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Abstract

Sickle cell disease (SCD) is the most common monogenic disorder in the world. Notably, there is extensive clinical heterogeneity in SCD that cannot be fully accounted for by known factors, and

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Declaration of Interests

The authors declare no competing interests.

in particular, the extent to which the phenotypic diversity of SCD can be explained by genetic variation has not been reliably quantified. Here, in a family-based cohort of 449 patients with SCD and 755 relatives, we first show that 5 known modifiers affect 11 adverse outcomes in SCD to varying degrees. We then utilize a restricted maximum likelihood procedure to estimate the heritability of 20 hematologic traits, including fetal hemoglobin (HbF) and white blood cell count (WBC), in the clinically relevant context of inheritance from healthy carriers to SCD patients. We report novel estimations of heritability for HbF at 31.6% (±5.4%) and WBC at 41.2% (±6.8%) in our cohort. Finally, we demonstrate shared genetic bases between HbF, WBC, and other hematologic traits, but surprisingly little overlap between HbF and WBC themselves. In total, our analyses show that HbF and WBC have significant heritable components among individuals with SCD and their relatives, demonstrating the value of using family-based studies to better understand modifiers of SCD.

Keywords

fetal hemoglobin; heritability; sickle cell disease

Introduction

Sickle cell disease (SCD), caused by the substitution of valine for glutamic acid in the β-globin chain of adult hemoglobin (HbA), is the most common monogenic disorder in the world. Notably, there is extensive clinical heterogeneity in SCD that cannot be fully accounted for by known factors, and in particular, the extent to which the phenotypic diversity of SCD can be explained by genetic variation has not been reliably quantified. Here, in a family-based cohort of 449 patients with SCD and 755 relatives, we show that 5 modifiers affect 11 adverse outcomes in SCD to varying degrees. We then estimate the heritability of 20 hematologic traits, including fetal hemoglobin (HbF) and white blood cell count (WBC), in the clinically relevant context of inheritance from healthy carriers to SCD patients.

In SCD, under conditions of deoxygenation, mutated sickle hemoglobin (HbS) polymerizes and damages erythrocytes, leading to vaso-occlusive events and hemolytic anemia.[1] Despite this common pathophysiology, SCD exhibits extensive clinical heterogeneity, ranging from mild phenotypes that remain undetected for decades to severe forms with multi-organ damage and early mortality.[2]

To resolve this heterogeneity, several traits have been found to modify the clinical course in SCD, of which fetal hemoglobin (HbF) and white blood cell count (WBC) are two of the most prominent. HbF inhibits the polymerization of HbS;[3,4] consequently, SCD patients with higher HbF have less severe complications and longer life expectancy,[5,6] and those with deletional hereditary persistence of HbF are almost entirely asymptomatic.[7,8] Meanwhile, higher WBC is associated with increased inflammation and is a strong predictor of acute chest syndrome (ACS), stroke, and early mortality in SCD.[3,9,10] Therefore, elucidating the genetic architecture of these traits holds important prognostic and therapeutic implications.

Genetic studies have identified numerous regions (e.g. *BCL11A*, *HBB*, and *HBS1L-MYB* loci) associated with increased HbF and WBC. However, these analyses were conducted in either healthy populations[11] or unrelated cohorts of individuals with SCD,[12,13] failing to capture how variation in HbF and other risk factors can be inherited from healthy carriers to SCD individuals within families. HbF is extremely difficult to sensitively measure in non-anemic individuals, whereas in the context of disease transmission, the heritability of HbF has generally been thought to be insignificant after adjusting for the overwhelming impact of SCD. For these reasons, no studies have estimated the heritability of HbF and WBC in a mixed SCD cohort, despite substantial evidence for their importance in the disease.

Here, using data collected from 449 SCD patients and 755 non-SCD relatives, we investigate the importance of a variety of hematologic traits in SCD. First, we apply logistic regression to model the effects of HbF, WBC, and 3 other modifiers on 11 adverse outcomes in SCD. Next, we estimate the proportion of phenotypic variance in 20 hematologic traits, including HbF and WBC, due to the additive effects of genes (i.e., the heritability) within the clinically relevant context of inheritance from healthy carriers to SCD patients.

