

It is believed that much of the clinical variability among patients with sickle cell disease (SCD) may be genetically determined, resulting from the co-inheritance of “epistatic” genes which interact with the basic sickling defect to modify the disease pathophysiology. We recently conducted a pilot study in 103 children and found that the Lewis negative Le (a-b-) phenotype was associated with a 2-fold higher hospitalization rate for sickle cell disease related complications compared to Le (a+b+) and Le (a-b+) patients. The Le (a-b-) phenotype is also known to be associated with a 2-fold increased risk of ischemic heart disease. No mechanism has yet been identified, but we hypothesize that the association between Lewis RBC phenotype and SCD severity may be mediated by differences in the plasma level of sialyl-Lewis a (sLe^a), a high-affinity selectin ligand. The objectives of this study are: a) to confirm our initial findings in a larger group of children drawn from multiple centers; b) to determine whether the Lewis (a-b-) phenotype is also associated with disease severity in adults; c) to determine whether the Lewis phenotype or plasma sLea level predict specific types of complications (e.g., stroke, ACS); d) to establish whether Lewis acts independently of HbF, beta globin haplotype and alpha thalassemia; e) to look for any link between other blood group polymorphisms (e.g., Duffy, MNS) and SCD severity.

Lewis antigen status will be determined serologically, along with 20 other blood group antigens. We will also perform Se and Le genotyping by PCR-RFLP and quantify plasma sLea by ELISA. Disease severity will be collected via standardized report forms and entered into the CSCC Common Database. It is anticipated that retrospective data will be available from the Database for many patients. The participation of multiple centers in this project is essential, since it requires the collection of high-quality clinical data on large numbers of patients. Given the large increment in hospitalizations associated with Le (a-b-) in our pilot study, we believe that this marker may be useful as an early predictor of severity in SCD, and may help with the targeting of aggressive interventions (BMT, chronic transfusion) to higher-risk SCD patients.