Supplemental Table 1. Characteristics of the entire analytic sample and by genotype severity, excluding those with a history of stroke (n=11).

	Entire analytic sample Mean (SD)* n=77	**"Severe" genotype Mean (SD)* n=47**	**"Moderate" genotype Mean (SD)* n=30**	**P-value†**
Age	36.1 (11.7)	33.1 (10.0)	40.8 (13.0)	0.01
Male sex*	27 (35.1%)	16 (34.0%)	11 (36.7%)	0.87
Education	13.1 (1.7)	13.0 (1.7)	13.2 (1.7)	0.76
Mild Cognitive Impairment*	12 (15.6%)	10 (21.3%)	2 (6.7%)	0.28
DSST T-score	47.9 (10.9)	45.1 (10.6)	52.1 (10.2)	0.01
O^2 Saturation	97.8 (1.8)	97.6 (1.8)	98.0 (1.7)	0.31
WBC count	9.4 (3.3)	9.6 (3.1)	9.1 (3.7)	0.90
Hemoglobin	10.1 (1.9)	9.2 (1.6)	11.5 (1.6)	<0.0001
Platelet count	311.8 (171.9)	345.8 (193.5)	259.7 (117.0)	0.22
Reticulocytes	1.5 (3.5)	1.7 (4.1)	1.2 (2.0)	0.49
LDH (IU/L)	299.5 (149.0)	314.7 (145.9)	274.1 (153.4)	0.40
Ferritin (ng/mL)	716.2 (1273.4)	877.2 (1356.4)	431.4 (1077.8)	0.10
Creatinine (mg/dL)	0.7 (0.2)	0.7 (0.3)	0.8 (0.2)	0.97
SBP (mm/Hg)	114.2 (13.6)	112.0 (13.9)	117.4 (12.6)	0.27
DBP (mm/Hg)	70.9 (8.9)	69.5 (8.8)	72.9 (9.8)	0.14
MAP (mm/Hg)	85.3 (9.4)	83.6 (8.8)	87.7 (9.7)	0.14
Hydroxyurea use*	38 (49.4%)	29 (61.7%)	9 (30.0%)	0.01
Opiate use*	24 (31.2%)	15 (31.9%)	9 (30.0%)	0.98
Transfusion history*	16 (20.8%)	11 (23.4%)	5 (17.2%)	0.63
Stroke history*	0 (0%)	0 (0%)	0 (0%)	N/A
SCI history	4 (5.2%)	3 (6.4%)	1 (3.3%)	0.65

DSST, digit symbol substitution test; WBC, white blood cell; LDH, lactate dehydrogenase; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SCI=silent cerebral infarct

* N(%) are reported.

† Age-adjusted p-value calculated with linear regression for continuous variables and logistic regression for categorical variables all variables; the models with age and standardized DSST T-score were unadjusted.

Supplemental Table 2. Association of genotype and DSST T-score, adjusted by factors that were associated with genotype severity, excluding participants with a history of stroke (n=11).

Covariates (X)	Model adjusted for X β (SE); p-value	VIF**
Unadjusted	-7.04 (2.44); 0.01	1.00
Hemoglobin	-6.27 (3.01); 0.05	1.51
Ferritin	-7.49 (2.49); 0.01	1.03
DBP	-7.36 (2.56); 0.01	1.04
MAP	-7.47 (2.57); 0.004	1.05
Hydroxyurea use	-7.04 (2.58);0.01	1.11
Fully adjusted*	-7.70 (3.57); 0.03	1.77

DSST, digit symbol substitution test; DBP, diastolic blood pressure; MAP, mean arterial pressure
The βs(SEs) and p values are for the variable “genotype” (severe vs. moderate-severe), for the model of “genotype” predicting standardized DSST score, adjusted for the covariate reported in the corresponding row of the table.
*Fully adjusted model includes genotype, hemoglobin, ferritin, DBP, MAP, hydroxyurea use and stroke/SCI history as predictors. **VIF=variance inflation factor of genotype in unadjusted and adjusted models.

Supplemental Table 3. Associations of genotype and DSST T-score, individually adjusted for covariates that were associated with genotype severity, among 72 participants with complete data on all covariates.

Covariates (X)	**Model adjusted for X** **β (p-value); R^2**	**VIF****
Unadjusted	-7.94 (2.88); 0.01	1.00
Hemoglobin	-7.44 (3.76); 0.05	1.68
Ferritin	-7.44 (3.03); 0.02	1.08
DBP	-8.60 (3.00); 0.01	1.08
MAP	-8.52 (3.01); 0.01	1.09
Hydroxyurea use	-8.18 (3.08); 0.01	1.13
Fully adjusted*	-8.15 (4.11); 0.05	1.93

DSST, digit symbol substitution test; DBP, diastolic blood pressure; MAP, mean arterial pressure The βs(SEs) and p values are for the variable "genotype" (severe vs. moderate-severe), for the model of "genotype" predicting standardized DSST score, adjusted for the covariate reported in the corresponding row of the table.

*Fully adjusted model includes genotype, hemoglobin, ferritin, DBP, MAP, hydroxyurea use and stroke/SCI history as predictors. **VIF=variance inflation factor of genotype in unadjusted and adjusted models.