

Index

A

- ABCB19, mitoferrin I stabilization, 124
Acute chest syndrome. *See* Sickle cell anemia
Acute splenic sequestration crisis. *See* Sickle cell anemia
ADA. *See* Adenosine deaminase
Adair, Gilbert, 2
Adenosine deaminase (ADA), gene therapy for deficiency, 356–357
AGM. *See* Aorta-gonad-mesonephros
AHSP. *See* α -Hemoglobin stabilizing protein
ALAS. *See* Aminolevulinate synthase
 α -Globin
 comparative biology. *See* Hemoglobin
 mutations. *See* α -Thalassemia
 normal variants of gene cluster, 187
 structure and expression of gene cluster, 184–187
 unstable variants, 392–393
 α -Hemoglobin stabilizing protein (AHSP),
 β -thalassemia pathophysiology, 200
 α -Thalassemia
 epidemiology, 246–247, 285–286
 gene defects of α -globin gene cluster
 α -ZF mutation, 192
 deletions in duplicated structural genes, 189–191
 duplications, 188
 large deletions beyond gene cluster, 191–192
 normal variants versus pathological variants, 187–188
 overview, 183–184
 translocations, 188
 upstream regulatory element
 competition for elements, 193–195
 deletions, 193
geographic distribution, 139
hemoglobin E interactions, 230–231
hemoglobin H disease. *See also* Hemoglobin Bart's
 hydrops fetalis syndrome
diagnosis, 249–251
laboratory screening, 249–251
management, 251
severity, 247–249
malaria natural selection effect on distribution, 153–154
management
 iron chelation therapy
 costs, 280–281
- deferasirox, 279
deferiprone, 279–280
deferoxamine, 277–279
initiation, 275–276
monitoring, 275, 277, 280
principles, 271–272
mental retardation syndromes
ATR-16 syndrome
 chromosomal abnormalities, 257–258
 genetic defects, 256
ATR-X syndrome
 ATRX identification and characterization, 261–264
 clinical features, 259–260
 genotype–phenotype correlation, 262–263
 hematology, 260–261
 severity, 263
 X-linked heredity, 261
 overview, 138, 255–256
mild forms, 247
molecular diagnosis, 291
myelodysplastic syndrome association. *See* α -Thalassemia-myelodysplasia, 138
overview, 137, 245–246
phenotypes, 184
prevention programs
 genetic counseling, 293
 population control, 286–287
 preimplantation diagnosis, 294–295
 prenatal diagnosis, 293–295
 prospects, 296
sickle cell anemia severity impact, 307
 α -Thalassemia-myelodysplasia (ATMDS)
 ATRX mutations, 266
 overview, 138, 264–265
Aminolevulinate synthase (ALAS)
 ALAS-2 mutation
 X-linked protoporphyrin, 127
 X-linked sideroblastic anemia, 124, 127–128
 heme synthesis, 116–117
 isozymes, 117
 regulation, 121–122
Anemia. *See* Iron deficiency anemia; Sickle cell anemia;
 X-linked sideroblastic anemia
Aorta-gonad-mesonephros (AGM), erythropoiesis, 15–17
Aspirin, β -thalassemia intermedia management, 223

Index

- Atherosclerosis, hemoglobin as disease modifier, 410–411
- ATMDS. *See* α -Thalassemia-myelodysplasia
- ATR-16 syndrome
- chromosomal abnormalities, 257–258
 - genetic defects, 256
 - overview, 191–192
- ATRX
- ATR-X syndrome genotype–phenotype correlation, 262–263
 - characteristics of gene and protein, 261–262
 - protein function, 263–264
 - α -thalassemia-myelodysplasia mutations, 266
- ATR-X syndrome
- ATRX identification and characterization, 261–264
 - clinical features, 259–260
 - genotype–phenotype correlation, 262–263
 - hematology, 260–261
 - severity, 263
 - X-linked heredity, 261
- 5-Azacytidine, hemoglobin F induction, 90, 97
- B**
- BCL11A
- hemoglobin F induction studies, 91–94, 96–97
 - hemoglobin gene expression regulation, 61, 68, 75–77
 - polymorphisms and β -thalassemia impact, 203–204
- β -Globin
- comparative biology. *See* Hemoglobin
 - mutations. *See* β -Thalassemia
 - unstable variants, 392–393
- β -Thalassemia. *See also* Hemoglobin E β -thalassemia
- classification, 213
 - clinical presentation
 - anemia, 205–206
 - hemoglobin E β -thalassemia, 200–201
 - heterozygous disease, 199–200
 - homozygous disease, 200
 - iron overload manifestations
 - bone effects, 208
 - cardiac manifestations, 206–207
 - endocrine dysfunction, 207
 - hepatic manifestations, 207–208
 - overview, 204–205
 - tissue measurement, 206
 - epidemiology, 285–286
 - gene therapy
 - clinical trials, 361–363
 - erythroid cell models, 361
 - immunodeficiency disease management, 355–357
 - mouse models, 360–361
 - overview, 240, 355
 - selective amplification *in vivo*, 361

