

## Genome-wide association study of HAM/TSP susceptibility in Brazil reveals both immune and neural genetic links

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### Background:

Despite decades of intensive research, HAM/TSP pathogenesis is poorly understood, but genetics have been shown to play a prominent role. Recent GWAS results from Japan have demonstrated a genetic link restricted to HLA class I and II polymorphisms, but replication in other HTLV endemic areas is lacking.

### Methods:

From October 2017 to December 2019, we recruited a total of 911 people living with HTLV-1 (PLHTLV-1, 378 HAM/TSP and 533 asymptomatics) through a nation-wide effort in Brazil. Seropositivity for HTLV-1 was confirmed with Western Blot and nested PCR. Clinical status (asymptomatic or definite HAM/TSP) was defined in accordance with Castro-Costa published criteria. We used the Axiom Precision Medicine microarray (Affymetrix) comprising 902,527 SNPs. Following a rigorous QC check (excluding individuals with low quality DNA, missingness rate >5%, outlying heterozygosity, kinship; excluding SNPs deviating from HWE or  $MAF < 0.001$ ), we obtained a final dataset of 701 individuals (317 HAM/TSP, 372 asymptomatics).

### Results:

A total of 42 SNPs in 20 genes were observed with p-values between  $3 \times 10^{-7}$  and  $9 \times 10^{-5}$ , most of which remained significant when correcting for proviral load. In agreement with the current paradigm of HAM/TSP pathogenesis, 15 were immune genes and/or expressed in leukocytes but not erythroid cells or platelets. However, no significant SNPs in HLA genes were observed. Notably, 6 genes (*NGFR/CTNND2/USH2A/KCNQ3/SYT12/PDE7B*) are enriched for GO term “synapse” and expressed in the central nervous system. Hinting at a molecular mechanism, most top SNPs were situated within or nearby ENCODE Candidate Cis-

Regulatory Elements, and within <100bp of a STAT1-binding motif, in agreement with previous epigenomic and transcriptomic findings in HAM/TSP.

**Conclusion:**

Non-HLA immune and neural genetic links are observed in a Brazilian GWAS study of HAM/TSP. STAT1-binding motifs in close vicinity to top SNPs represent a possible molecular mechanism supported by currently available multi-omics data in HAM/TSP.

**Disclosure of Interest Statement:**

The authors have no conflict of interest.