



Figures and figure supplements

Characterisation of the opposing effects of G6PD deficiency on cerebral malaria and severe malarial anaemia

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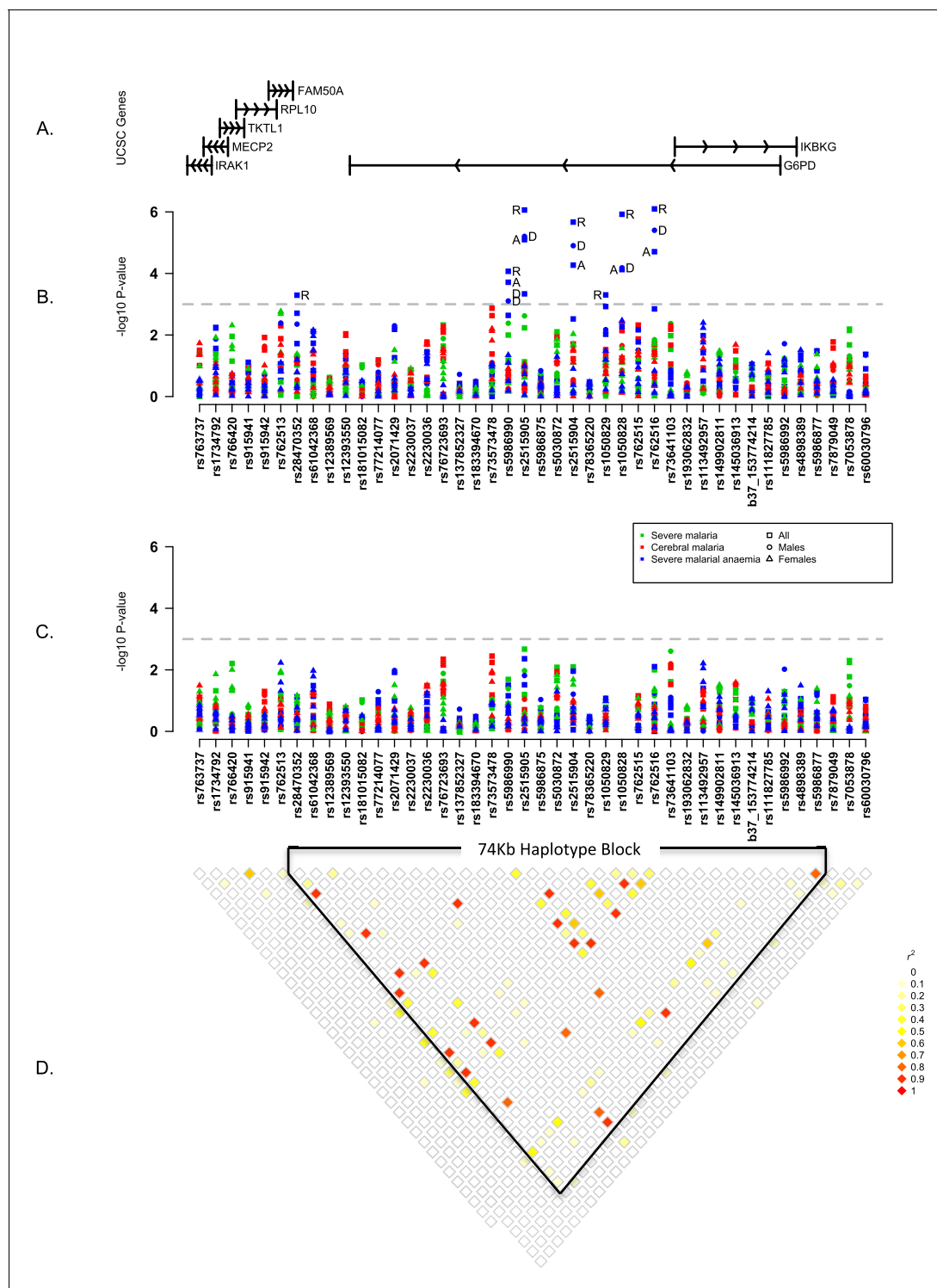


