HHS Public Access

Author manuscript

Curr Opin Hematol. Author manuscript; available in PMC 2023 December 29.

Published in final edited form as:

Curr Opin Hematol. 2017 May ; 24(3): 173–182. doi:10.1097/MOH.0000000000000333.

Genetic control of erythropoiesis

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Abstract

Purpose of review—The discovery of several genetic variants associated with erythroid traits and subsequent elucidation of their functional mechanisms are exemplars of the power of the new genetic and genomic technology. The present review highlights findings from recent genetic studies related to the control of erythropoiesis and dyserythropoiesis, and fetal hemoglobin, an erythroid-related trait.

Recent findings—Identification of the genetic modulators of erythropoiesis involved two approaches: genome-wide association studies (GWASs) using single nucleotide polymorphism (SNP) arrays that revealed the common genetic variants associated with erythroid phenotypes (hemoglobin, red cell count, MCV, MCH) and fetal hemoglobin; and massive parallel sequencing such as whole genome sequencing (WGS) and whole exome sequencing (WES) that led to the discovery of the rarer variants (*GFI1B, SBDS, RPS19, PKLR, EPO, EPOR, KLF1, GATA1*). Functional and genomic studies aided by computational approaches and gene editing technology refined the regions encompassing the putative causative SNPs and confirmed their regulatory role at different stages of erythropoiesis.

Summary—Five meta-analysis of GWASs identified 17 genetic loci associated with erythroid phenotypes, which are potential regulators of erythropoiesis. Some of these loci showed pleiotropy associated with multiple erythroid traits, suggesting undiscovered molecular mechanisms and challenges underlying erythroid biology. Other sequencing strategies (WGS and WES) further elucidated the role of rare variants in dyserythropoiesis. Integration of common and rare variant studies with functional assays involving latest genome-editing technologies will significantly improve our understanding of the genetics underlying erythropoiesis and erythroid disorders.

Keywords

erythroid traits; erythropoiesis; genetic variants

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Conflicts of interest

There are no conflicts of interest.

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INTRODUCTION

Healthy human adults produce approximately 2.5 × 10^{11} new red blood cells (RBCs) per day and clear an equal number of RBCs [1]. Failure to maintain this output and clearance results in anemias of various sorts and erythrocytosis [2]. Maintenance of this rapid turnover requires efficient erythropoiesis through proliferation and differentiation of the immature erythroid progenitor population, a progeny of self-renewing stem cells [2]. Early studies routinely measured various erythroid parameters (Table 1) with the purpose of deciphering the genetic variability, as well as underlying genes and sequence variants associated with erythropoiesis, during health and disease [3]. These erythroid parameters vary significantly among individuals, with 40–90% of this phenotypic variation being heritable [4■■]. Genetic and environmental factors, as well as age and sex, contribute to this variability as confirmed by early twin studies [5–7]. Of the erythroid traits, fetal hemoglobin (HbF) showed the highest genetic heritability [3]. The present review provides an update on how common and rare genetic variations affect the process of erythropoiesis, and how integration of experimental (functional) and bioinformatics approaches can enhance our understanding on the genetic control of erythropoiesis.

GENOME-WIDE ASSOCIATION STUDIES AND IDENTIFICATION OF COMMON VARIANTS AFFECTING ERYTHROPOIESIS

Identification of variants regulating fetal hemoglobin: an exemplar of genome-wide association studies

HbF is an erythroid parameter that has been the focus of much of the recent research efforts, as its induction ameliorates clinical symptoms associated with the β-hemoglobinopathies [8]. In normal healthy adults, HbF is present at residual levels (<0.6%) restricted to a small number of erythrocytes termed F cells. The percentage of F cells and HbF are highly correlated ($R^2 = 0.97$). HbF and F cells are quantitative traits, with a predominantly genetically controlled heritability of 0.87 [3], compared to the other erythroid traits (Hb, Hct, RBC, MCV, MCH, MCHC) that were measured in the same twin study. HbF varies considerably (up to 20-fold) in healthy adults; the variable increases are amplified in patients with sickle cell anemia and β-thalassemia. This variable persistence of HbF in adults constitutes the historical entity of heterocellular hereditary persistence of fetal hemoglobin (HPFH); multiple genes, together with a small environmental component, determine the HbF value measured in any individual. *Xmn*1-*HBG2* (rs7482144) on chromosome 11p, *HBS1L-MYB* intergenic region on chromosome 6q23, and *BCL11A* on chromosome 2p16 are the three major quantitative trait loci (QTL) for HbF, contributing to the complex inheritance of heterocellular HPFH. The remaining variation (‘missing heritability’) is likely to be accounted for by many loci with relatively small effects, and/or rare variants with significant quantitative effects on gamma-globin gene expression that are typically missed by GWAS population studies [8,9]. One such rare variant is *KLF1* (also known as *EKLF*) [10■■].

