

Trans-ethnic and ancestry-specific blood-cell genetics in 746,667 individuals from 5 global populations

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SUMMARY (148 words)

Most loci identified by GWAS have been found in populations of European ancestry (EA). In trans-ethnic meta-analyses for 15 hematological traits in 746,667 participants, including 184,535 non-EA individuals, we identified 5,552 trait-variant associations at $P < 5 \times 10^{-9}$, including 71 novel loci not found in EA populations. We also identified novel ancestry-specific variants not found in EA, including an *IL7* missense variant in South Asians associated with lymphocyte count *in vivo* and IL7 secretion levels *in vitro*. Fine-mapping prioritized variants annotated as functional, and generated 95% credible sets that were 30% smaller when using the trans-ethnic as opposed to the EA-only results. We explored the clinical significance and predictive value of trans-ethnic variants in multiple populations, and compared genetic architecture and the impact of natural selection on these blood phenotypes between populations. Altogether, our results for hematological traits highlight the value of a more global representation of populations in genetic studies.

INTRODUCTION

Blood-cell counts and indices are quantitative clinical laboratory measures that reflect hematopoietic progenitor cell production, hemoglobin synthesis, maturation and release from the bone marrow, and clearance of mature or senescent blood cells from the circulation. Quantitative red blood cell (RBC), white blood cell (WBC) and platelet (PLT) traits exhibit strong heritability ($h^2 \sim 30-80\%$) (Evans et al., 1999; Hinckley et al., 2013) and have been the subject of various genome-wide association studies (GWAS), including a large study that identified >1000 genomic loci in ~150,000 individuals of European-ancestry (EA) (Astle et al., 2016).

Importantly, the distribution of hematologic traits and prevalence of inherited hematologic conditions differs by ethnicity. For example, the prevalence of anemia and microcytosis is higher among African-ancestry (AFR) individuals compared to EA individuals in part due to the presence of globin gene mutations (e.g. sickle cell, α/β -thalassemia) more common among African, Mediterranean and Asian populations (Beutler and West, 2005; Raffield et al., 2018; Rana et al., 1993). AFR individuals tend to have lower WBC and neutrophil counts partly because of the Duffy/*DARC* null variant (Rappoport et al., 2019). Among Hispanics/Latinos (HA), a common Native American functional intronic variant of *ACTN1* is associated with lower PLT count (Schick et al., 2016).

Despite these observations, non-EA populations have been severely under-represented in most blood-cell genetic studies to date (Popejoy and Fullerton, 2016; Popejoy et al., 2018; Wojcik et al., 2019). Multiethnic GWAS have been recognized as more powerful for gene mapping due to ancestry-specific differences in allele frequency, linkage disequilibrium (LD), and effect size of

causal variants (Li and Keating, 2014). Since blood cells play a key role in pathogen invasion, defense and inflammatory responses, hematologic-associated genetic loci are particularly predisposed to be differentiated across ancestral populations as a result of population history and local evolutionary selective pressures (Ding et al., 2013; Lo et al., 2011; Raj et al., 2013). Given the essential role of blood cells in tissue oxygen delivery, inflammatory responses, atherosclerosis, and thrombosis (Byrnes and Wolberg, 2017; Chu et al., 2010; Colin et al., 2014; Tajuddin et al., 2016), factors that contribute to such inter-population differences in blood-cell traits may also play appreciable roles in the pathogenesis of chronic diseases and health disparities between populations.

RESULTS

Trans-ethnic and ancestry-specific blood-cell traits genetic associations

We analyzed genotype-phenotype associations at up to 45 million autosomal variants in 746,667 participants, including 184,424 individuals of non-EA descent, for 15 traits (**Figure 1**, **Supplementary Tables 1-4**, and **Methods**). The association results of the EA-specific meta-analyses are reported separately in a companion paper. In the trans-ethnic meta-analyses, we identified 5,552 trait-variant associations at $P < 5 \times 10^{-9}$, which include 71 novel associations not reported in the EA-specific manuscript (**Supplementary Table 5**). Of the 5,552 trans-ethnic loci, 128 showed strong evidence of allelic effect heterogeneity across populations ($P_{\text{ancestry.hetero}} < 5 \times 10^{-9}$) (**Supplementary Figure 1** and **Supplementary Table 5**). Ancestry-specific meta-analyses revealed 28 novel trait-variant associations (**Figure 1** and **Supplementary Tables 6-10**). However, 19 out of these 21 novel AFR-specific associations map to chromosome 1 and are associated with WBC or neutrophil counts, therefore reflecting long-range associations due to the admixture signal at the Duffy/*DARC* locus (Reich et al., 2009). We attempted to replicate all novel trans-ethnic or ancestry-specific genetic associations in the Million Veteran Program (MVP) cohort (Gaziano et al., 2016). Of the 89 variant-trait associations that we could test in MVP, 86 had a consistent direction of effect (binomial $P = 6 \times 10^{-24}$), 72 had an association $P < 0.05$ (binomial $P = 8 \times 10^{-79}$), and 44 met the Bonferroni-adjusted significance threshold of $P < 6 \times 10^{-4}$ (**Supplementary Table 11**).

For 3,552 loci with evidence of a single association signal based on conditional analyses in EA (**Supplementary Methods**), we generated fine-mapping results for each trans-ethnic or ancestry-specific dataset using an approximate Bayesian approach (**Methods**)(Wellcome Trust Case

Control et al., 2012). The 95% credible sets were smaller in the trans-ethnic meta-analyses than in the EA or EAS meta-analyses (**Figure 2A**), indicating improved resolution owing to both increased sample size and different LD patterns. When comparing loci discovered in both the trans and EA analyses, we found that the 95% credible sets were 30% smaller among the trans results (median (interquartile range) number of variants per 95% credible set was 4 (2-13) in trans vs. 5 (2-16) in EA, Wilcoxon's $P=3 \times 10^{-4}$). For instance, a locus on chromosome 9 associated with PLT counts included seven variants in the EA 95% credible set but only one in the trans set, an increase in fine-mapping resolution likely driven by limited LD at the locus in EAS (**Figure 2B**). In the trans and EA results, respectively, we identified 433 and 403 loci with a single variant in the 95% credible sets (**Figure 2C**).

Next, we assessed our fine-mapped 95% credible sets for the presence of functional variants, which we defined as variants with coding consequences or those mapping to hematopoietic accessible chromatin. Genomic annotation of the 95% credible sets of the trans, EA and EAS hematological trait-associated loci revealed that the proportion of likely functional variants was higher among those with high PPI (**Figure 2D**). The enrichment within high-PPI categories was particularly notable for missense variants, but also observed for intronic and intergenic variants that map to open chromatin regions in precursor or mature blood cells (**Figure 2D**)(Corces et al., 2016). We used g-chromVAR to quantify the enrichment of trans, EA and EAS 95% credible set variants within regions of accessible chromatin identified by ATAC-seq in 18 hematopoietic populations (Corces et al., 2016; Ulirsch et al., 2019). We noted 22 significant trait-cell type enrichments using the trans-ethnic credible sets, all of which were lineage specific, including RBC traits in erythroid progenitors, platelet traits in megakaryocytes, and monocyte count in granulocyte-macrophage

progenitors (GMP) (**Figure 2E** and **Supplementary Table 12**). Cell-type enrichments were largely consistent between fine-mapped traits found in the trans, EA and EAS loci. However, we observed two noteworthy ancestry-specific differences: the EAS results revealed significant enrichments in basophil count for the common myeloid progenitor (CMP) population and eosinophil count for the GMP population, but neither pairing reached significance in the larger EA meta-analyses (**Supplementary Figure 2**). These differences persisted even after controlling for the number of loci tested in each ancestry. This is further supported by our finding that the genetic correlations for these two traits between EA and EAS are the lowest among all studied blood phenotypes (see below).

