

Title: Assessing LRV1 role as risk factor for mucosal leishmaniasis occurrence and its relationship with TRL3 polymorphism.

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Mucosal leishmaniasis (ML) is a serious clinical form of leishmaniasis that is characterised by destruction of the nasal and/or the oral mucosae and due to unknown reasons appears as a late complication in 5%–10% of cutaneous leishmaniasis (CL) cases produced by species belonging to *Leishmania Viannia* subgenus. Experimental data suggests that strains of *Leishmania* spp. carrying an RNA virus known as Leishmania RNA virus type 1 (LRV1) triggers an immunological response that involves the endosomal Toll-like receptor 3 (TLR3) and has been associated with persistence and dissemination of *Leishmania (V.) guyanensis*. Moreover, TLR3 gene displays several single nucleotide polymorphisms (SNPs) associated with resistance or susceptibility to viral infectious diseases. The present work evaluated LRV1 and TLR3 gene polymorphisms as risk factors for the occurrence of ML throughout a retrospective case-control study involving 102 patients. Cases were defined as patients with ML (n=33) and controls corresponded to patients who had CL without mucosal lesions (n=69). A subgroup of controls (n=19) was followed up for a median time of 16 years to rule out ML occurrence. Clinical data were recorded from the patients' medical records and cryopreserved biopsies were used for *Leishmania* species identification, LRV type-1 (LRV1) detection and TLR3 (exons 2, 3, and 4) genotyping. Bivariate and logistic regression analyses were applied to estimate the risk factors associated with ML occurrence. The predominant *Leishmania* species in both groups was *L. (V.) braziliensis*. Multivariate logistic regression indicated that the unique factor linked with the occurrence of ML was the infection with *Leishmania* spp. carrying LRV1 [OR, 8.81, 95%CI 1.72–45.76 and p = 0.009]. Four SNPs on TLR3 gene were identified and showed no association to ML development. Therefore, LRV1 presence is an independent risk factor for developing ML.

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