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Genetic variants associated with non-typhoidal *Salmonella* bacteraemia in African children

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Abstract

Background—Non-typhoidal *Salmonella* (NTS) causes invasive and frequently fatal disease in African children. Existing strategies to prevent, diagnose, and treat NTS disease are inadequate. An improved understanding of the biology of invasive *Salmonella* infection will facilitate the development of novel NTS control measures. Despite evidence in mice and man showing a clear role for host genetics in NTS susceptibility, there are no published studies investigating host genetic susceptibility to NTS in African populations.

Methods—We conducted a genome-wide association study (SNP Array 6.0, Affymetrix, CA, USA) of NTS bacteraemia in Kenyan children, with replication in Malawian children. We assessed the function of NTS-associated variants in an expression quantitative trait locus (eQTL) dataset of interferon γ (IFNγ) and lipopolysaccharide-stimulated monocytes from 432 healthy European adults. Serum IFNγ (Bio-Plex immunoassay, Bio-Rad Laboratories, CA, USA) in Malawian NTS cases (n=106) during acute disease was correlated with genotype by linear regression.

Findings—After whole-genome imputation and quality control, 180 Kenyan cases and 2677 controls were included in an association analysis at 7 951 614 (additive model) and 4 669 537

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Contributors
JJG, AR, and TCM performed the sample handling and genotyping. JJG and AR performed the statistical and computational analyses. TNW and JAS recruited Kenyan study children. CAM recruited Malawian study children. VN, BPF, and JCK performed the eQTL studies. AR, TNW, JAS, SJC, and AVH designed the study. JJG drafted the abstract. All authors reviewed and approved the final abstract.

Declaration of interests
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(genotypic model) loci. After quality control, 143 Malawian cases and 336 controls were included in the replication analysis. An intronic variant in *STAT4* was associated (recessive model) with NTS in both Kenyan and Malawian children (Kenya $p=5 \cdot 6 \times 10^{-9}$, Malawi $p=0 \cdot 02$, combined $p=1 \cdot 4 \times 10^{-9}$; odds ratio 7 · 2, 95% CI 3 · 8–13 · 5). The NTS-associated variant was an eQTL for *STAT4* expression in IFNγ-stimulated monocytes ($p=9 \cdot 59 \times 10^{-6}$), the NTS risk allele being associated with lower *STAT4* expression. In Malawian children with NTS bacteraemia, the same NTS risk allele was associated with lower serum concentrations of IFNγ ($p=0 \cdot 02$) at presentation.

Interpretation—*STAT4* is highly plausible as a susceptibility locus for invasive NTS disease. *STAT4* mediates IFNγ release in T cells and natural killer cells in response to interleukin 12 (IL12). Individuals with rare mutations elsewhere in the IL12–IFNγ axis are at risk of disseminated NTS infection. We provide the first evidence, to our knowledge, of a host genetic determinant of NTS disease in African children, and of a *STAT4* variant conferring susceptibility to an infectious disease in man.

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