Received: 23 December 2021 | Revised: 18 February 2022 | Accepted: 27 February 2022

DOI: 10.1111/cts.13266

BRIEF REPORT

Population genetics of *PDE4B* (phosphodiesterase-4B) in neglected Native Americans: Implications for cancer pharmacogenetics

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Abstract

PDE4B (phosphodiesterase-4B) has an important role in cancer and in pharmacology of some disorders, such as inflammatory diseases. Remarkably in Native

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Funding information
This study was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Minas Gerais Research Agency (FAPEMIG, RED-00314-16, APQ-02188-18), National Program of Genomics and Precision Health from the Brazilian Ministry of Health (CNPq 403,502/2020–9), Pró-Reitoria de Pesquisa from the Federal University of Minas Gerais.

Americans, *PDE4B* variants are associated with acute lymphoblastic leukemia (ALL) relapse, as this gene modulates sensitivity of glucocorticoids used in ALL chemotherapy. *PDE4B* allele rs6683977.G, associated with genomic regions of Native American origin in US-Hispanics (admixed among Native Americans, Europeans, and Africans), increases ALL relapse risk, contributing to an association between Native American ancestry and ALL relapse that disappeared with an extra-phase of chemotherapy. This result insinuates that indigenous populations along the Americas may have high frequencies of rs6683977.G, but this has never been corroborated. We studied ancestry and *PDE4B* diversity in 951 healthy individuals from nine Latin American populations. In non-admixed Native American populations rs6683977.G has frequencies greater than 90%, is in linkage disequilibrium with other ALL relapse associated and regulatory variants in *PDE4B*-intron-7, conforming haplotypes showing their highest worldwide frequencies in Native Americans (>0.82). Our findings inform the discussion on the pertinence of an extra-phase of chemotherapy in Native American populations, and exemplifies how knowledge generated in US-Hispanics is relevant for their even more neglected and vulnerable Native American ancestors along the American continent.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
PDE4B (phosphodiesterase-4B) has an important role in cancer and in pharmacology of some disorders, such as inflammatory diseases. This study was inspired by an admixture mapping in US-Hispanics (the product of admixture among Native Americans, Europeans, and Africans), that reported that rs6683977.G in *PDE4B*, associated with genomic regions of Native American origin, increase the risk of acute lymphoblastic leukemia (ALL) relapse. This association disappeared in patients receiving an extra-phase of chemotherapy. Consistently, *PDE4B* is involved in metabolism of glucocorticoids used in ALL chemotherapy. This result on US-Hispanics suggests that indigenous populations along the Americas have high frequencies of rs6683977.G, but this has never been corroborated.

WHAT QUESTION DID THIS STUDY ADDRESS?
Does *PDE4B* allele rs6683977.G actually highly prevalent in Native American populations along the American continent?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
We studied *PDE4B* haplotype structure and ancestry in 951 individuals from eight indigenous and one admixed Latin American populations. rs6683977.G has frequencies greater than 90% in non-admixed Native American populations, is in strong linkage disequilibrium with other single-nucleotide polymorphisms (SNPs) associated with ALL relapse and with functionally regulatory variants in *PDE4B*-intron 7. Haplotypes, including ALL relapse risk and functional alleles, have the highest frequencies worldwide in Native Americans (>0.82).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
Our findings, by revealing the haplotype structure of *PDE4B*, contribute to the discussion about an extra-phase of chemotherapy in predominantly Native American populations. We also exemplify how to expand results on minority groups from developed countries (US-Hispanics) to their even more neglected ancestral populations (Native Americans), promoting an inclusive global precision medicine.

