Structural variation and genome diversity in natural populations of *Leishmania donovani*.

Imamura H[1], Mannaert A[1], Downing T[2], Berriman M[2], Sundar S[3], Rijal S[4], Dujardin JC[1]

[1] Institute of Tropical Medicine, Antwerp, Belgium; [2] Wellcome Trust Sanger Institute, Hinxton, United Kingdom, [3]Banaras Hindu University, Varanasi, India, [4]BP Koirala Institute of Health Sciences, Dharan, Nepal

In trypanosomatids, gene expression is primarily regulated at the post-transcriptional level rather than at initiation, allowing up-regulation of expression by copy-number amplification. This leads to genome plasticity, a mechanism used by several pathogens to adapt to changing environments. Next-generation sequencing methods now allow high-throughput studies of this phenomenon in natural populations. We recently sequenced over 100 clinical lines of *Leishmani donovani* from the Indian subcontinent and developed new methods for calling structural diversity. Little sequence variation was observed in contrast with a high degree of genome structural variation. Changes in gene dosage were achieved by four mechanisms: aneuploidy, amplifications of large chromosomal stretches, tandem array expansions and extra-chromosomal episomes. The extent and ubiquity of aneuploidy are particularly striking in *L. donovani*: about 95% of the lines showed an altered and unique karyotype and up to 27/36 chromosomes were tri- or tetrasomic. We propose a general model of gene dosage and discuss its potential biological impact as well as practical consequences for further research.