adverse events, and improved medication adherence across all partner sites. Significant concerns regarding patient and provider education for genetic testing, as well as lack of access to these resources in rural settings were common. Additionally, ethical strategies for collecting and returning genetic results for patients belonging to the aforementioned vulnerable populations was emphasized. While there is an overall interest in utilizing pharmacogenetics, significant concerns must be addressed, including, but not limited to, barriers in reimbursement, testing turn-around time, and effective integration into electronic health systems. The themes generated from these interviews will provide a framework for implementing a pharmacogenetics delivery model with our early adopter sites. Our project provides the opportunity to identify a broad range of implementation issues for further expansion across Montana and will serve as a model for pharmacogenetic implementation in rural settings.
Presenting author email: tianna.leitch@umontana.edu

1120

Racial differences in comparative efficacy and safety of thiazide-type (TT) and thiazide-like (TL) diuretics- Harnessing the potential of race in precision medicine

Lakshmi Manasa S. Chekka[1], Arlene B. Chapman[2], John G. Gums[1], Stephan T Turner, Rhonda M. Cooper-DeHoff[1], Julie A. Johnson[1]
1. Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL. 2. School of

Medicine, Emory University. 3. Department of Nephrology and Hypertension, Mayo Clinic

Research Category: Clinical implementation of genomics

Background: Recent hypertension (HTN) guidelines favor TL (Ex-chlorthalidone-CTD) over TT (Ex- hydrochlorothiazide-HCTZ) diuretics for longer action and better cardiovascular risk reduction. Also, CTD is considered twice as potent as HCTZ, yet HCTZ is prescribed 95% of times, due to inconclusive evidence from indirect comparisons of high dose thiazides (TZDs) or small low dose studies. Also, there are limited data on comparative efficacy of CTD and HCTZ in blacks which is likely to differ from whites, as blacks respond better to TZDs than whites. Our objective is to provide race specific comparisons of CTD and HCTZ at low doses (25mg/d) and study race as a contributor to drug response variability and in turn to precision medicine.
Methods: We used data from TZD monotherapy arms of PEAR (Pharmacogenomic evaluation of antihypertensive responses n= 376), PEAR-2 (n=326) prospective RCTs in mild-moderate HTN patients <65 years, treated with 12.5 mg/d HCTZ(PEAR), 15mg CTD (PEAR-2) * 2-3 weeks and titrated to 25mg/d * 6 weeks in both. Baseline, mid-visit and end of therapy home, office systolic/diastolic blood pressure (SBP/DBP), clinical parameters like serum sodium, potassium, glucose, uric acid etc were recorded. We compared BP and metabolic changes with HCTZ vs CTD therapy in whites and blacks with student-t or chi-square tests, statistical significance set a priori as p<0.05.
Results: SBP/DBP change on HCTZ vs CTD: 8±8/4±5, 12±9/7±5 mmHg in whites (p <10^-6); 12±10/7±6, 15±10/9±6 in blacks (p= 0.008- SBP, 0.054 - DBP). % patients who reached goal BP on HCTZ vs CTD differed in whites (p= 0.017) but not in blacks (p= 0.3) with similar trends in TZD adverse effects (hypokalemia, hyperuricemia etc)- stronger differences in whites than in blacks.
CONCLUSION: Our data showed the responsiveness of blacks to TZDs overpowered the potency differences between TZDs and choice of CTD over HCTZ is warranted in whites but not in blacks. Thus race is an important determinant of drug response variability and could help in precise therapy selection among hypertensives (specifically in the choice of TZD).
Presenting author email: mchekka@ufl.edu

1121
ZMAT4 and DOCK9 Variants Associated with Heart Failure in Breast Cancer Patients in the UK Biobank data

Marwa Tantawy[1], Sonal Singh[1], Guang Yang[1], Matthew A. Gitzendanner[2], Yiqing Chen, Yonghui Wu[3], Ruogu Fang[4], William Hogan[5], Yan Gong[1]

1. Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL. 2. Department of Biology, University of Florida. 3. Department of Health Outcome and Biomedical Informatics, Colle of Medicine, University of Florida. 4. J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida. 5. Department of Health Outcomes and Policy, University of Florida

Research Category: Pharmacogenomics

Breast cancer (BC) is the top cancer in women worldwide, and the incidence is increasing in developing countries. Most BC patients receive chemotherapy treatments, which reduces mortality by 33%. However, chemotherapy-induced cardiotoxicity such as heart failure (HF) has been identified as a major health concern among BC patients.
Our study aims to determine genetic variants associated with HF susceptibility among BC patients. We performed a genome-wide association analysis of 13,660 BC patients of European ancestry in the UK Biobank, including 62 patients who developed HF. The analysis was adjusted for age, sex, hypertension, and ancestry.
The most significant SNP associated with HF is an intronic variant rs72641596 in ZMAT4 (zinc finger matrin-type 4) (p value= 1.9x10-7) with an odds ratio (OR) of 3.127 and 95% confidence interval (CI) of (2.03-4.8). This gene is involved in DNA-protein binding and zinc ion binding, which has a vital role in maintaining cardiac function and contractility. Alterations in Zn2+ homeostasis is associated with dysregulated intracellular Ca2+ release, causing chronic HF. Another important SNP identified, is a missense variant rs62620184 in the DOCK9 (Dedicator of Cytokinesis 9) gene (p value= 7.5x10-6), with OR=3.4 and 95% CI of (2.02-6.03). This gene has Rho GTPase binding, Rho guanyl nucleotide exchange factor activity, and protein-binding functions. Besides, the unique altered transcript of DOCK9 in the remote myocardium has been shown to be related to cardiac arteriopathy.
In this study, we identified SNPs in ZMAT4 and DOCK9 to be associated with HF among BC patients. Further investigation is needed to understand the underlying mechanisms of these associations.
Presenting author email: mtantawy@cop.ufl.edu

1122
CYP2D6 Influences Aripiprazole Discontinuation in Pediatric Patients with Mood Disorders

Sahar A. Jallaq[1], Mark Verba[2], Jeffrey R. Strawn[3], Laura B. Ramsey[3]

1. Takebe Lab, University of Cincinnati. 2. Department of Pharmacology & Systems Physiology, University of Cincinnati. 3. Department of Pediatrics University of Cincinnati

Research Category: Pharmacogenomics

Mixed dopamine serotonin receptor antagonists can be effective treatments for mood disorders, however, patients often experience intolerable side effects, (e.g. weight gain, extrapyramidal symptoms, etc.). Selecting effective treatments that safely reduce symptoms is often difficult in children and adolescents with mood disorders. Consequently, many patients discontinue treatment due to lack of efficacy or side effects. Aripiprazole is mixed dopamine serotonin receptor antagonist that is primarily metabolized by the CYP2D6 enzyme. Genetic variation in CYP2D6 affects the pharmacokinetics of aripiprazole. Aripiprazole is amongst the few antipsychotic agents containing actionable pharmacogenetic (PGx) language in its FDA label, advising known CYP2D6 poor metabolizers (PMs) or those on concomitant CYP2D6 substrates to receive half of the usual dose.
We examined the effect of CYP2D6 metabolizer status on aripiprazole discontinuation in pediatric patients who received routine PGx testing. We retrospectively analyzed the electronic medical records of patients ≤20 years of age who were prescribed aripiprazole for a mood disorder (n=277) and had a CYP2D6 genotype. CYP2D6 metabolizer status was determined based on the 2019 Clinical Pharmacogenetics Implementation Consortium (CPIC) interpretation guidelines (activity score of 1 = intermediate

