

Lower frequency of *PNPLA3* in African populations and divergent associations with hepatocellular carcinoma

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BACKGROUND

Hepatocellular carcinoma (HCC) ranks as the 3rd leading cause of cancer-related deaths globally.

A single nucleotide polymorphism (SNP) in patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), rs738409, has been associated with HCC development in European and East Asian populations¹⁻³.

However, the relevance of this SNP remains unexplored in African populations, despite Africa containing the most genetically and phenotypically diverse populations and having the highest burden of HCC worldwide.

OBJECTIVES

Our study aimed to assess, for the first time, the association of *PNPLA3* with HCC in West Africa in two geographically and ethnically diverse populations, comparing it to mainly European-descent Americans.

METHODS

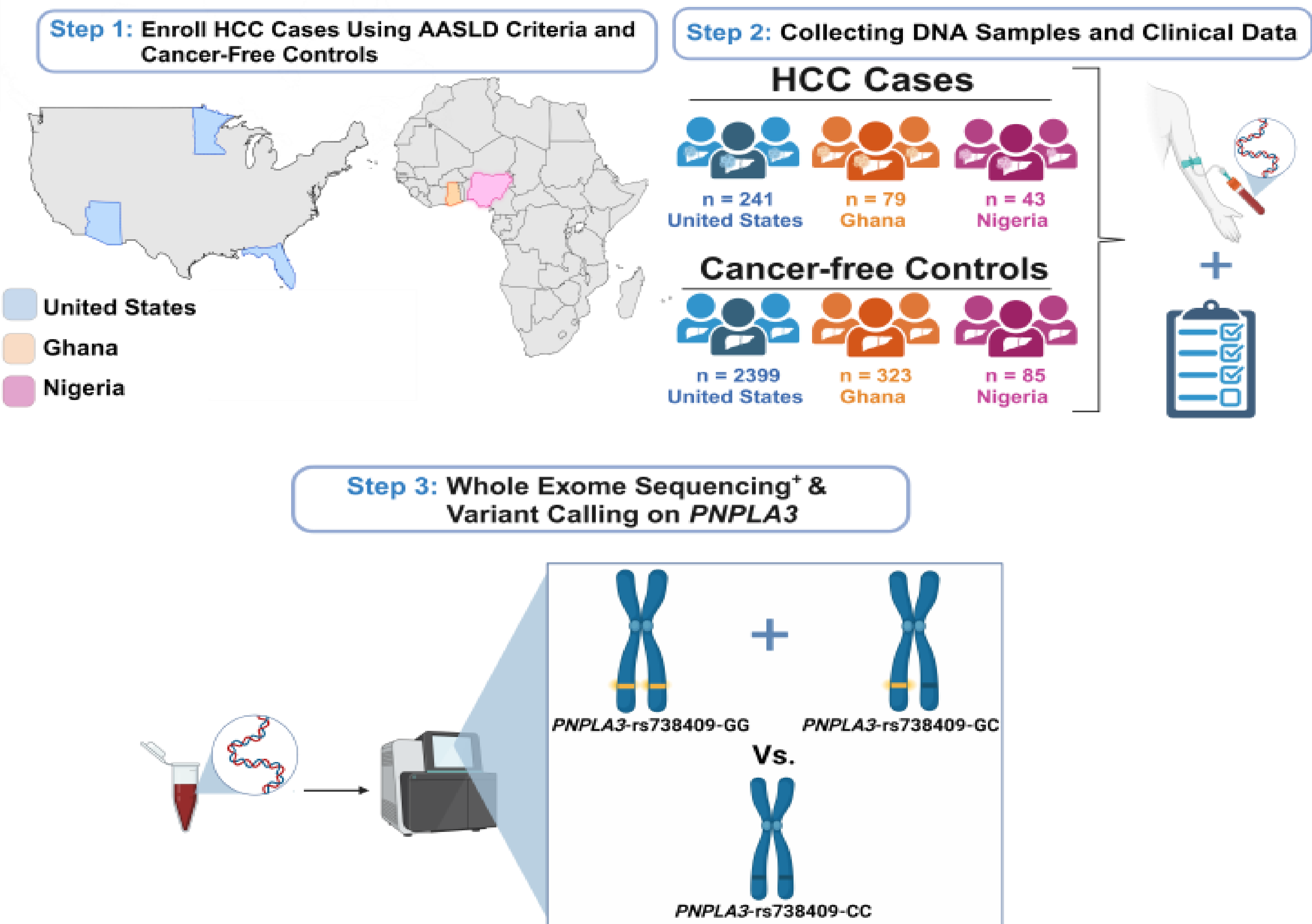


FIGURE 1: Study Design. We enrolled 363 patients diagnosed with HCC using AASLD guidelines from a predominantly European descent population in the United States (n = 241), and from Ghana (n = 79), and Nigeria (n = 43). Controls comprised 2,807 cancer-free patients from the same sites: United States (n = 2399), Ghana (n = 323), and Nigeria (n = 85). We performed whole-exome sequencing (Exome+, Helix, Inc.) and extracted data on *PNPLA3*-rs738409 for analyses. Prevalence of *PNPLA3*-rs738409 was compared using Chi-square test, odds ratios (OR), and 95% confidence intervals (CI).