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Identification of variants regulating erythropoiesis

The *HBS1L-MYB* locus on chromosome 6q23 was first shown to have a pleiotropic effect on non-HbF erythroid traits in 2007 [11]. Subsequently, five independent meta-analyses [12–16] involving a range of multiethnic cohorts (Table 2), identified 17 common variants, including *HBS1L-MYB* locus (Table 3), associated with erythropoiesis and erythroid disorders. Of these, five were previously discovered QTLs (*HFE, TFR2, TMPRSS6, HBS1L-MYB,* and *BCL11A*), and 11 were novel, some of which were annotated for genes known to be involved in iron homeostasis (*TFRC*) and erythropoiesis (*ABO, CCND3, CITED2, SH2B3, SPTA1*). Of the 17 loci, *HBS1L-MYB* locus, *ITFG3, TMPRSS6,* and glucose-6-phosphate dehydrogenase (*G6PD*) showed greatest pleiotropy, achieving genome-wide significant associations with five erythroid traits (Table 3).

HBS1L-MYB locus on chromosome 6q

High-resolution genetic mapping refined the 6q QTL to single nucleotide polymorphism (SNPs) in two clusters at −84 and −71 kb, respectively, upstream of *MYB,* one of the flanking genes. Functional studies in transgenic mice and primary human erythroid cells provide overwhelming evidence that the SNPs at these two regions disrupt binding of key erythroid enhancers affecting long-range interactions with *MYB* and *MYB* expression, providing a functional explanation for the genetic association of the 6q *HBS1L-MYB* intergenic region with levels of HbF and F cell as well as other erythroid traits. The MYB transcription factor is a key regulator of hematopoiesis and erythropoiesis, and modulates the erythroid traits via two mechanisms: indirectly through alteration of the kinetics of erythroid differentiation; low MYB levels accelerate erythroid differentiation leading to release of early erythroid progenitor cells that are larger, and still synthesizing predominantly HbF; and directly via activation of *KLF1* and other repressors (e.g. nuclear receptors TR2/TR4) of gamma-globin genes [17–19]. The polymorphisms at this locus have an occupancy of erythroid TFs (TAL1/SCL, E47, GATA1, and RUNX1/AML1) critical for erythroid cell differentiation [17].

The *HBS1L-MYB* intergenic enhancers do not appear to affect expression of *HBS1L*, the other flanking gene. Further, in-vitro cellular studies also excluded *HBS1L* as having a role in the regulation of HbF and erythropoiesis [20]. In whole-exome sequencing of rare uncharacterized disorders, loss-of-function mutations in the *HBS1L* gene were identified in a female child [21]. The child had normal blood counts and normal HbF levels.

BCL11A on chromosome 2p

Functional studies in primary human erythroid progenitor cells and transgenic mice demonstrated that *BCL11A* acts as a repressor of gamma-globin gene expression that is effected by SNPs in intron 2 of this gene [22]. Fine-mapping demonstrated that these HbF-associated variants, in particular, rs1427407 and rs7606173, localized to an enhancer that is erythroid-specific and not functional in lymphoid cells. *BCL11A* interacts with several co-repressor complexes occupying discrete regions in the *HBB* complex leading to reconfiguration of the locus [23,24]. The composite *BCL11A* erythroid-specific enhancer has three DNase I hypersensitive sites (DHSs) at +55, +58, and +62 kb from the

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transcription start site of this gene, with DHS at +58 having the greatest effect on *HBG* gene expression [22,25].

Experimental studies so far have shown that BCL11A deficiency results in HbF induction with minimal effect on erythropoiesis [26▪,27▪]. Although these studies, which were performed on mice models, showed no major perturbation in erythropoiesis, there were reductions in Hct, RBC, and Hb values. However, 2 *BCL11A* SNPs (rs2540917 and rs243070) have also been associated with MCV (Table 3), suggesting that *BCL11A* is a candidate gene for erythrocyte variation resulting from the perturbation of erythropoiesis, as supported from a recent finding that BCL11A is indispensable for hematopoietic stem cell (HSC) function [28].