Phenome-wide association studies (pheWAS)

When we queried the 5,552 trans-ethnic genome-wide significant variants associated with blood-cell traits in three distinct biobanks (EA individuals from UK Biobank (UKBB), Japaneses from Biobank Japan (BBJ), African Americans from BioVU (BioVU)), we identified 1,140 phenotype-variant associations (**Supplementary Table 13**). These include 106 variants in BBJ, four variants in BioVU, and 222 variants in the UKBB. Of the four variants significant in BioVU, three were located at the β -globin locus and reflect the known clinical sequelae of sickle cell disease. Of the 1,140 associations, 246 were shared across at least two biobanks (**Methods**). Many of the associations shared between BBJ and the UKBB were related to dyslipidemia and cardiovascular diseases (**Supplementary Table 13**). Because of the large differences in sample sizes between the three biobanks (**Methods**), we reasoned that lack of power was the likely explanation for why associations were not shared across biobanks. However, it appears that differences in allele

frequencies across the three primary ancestries also played a role. Overall, unique associations had greater differences in allele frequencies than shared associations (**Supplementary Figure 3**).

Trans-ethnic predictions of hematological traits

Polygenic trait scores (PTS) developed in a single ethnically homogeneous population tend to underperform when tested in a different population (Grinde et al., 2019; Marquez-Luna et al., 2017; Martin et al., 2019). We explored whether we could combine the genome-wide significant trans-ethnic variants identified in our analyses into PTS that can predict blood-cell traits in a multi-ethnic setting. First, we used trans-ethnic effect sizes as weights to compute PTS_{trans} for each trait, and tested their performance in independent EA, AFR and HA participants from the BioMe Biobank (**Methods**). As expected because our trans-ethnic meta-analyses are dominated by EA individuals, PTS_{trans} were more predictive in EA, although their performance in HA was comparable for several traits (lymphocyte and monocyte counts, mean PLT volume)(**Supplementary Figure 4A** and **Supplementary Table 14**). Moreover, for neutrophil and WBC counts, the variance explained by the PTS_{trans} was up to three times higher in AFR and HA than in EA samples due to the inclusion of the strong Duffy/*DARC* locus (**Supplementary Figure 4A**). Because these Duffy/*DARC* variants would not have been included in PTS derived uniquely from EA association results, this illustrates an interesting feature of using trans-ethnic variants for building polygenic predictors. Next, we asked if we could increase the variance explained by calculating PTS using the same trans-ethnic variants but weighting them using ancestry-specific as opposed to trans-ethnic effect sizes. PTS_{trans} outperformed ancestry-specific PTS_{AFR} and PTS_{HA} in BioMe AFR and HA participants, respectively (**Supplementary Figure 4B-C** and **Supplementary Table 14**). This result likely indicates that the discovery sample size for

these two populations is still too small to provide robust estimates of the true population-specific effect sizes.

Rare coding blood-cell-traits-associated variants

The identification of rare coding variants has successfully pinpointed candidate genes for many complex traits, including blood-cell phenotypes (Auer et al., 2014; Chami et al., 2016; Eicher et al., 2016; Justice et al., 2019; Marouli et al., 2017; Mousas et al., 2017; Tajuddin et al., 2016). Our trans-ethnic and non-EA ancestry-specific meta-analyses yielded 16 coding variants with minor allele frequency (MAF) <1% (**Table 1** and **Supplementary Table 15**). This list includes variants of clinical significance (variants in *TUBB1*, *GFI1B*, *HBB*, *MPL* and *SH2B3*) and variants that nominate candidate genes within GWAS loci (*ABCA7*, *GMPR*) (**Table 1**). Our analyses also retrieved a known missense variant in *EGLN1* (rs186996510) that is associated with high-altitude adaptation and hemoglobin levels in Tibetans (Lorenzo et al., 2014; Xiang et al., 2013). We noted a missense variant in *IL7* (rs201412253, Val18Ile) associated with increased lymphocyte count in South Asians (SAS) ($P=4.4 \times 10^{-10}$) (**Figure 3A** and **Supplementary Table 16**). This variant is low-frequency in SAS (MAF=2.6%) but rare in other populations (MAF <0.4%). *IL7* encodes interleukin-7, a cytokine essential for B- and T-cell lymphopoiesis (Lin et al., 2017). *IL7* is synthesized as a proprotein that is cleaved prior to secretion, and the *IL7*-Val18Ile variant localizes to the *IL7* signal peptide comprising the first 25 amino acids. To determine if this variant alters *IL7* secretion, we engineered HEK293 cells with either *IL7* allele (**Methods**). Although there was no difference in *IL7* RNA expression levels (*t*-test $P=0.63$), we found that the *IL7*-18Ile allele, which associates with higher lymphocyte counts in SAS individuals, significantly increased *IL7* protein secretion in this heterologous cellular system (+83%, $P=2.7 \times 10^{-5}$) (**Figure 3B**).

Unfortunately, the relatively small sample size of the SAS cohort prevented us from testing whether this *IL7* variant may be associated with other relevant phenotypes, such as cancer risk or susceptibility to infections (Lin et al., 2017).

Genetic architecture of blood-cell traits in EA and EAS populations

We used several different approaches to quantify similarities and differences in genetic architecture of hematologic traits across populations. Focusing on the two largest studied populations, EA and EAS, we calculated heritability for all blood traits and found them to be highly concordant between ancestries (Pearson's $r=0.75$, $P=0.0033$)(**Supplementary Table 17**)(Bulik-Sullivan et al., 2015b). Likewise, within-ancestry genetic correlation coefficients (r_g) between pairs of hematological traits were highly concordant across ancestries (Pearson's $r=0.97$, $P<2.2\times 10^{-16}$)(**Supplementary Figure 5**)(Bulik-Sullivan et al., 2015a). We then used the Popcorn method to directly measure genetic correlations for blood-cell traits between EA and EAS using summary statistics for common variants (Brown et al., 2016). For all 13 traits available in both EA and EAS, genetic correlations were high (lowest for basophils ($r_g=0.30$) and highest for MCH ($r_g=0.66$)), but significantly different than 1 ($P<3\times 10^{-6}$)(**Supplementary Table 18**). This suggests that even when considering only common variants, the genetic architecture of blood phenotypes is substantially different between populations.

Natural selection at blood-cell trait loci

Natural selection can account for differences in association results between populations, as highlighted by our analyses of rare coding variants which includes several loci known to be under selection (*CD36*, *HBB*, *EGLN1*)(**Table 1**). To further explore this possibility, we assessed whether

variants that tag selective sweeps (tagSweeps, variants with the highest integrated haplotype score (iHS)) within continental populations from the 1000 Genomes Project (1000G) are associated with blood-cell phenotypes (Johnson and Voight, 2018). We found a genome-wide enrichment of associations results between tagSweeps and hematological traits, particularly within EA, EAS and AFR populations (**Supplementary Figure 6** and **Supplementary Table 19**). To rule out simple overlaps due to the large number of sweeps and blood-cell trait loci, we compared the number of genome-wide significant tagSweeps in EA, EAS and AFR with the number of significant variants among 100 sets of matched variants (**Methods**). We found significant enrichment of selective sweeps for WBC (EA, EAS, AFR), monocytes (EA, AFR), eosinophils (EA), neutrophils (AFR), lymphocytes (EAS), and PLT (EA, EAS)(**Supplementary Table 20**).