Figure 1. Summary of single SNP tests of association at all sites combined. (A) Schematic of genes across the genotyped region plotted relative to evenly spaced positions of SNPs in (B). (B) Manhattan plot showing the results of all single SNP tests of association with all severe malaria and with cerebral malaria and severe malarial anaemia for males, females and all individuals combined for models of association with additive, dominant, recessive and heterozygous (females only) modes of inheritance. Mode of inheritance is indicated as additive (A), dominant (D), recessive (R) or heterozygous (H) only for SNPs with a P value $< 1 \times 10^{-3}$, as indicated by the horizontal dashed grey line. See **Figure 1—source data 1** for detailed association results. (C) As for (B), but results are adjusted for additive effects at G6PD+202. See **Figure 1—source data 2** for detailed association results with adjustment for G6PD+202. (D) Pairwise r^2 between pairs of SNPs in control individuals. Samples are excluded from analysis at sites where an

Figure 1 continued on next page

Figure 1 continued

SNP is monomorphic; this accounts for a variation in sample size across SNPs. Results for SNPs that are monomorphic or extremely rare across all sites (maximum minor allele frequency <0.01) are not shown. All results are adjusted for gender, ethnicity and the sickle-cell trait. See **Figure 1—figure supplement 1** for detailed forest plots of association at G6PD+202. See **Figure 1—figure supplement 2** for a summary of genetic heterogeneity of cerebral malaria and severe malarial anaemia within and across African sites.

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The following source data is available for figure 1:

Source data 1. Single SNP association test results.

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Source data 2. Single SNP association test results with adjustment for additive effect of G6PD+202.

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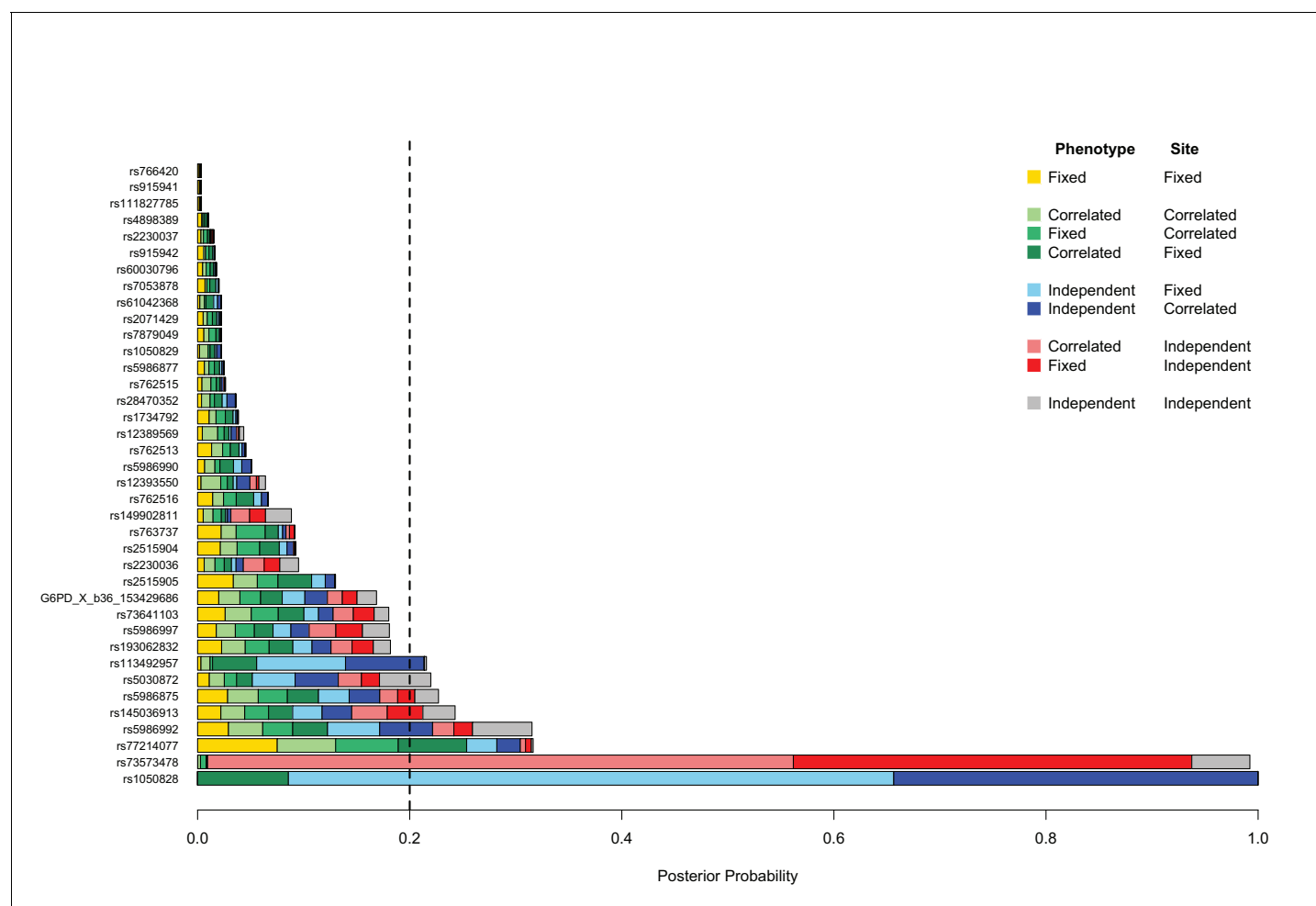