Variants associated with iron homeostasis and heme metabolism

Iron metabolism and erythropoiesis are closely related; iron being essential for hemoglobin synthesis during terminal erythropoiesis [29▪]. Genetic factors have a significant impact on iron homeostasis, defects in iron metabolism result in hereditary anemias and iron overload [29▪]. Early GWASs have implicated variants in the iron regulatory genes – *TMPRSS6*, *HFE, TFR2, TFRC* (Table 3) – in the variability of various erythroid traits. *TMPRSS6* inhibits hepcidin, which is essential for iron absorption and effective erythropoiesis. Complete loss-of-function mutations of *TMPRSS6* result in a rare disorder of iron-refractory iron deficiency anemia (IRIDA) [29▪]. Genetic variants in *TMPRSS6* may lead to iron deficiency anemia in individuals with or without other predisposing factors [30]. The hereditary hemochromatosis (*HFE*) protein is a key component of the signaling pathway through which transferrin stimulates hepcidin synthesis [31,32], thereby modulating erythropoiesis by affecting dietary iron absorption and erythroid iron intake [33]. Transferrin receptors *TFRC* (also called *TFR1*) and *TFR2* play a critical role in erythropoiesis. *TFRC* is one of the most abundant membrane proteins of the erythroblasts [34] and plays a dominant role in the delivery of transferrin-bound iron from the blood to developing erythroid precursors in the bone marrow, making it essential for erythropoiesis. *TFRC* deficiency results in defective hemoglobinization and anemia. *TRF2* is a component of *EPO* (erythropoietin) receptor (*EPOR*) complex in erythroid cells that modulates *EPO* sensitivity and maintains the balance between the RBC production and iron availability [35]. *TFR2* knockdown has shown to delay terminal differentiation, leading to inefficient erythropoiesis [36].

Another component of iron-regulatory system is *HMOX2*, which has an important role in erythroid differentiation and erythropoiesis [37]. The lead SNP rs7192051, discovered in the meta-analysis involving African-American ancestry, is located in the second intron of *HMOX2*, and is associated with lower MCH and MCV [12] (Table 3). However, validation of this association failed in two independent population-based African-American and European (CHARGE consortium) samples. Interestingly, another *HMOX2* SNP, rs4786504, is associated with an adaptive trait among Tibetans who live in high-altitude hypoxic conditions, where the variant is associated with increase in *HMOX2* expression, facilitating the breakdown of heme and helping to maintain low hemoglobin levels at high altitude [38].

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ABO blood group polymorphisms

The *ABO* blood group antigen system is complex; several weak phenotypes or subgroups are caused by SNPs mostly attributed to the coding variants [39–41]. However, there are *ABO* subgroups that are not related to variants in coding regions or splicing sites. For example, a positive regulatory element in intron 1 appears to enhance the activity of the *ABO* promoter in an erythroid cell–specific manner, through binding of erythroid-specific TF GATA binding protein 1 (GATA1) [42]. The *ABO* antigen is initially expressed on cells derived from erythroid blast colony forming units and colony forming units, with a gradual increase in expression during erythroid maturation [43,44]. Recent GWASs have identified the *ABO* gene locus as being significantly associated with erythroid traits (Table 3) [14,45,46]. Of the two SNPs (rs495828 and rs8176746) discovered in the Japanese GWAS study, rs8176746 which is nonsynonymous, serves as one of the deterministic variants of the B-antigen, and is associated with increase in erythroid parameters [14,46]. This SNP has also been mapped to the erythroid enhancer regions marked by p300 and colocalized erythroid transcription factors (TFs) KLF1 and TAL1 [47], suggesting a possible regulation of this gene during erythroid cell differentiation. Thus, it seems that the erythroid cell-specific regulatory activity of *ABO* expression is dependent on the binding of GATA1 and its co-factors (KLF1 and TAL1) during erythropoiesis [42]. In this context, the *ABO* SNPs discovered from GWAS, and their association with erythroid traits (Hb, Hct, and RBC) may further explain the molecular basis of the subphenotyes associated with this blood group during erythropoiesis.