In AFR and HA, the enrichments for WBC, neutrophils and monocytes were entirely driven by selective sweeps on chromosome 1 near Duffy/*DARC* (Reich et al., 2009). Only three additional loci shared evidence of associations with blood-cell traits and positive selection across populations: HLA, *SH2B3* (Zhernakova et al., 2010) and *CYP3A5* (Chen et al., 2009). We found eight and 100 non-overlapping selective sweeps with variants associated with hematological traits in EAS and EA, respectively (**Supplementary Table 21**). Six of the eight EAS-specific tagSweeps are also associated with blood-cell traits in EA participants, indicating that these regions do not account for population differences in hematological trait regulation (**Supplementary Table 21**). One of the remaining two variants is located at the *HBS1L-MYB* locus and, although it is not associated with blood-cell traits in EA, there are many other variants near *MYB* associated with blood phenotypes in EA (**Supplementary Table 6**). The remaining selective sweep highlighted by this analysis is located upstream of *IL6* (**Figure 4**). The tagSweep at this locus, rs2188580, is

strongly associated with PLT count in EAS ($P_{\text{EAS}}=2.8 \times 10^{-9}$, $P_{\text{EA}}=0.0022$), is differentiated between EAS and EA as indicated by the population branch statistic (PBS)(Yi et al., 2010)(C-allele frequency in EAS=44%, 4% in EA; standardized $\text{PBS}_{\text{EAS}}=7.353$), and overlaps selective sweeps identified in several EAS populations from the 1000G (e.g. $\text{iHS}_{\text{CHS}}=3.935$)(**Figure 4**). The *IL6* locus has previously been associated with WBC traits in EA (Astle et al., 2016), but our finding is the first report of its association with PLT. *IL6* encodes interleukin-6, a cytokine that is a maturation factor for megakaryocytes, the precursors of PLT (Kimura et al., 1990). Further supporting the role of IL6 signaling in PLT biology, a well-characterized missense variant in the IL6 receptor gene (*IL6R*-rs2228145)(van Dongen et al., 2014) is also associated with PLT count in EAS ($P=4.3 \times 10^{-6}$).

DISCUSSION

Our meta-analyses of 15 hematological traits in up to 746,667 individuals represents one of the largest genetic study of clinically relevant complex human traits across diverse ancestral groups. We have continued to expand the repertoire of loci and genes that contribute to interindividual variation in blood-cell traits, with potential implications for hematological diseases, but also other conditions such as cancer, immune and cardiovascular diseases. Our results hold a number of implications for future human genetic studies. First, we showed that adding even a “modest” number of non-EA participants to GWAS can yield important biology, such as the identification of a lymphocyte count-associated *IL7* missense variants in 8,189 South Asians (**Figure 3**). Second, loci that underlie variation in blood-cell traits represent a broad mixture of shared associations (i.e. similar allele frequencies and effect sizes across populations) and heterogeneous associations (i.e. dissimilar allele frequencies and effect sizes across populations). This result contributes to mounting evidence that a full accounting of the genetic basis of complex human traits will require a thorough catalog of global genetic and phenotypic variation. Third, because of heterogeneity across populations in both allele frequencies and patterns of LD, fine-mapping of association signals can be substantially aided by including multiple ancestries. This will have a dramatic impact on the success of large-scale efforts aimed at functionally characterizing GWAS findings. As more studies seek to unravel the causal variants that underlie complex traits associations, we anticipate that genetic evidence from diverse ancestries will play an important role.

SUPPLEMENTARY INFORMATION

Supplementary Information is linked to the online version of the paper.

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275

276 *Fine-mapping and functional annotation*

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280 *pheWAS, polygenic prediction, genetic architecture and natural selection*

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284 *Functional characterization of IL7*

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288 Summary genetic association, fine-mapping and g-chromVAR results are available online:
289 <http://www.mhi-humangenetics.org/en/resources>. Competing financial interests are declared in the

290 **Supplementary Information.** Correspondence and requests should be addressed to P.L.A
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Figure legends

Figure 1. Trans-ethnic and ancestry-specific meta-analyses of blood-cell traits. **(a)** Study design of the project. We used a fixed-effect meta-analysis strategy to analyze genetic associations within each of the five populations available, and a mega-regression approach that considers allele frequency heterogeneity for the trans-ethnic association tests. **(b)** Most blood-cell trait-associated loci physically overlap between populations. Despite different sample sizes between populations, we note that few loci are found in a single population, suggesting shared genetic architecture.

Figure 2. Fine-mapping of loci associated with hematological traits highlights likely functional variants. **(a)** We restricted fine-mapping to loci with evidence for a single association signal in European-ancestry (EA) populations. There are no such loci in Hispanic Americans. The 95% credible sets in the trans-ethnic meta-analyses are smaller than in the EA or East-Asian-ancestry (EAS) meta-analyses. **(b)** Trans-ethnic fine-mapping of a platelet locus. In EA individuals, the 95% credible set include 7 variants with posterior probability of inclusion (PPI) >0.04 and strong pairwise linkage disequilibrium (LD) with the sentinel variants rs10758481 ($r^2 > 0.93$ in GBR from 1000 Genomes Project, middle panel). LD is similarly strong in African-, Hispanic/South American-, and South-Asian-ancestry populations from the 1000 Genomes Project. However, LD is weaker in East Asians ($r^2 = 0.68$ in JPT from 1000 Genomes Project, bottom panel). In the trans-ethnic meta-analysis, rs10758481 has a PPI >0.99 (top panel). In EA and EAS, LD is color-coded based on pairwise r^2 with rs10758481. The dotted line indicates the genome-wide significance threshold ($P < 5 \times 10^{-9}$). **(c)** Number of variants in 95% credible sets in each population analyzed. In trans, EA and EAS, we identified 433, 403 and seven 95% credible sets with a single variant. **(d)** Annotation of variants in trans, EA and EAS shows a similar pattern, with a larger proportion of

likely functional variants (e.g. missense, intergenic and intronic variants within ATAC-seq peaks) among variants with higher posterior probability of inclusion (PPI). (e) g-chromVAR results for trans variants within 95% credible sets for 15 traits. The Bonferroni-adjusted significance level (corrected for 15 traits and 18 cell types) is indicated by the dotted line. mono, monocyte; gran, granulocyte; ery, erythroid; mega, megakaryocyte; CD4, CD4+ T cell; CD8, CD8+ T cell; B, B cell; NK, natural killer cell; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; MPP, multipotent progenitor; LMPP, lymphoid-primed multipotent progenitor; CMP, common myeloid progenitor; CLP, common lymphoid progenitor; GMP, granulocyte–macrophage progenitor; MEP, megakaryocyte–erythroid progenitor.

Figure 3. A South-Asian-ancestry *IL7* missense variant associates with increased lymphocyte count in humans and *IL7* secretion in an heterologous cellular system. (a) Lymphocyte count association results at the *IL7* locus in South Asians (SAS), European-ancestry participants (EA) and East Asians (EAS). In SAS, there are 7 genome-wide significant variants near *IL7*, but only rs201412253 is coding. Linkage disequilibrium (LD) r^2 is from 1000 Genomes Project SAS populations. In EA, the sentinel variant is located downstream of *IL7*; rs201412253 is rare (minor allele frequency= 4×10^{-4}) and not significant ($P=0.073$). In EAS, the locus is not associated with lymphocyte count. rs201412253 is monomorphic in 1000 Genomes Project EA and EAS so we could not calculate pairwise LD. (b) The 18Ile allele at *IL7*-rs201412253 increases *IL7* secretion in a heterologous cellular system. Our ELISA assay did not detect secreted *IL7* in clones generated with an empty vector. We tested eight independent clones for each *IL7* alleles. Each experiment was done in duplicate, and we performed the experiments three times (grey circles). The black

dots and vertical lines indicate means and standard deviations. We assess statistical significance by linear regression correcting for experimental batch effects.

Figure 4. Selective sweep and association with platelet count at the *IL6* locus in East Asians. The grey rectangle highlights a genomic region upstream of *IL6* that is strongly associated with platelet (PLT) count. This association signal is driven by results from East Asians (EAS), and is absent from other populations, including European- (EA) and African-ancestry (AFR) individuals (green). The region overlaps several selective sweeps detected in EAS from the 1000 Genomes Project (CDX, CHS, JPT, KHV). In orange, we provide standardized population branch site (stdPBS) metrics in EA and EAS, indicative of allele frequency differentiation at this locus between these two populations.

METHODS

Study design and participants

All participants provided written informed consent and the project was approved by each institution's ethical committee. **Supplementary Table 1** lists all participating cohorts. The SNPs we identified are available from the NCBI dbSNP database of short genetic variations (<https://www.ncbi.nlm.nih.gov/projects/SNP/>). No statistical methods were used to predetermine sample size. The experiments were not randomized and the investigators were not blinded to allocation during experiments and outcome assessment.