Methods

Subjects

The GEN-MOD cohort comprised SCD patients and family members recruited at the Red Cell Genetic Disease Unit of the Hôpital Henri Mondor in Créteil, France from 2003 to 2015. Participants were primarily of African descent from French-speaking African countries and the French Caribbean. This research was approved by the “Comité Consultatif de Protection des Personnes participant à une Recherche Biomédicale de Créteil-Henri Mondor” and the Boston Children’s Hospital Institutional Review Board (Protocol #05-06-077R). All individuals provided written informed consent to the study. The following criteria were used to enroll patients:

Inclusion criteria: All patients were diagnosed with SCD by hemoglobin electrophoresis, were over 15 years of age, and had been followed by Henri Mondor University Hospital for at least 12 months at the time of enrollment. The study required that each patient had at least 2 family members (i.e., blood relatives) willing to enroll in the study.

Exclusion criteria: Any patients who were enrolled in a SCD-related clinical trial, had been treated by a physician for pain crisis or acute chest syndrome (ACS) within the past 2 months, had taken hydroxyurea or received a blood transfusion within 90 days, were pregnant, or had clinical evidence of intercurrent illness (e.g., fever, flu) were excluded from the study. Patients with Hb SC disease and with Hb S/beta 0 thalassemia were not eligible for this study. Finally, individuals with both HbA < 30% and HbS < 30% were excluded.

After passing inclusion and exclusion criteria, there were a total of 449 individuals with SCD, 587 with sickle cell trait, and 174 with normal HbA (Appendix, Figure S1 in Supporting Information).

Data collection

Data was collected via participant interview. All participants completed surveys documenting clinical outcomes. Participants who enrolled as a family member received a survey with primarily questions regarding general health and demographics, whereas those who enrolled as a patient received more detailed survey with additional questions specific to various manifestations of SCD.

Blood samples were collected from all participants with venipuncture. Hemoglobin level, red blood cell (RBC) counts, mean red blood cell volume (MCV), white blood cell (WBC) counts, and platelet counts were determined with a Beckmann-Coulter automated blood cell analyzer. Ethylenediaminetetraacetic acid (EDTA) blood samples were used for measurements of complete blood counts. Levels of different hemoglobin types were measured via hemoglobin electrophoresis.

Statistical analysis

Statistical analyses were performed with R 3.5.1 and conducted using approaches described in the Appendix in Supporting Information.

Results

Comparing individuals with SCD to those without, mean HbF values were 6.75% (±5.30%) and 0.83% (±0.72%), respectively, while WBC were 10.56 (±3.62) $*10^3$ cells/μL and 5.83 (±3.23) $*10^3$ cells/μL. Individuals with SCD also had significantly increased reticulocyte and platelet counts (Table 1). Amongst individuals with SCD, HbF ranged from 0.2% to 38.2%, and WBC ranged from 4.3 to 45.3 $*10^3$ cells/μL, with both traits exhibiting a positively skewed distribution (Figure S2 in Supporting Information).

First, looking within 449 individuals with SCD, we quantified the effects of 5 modifiers - HbF, WBC, hematocrit, systolic blood pressure (SBP), and cigarette smoking - on 11 markers of SCD morbidity (Figure 1, Table S2 in Supporting Information). Interestingly, varying strata in HbF levels did not trend linearly with adverse outcomes. Compared to patients with HbF between 0–5% (bottom 45^{th} percentile in our SCD cohort), patients with HbF of 5–15% (45^{th} to 93^{rd} percentiles) exhibited little to no reductions in rates of anemia, blood transfusions, ACS, or leukocytosis (Figure S3 in Supporting Information). However, a high HbF of >15% was associated with significantly increased hematocrit and reduced blood transfusions (OR = 0.17 and 0.18; $p < 0.01$), as well as near-significant reductions in rates of leukocytosis (OR = 0.46; $p = 0.10$) and ACS (OR = 0.23; $p = 0.16$) (Figure 1A). Likelihood ratio tests revealed significantly non-linear relationships between HbF and all 4 of these outcomes (Appendix in Supporting Information), and furthermore, logistic regression modeling indicated steep drops in estimated probabilities of low hematocrit and ACS at HbF ≥ 15% (Figure S3 in Supporting Information). While other studies have proposed that various HbF thresholds exist for ameliorating severe SCD events such as pain crises and hospitalizations[14], our study builds on this by showing that an HbF threshold is also required to improve other markers of disease such as hematocrit, number of blood transfusions, and leukocytosis.

Examining other SCD modifiers, we found that elevated WBC was associated with reduced hematocrit and increased rates of priapism (Figure 1B). Higher hematocrit predicted increased rates of pain crisis (Figure 1C), consistent with previous studies associating hematocrit with increased blood viscosity,[15] and smoking strongly predicted increased rates of ACS and leukocytosis (Figure 1E).[16] Altogether, these results confirm and add finer resolution to the effects of 5 modifiers on specific aspects of SCD morbidity.

