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**TRYPANOSOME GENETIC DIVERSITY AND DIFFERENTIAL GENE EXPRESSION PROFILES ASSOCIATED WITH HUMAN AFRICAN TRYPANOSOMIASIS CLINICAL PHENOTYPES IN MALAWI**

**Abstract**

Clinical pathology of Rhodesian human African trypanosomiasis (r-HAT) in sleeping sickness endemic countries vary depending on disease foci. To gain more insight of r-HAT disease in Malawi, the current epidemiological trend of r-HAT in Malawi as well as gene expression profiles of sleeping sickness patients and *T. b. rhodesiense* isolates from Rumphi and Nkhotakota foci were analysed.

Data on r-HAT prevalence and demographics from epidemiological surveys carried out in Malawi from 2012 to 2020 was obtained from National Trypanosomiasis Control Programme. Additionally, clinical profiles as well as human and *T. b. rhodesiense* transcriptome profiles of HAT disease in Rumphi and Nkhotakota foci were analysed. r-HAT clinical phenotypes in Malawi demonstrated to be foci dependent; cases in Nkhotakota had more of a less severe clinical phenotype, compared to Rumphi who were characterised by severe clinical phenotype. There were differences in gene expression profiles in individuals with stage 1 and stage 2 disease regardless of foci, with innate immune response transcripts elevated in individuals with stage 1 disease and altered lipid metabolic processes in stage 2 disease associated with wasting. *T. b. rhodesiense* isolates from Nkhotakota were enriched with transcripts for cell cycle arrest and stumpy form markers, whereas isolates in Rumphi focus were enriched with transcripts for folate biosynthesis and antigenic variation biological pathways consistent with the more virulent disease observed in Rumphi and a more silent disease in Nkhotakota. Additionally, *T. b. rhodesiense* parasites from Nkhotakota and Rumphi foci are genetically distinct and individuals with APOL-1 G2 variant had severe r-HAT disease contrary to the current consensus that APOL-1 G2 variant may protect against *T. b. rhodesiense* infection.

The study has added insight to the current understanding on how clinical phenotypes of r-HAT in Malawi might be associated with differences in population structure of *T. b. rhodesiense* circulating in Rumphi and Nkhotakota foci. A surge of r-HAT and continuing incidences of the disease in Malawi should call for a review of Malawi’s r-HAT control and elimination strategies.

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