CCND3 and CITED2

Cyclin D3 (*CCND3*) plays a key role in HSC expansion; its absence in mice results in ineffective erythropoiesis and anemia [48]. *CCND3* variants (rs3218097, rs9349205, rs11970772, rs9349204) have also been implicated in their association with erythroid traits (MCV, MCH, RBC) by four different meta-analysis studies (Table 3). The region surrounding SNP rs9349205 was determined to be the region of erythroid enhancer element of *CCND3*, with TAL1, GATA1, and KLF1 chromatin occupancies [49]. The follow-up functional studies involving *CCDN3* knockout animal models and knockdowns involving humans *ex vivo* models confirmed that *CCND3* regulates the number of cell divisions during terminal erythropoiesis and that reduced levels of *CCND3* correlate with fewer terminal erythroid cell divisions, resulting in fewer but larger terminally differentiated erythrocytes [49].

GWAS meta-analyses also revealed significant association of Cbp/P300 Interacting Transactivator With Glu/Asp Rich Carboxy-Terminal Domain 2 (*CITED2*) variants (rs628751, rs632057, rs643381, rs590856, rs632057) with erythroid traits MCH and MCV (Table 3). *CITED2* is a master regulator of stem cell fate with a key role in the adult HSC maintenance [50]. A proper coordination among growth factors EPO, SCF, Forkhead box O3 (FOX3A), and *STAT5* is essential for the induction of *CITED2* expression and regulation of gene expression program in erythroblasts [51]. Also, *CITED2* regulates iron homeostasis and erythropoiesis via hypoxiainducible factor 1-alpha (HIF1A) and GATA1 [52,53].

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SH2B Adaptor Protein 3 polymorphism

A nonsynonymous SNP in *SH2B3* gene (rs318504), which results in R262W substitution, is significantly associated with high hemoglobin levels (Table 3) [16]. *SH2B3* negatively regulates hematopoietic cytokine signaling [54]. Targeted suppression of *SH2B3* expression in mice primary hematopoietic stem and progenitor cells (HSPCs) improves erythroid expansion and differentiation, and increases hemoglobin [55]. In humans, targeted *SH2B3* suppression and inactivation facilitated erythroid expansion and maturation by augmenting both the *EPO* and *KIT* signaling pathways [56■■]. Thus, *SH2B3* deficiency can enhance erythropoiesis *in vitro* and production of RBCs for transfusion purposes. Genetic variants of *SH2B3* at the population-level have been associated with increased RBC levels, thus recapitulating the results of the in-vitro functional studies.

Other genome-wide association studies identified common variants and their role in erythropoiesis

Three SNPs (rs218237, rs172629, rs218238) in the *PDGFRA-KIT* intergenic region were found to be associated with erythroid traits MCV and RBC (Table 3). These three SNPs are located in the intergenic region downstream of the platelet-derived growth factor receptor α polypeptide gene (*PDGFRA*) and upstream of the human homolog of the proto-oncogene c-kit gene (*KIT*). Until recently, the function of *PDGFRA* on erythropoiesis was unknown. A recent study [57] has identified *PDGFRA* as a negative regulator in erythroid differentiation, and is part of the miR-146b, *PDGFRA*, and *GATA1* regulatory circuit. KIT has a primary role in erythropoiesis. Considering their close proximity, we speculate that the three SNPs influence MCV and RBC through their regulation of *PDGFRA* and *KIT*.

Rare intronic and low frequency nonsynonymous coding variants in *ITFG3* (also known as *FAM234A*) are African-American-specific and were found to be associated with various erythroid traits (Table 3: Hb, MCH, MCHC, MCV, RBC). Although the role of *ITFG3* in erythropoiesis is unknown, the variants of this gene encompass the α-globin (*HBA2-HBA1*) locus and can be disrupting long-range enhancers of alpha-globin [58■■].

Two SNPs, rs762516 and rs1050828, in *G6PD* on the X chromosome have been associated with multiple erythroid traits (Table 3: Hct, Hb, MCV, RBC, RDW); rs1050828 is associated with increased risk of anemia in African-American women [12]. *G6PD* is indispensible for erythropoiesis and its deletion or deficiency results in accelerated erythropoiesis with increased red cell deformability in fetal erythrocytes and abrogation of the embryonic-adult hemoglobin developmental switch [59,60].

Similarly, variants in spectrin (*SPTA1*), protein kinase C epsilon (*PRKCE*) and endolyn (*CD164*) are associated with erythroid traits through their effect on erythropoiesis. An intronic (rs857721) [13] as well as a nonsynonymous variant (rs857725) in *SPTA1* [61] are associated with MCHC. Mutations in *SPTA1* are implicated in erythroid differentiation, regulation of cell cycle, and ineffective erythropoiesis [62,63]. *PRKCE* variant rs10495928 is associated with Hb and Hb-related traits in African Americans, Europeans, and Japanese [12]. Similarly, *CD164* variant (rs9386791) is associated with lower MCH in African Americans, whereas other variants are associated with RBC, MCH, and MCV in Japanese

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(rs11966072) and with MCV in Europeans (rs9374080). This suggests ethnic-specific allelic heterogeneity for erythroid traits for these two genes.