Next, we leveraged the comprehensive kinship information in our full cohort (n = 1210) to estimate the heritability of 20 SCD-relevant traits, including HbF and WBC. Using a variance components model with fixed effects of SCD status, sickle trait status, age, and sex (Appendix in Supporting Information), we found that most hematologic markers exhibited substantial heritable components (Figure 2A, Table 1). Strikingly, HbF and WBC were amongst the most heritable traits studied, with heritability estimates of 31.6% (±5.4%) and 41.2% (±6.8%), respectively, demonstrating that even after accounting for the significant influence of SCD, 31.6% and 41.2% of the residual phenotypic variation in HbF and WBC can be explained by other genetic factors in families with SCD transmission.

Finally, we used a bivariate restricted maximum-likelihood procedure[17] to estimate genetic correlations between HbF and WBC and other hematologic traits (Appendix in Supporting Information). We discovered a significant negative genetic correlation between HbF and reticulocyte count, and positive correlations between HbF and hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV) (Figure 2B, Table S3 in Supporting Information). Meanwhile, in addition to strong correlations with white cell subtypes, WBC exhibited positive correlations with MCH, MCV, platelet count, and reticulocyte count (Figure 2C). Interestingly, HbF and WBC had almost no genetic correlation with one another (0.084 ±0.13), suggesting that although both are potent modifiers of SCD, they share little overlap in their genetic underpinnings and may serve as independent risk factors. Together, these results suggest that while the presence of SCD alleles is sufficient to cause disease, multiple discrete polygenic signals underlie modified disease severity.

Discussion

HbF induction is extremely promising for the treatment of patients with SCD. However, it is unclear to what extent HbF is inherited or how much its expression can be changed on a patient-to-patient basis. Heritability, or the fraction of phenotypic variance attributable to genetic factors, quantifies the genetic contribution to a trait and forms the foundation for studying the genetic architecture of complex diseases.[18,19] Genome-wide association studies (GWAS) have emerged as powerful tools for heritability estimation, but an outstanding issue with this approach is that a substantial fraction of heritability cannot be captured by GWAS variants at insufficient sample sizes.[20] Thus, an important advantage of estimating heritability from family-based cohorts, as performed here, is that it infers the expected genetic relatedness from known relationships and does not suffer from missed heritability. As recent studies have employed similar approaches using large electronic health records to estimate the heritability of other phenotypes,[19] we suspect our approach will be applicable to understanding variance among other Mendelian and complex phenotypes.

Previous family-based studies have measured genetic contributions to HbF and HbF-producing cells.[21–23] These examined either healthy populations or twins with SCD, but none have incorporated both individuals with SCD *and* healthy carriers (Table S4 in Supporting Information). Of note, it is difficult to study HbF in healthy cohorts, since the near-zero HbF levels of non-anemic individuals cannot be sensitively measured. In contrast, our study leveraged a large cohort of related individuals both with SCD and without to directly measure the heritability of HbF, which provides a more clinically relevant estimate. Our estimates demonstrate the value of studying heritability in the context of inheritance from healthy carriers to SCD patients, showing that genetic factors continue to influence HbF and other hematologic traits outside of the inherited effects of SCD itself.

