EXTRACTED DATA (SYNTHESIS MATRIX)

Authors (year)	Country (setting)	Design	Participant characteristics	Genotype co-inheritance patterns analysed	Specific RBC polymorphisms studied	Malaria outcome / phenotype measured	Interaction direction ^a	Epistatic interaction outcome (authors' wording)	Context modifiers / analytic checks	Effect magnitude – best-adjusted estimate (95 % CI)
Williams et al. (2005)	Kenya (Kilifi HDSS; birth & community cohorts)	Prospective cohort	3 995 newborns; follow-up of 370 survivors to age < 8 y	HbAS + α^+-thal (–α/αα & –α/–α)	HbS; α^+-thalassaemia	Uncomplicated malaria incidence; hospitalised severe malaria; parasite density; mortality	Antagonistic	"Dual genotype abolished the 81 % protection of HbAS against severe disease"	Adjusted for age, sex, ethnicity, ITN intervention arm, distance to clinic	Severe-malaria IRR: HbAS 0.19; –α/–α 0.54; HbAS + –α/–α 0.90 (0.30–2.74)
Atkinson et al. (2014)	Kenya (Kilifi hospital)	Case–control	996 severe cases; 1 220 communit	Hp2-1 + α^+-thal; Hp2-2 + α^+-thal	Haptoglobin Hp2-1/Hp2-2; α^+-thalassaemia	WHO-defined severe malaria; in-	Synergistic (Hp2-1); antagoni	"Hp2-1 + –α/–α halves severe-malaria	Adjusted logistic model for age, sex,	Severe-malaria OR: Hp2-1 + –α/–α 0.48 (0.32–0.73);

			y controls (< 14 y)			hospital death	stic (Hp2-2)	odds; Hp2-2 + –α/–α abolishes protectio n"	ethnicity , HbAS and α⁺-thal stratifica tion	Hp2-2 + – α/–α 1.10 (0.78–1.55)
Abad et al. (2025)	Ghana & DRC (comm unity surveys)	Cross-sectional	424 volunteers (all ages; 55 % female)	Multilocu s: counts of PIEZO1 E756del, G6PD A⁻, HbS, PKLR variants	PIEZO1 E756del (±E750Q); G6PD A⁻; HbS/HbC; PKLR E277K/L241V	High-density parasitae mia by duplex qPCR	Additive	"Individ uals with multiple protectiv e alleles had lower rates of high-density parasitae mia, suggestin g an additive effect"	Adjusted for age, sex; pregnan cy analysed separatel y; Fisher's exact & logistic regressio n; LD checks for PIEZO1 variants	≥ 2 variants vs none OR 0.32 (0.14–0.74); PIEZO1 OR 0.48 (0.23–0.99); G6PD A⁻ OR 0.45 (0.21–0.97); HbS OR 0.41 (0.17–0.99); R = –0.13, p = 0.036

Mpimbaza et al. (2018)	Uganda (Jinja hospital clinic)	Matched case–control	325 severe; 325 uncomplicated; 325 community; median age 2 y	HbAS + α^{+}-thal (heterozygous)	HbS; α^{+}-thalassaemia; G6PD A^{-}	Severe vs uncomplicated malaria	Antagonistic	"Dual carriers lost the single-locus protection of HbAS against severe disease"	Matched by age, sex, village; adjusted for ethnicity, ITN use; G6PD as covariate	Severe vs uncomplicated OR 0.45 (0.11–1.84)
Guindo et al. (2011)	Mali (Bamako hospital)	Case–control	220 severe vs 404 uncomplicated cases (≤ 15 y)	HbAS × G6PD A^{-} (female vs male strata)	HbS; G6PD A^{-}	Severe malarial anaemia	Antagonistic (females); neutral (males)	"In sickle-trait females, heterozygous G6PD A^{-} greatly increased SMA risk; no	Adjusted for age, ethnicity; α^{+}-thal not typed; small female dual-carrier	Females OR 15.0 (2.07–132.3); Males OR 0.47 (0.07–2.40)

