Supplementary Online Content

Kirkham JK, Estepp JH, Weiss MJ, and Rashkin SR. Genetic variation and sickle cell disease severity: a systematic review and meta-analysis. *JAMA Netw Open*. 2023;5(10):e2337484. doi:10.1001/jamanetworkopen.2023.37484

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Search Terms
The following terms were used to search each database, respectively. The search was performed on May 16, 2023, and all manuscripts published prior to that date were considered.

PubMed: (sickle OR "sickle cell disease" OR “sickle cell anemia” OR “Hemoglobin SS” OR “Hemoglobin SC” OR “Hemoglobin SD” OR “sickle hemoglobin” OR "Anemia, Sickle Cell"[Mesh]) AND ("Genome-Wide Association Study"[Mesh] OR “GWA” OR “GWAS” OR "Genetic Association Studies"[Mesh] OR "Genetic Predisposition to Disease"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "single nucleotide polymorphism*" OR "SNP" OR “SNPs” OR "Genetic Variation"[Mesh] OR "genetic variant*" OR "gene variant*" OR "Genes, Modifier"[Mesh] OR "gene modifier*" OR "genetic modifier*" OR "Haplotypes"[Mesh] OR "haplotype*" OR "candidate gene*" OR "candidate variant*" OR "Quantitative Trait Loci"[Mesh] OR “eQTL” OR “QTL” OR "Genetic Loci"[Mesh] OR "locus" OR "loci" OR “alpha thalassemia”)

Web of Science: ALL=((sickle OR "sickle cell disease" OR “sickle cell anemia” OR “Hemoglobin SS” OR “Hemoglobin SC” OR “Hemoglobin SD” OR “sickle hemoglobin”) AND ("Genome-Wide Association Stud*" OR “GWA” OR “GWAS” OR "Genetic Association Stud*" OR "Genetic Predisposition to Disease" OR "genetic polymorphism*" OR "single nucleotide polymorphism*" OR "SNP" OR “SNPs” OR "Genetic Variation" OR "genetic variant*" OR "gene variant*" OR "gene modifier*" OR "genetic modifier*" OR "haplotype*" OR "candidate gene*" OR "candidate variant*" OR "Quantitative Trait Loc*" OR “eQTL” OR “QTL” OR "Genetic Loc*" OR "locus" OR "loci" OR “alpha thalassemia”))

Scopus: TITLE-ABS-KEY((sickle OR "sickle cell disease" OR “sickle cell anemia” OR “Hemoglobin SS” OR “Hemoglobin SC” OR “Hemoglobin SD” OR “sickle hemoglobin”) AND ("Genome-Wide Association Stud*" OR “GWA” OR “GWAS” OR "Genetic Association Stud*" OR "Genetic Predisposition to Disease" OR "genetic polymorphism*" OR "single nucleotide polymorphism*" OR "SNP" OR “SNPs” OR "Genetic Variation" OR "genetic variant*" OR "gene variant*" OR "gene modifier*" OR "genetic modifier*" OR "haplotype*" OR "candidate gene*" OR "candidate variant*" OR "Quantitative Trait Loc*" OR “eQTL” OR “QTL” OR "Genetic Loc*" OR "locus" OR "loci" OR “alpha thalassemia”))

Data Extraction
Data from the 571 included manuscripts[1-571] were extracted by one of two investigators (JKK and SRR), with discussions to resolve any uncertainty. Information was extracted regarding study design, phenotype definitions, genotype ascertainment methods and quality control performed, statistical analysis, and all genetic association results from the main text and available supplemental materials (**eTable 2**). Each extracted result was determined to be significant based on the reporting manuscript’s criteria as these definitions have shaped the current knowledge base, even though results reported without any multiple testing correction may be more likely to be false positive associations, incorrectly indicating an association is significant. For papers with undefined significance thresholds, if the analysis was genome-wide, a significance threshold of $5x10^{-8}$ was used, and 0.05 was used otherwise.