Figure 1—figure supplement 1. Genetic heterogeneity of severe malaria sub-phenotypes within and across African sites. Bar plots show the posterior probability on each of nine models of association in which effects on cerebral malaria and severe malarial anaemia sub-phenotypes are fixed, independent or correlated *within* a site combined with being fixed independent or correlated *across* all the sites, as indicated by the different colours; the remainder of the posterior probability is on the null model. The null model is assumed to be most likely 80% of the time; the remaining models are equally likely. Approximate Bayes Factors (ABFs), calculated as the ratio of the marginal likelihoods of a given model and the null model in which there is no effect on any of the subtypes, are used to compare the evidence between models. (See Methods and materials for details and specification of priors.) Estimated effects are calculated for all individuals within each site and adjusted for the sickle-cell trait, ethnicity and sex. Dashed line at posterior probability = 0.2 indicates where the posterior expectation of a non-null model is greater than the prior expectation. Only variants with valid estimates of effect at at least two sites are shown.

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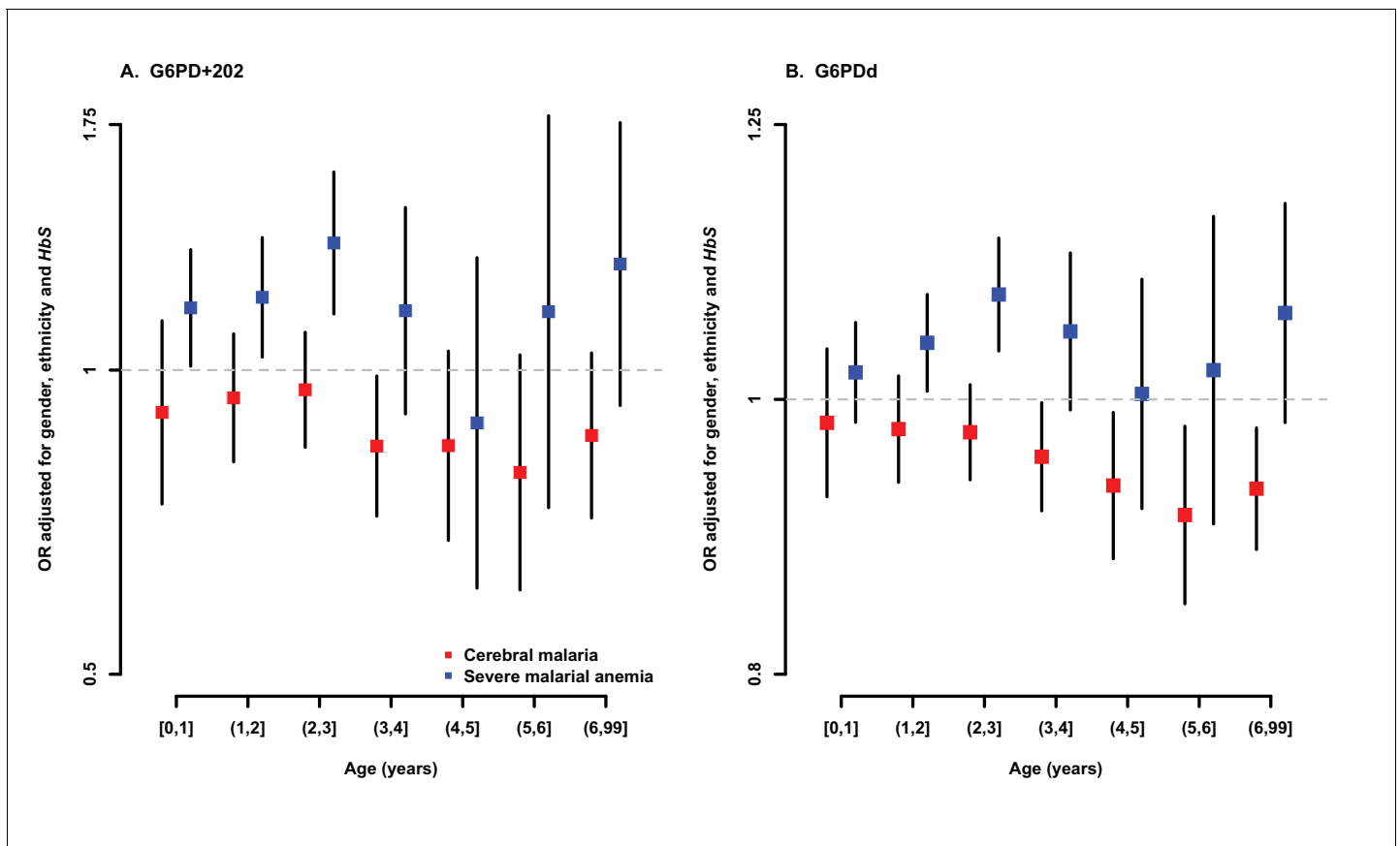


Figure 1—figure supplement 2. Association between G6PD deficiency and severe malaria sub-phenotypes stratified by age. ORs and 95% confidence intervals for association with (A) G6PD+202 assuming an additive mode of inheritance, and (B) for each 10% increase in G6PDd score, adjusted for gender, ethnicity and sickle-cell trait (*HbS*) in yearly age categories. Results are shown for association with cerebral malaria and severe malarial anaemia for all samples combined excluding (A) Vietnam and Papua New Guinea, where G6PD+202T is not found, and (B) Vietnam, where the median age of cases is outside the range considered here.