transduction optimization, 364–365

vectors

- gammaretroviral vectors, 358–359
- lentiviral vectors, 359–360
- limitations, 356–357
- locus control region, 358–359
- retroviral vector modification for safety, 357–358

genetic modifiers, 201–204

geographic distribution, 139

hematopoietic stem cell transplantation

- adults, 345

- alternative donors, 345–346

- mixed chimerism, 347

- outcomes

- haploidentical donors, 346–347

- matched donors, 345

- risk class approach, 344–345

hemoglobin F expression and severity of disease, 88

malaria natural selection effect on distribution, 153–154

management

- iron chelation therapy

- costs, 280–281

- deferasirox, 279

- deferiprone, 279–280

- deferoxamine, 277–279

- initiation, 275–276

- monitoring, 275, 277, 280

- principles, 271–272

mild phenotype prediction, 291–293

molecular diagnosis, 291

mutations

- deletions

- β -globin gene, 170, 172

- classification, 170–171

- upstream deletions, 172

- dominantly inherited disease

- alleles, 168–169

- codon deletion or insertion, 174–175

- elongated or truncated β -globin variants, 175

- missense mutations, 173–174

- nonsense mutation, 175

- overview, 172–173

- recessive versus dominant inheritance, 175–176

nondeletional forms

- initiation codon of β -globin mutations, 169

- point mutations, 162–166

- posttranscriptional modification

- mutants, 169

- RNA processing mutants, 166–169

- termination codon of β -globin mutations, 169–170

- transcriptional mutants, 160–161, 166

normal HbA₂ β -thalassemia, 176

- overview, 159–160
silent β -thalassemia, 176–177
trans-acting mutations, 177
transposon induction, 177
uniparental isodidomy, 178
- overview, 136–137
pathophysiology, 201
pluripotent stem cell modeling of disease, 376
prevention programs
carrier detection, 288–290
education, 287–288
genetic counseling, 293
outcomes, 295–296
population control, 286–287
preimplantation diagnosis, 294–295
prenatal diagnosis, 293–295
prospects, 296
- β -Thalassemia intermedia
clinical morbidity and pathophysiology
endocrine dysfunction, 221
gallstone, 221
hypercoagulability and thromboembolism,
216–219
iron overload, 215–216
leg ulcer, 221
pseudotumors, 220–221
pulmonary hypertension, 219–220
genetic defects, 214–215
management
anticoagulation therapy, 223
hemoglobin F induction, 223
iron chelation, 222
red blood cell transfusion, 222
splenectomy, 222–223
overview, 213–214
- BMP6, osteonecrosis variants in sickle cell
disease, 320
- Bohr, Christian, 2–3
- Bone marrow transplantation. *See* Hematopoietic
stem cell transplantation
- Bone morphogenetic protein-6 (BMP-6), hepcidin
synthesis regulation, 106–107
- C**
- CD163, hemoglobin scavenger system, 416–417
- Chronic granulomatous disease (CGD), gene therapy,
356–357, 363
- Cooley, Thomas, 4
- Coporphyrinogen, import by mitochondria, 119
- Coporphyrinogen oxidase (CPOX), heme synthesis,
119–120
- Corfu mutation, β -thalassemia, 176
- CREB-binding protein. *See* p300
- CTCF globin gene expression regulation, 60
- Cytoglobin, comparative biology in vertebrates, 50–51
- D**
- Decitabine, sickle cell anemia management, 336
- Deferasirox
dosing, 276
pharmacology, 279
safety and tolerability, 279
- Deferiprone
advantages, 280
pharmacology, 279–280
safety and tolerability, 280
- Deferoxamine
advantages, 278
dosing, 276
pharmacology, 277–278
safety and tolerability, 278–279
- E**
- Embryonic stem cell (ESC)
banking of cells, 378–379
costs of therapy, 377–378
differentiation protocols, 376–377
disease modeling applications
hemoglobinopathies, 374–375
overview, 374
gene therapy, 377
pluripotency factors, 373–374
- EPO. *See* Erythropoietin
- EPP. *See* Erythropoietic protoporphyrinia
- Erythroblast-macrophage protein. *See* Macrophage-
erythroblast attacher
- Erythroid Krüppel-like factor. *See* KLF1
- Erythropoiesis
erythroblastic islands and terminal
differentiation, 21–22
hematopoietic system ontogeny, 13–17
hemoglobin E β -thalassemia and excess, 236
lineage differentiation
adult hematopoiesis, 18
ontogeny, 17–18
niche, 19–20
regulation, 19–21
transcriptional regulation, 22–24
- Erythropoietic protoporphyrinia (EPP)
ferrochelatase mutation, 125
overview, 125–127
pathophysiology, 122
- Erythropoietin (EPO)
anemia and underproduction, 38
central nervous system function, 33–34
erythrocytosis and overproduction, 38–39
erythropoiesis role, 20, 31
expression regulation
HNF-4, 37
hypoxia-inducible factor, 35–37
overview, 34–35