PDE4B encodes a phosphodiesterase that degrades cyclic-AMP (cAMP).[1,2] Its inhibitors are commonly used in several treatments of disorders, including skin and pulmonary diseases.[3] Additionally, *PDE4B* expression has also been related with corticosteroids' role in cancer treatment, as in acute lymphoblastic leukemia (ALL).[4] Following B-cell receptor activation, cAMP downmodulates signaling pathways responsible for cell proliferation. *PDE4B* overexpression abrogates the cAMP inhibition of cell proliferation and modulates glucocorticoid (i.e., dexamethasone and prednisone[5,6]) sensitivity/resistance in ALL treatment. Thus, *PDE4B* genetic variants that modulate its expression are relevant for ALL treatment.[5,7]

Ancestry is associated with incidences or treatment outcomes of several types of cancer.[8] However, our understanding of these associations is hampered because most studies are performed in European/US populations.[9] Studies focusing on non-European and vulnerable populations are critical in human genomics and pharmacogenetics.[10] In particular, Native Americans are neglected in studies about genetic diversity and the genetic basis of diseases.[9–13]

ALL is the most common cancer in children less than 5 years old and its incidence is higher in countries with high Native American ancestry.[14] An admixture mapping including US-Hispanics (admixed among Native American, European, and African ancestries), reported that alleles *PDE4B*-rs6683977.G (intron 7, plus [+] strand) and *MYT1L*-rs17039396.A, commonly present in genomic regions of Native American origin, increase the risk of ALL relapse,[5] even after adjusting for known prognostic factors. These local-chromosome ancestry-based associations account at least in part for the association between Native American ancestry and ALL relapse.[15] Importantly, this association disappeared in patients submitted to an extra phase of chemotherapy, suggesting that at population level, ancestry-adjusted therapy may mitigate the higher risk of relapse.[5] The association of *PDE4B*-rs6683977.G with ALL relapse has been confirmed in an ethnically diverse cohort of St. Jude Hospital, Tennessee/United States, and other three intron 7 *PDE4B* single-nucleotide polymorphisms (SNPs; rs546784.A, rs641262.A, and rs524770.A) were associated with ALL relapse.[7]

The associations between *PDE4B*-rs6683977.G and *MYT1L*-rs17039396.A and ALL relapse in US-Hispanics insinuates that populations that are predominantly indigenous along the Americas have high frequencies of these ALL relapse associated variants, but this has never been corroborated, which is indicative of how Native American populations are neglected in genetic studies. To address this issue, we test the hypothesis that *PDE4B*-rs6683977.G and *MYT1L*-rs17039396.A (and their associated genomic regions) show higher frequency and are highly differentiated in indigenous populations of the Americas in respect to other continental groups.

There is a nomenclature caveat regarding *PDE4B*-rs6683977.G (Data S1). This SNP has two alleles: C and G. A methodological caveat that requires caution occurs with SNPs with the pairs of alleles C/G or A/T.[16] These kinds of SNPs are ambiguous because the alternative alleles (that by definition are present in the different homologous chromosomes) are sometimes confused with the complementary bases of the double DNA strands. The original study reporting the association between *PDE4B*-rs6683977 and ALL relapse designated the risk allele as *PDE4B*-rs6683977.C because it was referring to the minus (−) DNA strand of chromosome 1.[5,7] However, to follow the convention (such as the 1000 Genome Project [1000GP][17]) and to be consistent with strand nomenclature,[16] here, we report the risk allele in this study referring to the plus (+) DNA strand of chromosome 1, as *PDE4B*-rs6683977.G.

We studied 951 healthy individuals from eight Native American populations from Mexico (Tarahumara and Huichol), Peru (Quechua and Aymara from the Andes, Machiguenga, and Ashaninka from the Amazon) and Brazil (Tupiniquim and Guarani from South-East of the country) and a Brazilian admixed population from Minas Gerais state (AMG, also from South-East of the country). We generated genomic data for *PDE4B* and *MYT1L* regions, including *PDE4B*-rs6683977 and *MYT1L*-rs17039396 allele frequencies after genotyping 790 and 489 individuals, respectively (Table S1 and Figure S1). We estimated continental admixture proportions for each studied Latin American population (Data S1, Tables S1 and S3). Data from the 1000GP[17] were considered for comparison. Here, we focus on *PDE4B* results. The results regarding *MYT1L* are in Data S1. Institutional review boards of participant institutions approved this study.