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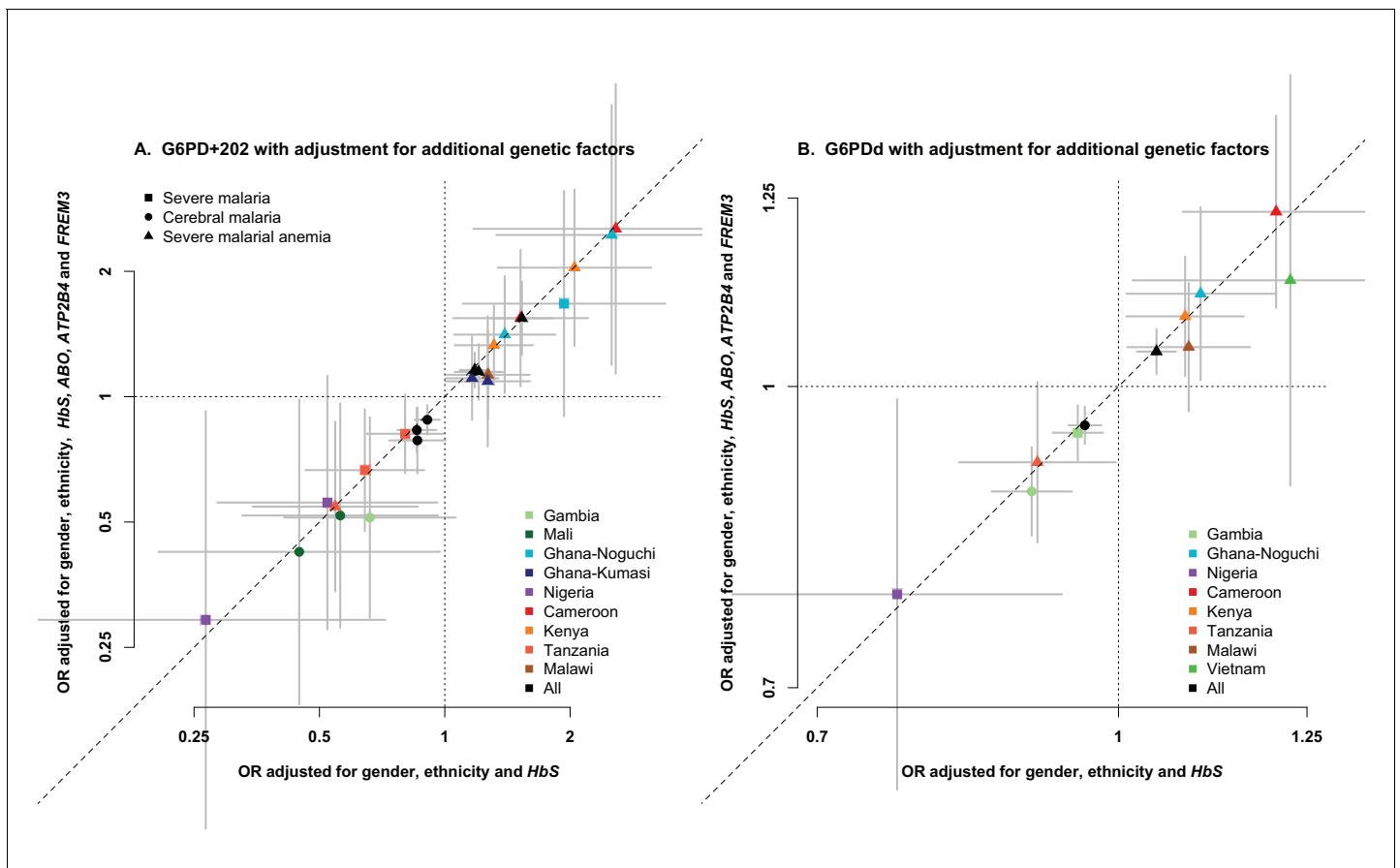


Figure 1—figure supplement 3. Association between G6PD deficiency and severe malaria with and without adjustment for additional genetic factors. ORs and 95% confidence intervals for association with (A) G6PD+202 under additive, dominant and recessive modes of inheritance, and (B) for each 10% increase in G6PDd score, adjusted for gender, ethnicity and the sickle-cell trait (*HbS*) compared to results with additional adjustment for *HbC*, *ABO*, *ATP2B4* and *FREM3* (as proxy for *GYPE*). Results are shown for all associations with $p < 0.05$ in tests of association with all severe malaria and with cerebral malaria and severe malarial anaemia at each site and for all samples combined.

