

**Abstract Title:** Proteomic analysis reveals differential protein expression with respect to blood transfusion in Sickle Cell Disease (SCD) patients

**Abstract Topic:** Statistical Genetics & Genetic Epidemiology Presenting

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**Aims:-** Sickle cell disease (SCD) is characterized by a single mutation in the beta hemoglobin gene. Although patients have the same underlying mutation, the clinical outcomes are highly variable. Blood transfusions are commonly used to ameliorate the symptoms of SCD. In this study, our aim was to understand the relationship between use of blood transfusion as therapy for SCD and protein expression in patients.

**Methods:-** We performed a mass spectrometry-based proteomic analysis of plasma samples from 109 adult patients with known transfusion histories from the Outcome Modifying Genes in SCD (OMG- SCD) cohort, quantifying 1190 proteins. We performed logistic regression to identify differentially expressed proteins, incorporating age, sex, and disease genotype as covariates.

**Results:-** Thirteen proteins, namely VASN, IBP7, PI16, CADM1, FBLN3, HEG1, APOL1, CD44, PCOC1, CO7, LYVE1, ATLA, and PTGDS, were differentially expressed in the highly transfused subset of patients (n=37 with > 20 transfusions) after adjusting for False Discovery Rate (FDR), with APOL1 being expressed at a lower level and the remaining proteins expressed more highly. To exclude false signals arising from other SCD symptoms, we also conducted proteomic analyses on stroke, acute chest syndrome, leg ulcers, and pain. None of the identified proteins were FDR significant in these other analyses. We found that two proteins, CO7 and PCOC1, were also FDR significant proteins identified in proteomic analysis of a composite end-organ damage severity score, suggesting their potential relevance to disease severity. We further investigated the proteomic landscape in a subset of severe SCD cases (SS genotype, n = 91) with respect to transfusion history. In addition to the previously identified 13 proteins, three novel proteins, NEGR1, COMP, and CAD13, were identified.

**Conclusions:-** Our study highlights the utility of plasma proteomics to uncover the complex molecular landscape underlying SCD. The identified proteins, including some previously associated with SCD pathophysiology, as well as others newly identified by this study, offer valuable targets for further investigation and potential development of precision therapeutic interventions. To further elucidate the biological implications, we are exploring the pathways associated with these identified proteins. By unraveling the intricate biological mechanisms and pathways involved in severe SCD, we aim to contribute to the advancement of personalized medicine approaches and provide valuable insights into the molecular profiles specific to severe SCD.

**Keywords:** Proteomics; Mendelian disorder; Genomics; Computational tools; Public health