metabolizer, IM). Then, the reason for treatment failure was abstracted from clinician notes. The cohort was 66% female, 84% white, and aged 14.3 (±2.4) years. Of the 277 patients, 57% were normal metabolizers (NMs), 37% were IMs, 5% were PMs, and 1.4% were ultrarapid metabolizers (UMs). Accounting for phenoconversion through concomitant use of CYP2D6 substrates resulted in 27% pNMs, 24% pIMs, 48% pPMs, and <1% pUMs. CYP2D6 pPMs discontinued treatment due to side effects more often than any other CYP2D6 group (67% for pPM, 51% pIM, 57% pNM, Chi-square p=0.024). However, pPM patients were prescribed higher doses of aripiprazole than other CYP2D6 groups (mean 9.1 vs 7.3, 7.8, and 5 in pIMs, pNMs, and pUMs, respectively), which is inconsistent with the FDA label. In conclusion, utilization of PGx results may help optimize dosing and reduce aripiprazole discontinuation due to side effects.
Presenting author email: jallaqsr@mail.uc.edu

1123
Association of Genetic Polymorphisms NCF4 rs1883112, CBR3 rs1056892, and ABCC1 rs3743527 with the Cardiotoxic Effects of Doxorubicin in Children with Acute Lymphoblastic Leukemia.

Jesús Alonso Gándara-Mireles, Ismael Lares-Assef, Elio Aáron Reyes-Espinoza, Javier Blanco, Antonio Emilio González-Font, Lourdes Patricia Cordova-Hurtado, Verónica Loera-Castañeda, Ignacio Villanueva-Fierro, Horacio Almanza-Reyes

Research Category: Pharmacogenomics

Introduction: In Mexico, acute lymphoblastic leukemia (ALL) is the most common type pediatric leukemia accounting for up to 50 % of total pediatric cancer cases. The use of anthracyclines for the chemotherapy of pediatric ALL is linked to the development of cardiotoxicity in certain cases.
Objective: To examine the presence of associations between NCF4 rs1883112, CBR3 rs1056892 and ABCC1 rs3743527 genotype status and echocardiographic parameters indicative of doxorubicin-cardiotoxicity in children with ALL.
Methods: DNA samples obtained from 67 cases with ALL (2 to 18 years old) and 67 controls without ALL (young adults) were genotyped by real-time polymerase chain reaction (qPCR). Echocardiograms of 67 patients ALL cases were examined. Left Ventricular Ejection Fraction (LVEF) was considered a marker of systolic toxicity, and diastolic filling ratio (E/A) was considered a marker of diastolic toxicity.
Results: According to the association of the codominant, dominant and recessive inheritance models of NCF4 polymorphisms rs1883112; CBR3 rs1056892; and ABCC1 rs3743527 with DOX cardiotoxicity, it was found that in the case of NCF4 rs1883112 polymorphism, the wild genotype of the codominant model determines a risk effect for DOX cardiotoxicity [OR = 4.5584 (CI = 1.4351 to 14.4794), p = 0.0101]; similarly, the dominant model determines a risk effect for DOX cardiotoxicity, with a highly significant association [OR = 4.0982 (CI = 1.3977 to 12.0163), p = 0.0182]. In the case of CBR3 Polymorphism rs1056892, no significant association was found between the different inheritance models with cardiotoxicity by DOX, for each echocardiographic parameter. Regarding the association of the different inheritance models of ABCC1 rs3743527 polymorphism with DOX cardiotoxicity, it was found that both, the heterozygous genotype codominant model and the dominant model provide a protective effect statistically significant for DOX cardiotoxicity [OR = 0.2769 (CI = 0.0868 to 0.8833), p = 0.0300] and [OR = 0.3077 (CI = 0.1048 to 0.9033), p = 0.0319], respectively. We can observe that women have a higher percentage of systolic damage considering LVEF as the value that has more impact to measure the damage that is present in 86.3% of the woman, while 54.5 % of them have diastolic damage, with a significant difference according to sex (x2 = 31.3, p<0.001) between % systolic and diastolic damage, with higher values in girls 31.8 % vs 6.7 % in boys.
Presenting author email: alonso_930@hotmail.com

