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Weighted Pathway Genetic Load Analysis of Hyperbilirubinemic Infants Indicates a Potential Genetic Component for Susceptibility to Bilirubin Neurotoxicity

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Weighted Pathway Genetic Load Analysis of Hyperbilirubinemic Infants Indicates a Potential Genetic Component for Susceptibility to Bilirubin Neurotoxicity

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Background: Severe kernicterus spectrum disorder (KSD) is described as motor and auditory deficits resulting from brain damage caused by hyperbilirubinemia (HB). Interestingly, the severity of HB does not always sufficiently predict the severity of injury. Numerous genetic mutations result in severe HB in neonates, but the role of genetics to bilirubin neurotoxicity remains unclear. The lack of a strong monogenetic link to result in severe HB in neonates, but the role of genetics to bilirubin neurotoxicity remains unclear. The lack of a strong monogenetic link to susceptibility to bilirubin-induced brain damage may be due to impaired bilirubin response pathways.

Objective: The objective of this work is to use a modified pathway genetic load (mPGL) score method to perform a targeted genetic analysis of whole exome data from patients with various degrees of neonatal HB, with an ultimate goal of developing a neonatal screen to susceptibility to bilirubin neurotoxicity.

Study Design:
• Retrospective Cohort Study
• Inclusion Criteria
  • History of severe HB (total bilirubin (TB) > 15 mg/dL in the first month of life)
  • > 36 weeks gestational age
• Exclusion Criteria (at time of HB exposure)
  • Active infection
  • Hypoxic ischemic encephalopathy
  • Other metabolic developmental abnormalities
• Study sites (Cases / Controls)
  • USA – Children’s Mercy Hospital – (8/16)
  • Mexico – Hospital Infantil de Mexico Federico Gomez (7/23)
  • Thailand – Shoklo Malaria Research Unit (13/0)

Sequencing and Variant Calling:
Whole Exome Sequencing (WES) was performed on DNA samples at either CMH or HIMFG via Illumina Next Generation Sequencing. Variant data was validated via the CMH bioinformatics pipeline. Variants were called using Variant Integration and Knowledge Interpretation in Genomes (VIKING) software developed at Children’s Mercy Hospital [1].

mPGL and mPGL+ scoring:
Known and predicted pathogenic variants were identified in two gene lists, counted, and weighted by zygosity to produce modified Pathway Genetic Load (mPGL) and mPGL+ scores for each individual [2]. Gene lists for variant filtering were curated based on known genetic contributors to jaundice (Tier 1) and bilirubin responders in human neuronal and mouse neuronal and glial cell culture (Tier 2). mPGL+ scores were created by weighting each variant identified using the Combined Annotation Dependent Depletion (CADD) scoring system (https://cadd.gs.washington.edu) [3].

For dichotomous analysis samples were separated into four groups (Figure 1) where mild jaundice was considered a peak bilirubin of 15 – 25 mg/dL, and severe jaundice was >25 mg/dL. KSD severity was determined by clinical evaluation. Familial control samples were also collected for future inheritance analysis. Average mPGL and mPGL+ scores for each tier were analyzed via one-way ANOVA with Tukey’s multiple comparison post-test (p<0.05). For continuous analysis mPGL and mPGL+ scores were plotted against KSD severity and analyzed by linear regression analysis.

Results and Conclusions:
• Only 1 group comparison in the mPGL+ Tier 1 analysis proved to be statistically significant, High Bilirubin & Mild KSD vs. Low Bilirubin & Severe KSD.
• We hypothesized that increased mPGL scores would correlate with increased susceptibility to bilirubin neurotoxicity but these results show the opposite effect and indicate a need for increased study and thoughtful evaluation of the mPGL score and the gene lists used here.

Identification of critical pathway genetic load scores related to susceptibility to bilirubin neurotoxicity in neonates is enhanced by weighting genetic variants using CADD scoring.

Next Steps:
• Proceed to a prospective study in an effort to reduce complicating clinical variables and include free bilirubin measurements for data analysis.

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References:
1. S. E. Soden et al., Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. Sci Transl Med 8, 365ra168 (2016).