sensitivity. These chemical-genetic interaction (CGI) screens can be performed in human cell lines using a pooled lentiviral CRISPR-Cas9 approach to assess drug sensitivity/resistance of single-gene knockouts across the human genome. A targeted, rather than genome-wide, library can enable scaling these screens across many drugs. CGI profiles can be derived from phenotypic screen readouts. These profiles are analogous to genetic interaction (GI) profiles, which represent sensitivity/resistance of gene knockouts to a second gene knockout rather than a drug. To computationally predict a drug's genetic target, we leverage the property that a drug's CGI profile will be similar to its target's GI profile. RESULTS/ANTICIPATED RESULTS: Five proof-of-principle screens will be conducted with compounds that have existing genome-wide profiles and well-characterized MOA. I will generate CGI profiles for these five compounds and identify genes that are drug-sensitizers or drug-suppressors. I will then evaluate whether targeted library screens can recapitulate the CGIs found in genome-wide screens. Finally, I will develop a computational tool to integrate these CGI profiles with GI profiles (derived from another project) to predict gene-level and bioprocess-level drug targets. These predictions (from both targeted and genome-wide profiles) will be benchmarked against a drug-target and drug-bioprocess standard. DISCUSSION/SIGNIFICANCE OF FINDINGS: This work will develop a scalable, targeted chemical-genetic screen approach to discovering how putative therapeutics work. The targeted screen workflow provides a method for higher-throughput drug screening. The computational pipeline provides a powerful tool for exploring the MOA of uncharacterized drugs or repurposing FDA-approved drugs.

38081

A Whole Blood Signature of Neutrophil Expression and Adaptive Immune Downregulation Characterizes Sepsis Mortality

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ABSTRACT IMPACT: This work identifies host immune perturbations in sepsis mortality that suggests targets for a precision medicine paradigm in the host response to infection. OBJECTIVES/GOALS: To compare the early whole blood transcriptome during sepsis between 30-day survivors and non-survivors in the Intensive Care Unit (ICU), and to evaluate for pathway enrichment that might explain sepsis lethality. METHODS/STUDY POPULATION: We enrolled 162 sepsis patients in the first 24 hours of ICU admission, particularly targeting individuals requiring vasopressors. Peripheral whole blood was collected in PAXgene vacutainers. Isolated RNA was analyzed with Affymetrix Human Genome ST 2.0 microarray. Differential gene expression was performed with Bioconductor/R/limma using log2 fold-change +/-0.6 as a threshold for differential expression, and a Benjamini-Hochberg adjusted p-value <0.05 to declare significance. Functional gene enrichment was performed using the Gene Ontology (GO) database with PANTHER overrepresentation test (Fisher's Exact) on all transcripts with adjusted p-value <0.05. Pathways analysis was performed with the Reactome Project using the raw fold change and significance data to identify dysregulated pathways. RESULTS/ANTICIPATED RESULTS: There were 58 non-survivors (36% mortality). We identified 39 genes as differentially expressed between sepsis non-survivors and survivors; 31 were upregulated in non-survivors and 8 had reduced expression. Several of the most overexpressed transcripts are neutrophil-specific, including LCN, MPO, OLF4M4, DEFA3, and DEFA4. A functional gene overrepresentation test further supports this finding, as the most enriched gene ontologies were neutrophil-mediated killing, neutrophil cytotoxicity, neutrophil extravasation, and respiratory burst, all demonstrating higher than 10-fold enrichment and FDR < 0.02. Pathway analysis of the peripheral blood transcriptome was notable for immune response derangement, specifically down-regulation of both innate and adaptive immune pathways (FDR < 0.00001). DISCUSSION/SIGNIFICANCE OF FINDINGS: We identified increased expression of neutrophil-related genes in sepsis non-survivors, replicating candidates previously identified in pediatric sepsis mortality and ARDS. These immune perturbations in sepsis mortality may represent key targets for eventually employing precision medicine strategies in sepsis.

54443

Pharmacogenomic Profiling of East and West African Populations

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ABSTRACT IMPACT: Genomic variation likely plays a role in differences in rates of adverse reactions and efficacy for African populations, and this research will add to the understudied field of pharmacogenomics in African populations. OBJECTIVES/GOALS: We aim to characterize the frequency of variants in clinically relevant genes in East and West African populations to assess the prevalence of potential drug-gene interactions. METHODS/STUDY POPULATION: Our pilot study will consist of 100 Somali patients enrolled at Mayo Clinic Rochester and 100 Ghanaian patients recruited at Teaching Hospitals in Ghana. Germline DNA will be extracted from pre-existing blood samples. Sequencing will be performed using Admera Health's PGxOne Plus test, interrogating a panel of 62 genes. Variants will be reported along with the predicted response for a list of drugs. Differences between frequencies of variants in East and West African populations will be analyzed. We will look for correlations with reported adverse reaction rates. We will then compare our findings with allele frequency data from publicly available data bases. Additionally, we will analyze the flanking regions of the panel for novel variants, using machine learning to predict gene-drug interactions. RESULTS/ANTICIPATED RESULTS: African populations are known to have more genetic diversity than any other population. Additionally, only African-Americans, African-Caribbeans from Barbados, Esan and Yoruba Nigerians, Gambians, Kenyans, and Sierra Leoneans are accounted for within the publicly available data bases most often used for variant studies. Thus, it is anticipated that we will find differences in the variant allele frequencies of our populations compared to European allele frequencies, and differences in frequencies between the East and West African populations. In the 200 base pair flanking regions that are sequenced in the assay along with the known variant regions, we may find novel previously unreported variants. DISCUSSION/

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SIGNIFICANCE OF FINDINGS: The lack of knowledge of pharmacogenomic variation in African populations contributes to ethnic disparities in patient outcomes. This study addresses this gap by adding to our comprehension of variants in clinically relevant genes, giving insight into underlying mechanisms of ethnicity-based drug responses.