Phenotypes

Complete blood count (CBC) and related blood indices were analyzed as quantitative traits. The descriptive statistics for each phenotype in each cohort analyzed are in **Supplementary Table 2**. Exclusion criteria and phenotype modeling in the UK Biobank (UKBB)(European-ancestry individuals), INTERVAL, and Biobank Japan (BBJ) have been described previously (Astle et al., 2016; Kanai et al., 2018). For all other studies, we followed the protocol developed by the Blood-Cell Consortium (Chami et al., 2016; Eicher et al., 2016; Tajuddin et al., 2016). Briefly, we excluded when possible participants with blood cancer, acute medical/surgical illness, myelodysplastic syndrome, bone marrow transplant, congenital/hereditary anemia, HIV, end-stage kidney disease, splenectomy, and cirrhosis, as well as pregnant women and those undergoing chemotherapy or erythropoietin treatment. We also excluded extreme blood-cell measures: $WBC > 200 \times 10^9$ cells/L, $HGB > 20$ g/dL, $HCT > 60\%$, and $PLT > 1000 \times 10^9$ cells/L. For WBC subtypes, we analyzed $\log_{10}$ -transformed absolute counts obtained by multiplying relative counts with total WBC count. For all phenotypes in all studies, we corrected the blood-cell phenotypes

for sex, age, age-squared, the 10 first genetic principal components, and other cohort-specific covariates (e.g. recruitment center) using linear regression analysis. We applied rank-based inverse normal transformation to the residuals from the regression analysis and used the normalized residuals to test for association with genetic variants.

Genotype quality-control and imputation

The genotyping array and quality-control steps used by each cohort as well as their quality-control steps are listed in **Supplementary Table 3**. Unless otherwise specified, all studies applied the following criteria: samples were removed if the genotyping call rate was <95%, if they showed excess heterozygosity, if we identified gender mismatches or sample duplicates, or if they appeared as population outliers in principal component analyses nested with continental populations from the 1000 Genomes Project (Genomes Project et al., 2012). We removed monomorphic variants, as well as variants with Hardy-Weinberg $P < 1 \times 10^{-6}$ and call rate <98%.

Genotype imputation for the UKBB, INTERVAL, and BBJ have been described in details elsewhere (Astle et al., 2016; Bycroft et al., 2018; Kanai et al., 2018). For all other studies, unless specified in **Supplementary Table 3**, we applied the following steps for genotype imputation of autosomal variants. We aligned all alleles on the forward strand of build 37/hg19 of the human reference genome (<http://www.well.ox.ac.uk/~wrayner/strand>) and converted files into the VCF format. We then applied checkVCF (<http://genome.sph.umich.edu/wiki/CheckVCF.py>) to confirm strand and allele orientation. We carried out genotype imputation using the University of Michigan (<https://imputationserver.sph.umich.edu>) or the Sanger Institute (<https://imputation.sanger.ac.uk/>) imputation servers. We phased genotype data using SHAPEIT (Delaneau et al., 2013), EAGLE

(Loh et al., 2016), or HAPI-UR (Williams et al., 2012). For populations of European ancestry, we used reference haplotypes from the Haplotype Reference Consortium (HRC r1.1 2016) for imputation (McCarthy et al., 2016), whereas reference haplotypes from the 1000 Genomes Project (Phase 3, Version 5)(Genomes Project et al., 2012) were used for non-European ancestry participants.

Study-level statistical analyses

We tested an additive genetic model of association between genotype imputation doses and inverse normal transformed blood-cell phenotypes. We analyzed the major ancestry groups (European (EA), East Asian (EAS), African (AFR), Hispanic-Latino (HL), South Asian (SAS)) separately and used linear mixed-effect models implemented in BOLT-LMM (Loh et al., 2018), EPACTS (<https://genome.sph.umich.edu/wiki/EPACTS>), or EMMAX (Kang et al., 2010) to account for cryptic and known relatedness. Autosomal single nucleotide variants were analyzed in all contributing studies. For simplicity, we only analyzed insertion-deletion (indel) variants from UKBB and INTERVAL, since a similar reference panel was used for genotype imputation.

Centralized quality-control and meta-analyses

We performed a centralized quality-control check on the association results of each single study using EasyQC (v9.0)(Winkler et al., 2014). By mapping variants of each study to the appropriate ethnicity reference panel (HRC for EA and 1000 Genomes Project Phase3 for non-EA participants), we were able to harmonize alleles and markers across all studies. We were also able to assess the presence of flipped alleles per study and check for excessive allele frequency discrepancies using allele frequency reference data. We also inspected quantile-quantile (QQ)

plots generated by EasyQC and the corresponding genomic inflation factors as well as SE-N plots (inverse of the median standard error vs. the square root of the sample size) to evaluate potential issues with, for example, trait transformation or unaccounted relatedness. We removed variants with imputation quality metric (INFO score) ≤ 0.4 . Except for three studies, we also removed variants with minor allele count (MAC) ≤ 5 . For UKBB EA, Women Health Initiative (WHI), and GERA (EA), we instead applied a MAC ≤ 20 filter because empirical observations suggested that unusual inflation of the test statistics (i.e. extreme effect sizes and standard errors) was due to rarer variants. To simplify handling of tri-allelic and indel variants, which have the same genomic coordinates but different alleles, we created a unique variant ID for each tested variant. Specifically, we assigned a chromosome:position(hg19)_allele1_allele2 unique ID to each variant, in which the order of the allele in the ID was based on the lexicographical order or the indel length. We performed inverse variance-weighted fixed-effect meta-analyses with GWAMA (v2.2.2)(Magi and Morris, 2010) and trans-ethnic meta-analyses with MR-MEGA (v0.1.5)(Magi et al., 2017). For MR-MEGA, we calculated four axes of genetic variation, the default recommendation, to separate global population groups.

Statistical significance, genomic inflation and locus definition

For each meta-analysis, we calculated the genomic inflation factor (λ_{GC}) for all variants, which were modest when considering the large sample sizes (λ_{GC} range: 0.9-1.2) (**Supplementary Table 4**). We used $\alpha \leq 5 \times 10^{-9}$ after GC-correction to declare statistical significance, accounting for the inflation of the test statistics and the number of blood-cell traits analyzed. To count the number of loci that we discovered, we first identified the most significant variants (with $P \leq 5 \times 10^{-9}$) and extended the physical region around that variant 250-kb on each side. Overlapping loci were

merged, and we used the most significant variant within the interval as the sentinel variant. In this manuscript, we defined as novel a locus if no variants were previously reported in the literature to be associated with the specific blood-cell trait and if the locus is not reported in the companion manuscript that focuses on EA-specific genetic discoveries.

Million Veteran Program (MVP) blood-cell trait analyses for replication

Phenotyping. Phenotyping methods published by the EMERGE Consortium and available on PheKB (<https://phekb.org/>) were used for retrieving lab data and exclusion criteria for all blood cell indices. This information was pulled from the VA electronic medical records for all MVP participants. Lab data was subject to the Boston Lab Adjudication Protocol. This entails five steps: (i) compile an initial spreadsheet of possible relevant lab tests, (ii) Subject Matter Expert (SME) does an initial review of possible tests, (iii) analyst adds relevant LOINC codes for SME review, (iv) second Subject Matter Expert (SME) review, (v) creation of a Lab Phenotype Table/Data Set. After restricting to only outpatient labs and applying the EMERGE exclusion criteria, for each trait and each person, the minimum, maximum, mean, median, SD, and number of labs was recorded. Values were compared to those from UKBB (Astle et al., 2016).

Genotyping. DNA extracted from whole blood was genotyped using a customized Affymetrix Axiom biobank array, the MVP 1.0 Genotyping Array. With 723,305 total DNA sequence variants, the array is enriched for both common and rare variants of clinical importance in different ethnic backgrounds (Klarin et al., 2018).