Index

Erythropoietin (EPO) (*Continued*)

- p300, 37–38
- history of study, 29–30
- ischemia/reperfusion injury studies, 34
- production, 30–32
- receptor interactions, 32–33
- structure, 32
- therapy, 39–41

F

Fas, erythroid homeostasis role, 20, 22

FECH. *See* Ferrochelatase

Feline leukemia virus C receptor (FLVCR),
heme transport, 122

Ferritin, hemoglobin H disease levels, 250

Ferrochelatase (FECH)

- erythropoietic protoporphyrin mutation, 125
- heme synthesis, 120–121

- multienzyme complexes, 122–123

Fetal hemoglobin. *See* Hemoglobin F

FLVCR. *See* Feline leukemia virus C receptor

FOG-1

- GATA mediation in hemoglobin gene expression regulation, 69–72

- NuRD interactions, 71, 75

FOP1, hemoglobin F induction studies, 95

G

Gallstone

- β-thalassemia intermedia, 221
- hemoglobin E β-thalassemia, 236

Garrod, Archibald, 4

GATA1

- β-thalassemia mutation, 177
- globin gene expression regulation, 60
- hemoglobin F induction studies, 91
- hemoglobin gene expression regulation, 68–72

GATA2

- erythropoiesis regulation, 22
- GATA1 interactions, 70

Gene therapy, β-thalassemia

- clinical trials, 361–363
- erythroid cell models, 361
- immunodeficiency disease management, 355–357
- mouse models, 360–361
- overview, 240, 355
- selective amplification *in vivo*, 361
- transduction optimization, 364–365

vectors

- gammaretroviral vectors, 358–359
- lentiviral vectors, 359–360
- limitations, 356–357
- locus control region, 358–359
- retroviral vector modification for safety, 357–358

Genome-wide association study (GWAS)

- hemoglobin E β-thalassemia, 239
- sickle cell anemia
 - overview, 316–317
 - population coverage, stratification, and admixture, 317–318
 - published studies, 318–320
 - replication, 318
 - sequencing of variants, 318
 - statistical power, 317
 - stroke, 320

Graft-versus-host disease (GVHD), hematopoietic stem cell transplantation, 344, 349–350

GVHD. *See* Graft-versus-host disease

GWAS. *See* Genome-wide association study

H

Haptoglobin (Hp)

- hemoglobin scavenger system, 415
- therapeutic applications, 419

HbAE Bart's disease, 232

HbAEF Bart's disease, 232

HBOC. *See* Hemoglobin-based oxygen carrier

HBSIL, hemoglobin F induction studies, 94

HDAC. *See* Histone deacetylase

Heart rate variability (HRV), hemoglobin E β-thalassemia, 235

Hematopoiesis. *See* Erythropoiesis

Hematopoietic stem cell (HSC), ontogeny and development, 14–16

Hematopoietic stem cell transplantation (HSCT)