One manuscript included genome-wide summary statistics for all 237,078 variants tested, and another included the top 4,000 results for each of three different analyses (12,000 total). While we extracted these results (**eTable 3**) and included them in the meta-analyses, we excluded them from tabulation of results to avoid over-inflation of counts.

Study Design Evaluation
Study design was determined by the original author’s designation, when available. As most publications did not clearly self-identify an approach, the primary method of data collection and analysis was determined as follows: For studies in which data collection was done at a single point of time, with respect to each individual subject, and there was not a longitudinal approach to data analysis, the study was categorized as cross-sectional. Studies which selected controls using a pre-determined ratio in respect to the cases of interest were categorized as case-control. All case-control studies, save one, were retrospective in nature. Investigations of a cohort involving collection of data over numerous time points, in relation to each individual subject, were categorized as either prospective or retrospective cohort studies, based on whether the exposure of interest (i.e., genetic mutation) was identified and subjects were consented prior to or after the period of data collection. Finally, studies in which an intervention was selectively applied between

a control group and an experimental group, even if the intervention was not thought to have a direct connection to the exposure (i.e., genetic mutation) data being extracted, were categorized as clinical trials. If a single report made use of multiple cohorts and each cohort was investigated using a different study design, then multiple study designs were listed.

Phenotype Categorization

We classified each result into one of 25 general categories based on reported phenotype (**eTable 4**), with the aim of consolidating diverse phenotypes into common disease manifestations or organ-system categories. These categories were then grouped into broad sets based on the type of complication or measure: 1) acute SCD-related complications, 2) chronic SCD-related complications, 3) hematological parameters and biomarkers or disease severity, and 4) general or mixed measurements of SCD severity.

Prevalence estimates for each phenotype category were determined from the most recent published measurements within the adult SCD population within the United States, regardless of SCD subtype, when available.[310,430,441,449,572-583] When United States prevalence measurements were not available, data from countries with the most similar healthcare infrastructure and life expectancy were utilized. Specifically, estimates for "Infection (excludes respiratory infections)", "Priapism", "Acute splenic sequestration", and "Kidney dysfunction" were from the United Kingdom, Nigeria, France, and France, respectively. Additionally, only pediatric estimates were available for "Acute splenic sequestration", "Hyperbilirubinemia, cholelithiasis, cholecystitis, or cholecystectomy", "Splenic dysfunction", and "Anemia".

Gene Annotation Harmonization

Gene annotations were standardized across all extraction results, using reported annotations, dbSNP, and NCBI Gene. Intergenic single nucleotide polymorphisms (SNPs) were annotated to the nearest up- and downstream genes. Gene-dense regions were clustered due to multiple possible SNP-gene annotations, including the extended beta-globin locus, the olfactory receptor gene cluster, the HLA region, and the HPA gene family. For gene labels not found in NCBI Gene's list of canonical gene identifiers and synonyms (downloaded June 27, 2023), we used dbSNP and the reporting paper's annotations to ensure all unique genes with significant associations were captured. We then obtained Entrez IDs for each gene, which were used as input for the pathway analyses.

Unique Sample Size Tabulation

An estimate of the total number of unique individuals studied, including the number of pediatric patients, was determined for the studies reviewed, accounting for repeated evaluation of the same cohort. Extracted sample sizes were totaled, assuming the most overlap possible where not specifically excluded by the original authors' cohort description or determined to be temporally or geographically distinct, based on subject age, publication date, and available information on location. This summation represents the fewest unique individuals that would satisfy the cohort sizes outlined in all reviewed publications, though it likely underestimates the total subject count in an effort to avoid counting individuals more than once. There was no attempt to account for the potential of migration, so two geographically distant recruiting centers were assumed to represent non-overlapping cohorts. If no cohort location was reported in the manuscript, the corresponding author's institution was used. As 17 manuscripts include a mixed United States and Canada cohort, the total patient count from these two countries were combined. Cohorts located in any region of the French Republic, including the overseas departments of French Guiana, Guadeloupe, Martinique, and Mayotte, were grouped with metropolitan France under the simplified heading of France. The number of studies reporting on individuals from each country was also tabulated. As 55 studies reported on cohorts from at least two different countries, the total number of times all cohorts have been studied was greater than the total number of studies reviewed.