In sum, this study utilized a large cohort of SCD patients and family members to measure the heritability of 20 hematologic traits. We find that surprisingly, genetic variation can explain 31.6% and 41.2% of this cohort's variance in HbF and WBC, even after accounting for the effects of SCD transmitted from carrier parents to children with SCD. More broadly, these results suggest that family-based studies will be valuable for gaining further insights into the susceptibility of clinically heterogeneous disorders such as SCD and their underlying genetic modifiers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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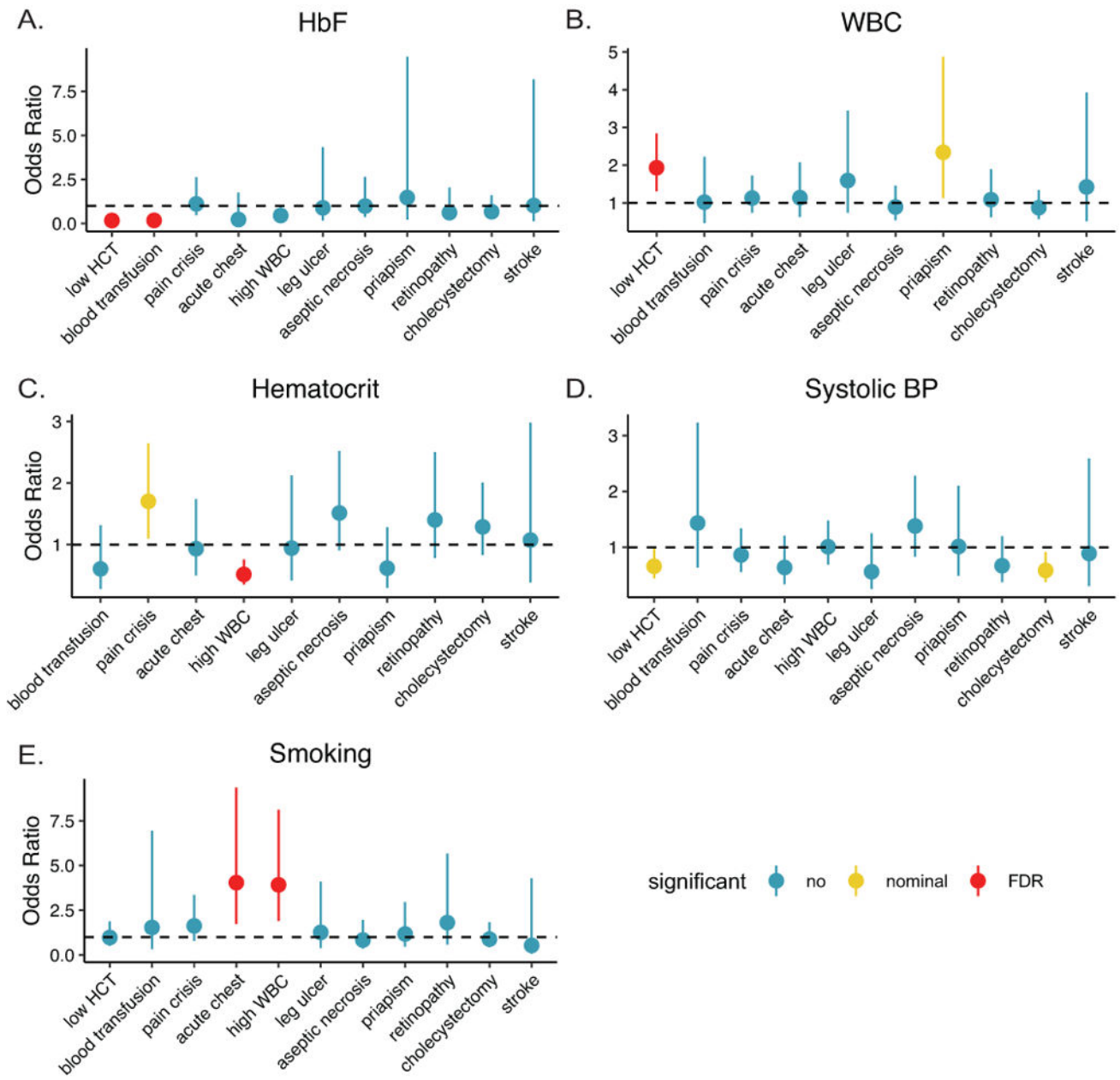

Figure 1: Effects of 5 risk factors on 11 markers of sickle cell morbidity.

Odds ratios (OR) and 95% confidence interval bounds for the effects of high (A) fetal hemoglobin, (B) white blood cell count (WBC), (C) hematocrit, (D) systolic blood pressure, (E) and cigarette smoking on 11 markers of SCD morbidity: low hematocrit, history of blood transfusions, pain crisis, acute chest syndrome, high WBC, leg ulcers, aseptic necrosis of the hip or shoulder, priapism, retinopathy, cholecystectomy, and stroke. Estimates were derived from a logistic regression model, adjusting for age and sex. In order to scale all outcomes such that a higher OR indicates increased morbidity, the outcome for hematocrit was reversed (i.e., an association with *low* hematocrit corresponds to an OR > 1). Yellow shading indicates nominal significance ($p < 0.05$); red indicates significance after adjusting for false discovery rate (FDR-adjusted $p < 0.05$).