Latin American populations with the highest Native American ancestry show the highest *PDE4B*-rs6683977.G frequencies (Spearman correlation rho = 0.684, $p < 0.0025$; Table S1), with most indigenous populations with frequencies greater than 90% (Figure 1a). Compared with the 1000GP populations, *PDE4B*-rs6683977.G frequencies have the lowest values in Europeans (44%), followed by South Asians (65%), with higher frequencies, similar to Native Americans, in East Asians (84%) and Africans (96–99%). Thus, European admixture influences the lower *PDE4B*-rs6683977.G frequencies in indigenous Tupiniquim, the admixed Brazilians (Minas Gerais),

and 1000GP admixed American continent populations (Figure 1a, Table S1). Among the 17 populations reported in Figure 1a, only admixed Puerto Ricans and indigenous Guarani from Brazil (with 67% of Native American ancestry) show exceptionally high frequencies of *PDE4B*-rs6683977.G with respect to expectations based on their admixture proportions.

PDE4B-rs6683977, LINKAGE DISEQUILIBRIUM WITH OTHER ALL RELAPSE AND FUNCTIONAL REGULATORY VARIANTS

Functional genomic studies were unable to identify if rs6683977 directly affects *PDE4B* expression, but other

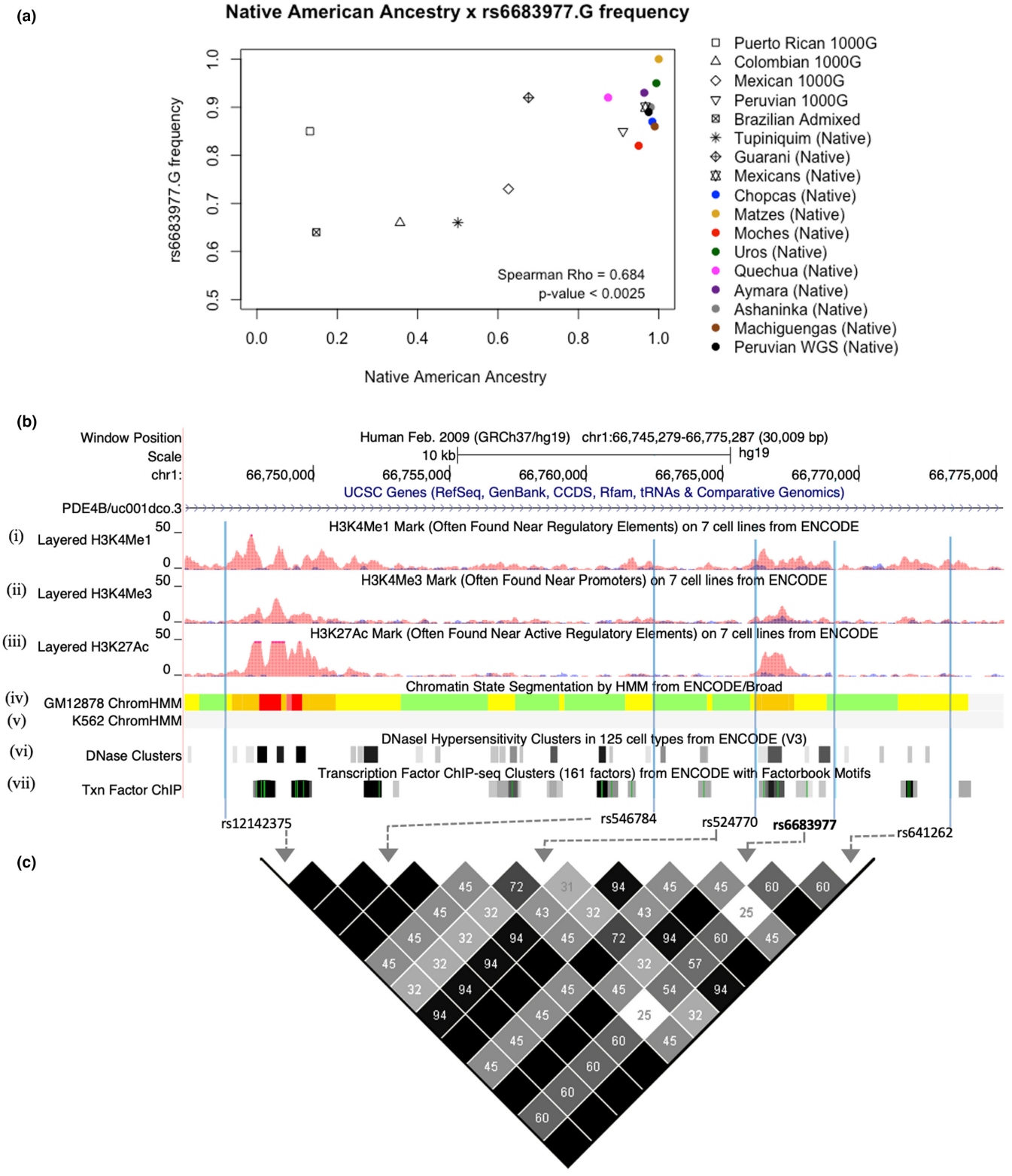

FIGURE 1 Allele frequency, functional signals, and linkage disequilibrium surrounding *PDE4B*-rs6683977 in Native Americans. (a) *PDE4B*-rs6683977.G allele frequencies as a function of Native American ancestry proportions in Native or admixed populations of the Americas. Admixed US Hispanics/Mexican (MXL), and Latin Americans from Puerto Rico (PUR), Colombia (CLM), and Peru (PEL) from 1000GP, Brazilian admixed population (Minas Gerais state), Native Americans from Peru (Quechuas, Aymaras, Ashaninkas, Machiguengas, Choppcas, Matzes, Moches, and Uros), Mexico (Tarahumaras and Huicholes), and Brazil (Tupiniquins and Guaranis). See Table S1 for details. (b) UCSC Genome Browser visualization of 30,009 bp of *PDE4B* (GRCh37/hg19 - chr1:66745279–66775287). Browser comprises (see Supplementary Material for details): three tracks of histone marks (H3K4Me1 [i], H3K4Me3 [ii], and H3K27Ac [iii]) for the lymphoblastoid GM12878 (pink) and myelogenous leukemia K562 (purple) cell lines; two tracks with results of modeling the presence of chromatin marks for GM12878 (iv) and K562 (v) cells (ChromHMM - red: promoter, orange: strong enhancer, yellow: weak enhancer, dark-green: transcriptional transition/elongation, light-green: weak transcribed); and two tracks of (vi) cis- (DNaseI Hypersensitivity Clusters) and (vii) transregulatory elements (Transcription Factor ChIP-seq Clusters). (c) Linkage disequilibrium between variants in Peruvian populations of the Whole Genome Sequencing database (Machiguengas, Choppcas, Matzes, Moches, and Uros, considered as a unique population, $n = 102$ individuals), including the *PDE4B*-rs6683977, and other ALL-relapse and *PDE4B* expression markers sorted by their chromosome positions: rs12142375, rs6668516, rs546784, rs6683604, rs12137080, rs524770, rs12137115, rs495477, rs494735, rs6683977, rs638111, and rs641262. Gray scale denotes r^2 between SNPs (black: $r^2 = 1$). Table S1 shows results from other databases, confirming that SNPs rs546784 and rs641262 are included in another dataset including other individuals and Native American populations (the Targetseq Dataset), where rs546784 and rs641262 are also in high LD ($r^2 > 0.80$) with rs6683977. 1000GP, 1000 Genome Project; ALL, acute lymphoblastic leukemia; ENCODE, Encyclopedia of DNA Elements; SNP, single-nucleotide polymorphism; WGS, whole-genome sequencing