β-thalassemia

- adults, 345
- alternative donors, 345–346
- mixed chimerism, 347
- outcomes
 - haploidentical donors, 346–347
 - matched donors, 345
- risk class approach, 344–345

sickle cell anemia

- hemoglobin F increase after failed transplantation, 350–351
- mixed chimerism, 349–350
- outcomes, 348–349
- overview, 347–348
- regimen modification, 350

Heme

disorders

- erythropoietic protoporphyrin, 125–127
- overview, 124–125
- X-linked protoporphyrin, 127
- X-linked sideroblastic anemia, 127–128

low-density lipoprotein oxidation, 410

structure, 425

synthesis

- aminolevulinate synthase, 116–117
coporphyrinogen import by mitochondria, 119
coporphyrinogen oxidase, 119–120
ferrochelatase, 120–121
hydroxymethylbilane synthase, 118
multienzyme complexes, 122–124
overview, 116
porphobilinogen synthase, 117–118
protoporphyrinogen oxidase, 120
regulation, 121–122
uroporphyrinogen decarboxylase, 118–119
uroporphyrinogen synthase, 118
- Heme oxygenase-1 (HO-1)
hemoglobin scavenger system, 417
sickle cell anemia and malaria tolerance mechanism, 409
- Hemoglobin
comparative biology
gene clusters in jawed vertebrates
coordinated regulation between α -globin and β -globin gene clusters, 53
developmental regulation of expression, 51–53
evolution of multiple globin gene clusters, 53–54
lineage-specific gains and loss of β -like globin genes, 55–58
stability of α -globin gene cluster, 54–55
globin gene expression regulation, 58–61
globin heme protein family, 49–51
cooperativity, 388–390
developmental regulation of globin gene synthesis, 390–391
disorders. *See also specific disorders*
epistatic interactions, 154–155
frequency, 147–148
general classification, 134–135
natural selection for malaria protection
hemoglobin C, 151–152
hemoglobin E, 152–153
hemoglobin S, 148–151
thalassemia distribution impact, 153–154
fetal-to-adult hemoglobin switch. *See Hemoglobin F*
gene expression regulation
BCL11A, 68, 75–77
GATA, 68–75
KLF1, 76
overview, 67–68
history of study
diseases, 4–6
properties, 1–4
synthesis, 6–7
mean cell hemoglobin concentration and sickle cell anemia severity impact, 307
nitric oxide binding and disease modification, 411–413
- oxidation and disease modification, 413–415
scavenger system
CD163, 416–417
haptoglobin, 415
heme oxygenase, 417
hemopexin, 415–416
therapeutic applications, 417–419
structure, 387–388
synthesis, 386–387
variants
definition, 383
globin chain elongation mutants, 396–397
high oxygen affinity variants, 393–395
identification, 390
laboratory testing, 391–392
low oxygen affinity variants, 395
methemoglobin variants, 395–396
multiple function variants, 397–399
table of types, 384–386
unstable variants, 392–393
- Hemoglobin A, comparative biology in vertebrates, 50–51
- Hemoglobin Bart's hydrops fetalis syndrome (BHFS)
overview, 137, 245, 251–252
prenatal management, 252–253
prevention, 252–253
- Hemoglobin-based oxygen carrier (HBOC)
oxidation, 415
pulmonary hemodynamic studies, 411, 413
sickle cell anemia treatment, 406–407
- Hemoglobin Bristol-Alesha, 399
- Hemoglobin C, natural selection for malaria protection, 151–152
- Hemoglobin Constant Spring (HbCS), 137, 249, 397
- Hemoglobin Cranston, 397
- Hemoglobin E
 α -thalassemia interactions, 230–231
natural selection for malaria protection, 152–153
properties, 229–230
- Hemoglobin E β -thalassemia
clinical presentation, 200–201, 233–234
complications
cardiac disease, 235
endocrine dysfunction, 237
erythropoiesis excess, 236
gallstone, 236
hypertension, convulsions, and cerebral hemorrhage, 236
hypoxemia, 235–236
infection susceptibility, 235
iron overload, 236–237
jaundice, 236
splenomegaly, 234–235
thromboembolism, 236
genotype–phenotype correlation
 α -thalassemia coinheritance, 238