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RESULTS

Characteristic	United States (N = 2,640)		Ghana (N = 402)		Nigeria (N = 128)	
	HCC (n = 241)	Control (n = 2,399)	HCC (n = 79)	Control (n = 323)	HCC (n = 43)	Control (n = 85)
Age, years [median (min, max)]	65 (29, 88)	66 (29, 88)	51 (21, 72)	38 (18, 72)	44 (29, 76)	49 (18, 71)
Sex						
Male	164 (68%)	1629 (67.9%)	59 (74.7%)	188 (58.2%)	28 (65.1%)	23 (27.1%)
Female	77 (32%)	770 (32.1%)	20 (25.3%)	135 (41.8%)	15 (34.9%)	62 (72.9%)
Self-Reported Ethnicity						
White	216 (89.6%)	2159 (90%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black	0 (0%)	0 (0%)	79 (100%)	323 (100%)	0 (0%)	0 (0%)
Hispanic or Latino	11 (4.6%)	110 (4.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian	7 (2.9%)	70 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	7 (2.9%)	60 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Underlying Etiology for Liver Disease						
Cirrhosis	180 (74.7%)	300 (12.5%)	35 (44.3%)	111 (34.5%)	21 (48.8%)	0 (0%)
MASLD	90 (37.3%)	304 (12.6%)	0 (0%)	3 (0.9%)	1 (2.3%)	1 (1.2%)
Hepatitis C infection	85 (35.2%)	20 (0.8%)	5 (6.3%)	5 (1.5%)	5 (11.6%)	8 (9.4%)
Hepatitis B infection	10 (4.1%)	20 (0.8%)	54 (68.4%)	177 (54.8%)	24 (55.8%)	8 (9.4%)
Alcohol associated liver disease	57 (23.7%)	122 (5.1%)	10 (12.7%)	30 (9.3%)	7 (16.3%)	12 (14.1%)

TABLE 1: Demographic and clinical features of 363 HCC Cases and 2,807 cancer-free controls