Apart from the meta-analysis studies reported in this review, a separate GWAS study [61] identified genetic loci in genes *THRB*, *PTPLAD1*, *CDT1, EPO, ALDH8A1, FBXO7*, associated with erythroid traits that are known to play role in erythroid differentiation and cell-cycle regulation.

RARE VARIANTS: IDENTIFICATION AND STRATEGIES

The role of common genetic variation in hematological traits has been well characterized with the expansion of GWAS-based consortia, but rare genetic variants with minor allele frequency less than 1%, although with large effect size were typically not discovered in GWASs [64]. Recently, DNA sequencing-based approaches and custom arrays have been deployed on a large scale to comprehensively evaluate the contribution of rare genetic variants to complex traits and diseases [65].

Kruppel-like factor 1 variants

Kruppel-like factor 1 (*KLF1*) is a master regulator of erythropoiesis, regulating approximately 700 erythroid genes involved in wide array of molecular mechanisms [10■■,66,67]. Red cell disorders have rarely been attributed to *KLF1* variants, until high-throughput DNA sequencing identified numerous sporadic cases, prompting population surveys. Since 2008, a range of hematologic phenotypes associated with *KLF1* variants have been identified including inconsequential In(Lu) type of Lu(a-b-) blood group [68], increases in HbF as a primary phenotype or secondary to other red cell disorders [67,69], severe dyserythropoietic anemia [70], and an extreme case of hydrops fetalis [71]. Since 2010, more than 65 different *KLF1* variants have been identified; these variants have varied effects on the severity of ineffective erythropoiesis and their clinical significance [10■■]. Although *KLF1* variants appeared to be a ‘common’ variant and associated with milder thalassemia in southern China (where β-thalassemia is prevalent) compared with a northern Chinese population [72], several GWASs of HbF, including ones in sickle cell anemia patients of African descent, have failed to identify common variants in *KLF1* [73,74].

GATA binding protein 1 variants

GATA1 encodes a transcription factor required for erythroid differentiation [75]. Exome sequencing in two male siblings with Diamond-Blackfan anemia (DBA) has identified mutations (a G → C transversion) in the exon 2 at a splice site that impaired production of the full-length form of the protein [76]. Interestingly, a missense mutation consisting an identical G → C transversion in the zinc fingers of *GATA1* resulted in dyserythropoietic anemias and thrombocytopenias [77–79]. Although most studies attribute DBA pathogenesis to a defective ribosomal biogenesis [80], the discovery of *GATA1* mutations reveal the potential for other plausible underlying mechanisms and basis for this erythroid disorder. A methodical sequencing approach of other DBA cases will further reveal the scope and extent to which *GATA1* mutations contribute to this disease.

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Targeted next-generation sequencing

Targeted next-generation sequencing is popular due to its cost-efficiency, and provides rapid and accurate mutation analysis. This approach has been utilized in the detection of novel mutations associated with rare congenital anemias. For example, targeted sequencing of genes from the Oxford Red Cell Panel (ORCP) [81■] on a patient previously diagnosed with DBA, resulted in the discovery of hypomorphic mutation in the *Shwachman Bodian Diamond syndrome* (*SBDS*) gene and a revised diagnosis of Shwachman–Diamond syndrome (SDS). Similar corrections and revisions in diagnosis include a revision of Congenital Dyserythropoietic Anemia type I (CDA-1) to DBA with the discovery of a mutation in *RPS19*, previously shown to have a mechanistic role in erythropoiesis. Targeted resequencing using ORCP on a patient with an initial diagnosis of CDA revealed a mutation in Pyruvate Kinase, Liver And RBC (*PKLR*) gene and revised the diagnosis to Pyruvate Kinase deficiency. Mutations of the *EPOR* have been documented in families with isolated familial erythrocytosis [82]. Using targeted re-sequencing on a family of 33 individuals, the first *EPOR* mutation was confirmed [83]. This discovery propelled further research that led to the discovery of ten different truncating mutations as well as several point mutations [84]. Thus, targeted resequencing of a carefully curated panel of genes not only serves as an essential diagnostic tool for clinical purposes, but also provides new insights on the role of unsuspected genetic variants in the regulation of erythropoiesis.

