Investigating a causal role for neutrophil count on P. falciparum severe malaria: a Mendelian Randomization study

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BACKGROUND

- Severe malaria caused by P. falciparum is a debilitating disease which predominantly affects people living in sub-Saharan Africa and comes with a great burden to human life and economic development (Fig. 1)
- Neutrophils defend against bacterial infections but have been shown to be detrimental in malaria mouse models, suggesting that neutropenia may be protective against severe P. falciparum malaria
- Benign ethnic neutropenia (BEN) is present in many individuals of African descent, and this might offer protection against severe malaria
- We investigated the relationship between neutrophil count and severe malaria caused by P. falciparum in a population genetics and Mendelian Randomization (MR) framework

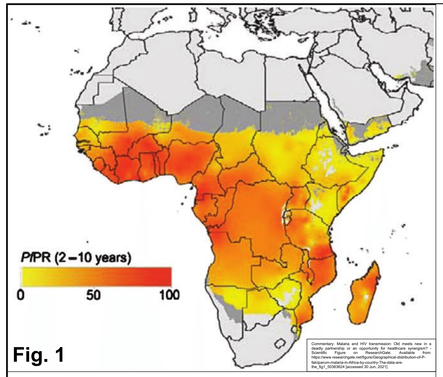

Fig. 1

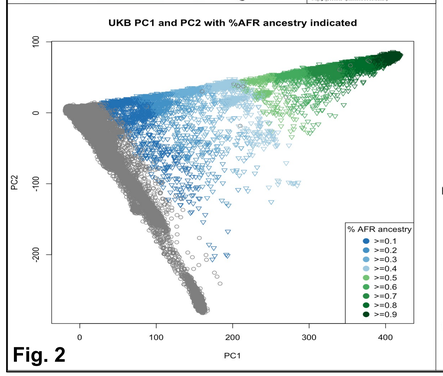

Fig. 2

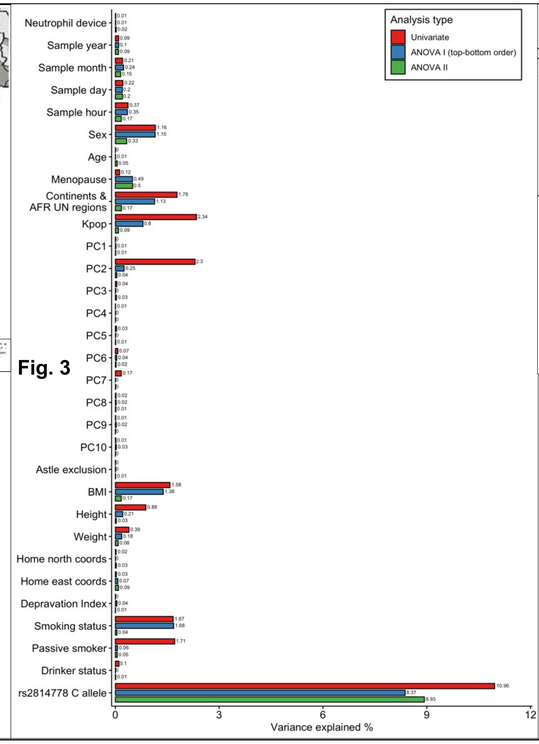

Fig. 3

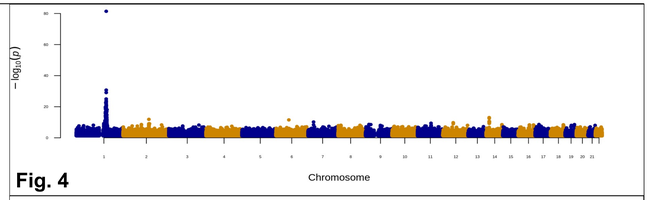

Fig. 4

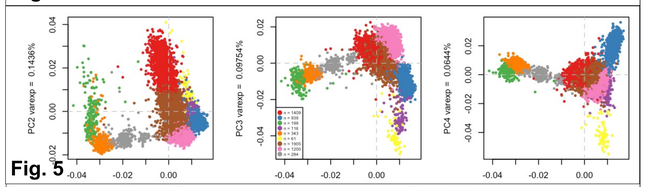
Fig. 5

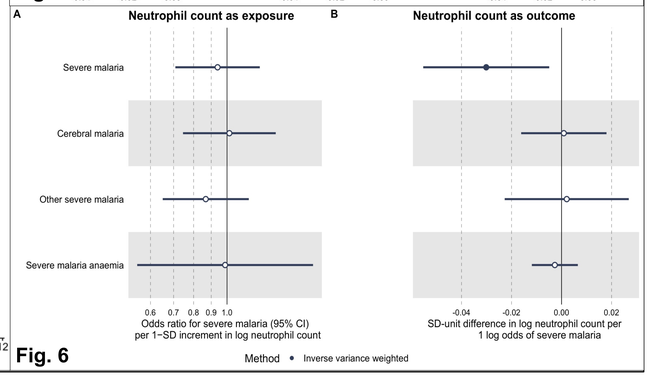

Fig. 6

METHODOLOGY

- Principal component (PC) analysis was done on all non-European people in UK Biobank (~80,000) using the 1000 Geomes dataset as reference
- Individuals with >80% Yoruban (YRI) ancestry were taken further (Fig 2)
- Outliers (N=197) and related people (N=544) were removed using EIGENSOFT
- People without neutrophil count data were filtered out (N=370), resulting in a final sample-size of 6,086
- A univariate, ANOVA type I and type II analyses were performed to show the variance explained by potential covariates on neutrophil count (Fig. 3)
- Main GWAS performed with BOLT/LMM, adjusting for age, sex, batch variables, and first 40 principal components (Fig. 4)
- High population structure was noted and a K-means clustering analysis was done to divide our dataset into clusters (N=9, Fig. 5)
- Sensitivity GWAS were done with SNPTEST on each cluster and the results were then meta-analyses using META
- We performed a pair-wise fixation index (F_{ST}) analysis
- This was followed by a conditional analysis for each GWAS
- Association testing results were then clumped with PLINK using MR parameters
- Two-sample bi-directional MR was done between BOLT/LMM GWAS of neutrophil count and severe malaria (Fig. 6)

RESULTS

- GWAS of neutrophil count identified 88 independent loci
- Results for each sub-phenotype of severe malaria show that the confidence intervals overlap the null, except in the case of overall severe malaria on neutrophil count [b: -0.03, CI(95%): -0.055-(-0.005), P=0.02]
- The small number of SNPs to be used in the MR reduced the efficacy of both main MR and sensitivity analyses

CONCLUSION

- The small sample-size was a limiting factor of statistical power for variants with a small effect and/or low effect allele frequency
- There is a large degree of population structure in people of African descent
- Genetic mechanism for neutrophil count differs between people of African vs. European descent
- This only highlights the need for large biobank studies in Africa

AFFILIATIONS

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