Index

- Hemoglobin E β -thalassemia (*Continued*)
anemia adaptation, 239
 β^E -globin mRNA splice variants, 238
 β -thalassemia mutations, 237–238
genome-wide association study, 239
hemoglobin F levels, 238
pyrimidine 5' nucleotidase deficiency, 238
severity, 237
laboratory findings, 231, 234
pathophysiology, 232–233
prevention, 240
treatment, 239–240
- Hemoglobin F
expression
regulation studies, 91–97
severity of blood diseases, 88–89
- HbA₂ β -thalassemia levels, 176
- hematopoietic stem cell transplantation failure
and increase, 350–351
- hemoglobin E β -thalassemia levels, 238
- hereditary persistence of fetal hemoglobin, 17–18,
89, 136–137, 203
- induction therapy
sickle cell anemia management, 336
 β -thalassemia intermedia, 223
therapeutic application, 91–97
- sickle cell anemia severity impact, 88, 307
- β -thalassemia impact, 202–203
- therapeutic induction, 89–90
- Hemoglobin H α -thalassemia. *See* α -Thalassemia
- Hemoglobin S
natural selection for malaria protection,
148–151
- sickle cell anemia polymerization, 343–344, 399
- Hemoglobin Zurich, 397–398
- Hemopexin (Hpx)
hemoglobin scavenger system, 415–416
therapeutic applications, 419
- Hepcidin
iron homeostasis, 106
synthesis regulation
erythropoiesis, 108
inflammation, 109
overview, 106–108
- Heredity hemochromatosis, 109–110
- Heredity persistence of fetal hemoglobin (HPFH),
17–18, 89, 136–137, 203
- Herrick, James, 9
- HIF. *See* Hypoxia-inducible factor
- High-performance liquid chromatography (HPLC),
hemoglobin variants, 391
- Histone deacetylase (HDAC), hemoglobin F induction
with inhibitors, 90
- HMBS. *See* Hydroxymethylbilane synthase
- HNF-4, erythropoietin gene regulation, 37
- HO-1. *See* Heme oxygenase-1
- Hookworm, iron deficiency anemia association, 428–429
- HPFH. *See* Hereditary persistence of fetal hemoglobin
- HPLC. *See* High-performance liquid chromatography
- Hpx. *See* Hemopexin
- HRV. *See* Heart rate variability
- HSC. *See* Hematopoietic stem cell
- HSCT. *See* Hematopoietic stem cell transplantation
- Hydrogen peroxide, hemoglobin oxidation, 413
- Hydroxycarbamide, hemoglobin F induction for
 β -thalassemia intermedia, 223
- Hydroxymethylbilane synthase (HMBS)
heme synthesis, 118
multienzyme complexes, 123
- Hydroxyurea
hemoglobin E β -thalassemia management, 240
hemoglobin F induction, 90
sickle cell anemia management, 335–336
- Hypoxemia, hemoglobin E β -thalassemia, 235–236
- Hypoxia-inducible factor (HIF)
erythropoietin gene regulation, 35–37
iron regulation, 106
prolylhydroxylase inhibitors, 41
VHL binding, 39
- I
- Induced pluripotent stem cell (iPSC)
banking of cells, 378–379
costs of therapy, 377–378
differentiation protocols, 376–377
disease modeling applications
hemoglobinopathies, 374–375
overview, 374
- gene therapy, 377
- pluripotency factors, 373–374
- iPSC. *See* Induced pluripotent stem cell
- Iron
accumulation rate in thalassemia, 272
- assessment
cardiac concentration, 273–274
extrahepatic iron, 274
ferritin in serum, 272–273
liver concentration, 273
nontransferrin-bound iron, 274
- cellular iron
functions, 103
transport, 103–105
uptake, 103
- disorders
anemia of inflammation, 109
deficiency, 109
hereditary hemochromatosis, 109–110
iron-refractory iron deficiency anemia, 109
overload
erythropoiesis inefficiency, 110
transfusion, 109