Analysis. The median lab value was the trait used for analysis. Linear regression models were run under an additive model in plink2 on 1000G (v3p5) imputed dosages. Analyses were run using models described above within each race/ethnicity stratum (AFR, ASN, EA, HA) classified based on their genotype data using HARE (Fang et al., 2019). Meta-analyses for the trans-ethnic analyses were completed in METAL (Willer et al., 2010).

Heritabilities and genetic correlations

We calculated heritabilities and genetic correlations between blood-cell traits within the EA and EAS populations using default parameters implemented in the LD score regression method (**Supplementary Table 17** and **Supplementary Figure 5**)(Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). For genetic correlation of the same phenotype between ancestral populations, we used Popcorn (Brown et al., 2016). Briefly, Popcorn uses a Bayesian framework to estimate, using genome-wide summary statistics, the genetic correlation of the same phenotype but in two different populations (in our case, between EA and EAS). It reports the trans-ethnic genetic-effect correlation (ρ_{ge}), i.e. the correlation coefficient of per-allele SNP effect sizes, but also the trans-ethnic genetic impact correlation (ρ_{gi}), which includes a normalization of the effect based on allele frequency (**Supplementary Table 18**). To address whether a difference in the sample size for the EA and EAS meta-analyses could impact the Popcorn results, we repeated our analyses using the current EAS results ($N_{max}=151,807$) and EA results from preliminary analyses of the UKBB dataset ($N_{max}=87,265$)(Astle et al., 2016). These analyses confirmed that for common variants, cross-ancestry EA-EAS genetic correlations are significantly different (but non-null). Both LD score regression and Popcorn are not amenable to admixed populations, and cannot

handle rare variants. For these reasons, we limited these analyses to the large EA and EAS populations and focused on common variants from the 1000 Genomes Project.

Statistical fine-mapping

No fine-mapping methods currently exist to handle admixed populations. Furthermore, for some of the ethnic groups analyzed here, we did not have access to a sufficiently large reference panel to properly account for LD, complicating conditional analyses and fine-mapping efforts. For these reasons, we fine-mapped the ancestry-specific fixed-effect meta-analyses by adapting the method proposed by Maller et al. (Wellcome Trust Case Control et al., 2012) in order to assign posterior probability of inclusion (PPI) to each variant and construct 95% credible sets.

This method makes the strong assumption that there is a single independent causal variant at the tested locus. For this reason, we limited our Bayesian fine-mapping to loci where we identified a single independent association signal by conditional analysis in EA individuals from the UKBB (Supplementary Methods). Because EA represented the largest group, we then inferred that there was also a single association signal in the other populations at these loci, an inference that may not always be right. Briefly, we added 250-kb on either side of genome-wide significant variants ($P < 5 \times 10^{-9}$) and merged loci when they overlapped. For the loci identified in the ancestry-specific meta-analyses, we converted P-values into approximate Bayes factors (aBF) using (Wakefield, 2009; Wellcome Trust Case Control et al., 2012):

$$aBF = \sqrt{\frac{SE^2}{SE^2 + \omega}} \exp \left[\frac{\omega \beta^2}{2SE^2(SE^2 + \omega)} \right]$$

where β and SE are the variant's effect size and standard error, respectively, and ω denotes the prior variance in allelic effects, taken here to be 0.04 (Wakefield, 2007). For the trans-ethnic results, we directly used Bayes factors calculated by MR-MEGA (Magi et al., 2017). We calculated PPI of each variant by dividing the variant's aBF by the sum of the aBF for all the variants within the locus. We generated the 95% credible sets by ordering all variants in a given locus from the largest to the smallest PPI and by including variants until the cumulative sum of the PPI $\geq 95\%$ (Mahajan et al., 2018). All variants that map to 95% credible sets are available online (see URL).

Functional annotation

To derive basic functional annotation information, we annotated all variants included in 95% credible sets from ancestry-specific and trans-ethnic meta-analyses with the Variant Effect Predictor (VEP) (<https://useast.ensembl.org/info/docs/tools/vep/index.html>), compiling both all consequences and the most severe consequence for Ensembl/GENCODE transcripts. We also specifically annotated rare coding variants using VEP (defined as any variant with MAF $< 1\%$ in a given analysis, with a GC-corrected P-value $< 5 \times 10^{-9}$, and annotated as a missense_variant, stop_gained, stop_lost, splice_donor, or a splice_acceptor, regardless of fine-mapping results). We removed all variants with a GC-corrected P-value $< 5 \times 10^{-9}$ in EA, in the MHC region, and, in analyses including individuals with at least some African ancestry, on chromosome 1 for neutrophils and total WBC count and for RBC traits near the chromosome 11 β -globin and the chromosome 16 α -globin loci.

Bias-corrected enrichment of blood trait variants for chromatin accessibility of 18 hematopoietic populations was performed using g-chromVAR, which has been previously described in detail (Ulirsch et al., 2019). In brief, this method weights chromatin features by fine-mapped variant posterior probabilities and computes the enrichment for each cell type versus an empirical background matched for GC content and feature intensity. For chromatin feature input, we used a consensus peak set for all hematopoietic cell types with a uniform width of 500 bp centered at the summit. For variant input, we included all fine-mapped variants within 95% credible sets of the trans-ethnic GWAS. We also ran g-chromVAR for each ancestry-specific meta-analysis, keeping all other parameters the same, but using fine-mapped variants with the 95% credible sets of each ancestry-specific study. Finally, to control for the number of loci tested within each ancestry-specific study, we first ranked the loci of the largest cohort (i.e. EA) by sentinel variant p-value, and then subset only the top n loci, where n equals the number of loci in the smaller cohort (e.g. EAS) for the same trait. We then ran g-chromVAR on the subset of variants falling within these top n loci.

Phenome-wide association study (pheWAS) analysis

UK Biobank (UKBB). We extracted pheWAS results for a list of 5552 variants in UKBB ICD PheWeb hosted at the University of Michigan (Accessed 21 August 2019). To account for severe imbalance in case-control ratios, we selected the output from the SAIGE analyses (<http://pheweb.sph.umich.edu/SAIGE-UKB/>) based on 408,961 samples from White British participants (Zhou et al., 2018). In total, 1403 phecodes were tested for association. All results were downloaded using R, and were parsed and organized into data table format using the `data.table`, `rvest`, `stringr`, `dplyr` and `tidyr` packages.

773
774 *Biobank Japan (BBJ)*. We performed a pheWAS for the lead variants identified by the trans-ethnic
775 meta-analyses. From the list of all the significantly associated variants with blood cell-related
776 traits, we extracted those genotyped or imputed in the BBJ project ($n_{\text{SNP}} = 4,255$). Next, we curated
777 the phenotype record of the disease status and clinical values for the same individuals analyzed in
778 the discovery phase ($n_{\text{indiv}} = 143,988$). Then, we performed the logistic regression analyses for 22
779 binary traits (20 diseases and 2 behavioral habits) which had a sufficient number of case samples
780 ($n_{\text{case}} = 2,500$). Regression models were adjusted for age, sex and 20 principal components as
781 covariates. Trait-specific covariates are described elsewhere (Kanai et al., 2018).

782
783 *BioVU*. BioVU is the biobank of Vanderbilt University Medical Center (VUMC) that houses de-
784 identified DNA samples linked to phenotypic data derived from electronic health records (EHRs)
785 system of VUMC. The clinical information is updated every 1-3 months for the de-identified
786 EHRs. Detailed description of program operations, ethical considerations, and continuing
787 oversight and patient engagement have been published (Roden et al., 2008). DNA samples were
788 genotyped with genome-wide arrays including the Multi-Ethnic Global (MEGA) array, and the
789 genotype data were imputed into the HRC reference panel (McCarthy et al., 2016) using the
790 Michigan imputation server (Das et al., 2016). Imputed data and the 1000 Genome Project data
791 were combined to carry out principal component analysis (PCA) and African-American samples
792 were extracted for analysis based on the PCA plot. PheWAS were carried out for each SNP with
793 the specified allele (Denny et al., 2010). Phenotypes were derived from billing codes of EHRs as
794 described previously (Carroll et al., 2014). Each phenotype ('phecode') has defined case, control
795 and exclusion criteria. We required two codes on different visit days to instantiate a case for each

phecode. In total, 1815 phecodes were tested for association. Association between each binary phecode and a SNP was assessed using logistic regression, while adjusting for covariates of age, sex, genotyping array type/batch and 10 principal components of ancestry.