Data Strength Category Definitions

We used the STrengthening the REporting of Genetic Association Studies (STREGA) guidelines[584] – an extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[585] – to create three data strength categories into which all results were classified, defined as:

1. Exploratory – results which conduct genotype-phenotype association with a formal, statistical test but lack some information required for inclusion in a meta-analysis.
2. Meta-Suitable – results which contain at least the minimum required information for inclusion in a meta-analysis statistically: a) clearly defined phenotypic outcome, including comparison groups, association

direction, units, and any data transformations performed (STREGA 7a, 8a); b) clearly defined genetic variables, including genetic model (i.e., additive, dominant), with all genotypes defined by allele and association direction (STREGA 7b); c) exact statistical test conducted (STREGA 12); d) number of individuals used in analysis (STREGA 13); e) association size (i.e., beta, odds ratio, hazard ratio, etc.) and direction and a measure of variability (i.e., standard error [SE], confidence interval [CI], P-value) (STREGA 16a).

3. Contemporary – results which contain all criteria required for meta-suitable as well as further elements crucial for genetic association studies: a) genotyping/sequencing methods and quality control steps, including consideration of Hardy-Weinberg Equilibrium (STREGA 8a, 12f, 12g); b) accounting for population stratification (STREGA 12h); c) multiple testing correction (STREGA 12i, 16d); d) assessment of and, where relevant, accounting for related samples (STREGA 12j); e) evaluation of and adjustment for potential confounders (STREGA 12a, 16a). While not explicitly listed in STREGA, due to the potential for false positives, we have also included external validation as a required element for this category.

Meta-analysis

Due to the high level of variability in study design, data transformation, and covariate adjustment among results included in the meta-analyses, in lieu of either a fixed- or random-effects meta-analysis, we used a weighted Z-score-based approach implemented by METAL,[586] as we indicated in an amendment to our PROSPERO registration. This method is robust to differences in ethnicity, phenotype distribution, and other factors, as association sizes are not directly combined. Instead, for each study, Z-scores are calculated, summarizing the magnitude and association direction using P-values. An overall Z-score and P-value are calculated from a weighted sum of the individual scores, where weights are proportional to the study's sample size. As this method requires P-values, for results with only SE and/or CI, we calculated P-values using the provided information and an appropriate formula. If only CI was provided, when the two SE estimates differed by more than 20% of the larger value, likely due to rounding in the published results, that result was excluded; otherwise, the two estimates were averaged. Meta-analysis results were determined to be significant if the P-value satisfied the Bonferroni-corrected threshold (0.05/62). As typical metrics of heterogeneity used for meta-analyses, such as Cochran's Q and I^2, rely on the pooled association size, we evaluated component studies for agreement with the meta-analysis result in terms of significance and directionality.