1124
Combinatorial Pharmacogenomic Algorithm is Predictive of Citalopram and Escitalopram Metabolism in Patients with Major Depressive Disorder

Aime Lopez Aguilar[1], Richard C. Shelton, Sagar V. Parikh[2], Rebecca A. Law, Anthony J. Rothschild[3], Michael E. Thase[4], Boadie P. Dunlop[5], Charles DeBattista[6], Charles R. Conway[6], Brent P. Forester[7], Matthew Macaluso[8], Daniel T. Hain, Krystal Brown, David J. Lewis, Michael R. Jablonski, John F. Greden[9]

1. Medical Science Liaison at Assurex Health/Myriad Neuroscience. 2. Heinz C. Prechter Bipolar Research Program, University of Michigan. 3. Department of Psychiatry, University of Massachusetts Medical School. 4. Department of Psychiatry, University of Pennsylvania. 5. Department of Psychiatry, Emory University. 6. Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center. 6. Department of Psychiatry, Washington University School of Medicine. 7. Division of Geriatric Psychiatry, McLean Hospital. 8. Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine. 9. Department of Psychiatry, University of Michigan

Research Category: Pharmacogenomics

The validity of pharmacogenomic tests used to guide clinical treatment for major depressive disorder (MDD) must be thoroughly investigated. An important component of clinical validity is the accurate prediction of metabolism, which is indicated by the ability to predict metabolizer phenotypes. Historically, the metabolic impact of individual genes was evaluated but we now know that multiple genes are often involved in medication metabolism. Here, the ability of individual pharmacokinetic genes (CYP2C19, CYP2D6, CYP3A4) and a combinatorial pharmacogenomic (PGx) test (GeneSight Psychotropic®; weighted assessment of all three genes) to predict citalopram/escitalopram (es/citalopram) blood levels in patients with MDD was evaluated.
The Genomics Used to Improve DEpression Decisions (GUIDED) trial included patients who were taking es/citalopram at screening and had available blood level data (N=191). The ability to predict log-transformed concentration/dose ratios was evaluated for the individual pharmacokinetic genes involved in es/citalopram metabolism (CYP2C19, CYP2D6, CYP3A4) and for a PGx test (GeneSight Psychotropic, weighted assessment of all three genes). Individual gene phenotypes assigned by the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines or the PGx test were assessed. PGx test report categories were based on the level of gene-drug interactions and the direction of the metabolic impact. Individual genes and the PGx test were evaluated separately and together in ANCOVA analyses adjusted for age and smoking status.

In an ANCOVA analysis, CYP2C19 alone was a significant predictor of es/citalopram blood levels when phenotypes were assigned by CPIC guidelines (p=0.006) or the PGx test (p=0.01). CYP2D6 alone was only significant when phenotypes were assigned by the PGx test (p=0.03). The PGx test was a significant predictor of es/citalopram blood levels (p=0.0003). In ANCOVA analyses that evaluated the unique variance explained by individual genes (CPIC- and PGx test-assigned phenotypes) and the PGx test, only the PGx test remained significant (p≤0.01). The results are from the numerically-transformed phenotypes and gene-drug interaction categories.
Compared to individual genes, this study demonstrates that the PGx test that incorporated CYP2C19, CYP2D6, and CYP3A4 together was a superior predictor of es/citalopram blood levels.
Presenting author email: aime.lopez@myriad.com