Merging across biobanks. We defined statistical significance within each biobank to be a Bonferroni corrected level of $0.05/pq$, where p is the number of phecodes tested and q is the number of variants tested. We merged results across UKBB and BioVU by matching on phecode, as these two biobanks used the same phecode system for classifying outcomes. To merge with BBJ, we cross-referenced the 22 outcomes in BBJ with the phecode library used by BioVU/UKBB. Matches were determined based on phenotype similarity between the BioVU/UKBB phenotype description and the outcomes described in Nagai et al. (Nagai et al., 2017).

Polygenic trait score (PTS) analyses

We restricted these analyses to variant-trait associations that reached genome-wide significance ($P < 5 \times 10^{-9}$) in the trans-ethnic MR-MEGA meta-analyses (**Supplementary Table 5**). For each of these variant-trait pairs, we calculated an effect size – hereafter referred to as trans weights – using the fixed-effect meta-analysis method implemented in GWAMA and all cohorts available (Magi and Morris, 2010). For the same variants, we also retrieved the ancestry-specific effect sizes (or weights). We calculated the PTS using plink2 by summing up the number of trait-increasing alleles (or imputation doses) that were weighted by their corresponding trans (PTS_{trans}) or ancestry-specific (PTS_{EA} , PTS_{AFR} , PTS_{HA}) weights. The variance explained by the PTS on corrected and normalized blood-cell traits was calculated in R using linear regression. For these analyses, we

had access to 2,651 AFR, 5,048 EA and 4,281 HA BioMe participants, as well as 2546 AFR ARIC participants, that were not used in the discovery effort.

Analysis of natural selection

To quantify the contribution of positive selection on blood-cell trait variation, we used the recent map of selective sweeps identified in the different populations of the 1000 Genomes Project (Johnson and Voight, 2018). We grouped the sweeps identified in the 26 1000 Genomes Project populations into five larger populations that correspond to our ancestry-specific meta-analyses: Europe-ancestry (CEU, TSI, GBR, FIN, IBS); East-Asian-ancestry (CHB, JPT, CHS, CDX, KHV); African-ancestry (YRI, LWK, GWD, MSL, ESN, ASW, ACB); South-Asian-ancestry (GIH, PJL, BEB, STU, ITU); and Hispanic/Latino-ancestry (MXL, PUR, CLM, PEL). Following the nomenclature by Johnson and Voight(Johnson and Voight, 2018), each selective sweep is summarized by the variant located within the sweep that has the highest iHS value. iHS (Integrated Haplotype Score) is a statistic to quantify evidence of recent positive selection. A high positive iHS score ($iHS > 2$) means that haplotypes on the ancestral allele background are longer compared to derived allele background. A high negative iHS score ($iHS < -2$) means that the haplotypes on the derived allele background are longer compared to the haplotypes associated with the ancestral allele. We retrieved the blood-cell trait association results for these sweep-tagging SNPs from the ancestry-specific meta-analyses (**Supplementary Table 19**). To determine if the inflation observed in the QQ plots was significant, we generated 100 sets of SNPs that match the selective sweep-tagging SNPs based on allele frequency, gene proximity, and the number of LD proxies in European-ancestry, East-Asian-ancestry and African-ancestry individuals using SNPsnap (Pers et al., 2015). For these analyses, we excluded the HLA region and variants in LD ($r^2 > 0.5$). We

computed empirical significance by tallying the number of sets with the same or more genome-wide significant variants than the canonical sets of selective sweep-tagging SNPs (**Supplementary Table 20**).

We also computed the population branch statistic (PBS)(Yi et al., 2010). PBS measures the amount of allele frequency change in the population since its divergence from the other two populations. For a target population, PBS is calculated as:

$$PBS = \frac{T^{target,sister} + T^{target,outgroup} - T^{sister,outgroup}}{2}$$

where $T = -\log(1 - F_{ST})$ is an estimate of the divergence time between two populations. Here, F_{ST} between each pair of populations was estimated using Weir and Cockerham's estimate (Weir and Cockerham, 1984). We then divided all variants with calculated PBS into 50 bins of equal size by derived allele count in the target population, and then standardized the raw PBS values within each bin. To calculate PBS for Europe-ancestry (CEU, TSI, GBR, and IBS, without FIN), we used YRI as an outgroup and East-Asian-ancestry (CHB, JPT, CHS, CDX, KHV) as a sister population; for East-Asian-ancestry, we used YRI as an outgroup and Europe-ancestry as a sister population; for YRI, we used East-Asian-ancestry as an outgroup and Europe-ancestry as a sister population.

IL7 functional analyses

We PCR amplified and cloned the *IL7* wildtype (rs201412253-Val18) and mutant (rs201412253-18Ile) open reading frame (ORF) in the pcDNA5/FRT vector (ThermoFisher Scientific) using HindIII and BamHI restriction sites (see **Supplementary Table 22** for ORF and primer

sequences). We validated the sequences of the two plasmids by Sanger Sequencing. Flip-In™-293 cells (ThermoFisher Scientific) at 80% confluency were transfected with 1:10 mixes of empty pcDNA5 or pcDNA5 derivatives coding for IL7-Val8 or IL7-18Ile and pOG44 FLP recombinase coding vector (ThermoFisher Scientific) using polyethylenimine. Transfectant clones were expanded and selected in DMEM medium supplemented with 10% Foetal Bovine Serum, 4 mM L-glutamine, 100 IU penicillin, 100 µg/ml streptomycin and 100 µg/ml hygromycin. We measured the secretion of IL7 in eight independent clones for each *IL7* allele (rs201412253-Val18 and rs201412253-18Ile) as well as in four clones generated with the empty vector by ELISA assay. We used the High Sensitivity Quantikine HS ELISA kit from R & D Systems (Cat # HS750). We seeded 100,000 cells per 12-wells plates and grew them for 6 days in DMEM glutamax plus 10% FBS before doing the ELISA. We measured each supernatant in duplicate and seeded each of the clones in triplicate. The whole experiment was done on three different weeks (three complete biological replicates). We extracted total proteins from cells with RIPA buffer and we quantified the lysates by BCA. We used this quantification to normalize the ELISA assays. We extracted total RNA from ~500,000 cells using the Qiagen RNEasy kit (cat # 74136). We checked the quality of the RNA by Bioanalyzer and quantified its concentration by Nanodrop. We reverse transcribed 1 µg of total RNA into cDNA using the ABI kit (Life Technologies Cat # 4368814). We used two pairs of primers for *IL7* and assays for three normalizing genes (*HPRT*, *GAPDH*, *TBP*, **Supplementary Table 22**). We followed the MIQE recommendations and performed the qPCR reactions with the Sybergreen Platinum (Life Technologies Cat # 11733-046) on a Biorad CFX384 thermocycler.