Whole-exome sequencing

Whole-exome and targeted re-sequencing approaches have been used to identify rare, loss (or gain)-of-function coding variants segregating within families with hematologic traits at the extremes of the phenotypic distribution. Whole exome sequencing (WES) approach, involving large population-based cohorts phenotyped for hematological traits, is in developmental stages. One notable example is a study by Polfus *et al.* [85■■] where WES association analyses of hematologic quantitative traits in 15,459 individuals from European and African-American ancestry have discovered rare synonymous variant in *GFI1B* (rs150813342), with the follow-up knockdown experiments in primary human HSPCs revealing an alternative splicing mechanism wherein rs150813342 variant suppresses the long isoform of *GFI1B* that is indispensable for megakaryopoiesis and not the short isoform, which is indispensable for erythropoiesis [85■■]. A recent study examining WES data from a cohort of more than 450 patients with a clinical diagnosis of DBA, led to the discovery of a homozygous recessive mutation in *EPO* which resulted in an R150Q substitution in the mature EPO protein, affecting the erythroid differentiation and proliferation [86].

Exome arrays

Large-scale studies, such as the 1000 Genomes Project and Exome Sequence Project (ESP), have catalogued coding DNA sequence variants, facilitating the study of these rare variants using standard genotyping arrays. Exome-wide genotyping arrays (exome chips) are now commercially available, and although computationally less challenging to analyze, they are not as comprehensive as the NGS technologies which may result in missing a large amount of very rare genetic variation. Furthermore, the exome arrays are based mostly

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on sequence data from the European population, hence rare variants in other populations may be missed. Despite these limitations, exome chips have already been used successfully to identify rare coding variants associated with erythroid traits. A recent exome array study has identified a rare low-frequency missense variant in the erythropoietin gene *EPO* (rs62483572) in the high-affinity receptor binding site and associated with lower Hct and Hb values [64]. Another study, consisting of meta-analyses of seven RBC phenotypes in multiethnic individuals from studies genotyped on an exome array, have discovered rare variants associated with erythroid traits, such as *MAP1A* (for Hb), *HNF4A* (for Hct and Hb), *CD36* (for RBC), and *ALAS2* (for MCV) [4■■].

CONCLUSION

GWASs have been extremely successful in uncovering thousands of associations between common variants and complex traits as well as diseases, but much of the heritability of these traits remains unexplained and unexplored. Within the Mendelian erythroid diseases, such as SCD and β-thalassemia, most of the discoveries from GWASs were focused on the erythroid trait HbF [9,87,88,89■]. Although this is a significant achievement when compared to GWAS-identified loci for all other traits, there is a scope for further identification and characterization of common as well as rare variants modulating HbF levels. Meta-analysis of GWASs, as well as recent rare variant studies, revealed novel loci annotated for genes known to be involved in erythropoiesis (Fig. 1). GWAS-identified trait-associated noncoding variants have small effect size, and thus the impact on the biological processes is often unknown. One way to address this challenge is to develop assays for high-throughput functional screening of GWAS loci, and complement the results with genome-editing in gene modulation assays. Another approach is to comprehensively evaluate the contribution of rare genetic variants by DNA sequencing, followed by functional characterization. Ultimately, integration of data from both common and rare variant studies, and follow-up gene functional assays will provide further insights on how the genetic variation in erythroid traits affects erythropoiesis (Fig. 2).

Acknowledgements

We would like to thank Rusinel Amarante for her help in preparation of the manuscript.

Financial support and sponsorship

This work was supported by the Intramural Research Program of the National Heart, Lungs, and Blood Institute, NIH.

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KEY POINTS

- Erythroid traits are heritable and clinically important biomarkers but much of the heritability of these traits remains unaccounted for.
- Understanding how genetic variants modulate erythroid traits in health (and disease) can provide us with new insights into the mechanistic underpinnings of erythropoiesis.
- GWASs and meta-analyses of GWAS data have identified robust associations between many common variants and erythroid traits in healthy and disease states, but these variants have small effect size, and their impacts on biological process such as erythropoiesis remain uncertain.
- Meta-analyses of GWAS data, as well as recent rare variant association studies have also identified novel genetic loci that showed pleotropic association with erythroid traits and were annotated for genes (*ABO, CCND3, CITED2, SH2B3, SPTA1, GFI1B, SBDS, RPS19, PKLR, EPO, EPOR, KLF1, GATA1*) involved in erythropoiesis.
- Integration of common and rare variant studies with functional assays involving latest genome-editing technologies will significantly improve our understanding of the genetics underlying erythropoiesis and erythroid disorders.