1125
The effects of rs4363657-C of SLCO1B1 on metabolite levels in individuals on simvastatin treatment

Lilian F. Silva
University of Eastern Finland

Research Category: Pharmacogenomics

Background: Statins lower effectively LDL cholesterol levels and decrease the risk of cardiovascular events. The SLCO1B1 gene is expressed in the liver and encodes for a protein that transports statins into the liver. The C allele of a genetic variant rs4363657 of SLCO1B1 (SLCO1B1 rs4363657-C) has been previously associated with increased risk of statin-induced myopathy and rhabdomyolysis. However, the mechanisms of how this genetic variant increases the risk of myopathy are largely unknown. Objective: We investigated the associations of SLCO1B1 rs4363657-C with 857 metabolites in 760 participants of a large Finnish population sample (METSIM study) who were on simvastatin treatment.
Methods: We genotyped SLCO1B1 rs4363657-C by TaqMan assays or Sequenom genotyping, and measured metabolites by mass spectrometry (Metabolon, USA). P<5.8E-5 was considered as statistically significant given 857 metabolites included in statistical analyses.
Results: We found that SLCO1B1 rs4363657-C was significantly associated with a wide range of metabolites in participants on simvastatin treatment, including previously reported lucochenodeoxycholate, glucuronide, glycodeoxycholate sulfate, hexadecanedioate, and tetradecanedioate. We found novel associations of SLCO1B1 rs4363657-C with bile acids (glycocholenate sulfate, taurocholenate sulfate), dicarboxylic acids (hexadecenedioate, octadecenedioate, octadecadienedioate), dipeptide (prolylserine), lipids (octadecenedioylcarnitine, 1-oleoyl-GPG, octadecanedioylcarnitine, 1-linoleoyl-GPG), and a steroid, pregnenolone sulfate. The metabolite profiles in participants carrying SLCO1B1 rs4363657-C and treated with simvastatin involve metabolites originated from gut microbiota or having potential effects on mitochondrial function and hormonal imbalance.
Conclusion: Our study reports novel findings of the metabolites and pathways affected by SLCO1B1 rs4363657-C. Further studies are needed to determine whether these metabolites are directly or indirectly related to statin induced myopathy.
Presenting author email: lilianf@uef.fi

1126
Association of Genetic Polymorphisms NCF4 rs1883112, CBR3 rs1056892, and ABCC1 rs3743527 with the Cardiotoxic Effects of Doxorubicin in Children with Acute Lymphoblastic Leukemia.

Jesús Alonso K. Gándara Miréles, Ismael Lares Assef, Elio Aáron Reyes Espinoza, Javier Guillermo Blanco, Antonio Emilio González Font, Verónica Loera Castañeda, Lourdes Patricia Córdova Hurtado, Ignacio Villanueva Fierro, Reyes Horacio Almanza

Research Category: Pharmacogenomics

Introduction: In Mexico, acute lymphoblastic leukemia (ALL) is the most common type pediatric leukemia accounting for up to 50 % of total pediatric cancer cases. The use of anthracyclines for the chemotherapy of pediatric ALL is linked to the development of cardiotoxicity in certain cases. Objective. To examine the presence of associations between NCF4 rs1883112, CBR3 rs1056892 and ABCC1 rs3743527 genotype status and echocardiographic parameters indicative of doxorubicin-cardiotoxicity in children with ALL.
Methods: DNA samples obtained from 67 cases with ALL (2 to 18 years old) and 67 controls without ALL (young adults) were genotyped by real-time polymerase chain reaction (qPCR). Echocardiograms of 67 patients ALL cases were examined. Left Ventricular Ejection Fraction (LVEF) was considered a marker of systolic toxicity, and diastolic filling ratio (E/A) was considered a marker of diastolic toxicity.
Results: According to the association of the codominant, dominant and recessive inheritance models of NCF4 polymorphisms rs1883112; CBR3 rs1056892; and ABCC1 rs3743527 with DOX cardiotoxicity, it was found that in the case of NCF4 rs1883112 polymorphism, the wild genotype of the codominant model determines a risk effect for DOX cardiotoxicity (OR = 4.5584 (CI = 1.4351 to 14.4794), p = 0.0101); similarly, the dominant model determines a risk effect for DOX cardiotoxicity, with a highly significant association (OR = 4.0982 (CI = 1.3977 to 12.0163), p = 0.0182). In the case of CBR3 Polymorphism rs1056892, no significant association was found between the different inheritance models with cardiotoxicity by DOX, for each echocardiographic parameter. Regarding the association of the different inheritance models of ABCC1 rs3743527 polymorphism with DOX cardiotoxicity, it was found that both, the heterozygous genotype codominant model and the dominant model provide a protective effect statistically significant for DOX cardiotoxicity [OR = 0.2769 (CI = 0.0868 to 0.8833), p = 0.0300] and [OR = 0.3077 (CI = 0.1048 to 0.9033), p = 0.0319], respectively. We can observe that women have a higher percentage of systolic damage considering LVEF as the value that has more impact to measure the damage that is present in 86.3% of the woman, while 54.5 % of them have diastolic damage, with a significant difference according to sex (x2 = 31.3, p<0.001) between % systolic and diastolic damage, with higher values in girls 31.8 % vs 6.7 % in boys.
Presenting author email: alonso_930@hotmail.com

