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Sequence is scaffold to study sleeping sickness

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Researchers have made a further step toward understanding sleeping sickness - a chronic disease caused by Trypanosoma parasites, which affect the human central nervous system. The team have generated a high-quality draft genome sequence for the strain of *Trypanosoma brucei* that is responsible for almost all reported cases of human African trypanosomiasis, also known as sleeping sickness.

The study is published on April 13 in the open access journal, *PLoS Neglected Tropical Diseases*.

The *T. brucei* genome sequence previously used for research was obtained from a bovine infecting strain, harmless to humans.

The team sequenced the entire genome of the pathogenic subspecies *T. b. gambiense* and compared this with the genome sequence of its non-human infecting relative, *Trypanosoma brucei brucei*. Both genomes are subspecies of the *T. brucei* family. The team wanted to answer two questions: is the existing *T. brucei brucei* sequence representative of the full diversity of *T. brucei* parasites? And, is there anything in the *T. b. gambiense* genome that might explain its ability to infect and thrive in human populations?

"Historically, sleeping sickness has been a severely neglected disease," says Dr Matt Berriman, leader of the Parasite Genomics group at the Wellcome Trust Sanger Institute and an author on the study, "with considerable impact on human health and the wellbeing and prosperity

of communities.

"To move research forward, we needed to answer a critical question: is the *T. b. brucei* reference genome sequence a suitable scaffold for exploring the genomes of the full diversity of *T. brucei*?"

The genome comparison threw up a remarkable level of similarity between *T. b. brucei* and *T. b. gambiense* - just a single locus was unique to *T. b. brucei*. Moreover, the sequences of comparable genes were, on average, 98.2 per cent identical. Because the genomes were so similar, the team could say with confidence that the *T. b. brucei* parasite and its genome are good models for future experiments to understand the biology of *T. b. gambiense*.

The similarity between the two genomes also suggested that the source of *T. b. gambiense*'s ability to infect humans cannot be explained simply by the addition or removal of a few genes.

"The two sequences we looked at were extremely similar," says Dr Andrew Jackson, from the Wellcome Trust Sanger Institute and lead author on the study, "with no obvious genetic causes for the differences between *T. b. gambiense* and *T. b. brucei*. Changes in the phenotype - the physical characteristics - seem to be down to more subtle changes in genetic information.

"Single letter changes in the genome; differences in the number of copies of genes; changes in how the activity of genes is regulated - all of these genetic nuances could play that crucial role in determining why *T. b. gambiense* behaves so differently to *T. b. brucei*."

With two high quality reference genome sequences in place for the *T. brucei* strains, the search for those small genetic differences is given a boost. It is this search that will fuel the pursuit of targeted drug

treatments to tackle *T. b. gambiense*.

Patients are often wary of treatment because the side effects of current treatments can be unpleasant and sometimes severe. We know that the different Trypanosoma subspecies are susceptible to different drugs and the genome sequences could help the search for new regions of the parasite's molecular make-up against which drugs might be targeted.

The research also looked in far more detail than ever before at the evolution of the parasite's complex system to dupe human and animal immune systems.

Trypanosomes possess a very effective set of proteins - called VSGs - which reside at the surface of the cell and can form a kind of invisibility cloak to protect the parasite from immune response. By successively activating members of this large protein family, the parasites can stay one step ahead of the host immune system and so thrive undetected in the human bloodstream.

"The armoury of VSGs at the parasite's disposal mean that it can stay one step ahead," explains Dr Christiane Hertz-Fowler, from the Sanger Institute and senior author on the study. "Because of their role, VSGs are among the most-rapidly evolving genes in parasite genomes. So we were surprised to find that as many as 88 per cent of VSGs remained consistent between our *T. b. brucei* and *T. b. gambiense* genomes. This has implications for epidemiological studies in the future.

"It means that researchers can produce a global library of VSGs found in *T. brucei* strains, allowing them to categorise *T. brucei* strains found in the field according the precise set of VSGs they possess."

This catalogue of VSGs might also provide further clues to human infectivity. The research community can now peer into the make-up of

genes at the cell surface - one of the best places to search for those subtle differences that empower *T. b. gambiense* to infect human populations.

The high quality reference sequences for the two subspecies of *T. brucei* lay the foundation for epidemiological studies looking at multiple samples. Teams can now look to next-generation sequencing technologies to study multiple isolates, which should throw further light on how the genetic make-up of these parasites can cause distinctive disease in humans.

More information: Jackson AP et al. (2010) The genome sequence of Trypanosoma brucei gambiense, causative agent of chronic Human African Trypanosomiasis. PLoS Neglected Tropical Diseases. Published online before print at: dx.plos.org/10.1371/journal.pntd.0000658

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