								effect in males"	cell (n ≈ 8)	
Udomsangpetch et al. (1993)	Myanmar (military hospitals)	Cross-sectional survey	383 adult males (19–45 y)	(i) α-thal × G6PD; (ii) β-thal × G6PD; (iii) HbAE × G6PD	α- & β-thalassaemia traits; HbE; multiple G6PD alleles	WHO clinical severity categories; peripheral parasitaemia (%)	Synergistic / protective	"No cerebral-malaria cases in dual-defect carriers; parasitaemia 1.98 % vs 3.05 % in non-carriers"	Adult-male cohort; χ^2 across strata; no multivariable adjustment	Cerebral-malaria risk: 0/25 vs 46/358 ($p \approx 0.04$); parasitaemia 1.98 % vs 3.05 %
Ahmed et al. (2020, Kenya)	Kenya (Vihiga hospital)	Case–control	574 children (6 mo–3 y)	Hb genotype (AA, AS, SS) × G6PD phenotype (normal,	HbAA/AS/SS; G6PD normal/intermediate/deficient	Severe malarial anaemia vs non-SMA	Bidirectional	"G6PD intermediate in HbAA increased SMA risk; HbAS +	Adjusted for age, sex, nutritional z-score, parasitaemia;	AA + intermediate OR 1.54 (1.01–2.34); AS + normal OR 0.34 (0.16–0.91); AS + deficie

				intermediate, deficient)				normal G6PD was protective"	fluorescent spot & PCR for G6PD; PCR for Hb genotype	nt OR 0.24 (0.05–1.37)
Purohit et al. (2023)	India (Burla tertiary centre)	Case–control	415 severe; 372 uncomplicated; 481 uninfected controls (15–65 y)	α^{+}-thal within HbAA, HbAS, HbSS strata	α-globin $-\alpha^{3\cdot7}/-\alpha^{4\cdot2}$; HbS	WHO-defined severe malaria & sub-syndromes	Protective (HbAA); antagonistic (HbAS); neutral (HbSS)	"α^{+}-thal lowers severe-malaria risk in HbAA, but reverses the protection of HbAS"	Adjusted for age, sex, tribal vs non-tribal ethnicity; matched hospital controls	HbAA + α^{+}-thal OR 0.61; HbAS + α^{+}-thal OR 4.11 (1.95–8.71)
Opi et al. (2018)	Kenya (Kilifi	Case–control	1 716 cerebral-	CR1 Sl_2/McC[b]	CR1 Sl (rs17047661); McC	Cerebral malaria;	Antagonistic	"Sl_2 halves	Mixed-effects	Cerebral malaria:

	HDSS case–control)		malaria cases (< 14 y) vs 3 829 controls	× α^{+}-thal; McC^{b} × α^{+}-thal; Sl_2/McC^{b} haplotypes	(rs17047660); α^{+}-thal ($-\alpha^{3\cdot7}$); HbAS; ABO	severe anaemia; respiratory distress; mortality		cerebral-malaria odds only in αα/αα children; α^{+}-thal abolishes this benefit"	model adjusted for ethnicity, residence, HbAS, α^{+}-thal, ABO; interaction term tested	aOR 0.67 (0.52–0.87); mortality: aOR 0.50 (0.30–0.80); McC^{b}: aOR 1.19 (1.02–1.38)
Awah & Uzoegwu (2006)	Nigeria (Elele community cohort)	Prospective cohort	75 children (1–18 y)	HbAS + G6PD deficiency	HbS; G6PD qualitative	Clinical malaria incidence; parasite density; severe-anaemia episodes	Synergistic / protective	"Dual carriers had no severe malaria and fewer clinical attacks"	Monthly active follow-up; passive surveillance; age-matched groups	Parasite density: 478±245 vs 4 350±865 parasites/µL; severe-anaemia 0 vs 0.08 episodes/1 000 p-m

