CAMKK2 POLYMORPHISMS AND THE ENCODED PROTEINS MAY CONTRIBUTE TO THE PATHOGENESIS OF HIV-SN

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Background: HIV-associated sensory neuropathy (HIV-SN) is a neurological condition that affects up to 60% of HIV$^+$ patients worldwide. Clinical presentations reflect neuronal loss in the dorsal root ganglion (DRG), degeneration of long axons and/or a reduced intra-epidermal nerve fibre density. Additionally, HIV-SN exhibits an inflammatory pathology with macrophage and cytokine infiltration around the DRG and epidermal nerves. We investigated the effect of single nucleotide polymorphisms (SNPs) in three adjacent genes *P2X7R, P2X4R* and *CAMKK2*, involved in inflammatory signalling and neuronal repair pathways. Expression of the encoded proteins was examined in skin biopsies.

Methods: 153 South African HIV$^+$ patients treated with stavudine were assessed for HIV-SN using the Brief Peripheral Neuropathy Screening Tool. DNA was genotyped for 45 SNPs across the three genes, haplotypes were derived using fastPHASE and genotype and haplotype associations with HIV-SN were identified. Distal leg skin biopsies were collected from HIV$^+$ patients with and without neuropathy and healthy controls (n=9). Immunohistochemistry (IHC) and confocal microscopy were used to visualise and assess differential expression of P2X7R, P2X4R and CaMKK2.

Results: *CAMKK2* exhibited the strongest genetic association with two SNPs and six haplotypes predicting HIV-SN in this cohort. This profound association was supported by IHC results with CaMKK2 upregulated and closely associated with nerves in patients with HIV-SN compared to HIV$^+$ patients without neuropathy and healthy controls.

Conclusion: Polymorphisms in CAMKK2 may mark susceptibility to HIV-SN in South Africans and the encoded protein may contribute to the underlying pathology of the disease. Further genetic and histological investigation is underway to identify critical SNPs and understand the role of CaMKK2 *in situ*. Data will also be presented from ongoing studies of neuropathy in Indonesian HIV$^+$ patients. The effect of the neurotoxic drug stavudine on the role of CaMKK2 will also be evaluated.

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