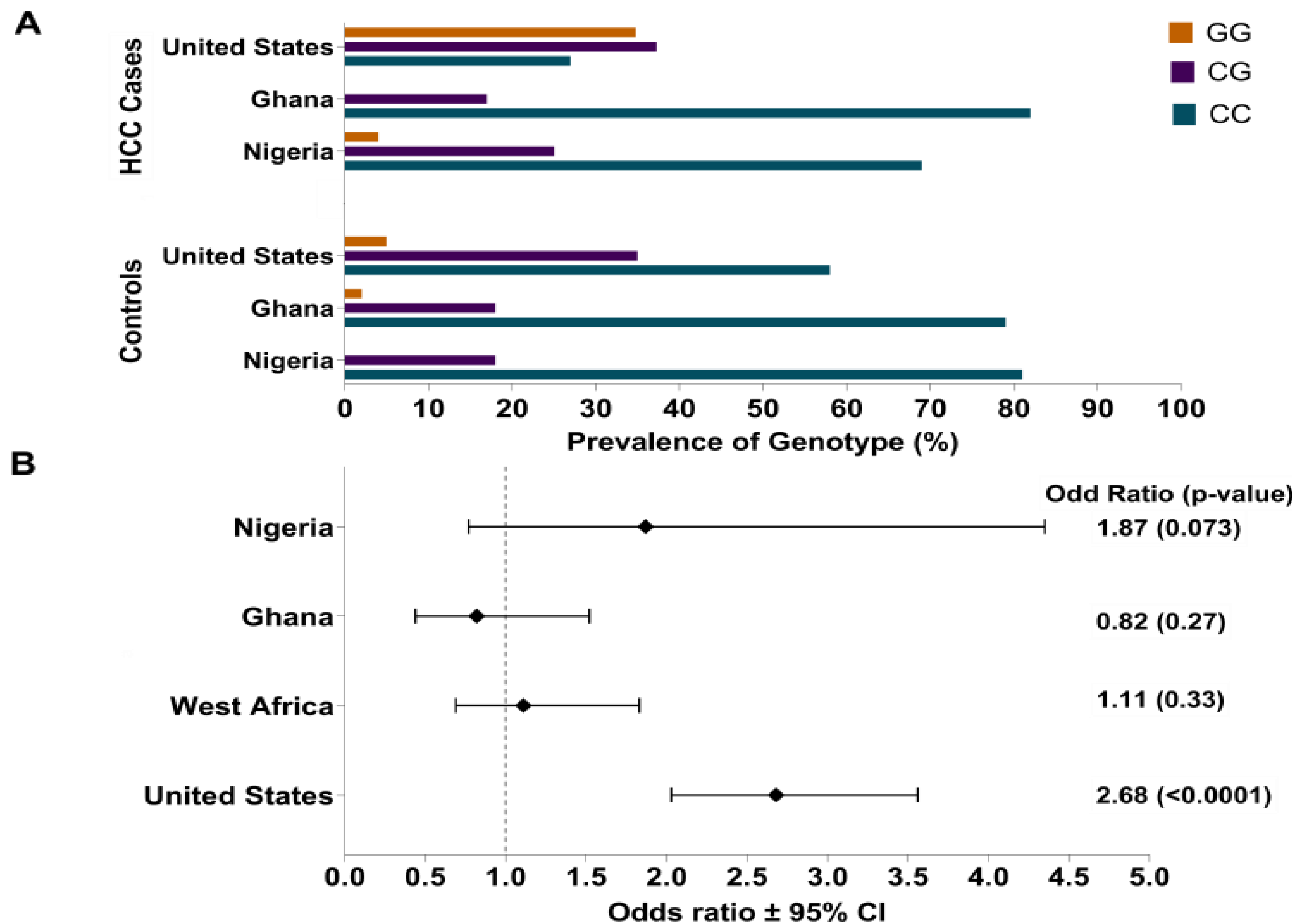


FIGURE 2: Allele frequency distribution of *PNPLA3* rs738409 C > G in three populations

DISCUSSION

In the HCC United States population, there was a significant association between *PNPLA3*-rs738409 (G) and HCC risk, with OR for GG/CG vs. CC of 2.68 (CI: 2.03-3.56, p < 0.0001), and with risk allele frequency of 0.46.

We did not find a significant association between *PNPLA3*-rs738409 & HCC risk in the combined HCC West African samples (OR = 1.11, CI: 0.69-1.83, p = 0.33), with overall risk allele frequency of 0.12.

When the West African samples were examined separately, we found a striking difference in the pattern of association.

Nigerian population demonstrated a trend toward an association between *PNPLA3*-rs738409 and HCC risk (OR = 1.87, CI: 0.77-4.35, p = 0.073), with risk allele frequency of 0.17

Ghanaian population did not show this trend (OR = 0.82, CI: 0.44-1.52, p = 0.27), with a lower risk allele frequency of 0.09.

CONCLUSIONS

- West Africans from Ghana and Nigeria have a **lower** *PNPLA3* minor allele frequency as compared to European Americans.
- There were **different** trends in the association between *PNPLA3* and HCC within Africans, with only the Nigerian population showing the trend toward elevated risk.
- A global multi-ethnic genetic association study is needed to **reduce** disparities in the clinical application of genetic test results in HCC.

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