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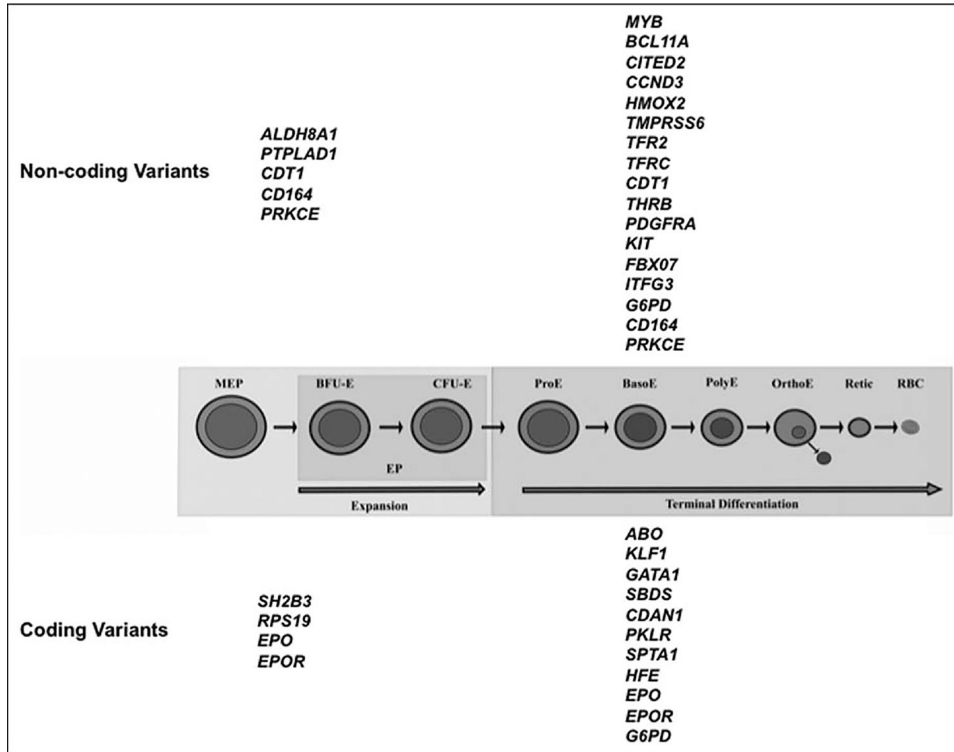

FIGURE 1.

Genes implicated in erythropoiesis are associated with erythroid traits. Different stages of erythroid differentiation, from the megakaryocyte erythroid progenitor (MEP) to the mature red blood cell (RBC), are shown here: Megakaryocyte erythroid progenitor; BFU-E, blast colony forming unit-erythroid; CFU-E, colony forming unit-erythroid; ProE, proerythroblast; BasoE, basophilic erythroblast; PolyE, polychromatic erythroblast; OrthoE, orthochromatic erythroblast; Retic, reticulocyte. Genes associated with noncoding variants are shown at the top, and genes associated with coding variants are shown at the bottom.