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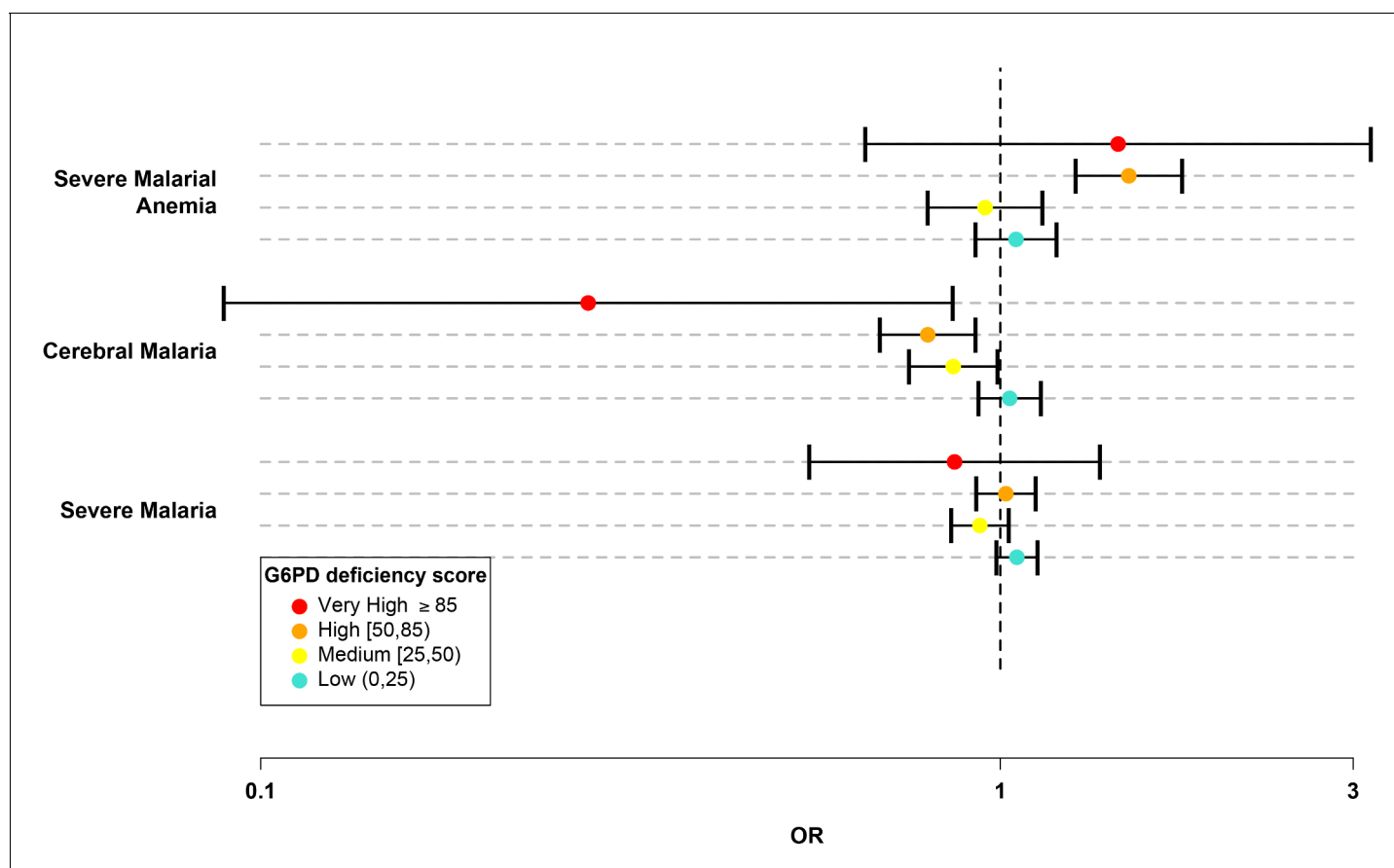


Figure 2. G6PD deficiency score forest plot. Forest plots showing 95% confidence intervals for the effect of each category of G6PDd score on all severe malaria and on two sub-phenotypes, cerebral malaria and severe malarial anaemia. Results are shown for all individuals across all sites combined and are adjusted for the sickle-cell trait, ethnicity and sex. See [Table 6](#) for details and [Supplementary files 1H–J](#) for results at all sites for males, females and all individuals combined.

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The following source data is available for figure 2:

Source data 1. G6PDd score association test results.

