

Publication

Aquaporin 2 mutations in *Trypanosoma brucei gambiense* field isolates correlate with decreased susceptibility to pentamidine and melarsoprol

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The predominant mechanism of drug resistance in African trypanosomes is decreased drug uptake due to loss-of-function mutations in the genes for the transporters that mediate drug import. The role of transporters as determinants of drug susceptibility is well documented from laboratory-selected *Trypanosoma brucei* mutants. But clinical isolates, especially of *T. b. gambiense*, are less amenable to experimental investigation since they do not readily grow in culture without prior adaptation. Here we analyze a selected panel of 16 *T. brucei* ssp. field isolates that (i) have been adapted to axenic in vitro cultivation and (ii) mostly stem from treatment-refractory cases. For each isolate, we quantify the sensitivity to melarsoprol, pentamidine, and diminazene, and sequence the genomic loci of the transporter genes TbAT1 and TbAQP2. The former encodes the well-characterized aminopurine permease P2 which transports several trypanocides including melarsoprol, pentamidine, and diminazene. We find that diminazene-resistant field isolates of *T. b. brucei* and *T. b. rhodesiense* carry the same set of point mutations in TbAT1 that was previously described from lab mutants. Aquaglyceroporin 2 has only recently been identified as a second transporter involved in melarsoprol/pentamidine cross-resistance. Here we describe two different kinds of TbAQP2 mutations found in *T. b. gambiense* field isolates: simple loss of TbAQP2, or loss of wild-type TbAQP2 allele combined with the formation of a novel type of TbAQP2/3 chimera. The identified mutant *T. b. gambiense* are 40- to 50-fold less sensitive to pentamidine and 3- to 5-times less sensitive to melarsoprol than the reference isolates. We thus demonstrate for the first time that rearrangements of the TbAQP2/TbAQP3 locus accompanied by TbAQP2 gene loss also occur in the field, and that the *T. b. gambiense* carrying such mutations correlate with a significantly reduced susceptibility to pentamidine and melarsoprol.

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