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Influence of CYP2C19 on proton pump inhibitor response

Rebeca Rivera[1], Ethan A. Poweleit[2], Lisa J. Martin[3], Jeffrey R. Strawn[4], Laura B. Ramsey[5]

1. Department of Physics, University of Puerto Rico at Rio Piedras. 2. Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center. 3. Cincinnati Children's Hospital Medical Center | CCHMC · Division of Human Genetics 4. Department of Psychiatry, University of Cincinnati. 5. Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center

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Proton pump inhibitors (PPIs) are used to treat acid-related disorders, such as gastroesophageal reflux (GERD). They act on parietal cells in the stomach inhibiting acid secretion by covalently binding to the H+/K+ -ATPase proton pump. Hepatic microsomal enzymes, such as the cytochrome P450 enzyme, CYP2C19, are responsible for PPI metabolism. PPI efficacy is dependent on the plasma concentration, which is affected by genetic variation in CYP2C19. The purpose of this project was to determine whether CYP2C19 metabolizer status influences PPI response in pediatric patients that have undergone pharmacogenomic (PGx) testing as part of routine care when admitted to the inpatient psychiatry unit. We retrospectively examined the electronic medical record data from youth ≤20 years of age (n=140) who were prescribed PPIs and underwent clinical CYP2C19 genotyping for *2, *3, *4, *5, *6, *7, *8, and *17. A normal function allele (1*) was inferred from the absence of the previous alleles. CYP2C19 metabolizer status was determined based on Clinical Pharmacogenetics Implementation Consortium (CPIC) standards. The cohort was 68% female, 79% white, and the mean age of the patients was 13.8 (±2.8). The most commonly prescribed PPI was omeprazole (49%), followed by lansoprazole (36%), pantoprazole (12%) and esomeprazole (2%). Many patients were prescribed other medications metabolized by CYP2C19, including escitalopram (31%), sertraline (27%) and oral contraceptives (28%). We were able to determine clinical response from the notes of 44 patients (32 responded). We found that the prescribed PPI dose (in omeprazole equivalents) was not related to CYP2C19 metabolizer status. However, response rate was lowest in rapid (RM) and ultrarapid (UM) metabolizer patients (8/14) compared to poor (PM) and intermediate (IM) metabolizer patients (11/13, Chi-square test for trend, p=0.11). This difference was more pronounced in adolescents 11-15 years of age, where only 1 of 6 RM/UM patients responded, compared to 7/9 normal metabolizers and 5/7 PM/IMs responded (chi-square test for trend, p=0.01). We conclude that CYP2C19 RM and UM patients undergoing psychiatric treatment may require increased doses of PPIs to improve their rate of response, especially during adolescence. When they are published, we plan to implement the PPI dosing guidelines based on CYP2C19 that CPIC is currently developing.

Presenting author email: rebeca.rivera4@upr.edu