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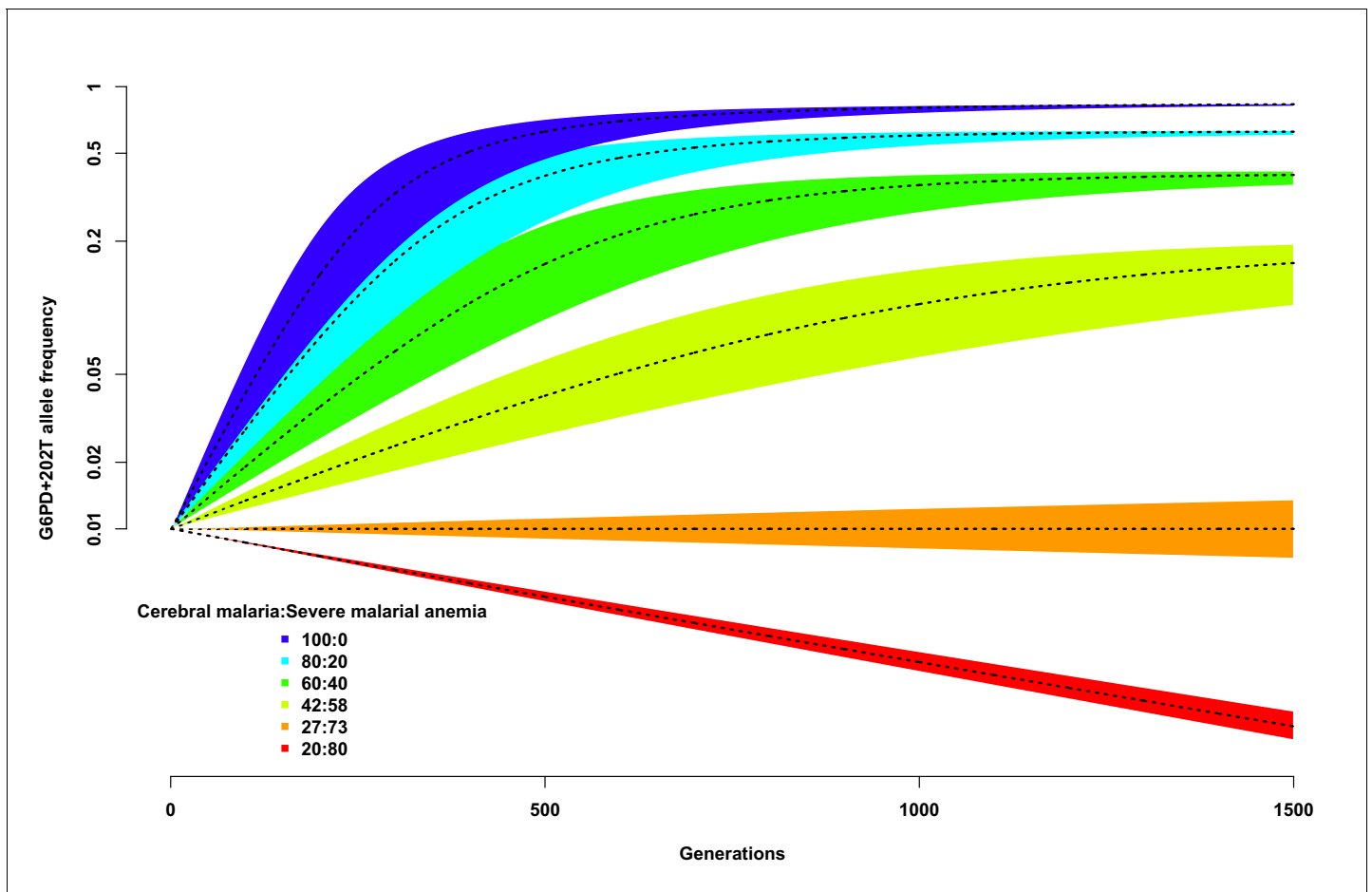


Figure 3. Allele frequency of G6PD+202T. Change in the allele frequency of G6PD+202T under the adapted Levene model. We assume an initial frequency of 0.01 in both males and females and that the change in allele frequency depends only on genotype fitness as a consequence of relative exposure to three selective forces: cerebral malaria, severe malarial anaemia and no selection (see Materials and methods). Here we have assumed that, in each generation, 50% of children suffer from severe malaria and show results for different ratios of cerebral malaria to severe malarial anaemia cases, as indicated for each coloured polygon. Within each of these polygons, the solid black lines shows the allele frequencies when the fatality rate of cerebral malaria (severe malarial anaemia) is 20% (10%); the lower bound to 15% (8%); and the upper bound to 25% (12%).