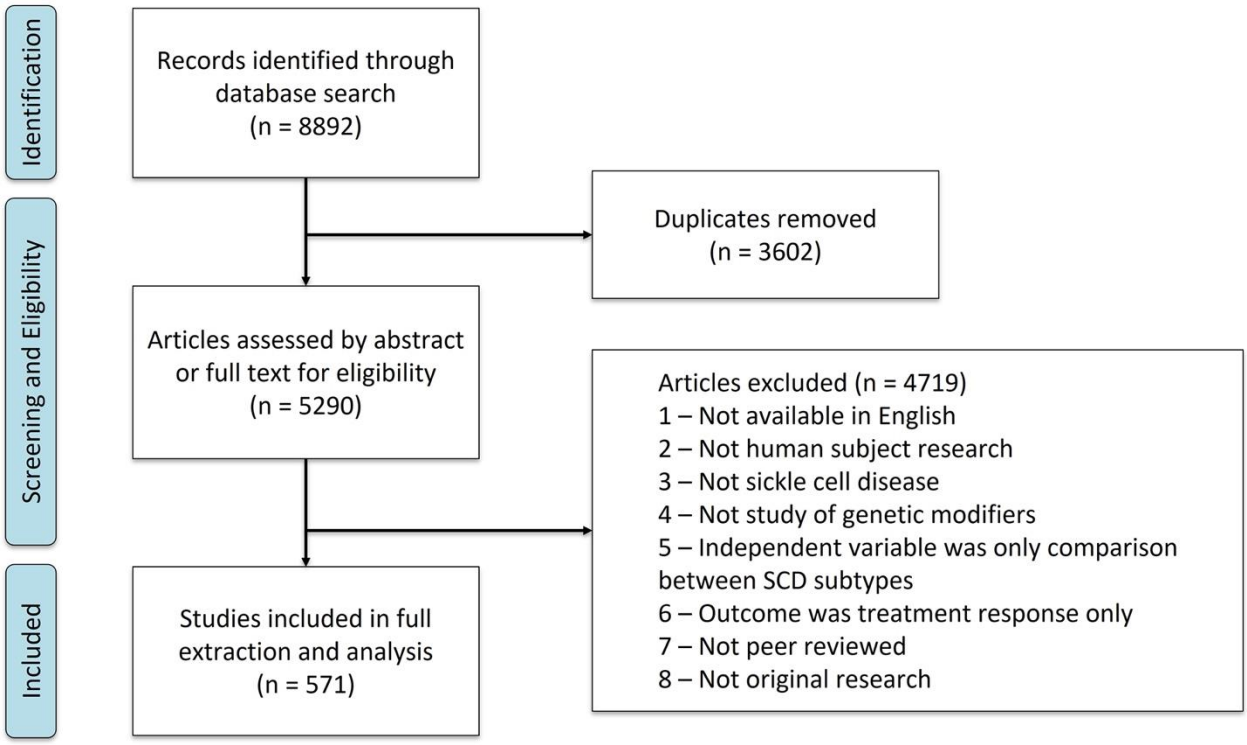
α-Thalassemia

As the relationship of concomitant α-thalassemia to SCD-related outcomes has been investigated for years, we compared all published results to summarize what is known. We restricted this assessment to extracted results classified as meta-suitable or contemporary. Additionally, we excluded results modeling one and two deletions separately; we further restricted to dominant genetic models unless the only evaluations performed for an outcome were additive per each allele copy.

