Variant in the *PDE4B* related to Acute Lymphoblastic Leukemia relapse is differentiated in Native Americans

Rennan G. Moreira, Fernanda Rodrigues-Soares, Eduardo Tarazona-Santos

Laboratório de Diversidade Genética Humana. Departamento de Biologia Geral, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil

Acute Lymphoblastic Leukemia (ALL) is the most common cancer in children, being responsible for almost 25% of the malignancies cases. Despite of recent advances in treatments, leading to more than 80% of cure rate, relapse is still common. In this sense, Pharmacogenetics is being increasingly applied on cancer cases as a new approach to improve treatment outcomes, opening new possibilities for reducing relapse events in ALL cases. Accordingly, ALL relapse risk varies considerably depending on the ethnicity. Yang et al. 2011 showed that Native American genomic component was associated with higher risk of ALL relapse in a study encompassing more than 2,500 ALL cases from the USA but also including worldwide samples for comparison. Authors identified strong association signals into the *PDE4B* (rs6683977) and *MYT1L* (rs17039396) genes in Hispanic samples. The *PDE4B* gene is involved in the metabolism of certain drugs used in cancer treatment, such as prednisone, what could suggest an effect on ALL relapse susceptibility. Thus, in order to support such findings, the main goal of this study is to evaluate genetic diversity of Native American populations from Peru and Brazil as well as of Brazilian admixed populations in the genomic regions surrounding rs6683977-*PDE4B* and rs17039396-*MYT1L*, and discuss their impact in mapping variants related to ALL relapse in additional populations with Native American ancestry. We used the BeadXpress Illumina system to genotype 76 SNPs - previously known as ancestry informative markers (AIMs) - and also 48 *PDE4B* and *MYT1L* SNPs (including the rs6683977 and rs17039396 variants) in 255 Native Americans from Peru, 88 from Brazil, and 98 admixed Brazilians. Results showed that whereas Native Peruvians have less than 5% of non-Native American ancestry, Native Brazilians present higher European and African admixture proportions. Native American ancestry proportion was inversely related to higher heterozygosity values in both genes. Population pairwise FST measures performed by each gene showed expected patterns of differentiation for human populations worldwide. However, when analyzing SNPs individually, the highest FCT value found in *PDE4B* SNPs is for rs6683977. Thus, considering allele frequencies and AMOVA analyses, we confirmed our expectation that the rs6683977-C-*PDE4B* allele is highly differentiated in Native Americans from Peru and Brazil, when comparing with Europeans. We did not see the same pattern for the ALL admixture mapping hit rs17039396 in *MYT1L*.