Awah et al. (2012)	Nigeria (Elele community survey)	Cross-sectional survey	400 volunteers (5–50 y)	Hb genotype × G6PD deficiency	Hb genotype; G6PD qualitative	Annual malaria-attack frequency; parasitaemia grade; severe-symptom episodes	Synergistic / protective	"G6PD-deficient HbAS heterozygotes experienced fewer attacks and none had severe malaria"	Stratified by age group and sex; χ^2 tests	MP+++ severe malaria: 0 % (dual) vs 3.4 % (HbAS only) and 7.9 % (HbAA only); <2 attacks: 58.3 % vs 70.9 % vs ?
Saguti et al. (2013)	Tanzania (Korogwe district hospital)	Retrospective case–control	148 children (1–15 y; 95 mild, 53 severe)	α^+-thal ($-\alpha^{3\cdot7}$) × GSTP1 I105V; GSTM1; GSTT1	α^+-thal ($-\alpha^{3\cdot7}$); GSTP1 I105V; GSTM1 null; GSTT1 null	Severe vs mild malaria	Antagonistic (inverse)	"GSTP1 mutants attenuate the protective effect of α^+-thalassaemia"	Adjusted for age (< 5 vs ≥ 5 y), sex, parasitaemia; mutual adjustment of	GSTP1 OR 2.58 (1.46–4.54); α^+-thal OR 0.81 (0.45–1.48); after GST adjustment α^+-thal OR 0.78 (0.43–1.45); in <5

									GST loci	y: GSTP1 OR 2.79 (1.54–5.06)
Shah et al. (2016)	Zambia (Choma hospital)	Case–control	133 children (< 6 y; 67 SMA, 66 uncomplicated)	CYB5R3 T117S × G6PD A^+/A^-	G6PD c.376G (A^+), c.202A/376G (A^-); CYB5R3 T117S	Severe malarial anaemia vs uncomplicated malaria	Bidirectional	"CYB5R3 T117S is protective in G6PD-normal children but harmful when co-inherited with G6PD variants"	Adjusted for weight, fever duration, prehospital treatment; tested interaction term	CYB5R3 × G6PDWT: OR 0.30 (0.10–0.90); CYB5R3 × G6PDvar: OR 3.10 (0.60–15.90); additive G6PD OR 2.6 (1.3–5.3)

RISK OF BIAS ASSESSMENT RESULTS

Study	Case selection	Control representativeness	Exposure genotyping	Confounding control	Precision	Outcome measurement	Missing data / exclusions	Overall RoB
Williams 2005 (Kenya)	Low	Low	Low	Moderate	Low	Low	Moderate	Moderate
Atkinson 2014 (Kenya)	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate
Abad 2025 (Ghana + DRC)	Moderate	Low	Low	Moderate	Low	Moderate	Low	Moderate
Mpimbaza 2018 (Uganda)	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate
Ahmed 2020 (Sudan)	High	High	Low	Moderate	Moderate	Low	Moderate	Serious
Udomsangpetch 1993 (Myanmar)	High	High	Moderate	High	Moderate	High	Low	Serious
Ahmed 2020 (Kenya, Vihiga)	Moderate	High	Low	Moderate	Moderate	Low	Low	Serious
Purohit 2023 (India)	Moderate	High	Low	Moderate	Moderate	Low	Low	Serious

Opi 2018 (Kenya)	Low	Low	Low	Moderate	Low	Low	Moderate	Moderate
Awah & Uzoegwu 2006 (Nigeria)	Moderate	High	Low	High	Moderate	Moderate	Low	Serious
Saguti 2013 (Tanzania)	High	High	Low	High	High	Low	Moderate	Serious
Shah 2016 (Zambia)	High	High	Low	Moderate	High	Low	Moderate	Serious
Awah 2012 (Nigeria)	Moderate	High	Low	High	Moderate	Moderate	Low	Serious
Guindo 2011 (Mali)	High	High	Low	Moderate	High	Low	Moderate	Serious