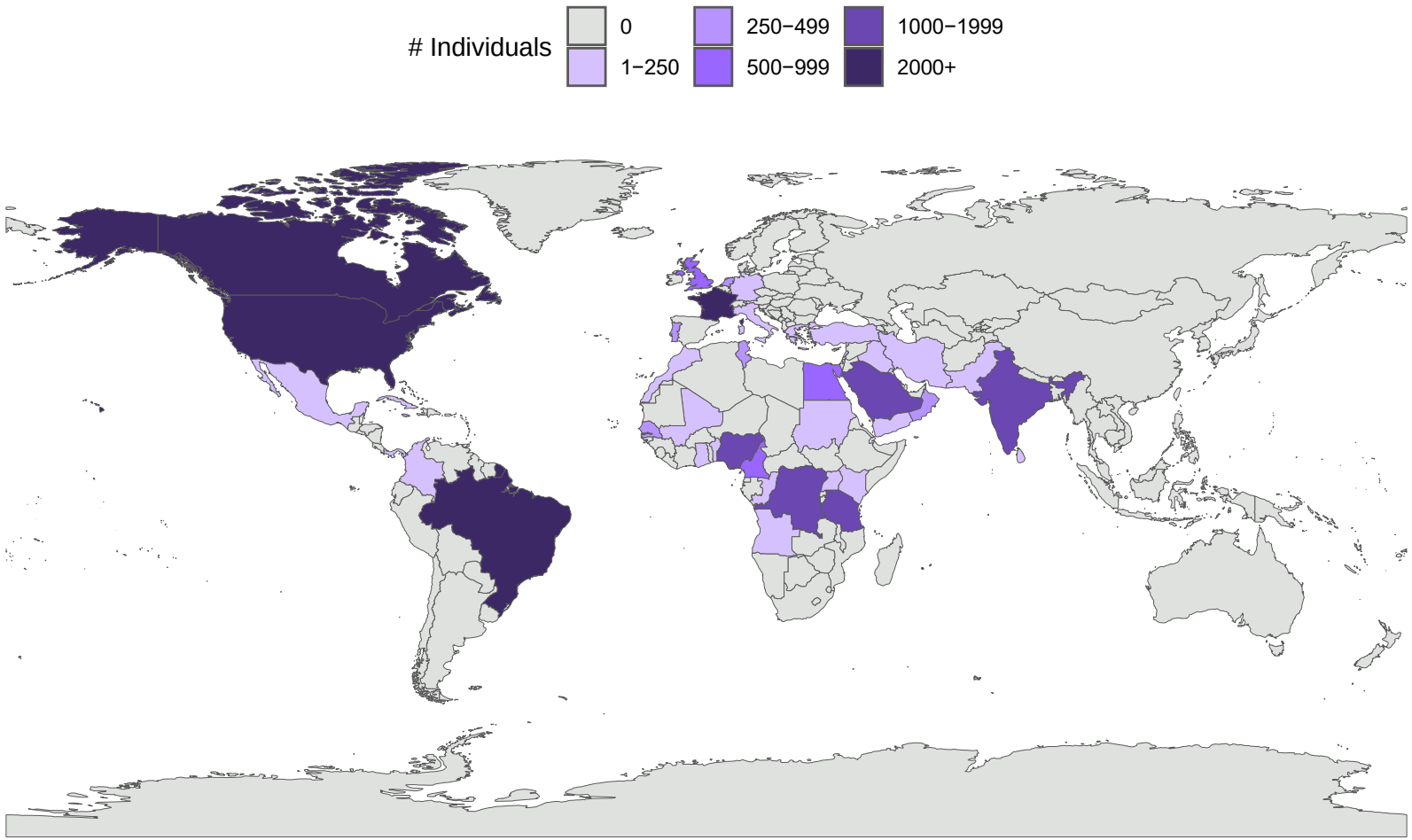
For comparison, non-continuous trait measures of association (i.e., odds ratio, hazard ratio) were log-transformed to convert to the beta scale (i.e., log odds ratio, log hazard ratio). For phenotypes with results from multiple cohorts, we first conducted fixed-effects meta-analyses to obtain an overall association size and CI, as our primary meta-analysis results did not provide global association sizes and CIs, and the fixed-effects P-values more closely matched our METAL P-values than the random-effects P-values. A forest plot was generated to evaluate the relationship between the presence of α-thalassemia deletions compared to no deletions on all reported outcomes.