- distribution and storage, 102
homeostasis
 cellular, 104
 systemic
 hepcidin role, 106–109
 overview, 102, 424
hypoxia sensing, 106
intake, 101–102
mitochondrial transport, 104–105
overload and β -thalassemia
 β -thalassemia intermedia, 215–216
 clinical manifestations
 bone effects, 208
 cardiac manifestations, 206–207
 endocrine dysfunction, 207
 hepatic manifestations, 207–208
 tissue measurement, 206
hemoglobin E β -thalassemia, 236–237
pathophysiology, 204–206
 treatment. *See* Iron chelation therapy
plasma concentration regulation, 102
proteins
 classification, 423
 synthesis regulation in erythroid
 cells, 105–106
recycling, 102
regulatory elements, 105
Iron chelation therapy
 β -thalassemia intermedia, 222
 costs, 280–281
 deferasirox, 279
 deferiprone, 279–280
 deferoxamine, 277–279
 initiation, 275–276
 monitoring, 275, 277, 280
Iron deficiency anemia
 clinical features, 425–427
 diagnosis, 425–427
 epidemiology, 425
 etiology
 blood loss, 427
 diet, 429–430
 hookworm, 428–429
 malabsorption, 429–430
 malaria comorbidity, 428
 pregnancy and maternal deficiency, 427–428
 overview, 109, 424–425
 prospects for study, 431–432
 refractory disease, 109
 treatment and prevention
 fortification, 430
 umbilical cord delayed clamping, 430–431
- J**
Jaundice, hemoglobin E β -thalassemia, 236
- K**
KLF1
 β -thalassemia mutation, 177
 erythropoiesis regulation, 23–24
 hemoglobin F induction studies, 91, 93–94, 96
 hemoglobin gene expression regulation, 76
- L**
LDL. *See* Low-density lipoprotein
Leg ulcer
 β -thalassemia intermedia, 221
 sickle cell anemia, 305
Low-density lipoprotein (LDL), oxidation
 by heme, 410
- M**
Macrophage-erythroblast attacher (MAEA), 21–22
MAEA. *See* Macrophage-erythroblast attacher
Magnetic resonance imaging (MRI)
 angiography in β -thalassemia intermedia, 219
 iron measurement in tissue, 206, 273–274
Malaria
 hemoglobin natural selection for protection
 hemoglobin C, 151–152
 hemoglobin E, 152–153
 hemoglobin S, 148–151
 iron deficiency anemia comorbidity, 428
 sickle cell anemia–induced tolerance
 mechanisms, 409
MC. *See* Mixed chimerism
Mean cell hemoglobin concentration.
 See Hemoglobin
Med1, hemoglobin gene expression regulation, 72
Methemoglobin, variants, 395–396
Mitochondria
 coporphyrinogen import, 119
 iron transport, 104–105
Mixed chimerism (MC), hematopoietic stem cell
 transplantation, 347, 349–350
MRI. *See* Magnetic resonance imaging
MYB, hemoglobin F induction studies, 94, 96
Myoglobin
 comparative biology in vertebrates, 50–51
 polymorphisms and β -thalassemia impact, 203
- N**
***Ncx1*, 17**
Neuroglobin, comparative biology in vertebrates, 50–51
NF-E4, hemoglobin F induction studies, 95
Nitric oxide (NO), hemoglobin binding and disease
 modification, 411–413
NO. *See* Nitric oxide
NuRD, FOG-1 interactions, 71, 75

Index

O

- Osteoporosis, β -thalassemia, 208, 221
Oxygen binding, hemoglobin variants
 binding curve, 391
 high oxygen affinity variants, 393–395
 low oxygen affinity variants, 395

P

- p300
 erythropoietin gene regulation, 37–38
 GATA1 interactions, 71–72
Pauling, Linus, 5
PBGs. *See* Porphobilinogen synthase
PCBPs. *See* Poly(RC)-binding proteins
Perutz, Max, 3–5
Pluripotent stem cell. *See* Embryonic stem cell; Induced pluripotent stem cell
Poly(RC)-binding proteins (PCBPs), iron binding, 103–104
Porphobilinogen synthase (PBGS), heme synthesis, 117–118
PPOX. *See* Protoporphyrinogen oxidase
Pregnancy
 β -thalassemia intermedia considerations, 221
 iron deficiency, 427–428
Protoporphyrinogen oxidase (PPOX)
 heme synthesis, 120
 multienzyme complexes, 122–123
PU.1, erythropoiesis regulation, 23
Pulmonary hypertension, hemoglobin binding of nitric oxide, 411, 413
Pulmonary hypertension, β -thalassemia intermedia, 219–220
Pyrimidine 5' nucleotidase, hemoglobin E
 β -thalassemia and deficiency, 238