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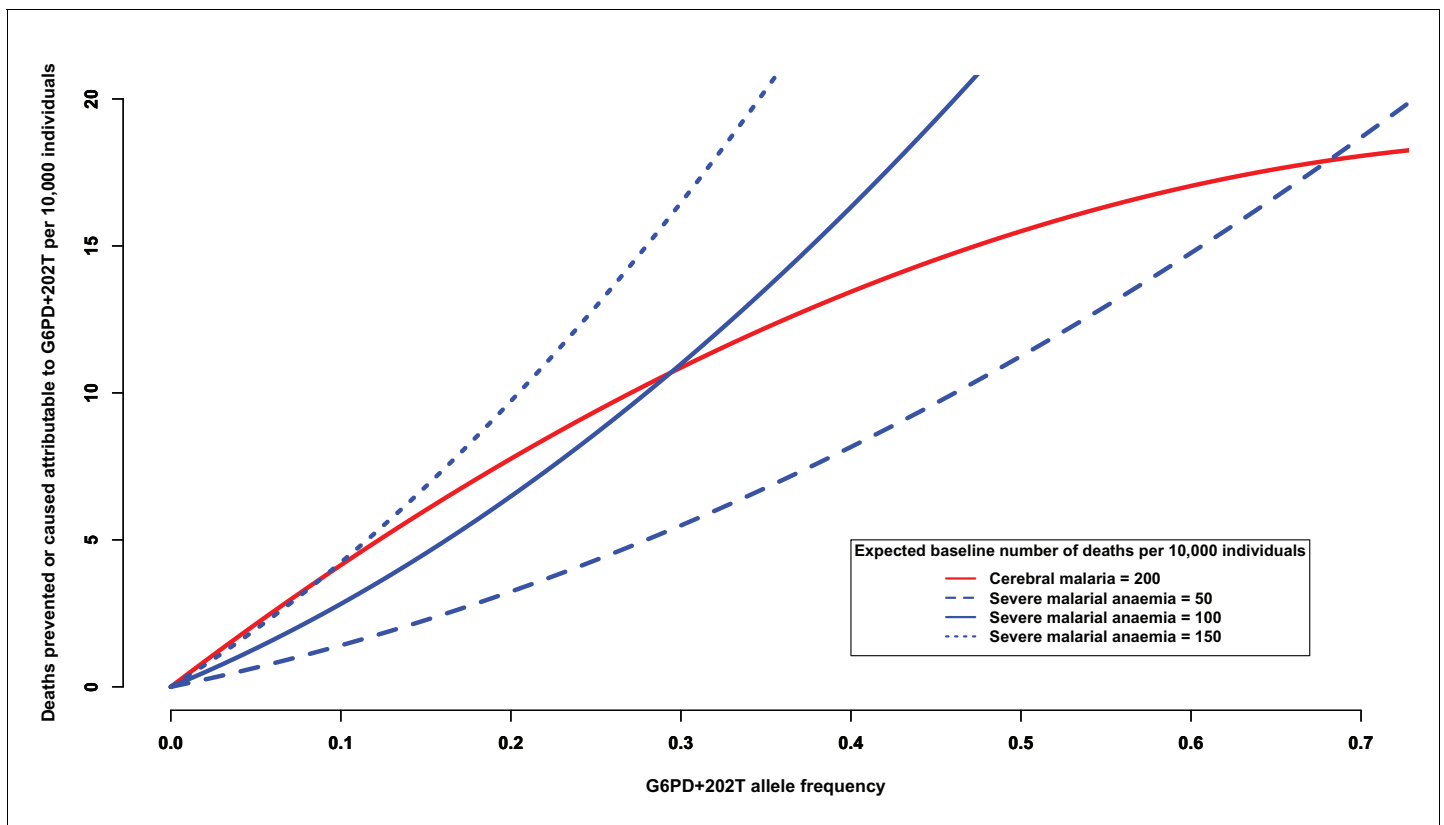


Figure 4. Deaths prevented or caused attributable to the genetic effects at G6PD+202T. The solid red line shows the number of deaths due to cerebral malaria that are prevented by the presence of G6PD+202T, assuming a baseline risk of death due to cerebral malaria of 200/10,000 individuals. The blue lines show the number of deaths due to severe malarial anaemia that are caused by the presence of G6PD+202T for various baseline risks of death due to severe malarial anaemia, as indicated. The baseline risk of death is the expected number of deaths per 10,000 wild-type individuals, i.e. when the frequency of G6PD+202T is zero. Results are shown as the allele frequency of G6PD+202T increases. Relative risks of disease are estimated by odds ratios observed in this study.

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