886 DATA AVAILABILITY STATEMENT

887 All results are available at the following URL: <http://www.mhi-humangenetics.org/en/resources>

888

889 URLs

890 checkVCF: <http://genome.sph.umich.edu/wiki/CheckVCF.py>

891 EPACTS: <https://genome.sph.umich.edu/wiki/EPACTS>

892 Imputation servers: <https://imputationserver.sph.umich.edu> or <https://imputation.sanger.ac.uk/>

893 NCBI dbSNP: <https://www.ncbi.nlm.nih.gov/projects/SNP/>

894 PheKB: <https://phekb.org/>

895 Strand alignment resources: <http://www.well.ox.ac.uk/~wrayner/strand>

896 UK Biobank SAIGE results: <http://pheweb.sph.umich.edu/SAIGE-UKB/>

897 Variant Effect Predictor: <https://useast.ensembl.org/info/docs/tools/vep/index.html>

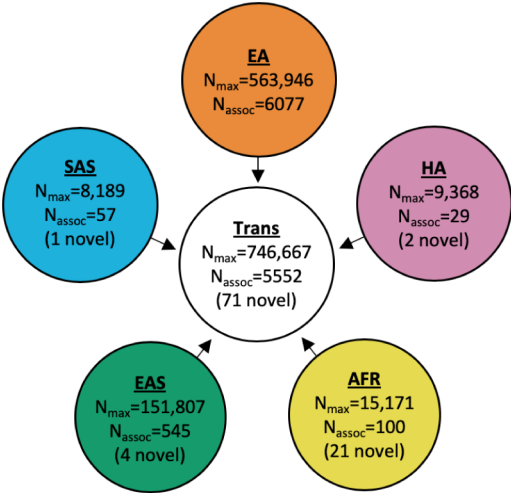
Table 1. Non-synonymous variants with a minor allele frequency (MAF) $\leq 1\%$ identified in non-European-ancestry (EA) populations or in the trans-ethnic meta-analyses. The population in which each variant was discovered is listed in the first column. Complete association results for each variant are available in **Supplementary Table 15**. Genomic coordinates (chr:position) are on build hg19. For the trans-ethnic results, mMAF corresponds to the mean MAF across all studies. EA, European-ancestry; EAS, East Asians; SAS, South Asians; AFR, African-ancestry; HA, Hispanics; PLT, platelet; NEU, neutrophil; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume; EOS, eosinophil; MON, monocyte; RDW, red blood cell distribution width; LYM, lymphocyte; RBC, red blood cell count; HGB, hemoglobin; WBC, white blood cell.

Population	Position	Phenotype	rsID	mMAF (%)	P-value	Gene	Annotation	Note
EAS	1:43805737	PLT	rs117656396	0.9	5.20×10^{-12}	<i>MPL</i>	missense	Thrombopoietin receptor; MAF <0.1% in EA and SAS.
EAS	3:133476778	MCH	rs143019827	0.4	4.52×10^{-9}	<i>TF</i>	missense	Transferrin (iron binding protein); monomorphic in non-EAS populations.
EAS	3:184046450	PLT	rs112809828	0.08	2.03×10^{-35}	<i>EIF4G1</i>	missense	MAF <0.01% in EA. Located ~45kb from thrombopoietin (<i>THPO</i>).
EAS	6:16295278	MCH/MCV	rs78806162	0.4	$4.79 \times 10^{-14} / 4.82 \times 10^{-12}$	<i>GMPT</i>	missense	MAF <0.1% in SAS; monomorphic in EA.
EAS	6:41621210	MCH/MCV	rs201503063	1	$4.28 \times 10^{-9} / 1.03 \times 10^{-9}$	<i>MDFI</i>	missense	Monomorphic in non-EAS populations.
EAS	7:100014072	MCH/MCV	rs6957339	0.07	$3.65 \times 10^{-21} / 1.02 \times 10^{-10}$	<i>ZCWPW1</i>	missense	MAF in EA <0.03%; more common in AFR and HA populations (MAF=0.2-0.6%). Located ~204kb from <i>TFR2</i> .
EAS	19:1049396	LYM/WBC	rs201347186	0.6	$8.78 \times 10^{-13} / 6.53 \times 10^{-22}$	<i>ABCA7</i>	missense	Previous GWAS identified common missense SNPs in <i>ABCA7</i> associated with NEU (Astle et al., 2016); monomorphic in non-EAS populations.
EAS	20:57599434	PLT	rs121918555	0.06	1.27×10^{-13}	<i>TUBB1</i>	missense	Mutation previously characterized in Japanese patients with congenital macrothrombocytopenia (Kunishima et al., 2009); monomorphic in non-EAS populations.
SAS	9:135863848	MPV/PLT	rs527297896	0.5	$2.24 \times 10^{-19} / 3.57 \times 10^{-18}$	<i>GF11B</i>	missense	Mutation previously identified in patients with thrombocytopenia without α -granule or bleeding defect (Rabbolini et al., 2017); monomorphic in non-SAS populations.
Trans	1:43803807	PLT	rs17292650	0.2	2.87×10^{-16}	<i>MPL</i>	missense	Thrombopoietin receptor; known common variant in AFR populations (MAF=4.2%)(Auer et al., 2012).
Trans	1:231557623	HCT	rs186996510	1	4.90×10^{-15}	<i>EGLN1</i>	missense	Low-frequency variant in EAS (MAF=4.1%) and AFR (3.2%), rare in SAS (0.6%) and EA (<0.01%). Associated with adaptation to

								hypoxia and HGB in Tibetans (Xiang et al., 2013).
Trans	7:80300449	RDW	rs3211938	0.3	5.75×10^{-14}	<i>CD36</i>	nonsense	Known common variant in AFR populations (MAF=9.3%)(Chami et al., 2016).
Trans	9:136083640	RBC	rs12336956	0.8	1.01×10^{-9}	<i>OBP2B</i>	missense	Association signal in EA (MAF=0.3%); MAF=3% in HL; MAF=19% in AFR. Located ~47kb from <i>ABO</i> .
Trans	11:5248232	LYM	rs334	0.2	9.50×10^{-16}	<i>HBB</i>	missense	Sickle cell anemia mutation, well known for RBC trait associations.
Trans	12:111856673	PLT	rs78894077	0.9	7.63×10^{-38}	<i>SH2B3</i>	missense	Common variant in EAS (MAF=3.6%). Associated with myeloproliferative neoplasms (Chen et al., 2016).
Trans	17:38062390	WBC	rs35266519	0.8	6.69×10^{-12}	<i>GSDMB</i>	missense	Rare across all populations. Previously reported for NEU count (Mousas et al., 2017).