74325

Vast sex-specific differences in transcriptional landscapes of pancreatic neuroendocrine tumors*

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ABSTRACT IMPACT: Here, we describe extensive sex-specific differences in the transcriptomes of pancreatic neuroendocrine tumors (PNETs). Given that the clinical course of PNETs differs by sex (female sex is associated with better survival), achieving a greater understanding of the specific molecular sexual dimorphisms is invaluable for advancing personalized treatment. OBJECTIVES/GOALS: Epidemiologic studies demonstrate that pancreatic neuroendocrine tumors (PNETs) exhibit sexual dimorphisms with regards to prognosis, disease recurrence, and complication rates. We sought to compare the transcription and DNA methylation landscapes of PNETs by sex, to elucidate molecular differences that may underlie this sex disparity. METHODS/STUDY POPULATION: RNAseq data was generated from PNETs surgically resected at our institution (9 Female; 12 Male patients). RNA was extracted with the RNeasy Mini Kit, stranded sequencing libraries were prepared with TruSeq, and paired end sequencing was done on the HiSeq 2500/4000 systems. Transcript-level quantification was performed with salmon, and DESeq2 was used for differential expression analysis. To account for significant variation due to covariates other than sex, surrogate variables were computed with the SVA package and adjusted for. The goseq package was used for gene set over representation analysis. Matched DNA methylation (DNAm) and RNAseq data was downloaded from GEO (16 F; 16 M). Raw DNAm data was processed with minfi. Differential methylation analysis was done with limma and bumphunter. Analysis was done in R. RESULTS/ANTICIPATED RESULTS: We found that 826 autosomal genes were differentially expressed (DE) by sex in PNETs (at FDR $\leq$0.1). Gene set over representation analysis performed on the DE genes revealed significant enrichment for several processes, including 'ascorbate & aldarate metabolism' and 'positive regulation of ERK1 & ERK2 cascade' (all FDR $\leq$0.1). When we compared DNAm profiles between sexes, we found 8 CpGs which were differentially methylated by sex (at FDR $\leq$0.1), 7 of which were proximal to genes. Methylation of one of the sex-associated CpGs, overlapping the gene TIMM8B, was found to be negatively correlated with gene expression (rho=-0.41; p-value=0.02). Interestingly, TIMM8B deletion has been previously reported in other non-pancreatic neuroendocrine tumors. There were no differentially methylated regions between sexes. DISCUSSION/SIGNIFICANCE OF FINDINGS: Our findings demonstrate that PNETs exhibit extensive sexual dimorphisms with regards to gene expression profiles but have largely congruent methylomes by sex. These molecular differences may contribute to the variability in clinical course between men and women, and their characterization is vital for the advancement of personalized medicine.

Dissemination and Implementation

82786

Quantification of the Accuracy of Stereotactic Radiosurgery using Surface Guided Imaging with 3D Printed Head Phantoms

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ABSTRACT IMPACT: This work assesses clinical implementation of a surface guided imaging system to improve the accuracy radiation delivery for treatment of brain lesions using a patient CT derived head phantom. OBJECTIVES/GOALS: Advancements in radiotherapy design have made clinical demand for efficient and accurate methods to deliver stereotactic radiosurgery (SRS) for treatment of intracranial lesions. This study assesses the potential of using surface guided imaging for setup using a 3D patient specific head phantom. METHODS/STUDY POPULATION: A single isocenter, multiple metastases SRS plan was generated on a CT derived RTsafe Prime phantom made of tissue equivalent materials and a polymer gel insert. Five targets of varying diameters were treated with 8Gy of radiation using two different positioning techniques. The first gel insert was irradiated within the phantom according to internal alignment with standard orthogonal x-ray imaging while the second setup used surface guided imaging, based on external anatomy. 42 hours after irradiation, the phantom was scanned in a head coil using a 1.5T MRI. MR images were fused with the patient CT data and structure set to further evaluate calculated and measured dose distributions. RESULTS/ANTICIPATED RESULTS: Discrepancies in phantom setup according to standard orthogonal x-ray imaging compared to surface guided imaging demonstrated to be <1mm in each translational (vertical, longitudinal, and lateral) and angular (rot, roll, pitch) directions. The 3D gel inserts permitted spatial analysis to compare dose distributions of measured values to those calculated in a treatment planning system (TPS). 3D GI (Gamma Index) analysis showed good alignment in high dose regions and resulted in passing rates >94% (5%/2mm) and >87% (3%/2mm). Finally, 3 of 5 targets showed better 3D GI passing rates and less geometric offset for positioning with the surface guided imaging. DISCUSSION/SIGNIFICANCE OF FINDINGS: 3D spatial analysis of human like phantoms demonstrated that patient positioning according to external anatomy performed comparable to standard methods aligning to the internal anatomy, for a multiple met SRS treatment.

97856

Implementation of DPYD and UGT1A1 pharmacogenetic testing to guide chemotherapy dosing

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ABSTRACT IMPACT: The implementation of DPYD and UGT1A1 pharmacogenetic testing, a promising tool of precision medicine,

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