Pathway Enrichment Analysis

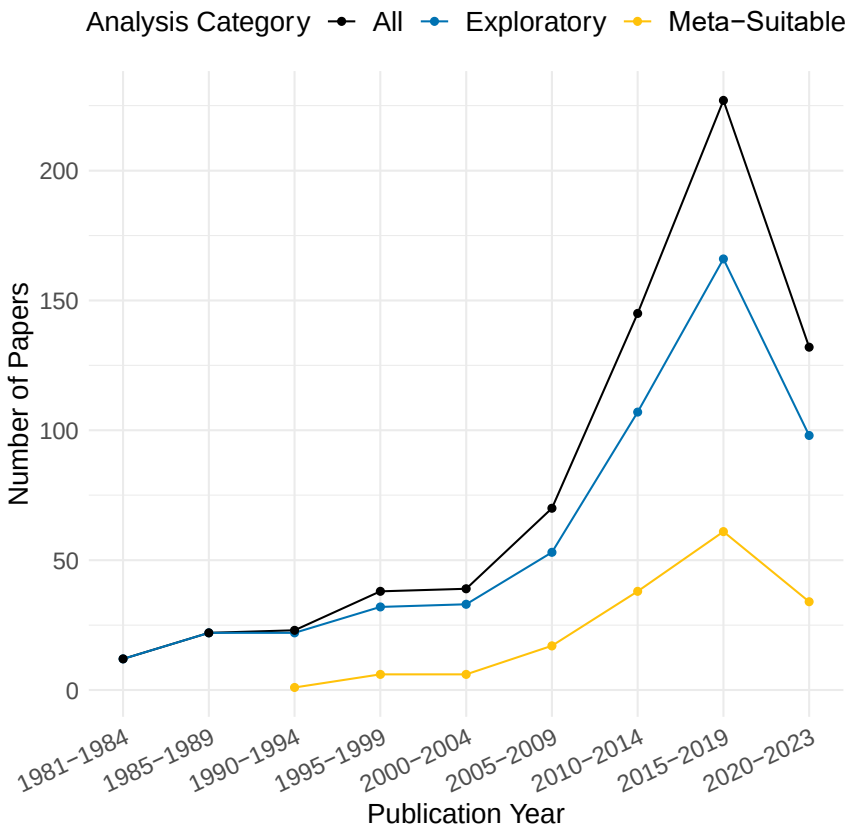
From the list of extracted results, we compiled a list of unique genes to which significant results were annotated. We used the R packages "clusterProfiler"[587] and "ReactomePA"[588] to conduct over-representation analyses using the Gene Ontology (GO)[589] and Reactome[590] databases. Briefly, a list of input genes was compared to curated pathway databases, testing whether there are any pathways containing more genes from the input list than expected by chance, correcting for multiple testing. We first conducted this assessment across all reported significant results, regardless of phenotype. We then repeated the analysis for each phenotype category with significant results in at least 35 genes. Each P-value was corrected internally for multiple testing using the Benjamini-Hochberg method[591], and pathways were considered significant and reported if both P and adjusted $P < 0.05$.



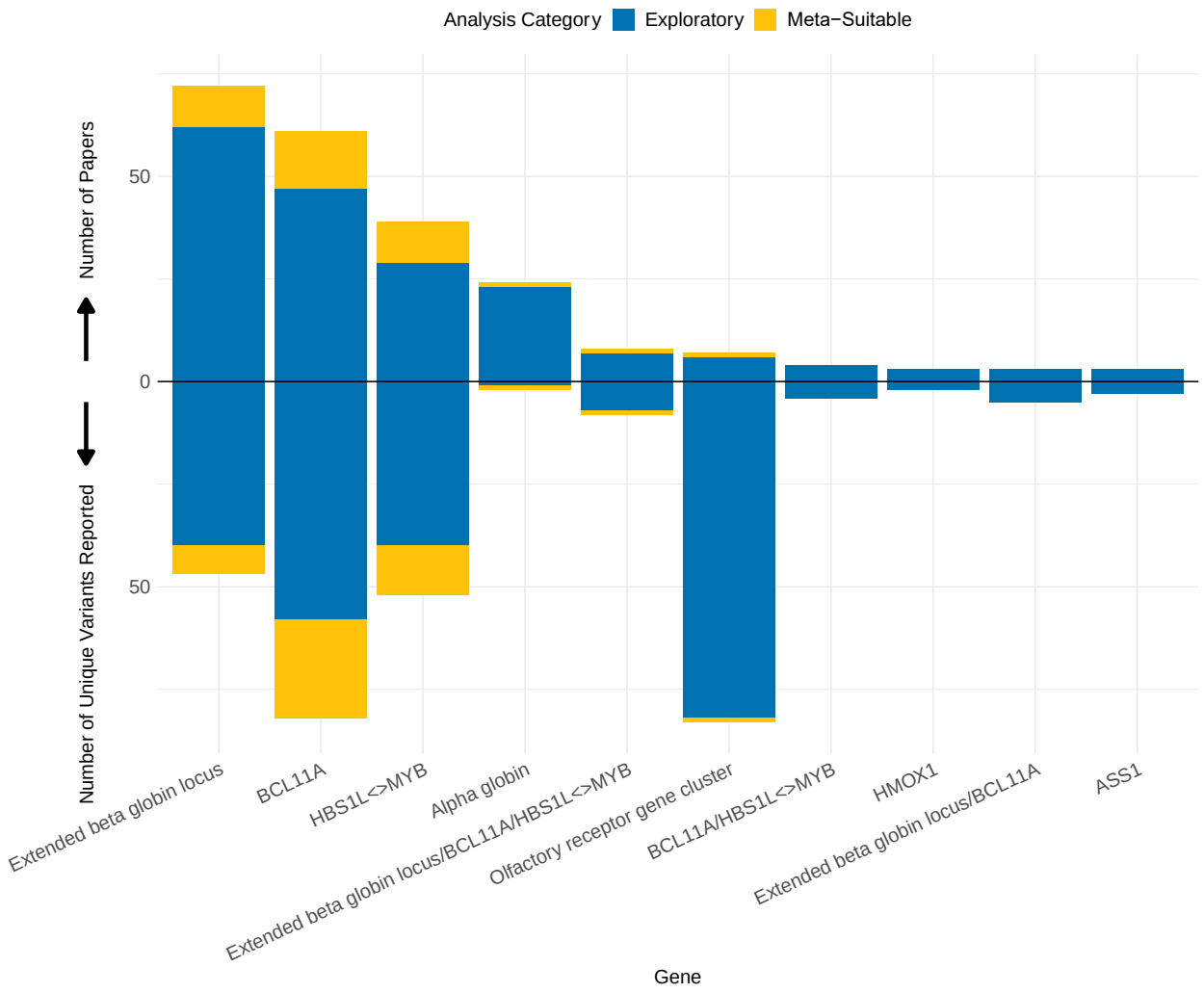
eFigure 1. **PRISMA Flow Diagram For Manuscript Identification, Screening, and Inclusion.** See eMethods for full search terms for each database.