FIGURE 1

a



b

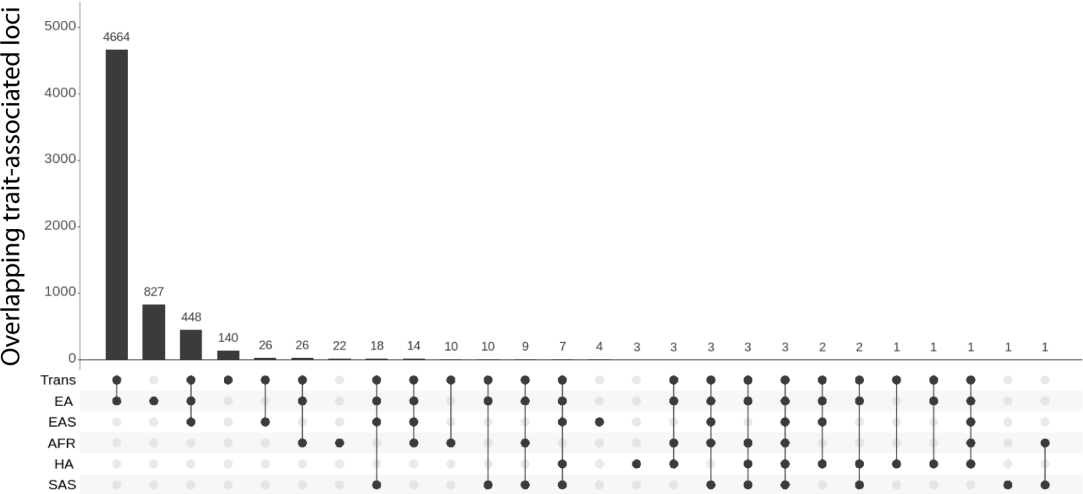


FIGURE 2

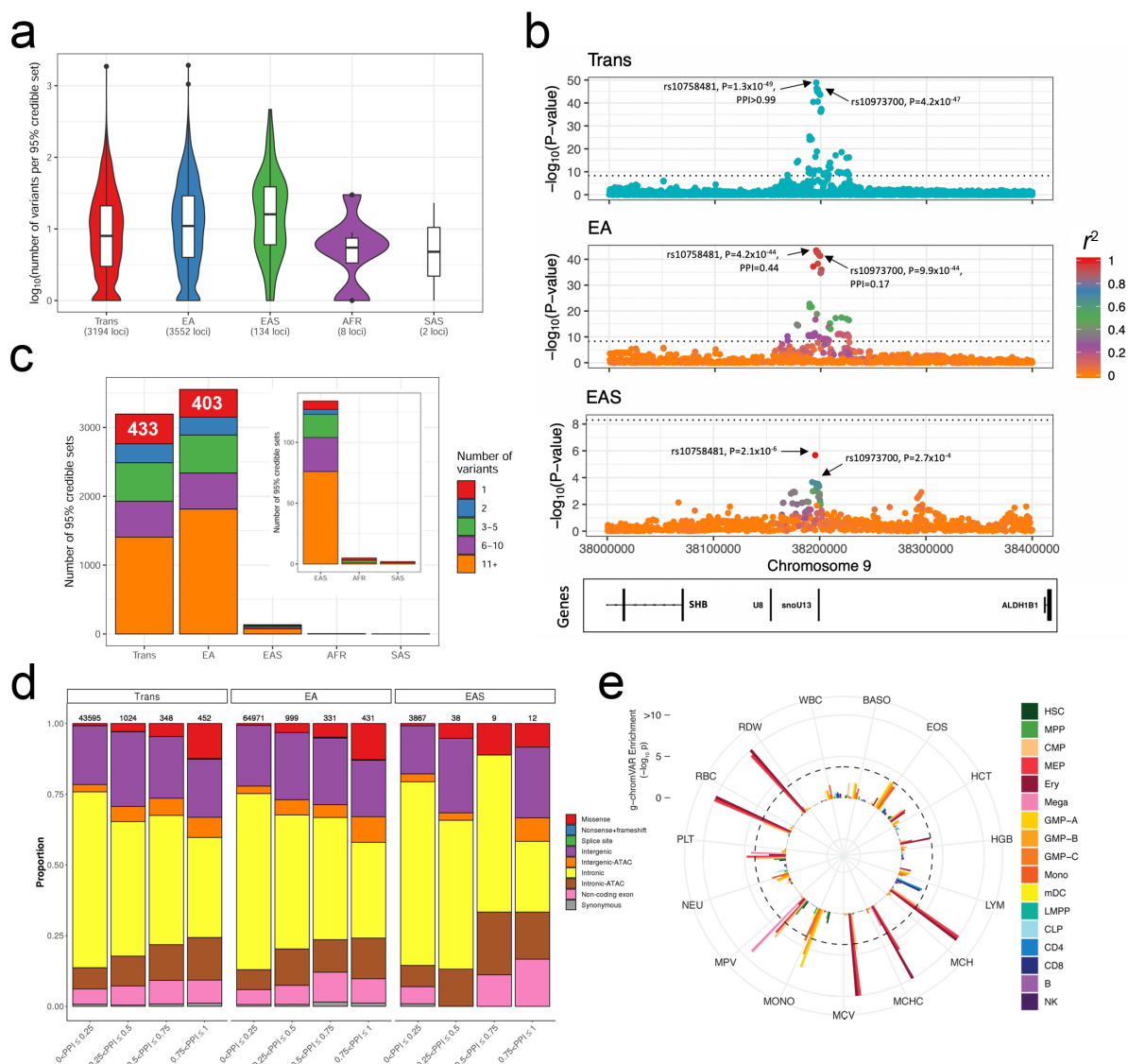


FIGURE 3

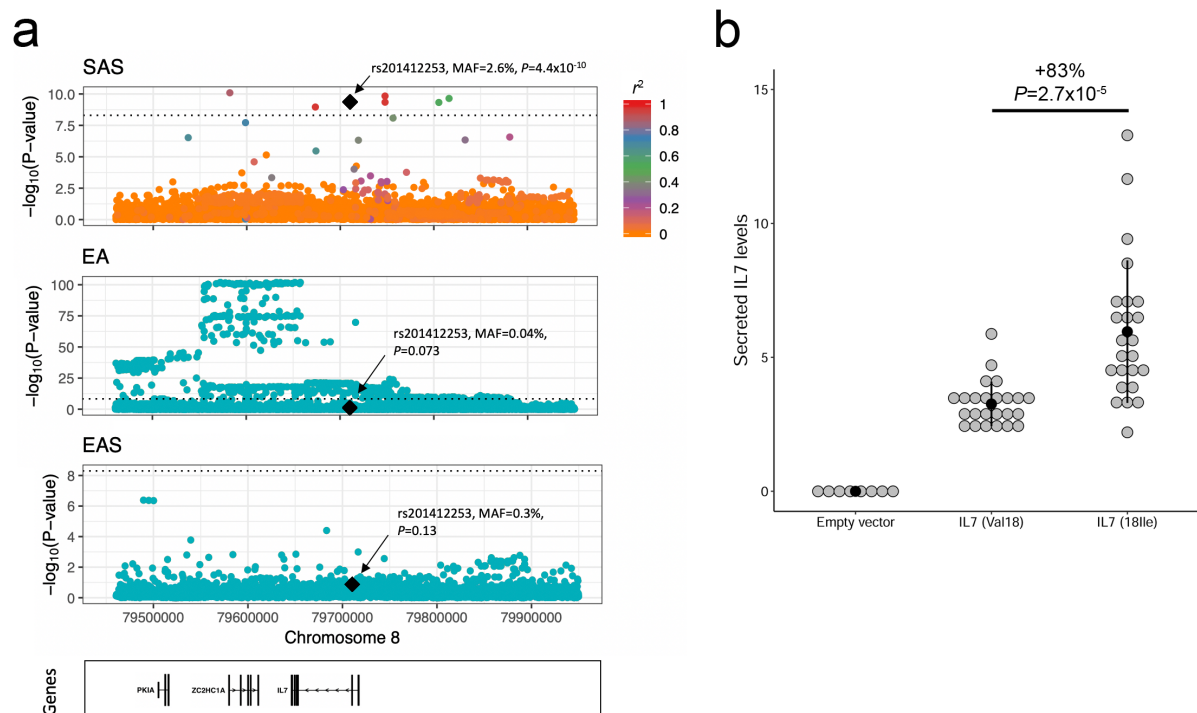
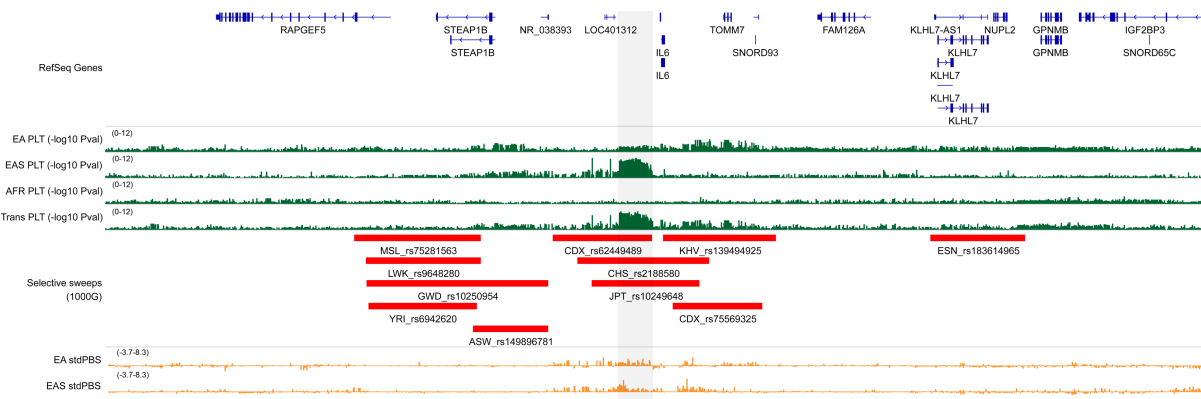


FIGURE 4



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