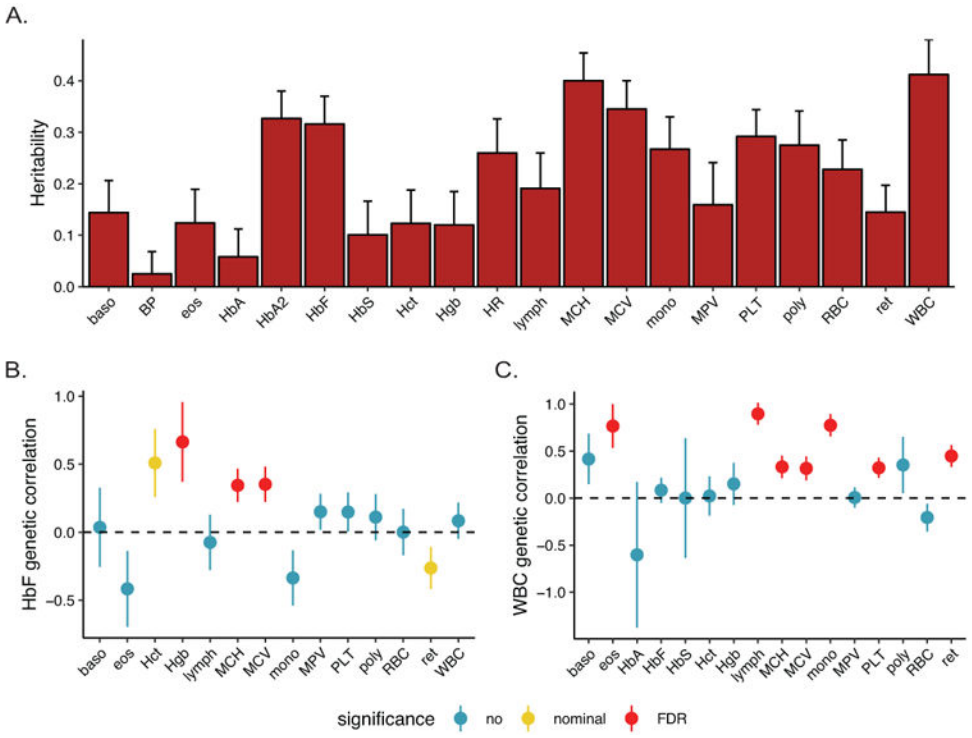

Figure 2: Measuring the heritability and shared genetic influences of fetal hemoglobin and white blood cell count.

(A) Heritability estimates of 20 clinical hematologic traits determined by variance components analysis. Genetic correlations between (B) fetal hemoglobin and (C) white blood cell count compared to other hematologic traits. Yellow shading indicates nominal significance ($p < 0.05$); red indicates significance after adjusting for false discovery rate (FDR-adjusted $p < 0.05$). Abbreviations: baso, basophil count; BP, systolic blood pressure; eos, eosinophil count; HbA, hemoglobin A; HbA2, hemoglobin A2; Hct, hematocrit; Hgb, hemoglobin; HbF, fetal hemoglobin; HR, heart rate; HbS, hemoglobin S; lymph, lymphocyte count; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; mono, monocyte count; MPV, mean platelet volume; PLT, platelet count; poly, polymorphonuclear leukocyte count; RBC, red blood cell count; ret, reticulocyte count; WBC, white blood cell count.

Table 1.

Summary statistics and heritability estimates of hematologic traits.

TRAIT	UNITS	NON-SCD	SCD	H2G	SE
baso	10^3 cells/uL	0.031 (0.054)	0.085 (0.111)	0.144	0.062
BP	mmHg	97.019 (15.198)	89.067 (31.405)	0.025	0.043
eos	10^3 cells/uL	0.18 (0.254)	0.272 (0.305)	0.124	0.065
HbA	%	60.707 (14.235)	0.782 (4.191)	0.058	0.054
HbA2	%	3.149 (0.56)	3.449 (0.734)	0.327	0.053
HbF	%	0.825 (0.724)	6.759 (5.319)	0.316	0.054
HbS	%	27.058 (15.14)	82.112 (8.359)	0.101	0.065
Hct	%	40.273 (4.183)	26.088 (4.907)	0.123	0.065
Hgb	g/dL	13.38 (1.5)	8.862 (1.444)	0.12	0.065
HR	bpm	71.982 (11.655)	75.428 (11.085)	0.26	0.066
lymph	10^3 cells/uL	2.155 (1.244)	3.542 (1.476)	0.191	0.069
MCH	pg	28.029 (2.685)	29.258 (4.115)	0.4	0.054
MCV	fL	84.578 (6.62)	86.817 (10.106)	0.345	0.055
mono	10^3 cells/uL	0.405 (0.31)	0.806 (0.482)	0.267	0.063
MPV	fL	9.089 (3.112)	8.651 (1.03)	0.159	0.082
PLT	10^3 cells/uL	245.238 (69.191)	389.645 (125.073)	0.292	0.052
poly	10^3 cells/uL	3.146 (1.806)	5.812 (2.621)	0.275	0.066
RBC	10^6 cells/uL	4.775 (0.556)	3.053 (0.81)	0.228	0.057
ret	10^3 cells/uL	13.851 (10.033)	84.168 (46.438)	0.145	0.052
WBC	10^3 cells/uL	5.921 (3.091)	10.556 (3.619)	0.412	0.068