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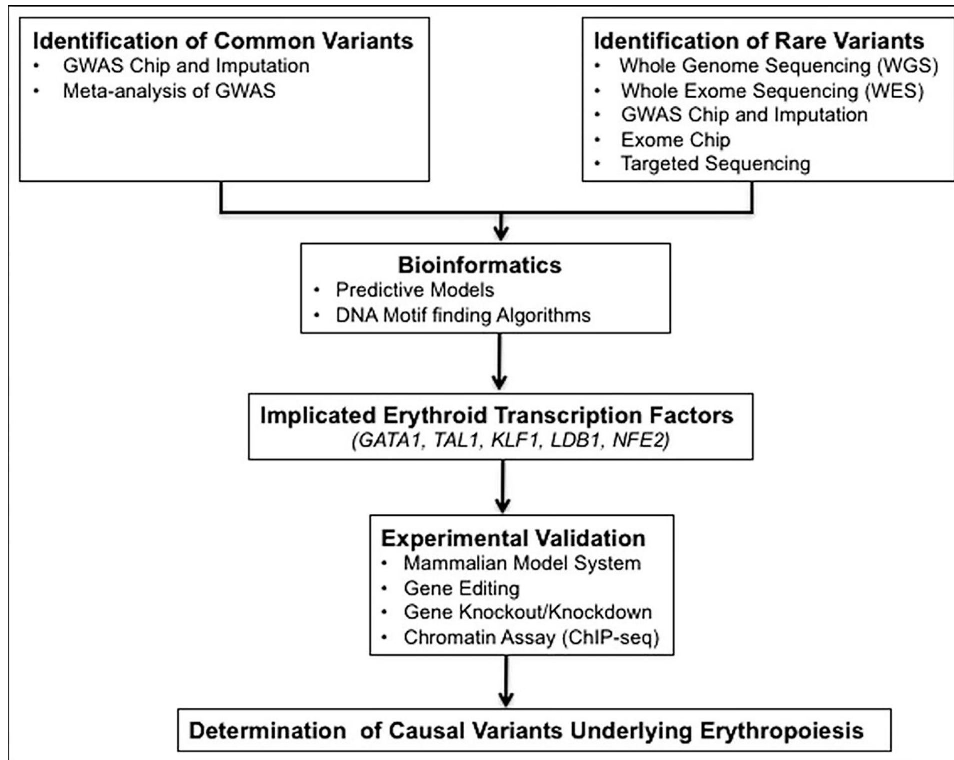

FIGURE 2.
Model of the integrated approach for the genetic determinants of erythropoiesis.

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Table 1.

Main erythrocyte phenotypes (traits) routinely measured in clinic

Erythroid trait	Definition	Unit
Mean corpuscular hemoglobin (MCH)	Average mass of hemoglobin per red blood cell	Picogram (pg)
Mean corpuscular volume (MCV)	Average volume of red blood cells	Femtoliter (fL)
Red blood cell (RBC) count	Count of red blood cells per microliter	Million cells per microliter ($\times 10^6/\mu L$)
Hemoglobin (Hb)	Hemoglobin concentration	Gram per deciliter (g/dL)
Hematocrit (Het)	Percentage of the blood volume occupied by erythrocytes	Percentage (%)
MCH concentration (MCHC)	Average concentration of hemoglobin in red blood cells (hemoglobin divided by hematocrit)	Gram per deciliter (g/dL)
RBC distribution width (RDW)	Distribution of red blood cell volume	Percentage (%)

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Table 2.

Meta-analysis studies researched for common variants associated with erythroid traits for this review

Ancestry	Sample number (*n*)	Erythroid traits	Number of significantly associated loci	Meta-analysis study reference
6 European cohorts	13943	RBC, Hb, MCH, MCHC, MCV	22	(HaemGen Consortium) [15]
6 European Cohorts	24167	RBC, Hb, Het, MCH, MCHC, MCV	23	(CHARGE consortium) [13]
10 Japanese disease groups	14700	RBC, Hb, Het, MCH, MCHC, MCV	49	[14]
32 European and 3 South Asian Cohorts	71861	RBC, Hb, Het, MCH, MCHC, MCV	75	[16]
7 African American cohorts	16500	RBC, Hb, Het, MCH, MCHC, MCV, RDW	7	(COGENT network) [12]

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Table 3.

Genomic loci associated with erythroid traits and erythropoiesis

Gene or genomic region	Chromosome	Erythroid trait	Meta-analysis study reference
HBS1L-MYB	6	Het, MCH, MCHC, MCV, RBC	[13–16]
ITFG3	16	Hb, MCH, MCHC, MCV, RBC	[12,13]
TMPRSS6	22	Hb, Het, MCH, MCHC, MCV	[13–16]
G6PD	X	Het, Hb, MCV, RBC, RDW	[12]
HFE	6	Hb, Het, MCH, MCV	[13,15,16]
ABO	9	Hb, Het, RBC, MCHC	[14]
CCND3	6	MCH, MCV, RBC	[13–16]
TFR2	7	Het, MCV, RBC	[13,15,16]
TFRC	3	MCH, MCV	[13,16]
PDGFRA-KIT	4	MCV, RBC	[13,14,16]
CITED2	6	MCH, MCV	[13,14,16]
HMOX2	16	MCH, MCV	[12]
SPTA1	1	MCHC	[13]
BCL11A	2	MCV	[13,16]
PRKCE	2	Het	[12]
CD 164	6	MCH	[12]
SH2B3	12	Hb	[16]