three SNPs in intron 7 were functionally validated as "positive regulatory elements" (PRE)[18]: rs494735, rs502958 and, in particular, rs12142375, which has an allele-specific regulatory effect (Figure 1b).[18] In Native Americans from Peru, rs6683977.G is in strong linkage disequilibrium (LD) with the PRE rs12142375.G ($r^2 = 1$, both at very high frequencies; Figure 1c), but not with the other two PRE SNPs. In these Peruvian populations *PDE4B*-rs6683977 is also in strong LD ($r^2 = 1$) with other variants in intron 7, including rs546784 and rs641262 (Figure 1c), associated with ALL relapse in the St. Jude multi-ethnic cohort.[7] Notably, we show that the sum of frequencies of *PDE4B* haplotypes including the ALL relapse risk alleles rs546784.T, rs6683977.G, rs641262.T, and the functional allele rs12142375.G is higher in Native Americans from Mexico (0.92) and Peru (0.82–0.95) than in other 1000GP populations, particularly in Europeans (0.43; Table S2).

Our study has the limitation of being a population genetics study on healthy individuals. Association and functional studies of *PDE4B*-rs6683977.G with relapse in patients with ALL from Latin American countries are a pending task. Clinical studies on the use of *PDE4B*-rs6683977.G haplotypes information to prescribe an extra-phase of ALL chemotherapy would be the gold standard.

In conclusion, the ALL relapse associated allele *PDE4B*-rs6683977.G is highly prevalent in Native American (Figure 1a), as well as in African and East Asian populations, but only in Native Americans both individual and local-chromosome ancestries are associated with ALL relapse in the multi-ethnic St. Jude cohort. This result posits the hypothesis, to be tested, that effect sizes of *PDE4B*-rs6683977.G on ALL relapse may vary with ancestry, as has been recently observed for susceptibility SNPs for ALL in the ERG gene in Hispanics.[19] *PDE4B*-rs6683977.G is in LD with other SNPs also associated with ALL relapse (Table S1)[7] and with functional variants in intron 7 (Figure 1c, Table S3) both in Native American and also East Asians. The intronic region encompassing *PDE4B*-rs6683977 has been functionally validated as a spatially active chromatin segment, harboring active enhancers,[20] even if this validation has been performed in cell lines with European ancestry background and not in cell lines derived from Native American individuals, a pending task. Functional databases (Data S1) reveal that the region around *PDE4B*-rs6683977, including other ALL relapse markers, has several DNase I hypersensitive binding sites, transcription factor ChIP-seq clusters and histone marks of active enhancers (H3K4me1, H3K4me3, and H3K27ac) in a European ancestry lymphoblastoid cell line (Figure 1b). Accordingly, the importance of *PDE4B* for the ALL treatment outcome is likely related to the association of its overexpression with glucocorticoids resistance.[1,2,5,6] Our findings are consistent with the role of admixture mapping hits found by Yang et al.,[5] expand their results by revealing the very high prevalence of *PDE4B*-rs6683977.G and associated haplotypes in neglected Native American populations, and provide further support to the therapeutic decision of an extra phase of chemotherapy[5] in populations with predominant Native American ancestry. Our study exemplifies how knowledge generated in US-Hispanics is relevant for their even more vulnerable and neglected Native American ancestors along the American continent.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

R.G.M., E.T.-S., and F.R.-S. wrote the manuscript. E.T.-S. and F.R.-S. designed the research. R.G.M., J.M.S.D., W.C.S.M., and F.R.-S. performed the research. R.G.M., J.M.S.D., M.L.S., W.C.S.M., Z.B., and F.R.-S. analyzed the data. A.C.P., M.S.-M., C.G.-H., C.Z., T.P.L., A.L., R.H.G., J.G.M., V.B., H.G., and T.D.O.'C. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Moreira RG, Saraiva-Duarte JM, Pereira AC, et al. Population genetics of *PDE4B* (phosphodiesterase-4B) in neglected Native Americans: Implications for cancer pharmacogenetics. *Clin Transl Sci*. 2022;15:1400-1405. doi: 10.1111/cts.13266