eFigure 2. Map of Included Patient Cohort Locations by Number of Individuals. Countries in which sickle cell cohorts were studied in at least one manuscript included in this review are colored in purple, shaded by number of individuals. If the origin of the cohort was not reported in the manuscript, the corresponding author's institution is shown. Cohorts located in any region of the French Republic, including the overseas departments of French Guiana, Guadeloupe, Martinique, and Mayotte, were grouped with metropolitan France under the simplified heading of France and shaded if individuals were included from any. As many cohorts in the United States and Canada recruited patients from the other, the total patient count from these two countries were grouped.



eFigure 3. Data Strength Categories by Time. The total number of papers published within each year range are plotted in black. Papers publishing exploratory or meta-suitable/contemporary results are within each year range are plotted in blue and yellow, respectively. Papers reporting results for both categories were counted in each.



eFigure 4. Number of Papers Reporting Significant Associations With Fetal Hemoglobin (HbF) and Number of Unique Variants for Genes With Significant Results Reported in at Least Three Manuscripts. Papers reporting exploratory results are tabulated in blue, and those reporting meta-suitable results are tabulated in yellow. Similarly, results classified as exploratory and meta-suitable were tabulated in blue and yellow, respectively. Some papers report results of both categories and were counted in both, and some variants were classified as both categories and were counted in both. Gene names separated by arrows (“<>”) indicate SNPs in the intergenic region were associated with HbF, and gene names separated by a slash (“/”) indicate that both genes were implicated, as in a polygenic score.

eTable 4. **Phenotype Categories With Major Constituent Phenotypes**. Specific phenotypes within each category are shown if they were reported at least twice and not described in the category name. ACS, acute chest syndrome; HbF, fetal hemoglobin; CNS, central nervous system; TCD, transcranial doppler; MRI, magnetic resonance imaging; BMI, body mass index.