R

- Red blood cell. *See* Erythropoiesis
RUNX1, erythropoiesis regulation, 23

S

- SCA. *See* Sickle cell anemia
SCE. *See* Stem cell factor
SCID. *See* Severe combined immunodeficiency
Severe combined immunodeficiency (SCID), gene therapy, 356–357
Sickle cell anemia (SCA)
 clinical features
 adults, 306
 early years, 303–304
 first year, 303
 late childhood, 304–305
 overview, 306
genome-wide association study
 overview, 316–317
 population coverage, stratification, and admixture, 317–318
 published studies, 318–320
 replication, 318
 sequencing of variants, 318
 statistical power, 317
 stroke, 320
genotype–phenotype correlations, 302–303
geographic distribution and variability, 301–302, 308
hematopoietic stem cell transplantation
 hemoglobin F increase after failed transplantation, 350–351
 mixed chimerism, 349–350
 outcomes, 348–349
 overview, 347–348
 regimen modification, 350
hemoglobin S polymerization, 343–344, 399
heritability, 315–316
history of study, 5–6, 9
malaria tolerance mechanisms, 409
management
 acute chest syndrome, 331–332
 acute splenic sequestration
 adult care, 334
 crisis, 331
 decitabine, 336
 education, 327–328
 hemoglobin F induction, 336
 hemoglobin-based oxygen carrier therapy, 406–407
 hydroxyurea, 335–336
 infection prevention and management, 328–329
 pain control, 329–331
 stroke management and screening, 332–334
 transfusion, 334–335, 374–375
mortality
 causes, 308
 infants, 326
 survival rates, 306
neonatal screening, 326–327
overview, 138–139
phenotype determination, 314–315
pluripotent stem cell modeling of disease, 375–376
prevention, 309
severity determinants
 α -thalassemia, 307
 environment, 307–308
 genetics, 308, 318–320
 hemoglobin F levels, 88, 307
 mean cell hemoglobin concentration, 307
Sideroblastic anemia. *See* X-linked sideroblastic anemia
SOX6, hemoglobin F induction studies, 92–93

SOX8, α -thalassemia deletion, 191

Splenectomy

β -thalassemia intermedia management, 222–223

hemoglobin H disease management, 251

Stem cell. *See* Embryonic stem cell; Hematopoietic stem cell transplantation; Induced pluripotent stem cell

Stem cell factor (SCF), erythropoiesis role, 20

Stroke

β -thalassemia intermedia, 219

sickle cell anemia

genetic variants, 320

management and screening, 332–334

T

TAL1

GATA interactions, 73

globin gene expression regulation, 60

hemoglobin F induction studies, 91

Thalassemia. *See also specific thalassemias*

history of study, 5–9

molecular diagnosis, 291

prevention programs

genetic counseling, 293

population control, 286–287

preimplantation diagnosis, 294–295

prenatal diagnosis, 293–295

prospects, 296

Thromboembolism

β -thalassemia intermedia, 216–219

hemoglobin E β -thalassemia, 236

Transferrin

iron storage, 102

receptor, 103

Transfusion

animal studies of old blood transfusion, 407–409

β -thalassemia intermedia management, 222

hemoglobin E β -thalassemia management, 239–240

iron overload induction, 109

red blood cell storage lesion, 407

sickle cell anemia management, 334–335, 374

U

UGT1A1, sickle cell anemia variants, 320

Umbilical cord, delayed clamping for iron deficiency anemia prevention, 430–431

Uniparental isodidom, β -thalassemia, 178

UROD. *See* Uroporphyrinogen decarboxylase

Uroporphyrinogen decarboxylase (UROD), heme synthesis, 118–119

Uroporphyrinogen synthase (UROS)

heme synthesis, 118

multienzyme complexes, 123

UROS. *See* Uroporphyrinogen synthase

V

VHL, hypoxia-inducible factor binding, 39

X

X-linked protoporphyrin (XLPP)

ALAS-2 mutation, 127

overview, 127

pathophysiology, 122

X-linked sideroblastic anemia (XLSA)

ALAS-2 mutation, 124, 127–128

overview, 127–128

XLPP. *See* X-linked protoporphyrin

XLSA. *See* X-linked sideroblastic anemia

XMN1, polymorphisms and β -thalassemia impact, 203

XPD, β -thalassemia mutation, 177