Phenotype Category	Specific phenotypes
Acute SCD-Related Complications	
Acute pain episode	Analgesic dosing, dactylitis, hand and foot syndrome, health care utilization, veno-occlusive crisis, other acute pain
ACS, pneumonia, respiratory infection	
Infection (excludes respiratory infections)	Bacteremia, bacterial infection, hepatitis C, malaria, meningitis, osteomyelitis, sepsis, urinary tract infection
Priapism	
Acute splenic sequestration	
Other acute phenotype	Age at presentation for acute complication, aplastic crisis, hospitalization for multiple or unspecified acute complications, thrombosis
Chronic SCD-Related Complications	
Allo- or autoantibody or transfusion reaction	
Cerebrovascular disease	Cerebrovascular accident (overt or silent), CNS bloodflow, CNS vasculopathy, TCD abnormality
Cardiopulmonary dysfunction	Cardiopulmonary complications, echocardiogram or cardiac MRI measurements, exercise tolerance tests, oxygen saturation, pulmonary hypertension
Kidney dysfunction	Blood urea nitrogen (BUN), chronic kidney disease (CKD), creatinine, cystatin C, end stage renal disease (ESRD), glomerular filtration rate (GFR), hyperfiltration, renal imaging measurements, urine studies
Hyperbilirubinemia, cholelithiasis, cholecystitis, or cholecystectomy	
Osteonecrosis	
Chronic pain	Composite pain index
Leg ulcers	
Iron overload	Iron chelation therapy, iron studies, liver iron content
Retinopathy	
Splenic dysfunction	Impaired splenic function, splenectomy, splenomegaly
Other chronic phenotype	BMI, bone age, diabetes, fertility and pregnancy outcome, height, hepatomegaly, osteoporosis, other chronic disease, vascular complication, vascular reactivity, weight
Hematologic Parameters and Biomarkers of Disease Severity	
HbF	F cells, gamma globin
Other hematologic parameter	Blood viscosity, complete blood counts, hemoglobin identification, hemorheology, leukocyte subsets, other red blood cell studies
Hemolysis	Aspartate aminotransferase (AST), lactate dehydrogenase (LDH), hemoglobinuria, hemolysis-associated complications, hemolysis score/index, hyperhemolysis, jaundice, red blood cell survival, reticulocyte count
Anemia	Anemia, erythropoietin level, hemoglobin, or transfusion history
Oxidative stress	Advanced oxidation protein products (AOPP), catalase (CAT), ferric reducing antioxidant power (FRAP), glutathione, malondialdehyde (MDA), myeloperoxidase (MPO), nitrate, nitrite, superoxide dismutase (SOD), thiobarbituric acid-reacting substances (TBARS), thiol, trolox equivalent antioxidant capacity (TEAC)
Other parameter or biomarker	Gene expression measurements, heart rate, serum electrolyte and protein concentrations, systemic blood pressure
General or Mixed Measurement of SCD Severity	Combination of acute and chronic complications, death, disease severity index, organ failure, total days in hospital

eTable 5. Number of Unique Patients and Studies by Country. Sample sizes were determined assuming the most overlap possible where not specifically excluded by the original authors' cohort description or otherwise determined to be distinct. This summation represents the fewest unique individuals that would satisfy the cohort sizes outlined in all reviewed publications (see **eMethods**). ND = Not determinable

Country	Total Unique Patients	Children	Studies Including Country's Patients
TOTAL	**29670**	**14970**	**571 (55 multinational)**
USA and Canada	9635	3728	166
Brazil	3397	1744	111
France	2445	1476	66
India	1631	1200	41
DRC	1356	361	5
Tanzania	1213	910	11
Nigeria	1202	539	13
Saudi Arabia	1194	330	28
United Kingdom	899	283	41
Cameroon	730	406	13
Bahrain	577	377	8
Egypt	508	358	24
Oman	495	495	6
Jamaica	407	356	26
Senegal	403	322	9
Tunisia	358	242	9
Netherlands	342	0	2
Portugal	296	252	7
Ghana	244	131	2
Kuwait	237	140	15
Angola	200	200	4
Sudan	166	33	1
Germany	164	131	1
Lebanon	163	25	2
Uganda	142	142	2
Benin	128	107	3
Iraq	128	64	1
Kenya	128	128	2
Congo	116	110	2
Yemen	102	102	2
Panama	100	100	2
Morocco	80	80	1
Greece	79	0	1
Cuba	65	ND	1
Colombia	60	ND	2
Italy	60	60	1
Sri Lanka	60	ND	1
Iran	52	14	2
Pakistan	41	ND	1
Turkey	31	0	1
Mexico	24	12	1
Mali	12	12	1

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