

ASSOCIATION STUDIES TO DETECT DRUG-GENE INTERACTIONS IN LARGE POPULATIONS

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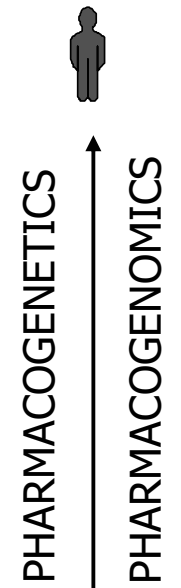
PHARMACOGENETIC DATABASES

SOCIAL AND PUBLIC POLICY ISSUES: OVERVIEW

- Population frequencies of many polymorphic genes of pharmacogenetic interest depend on race or ethnic specificity.
- Information about ethnic specificity has become an integral part of pharmacogenetic research.

THE PROMISE OF PHARMACOGENETICS

Ultimate goal: personalized therapy



Current: one drug fits all



Genetic Structure of Human Populations

Noah A. Rosenberg,^{1*} Jonathan K. Pritchard,² James L. Weber,³
Howard M. Cann,⁴ Kenneth K. Kidd,⁵ Lev A. Zhivotovsky,⁶
Marcus W. Feldman⁷

20 DECEMBER 2002 VOL 298 SCIENCE

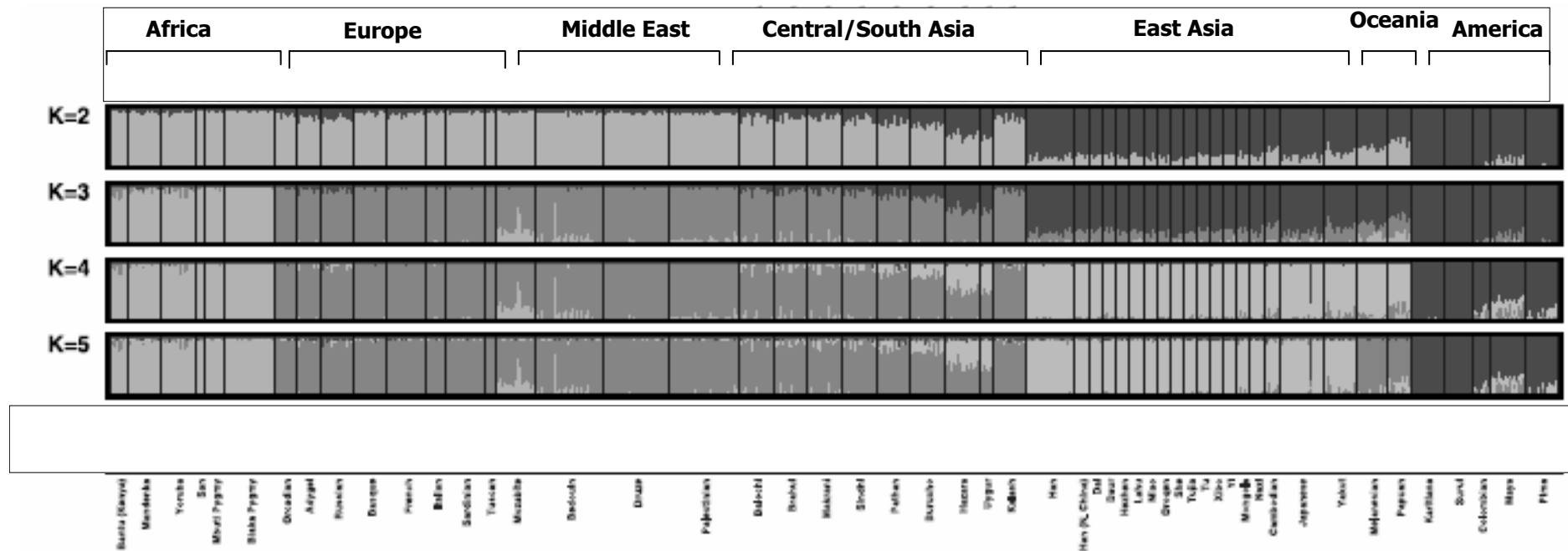
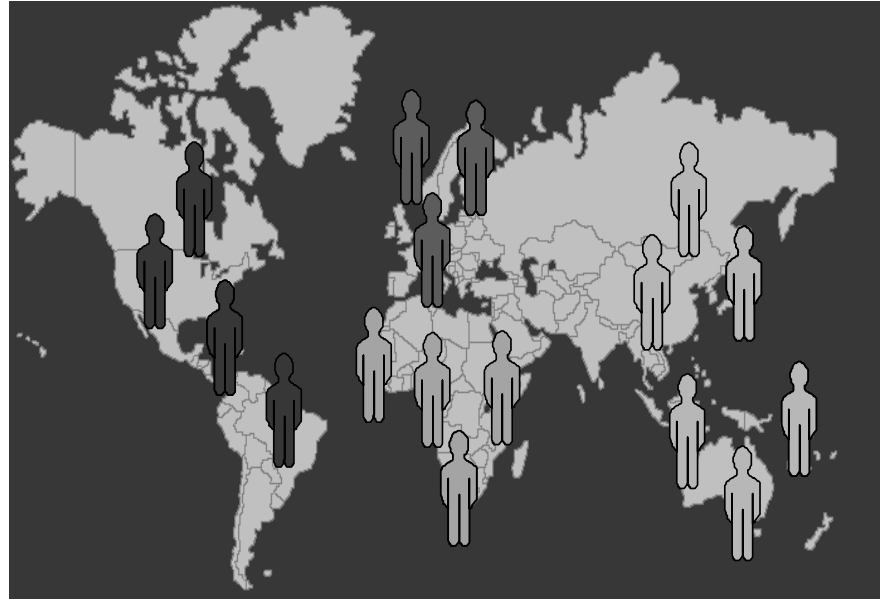


Fig. 1. Estimated population structure. Each individual is represented by a thin vertical line, which is partitioned into K colored segments that represent the individual's estimated membership fractions in K clusters. Black lines separate individuals of different populations. Populations are labeled below the figure, with their regional affiliations above it. Ten *structure* runs at each

K produced nearly identical individual membership coefficients, having pairwise similarity coefficients above 0.97, with the exceptions of comparisons involving four runs at $K = 3$ that separated East Asia instead of Eurasia, and one run at $K = 6$ that separated Karitiana instead of Kalash. The figure shown for a given K is based on the highest probability run at that K .



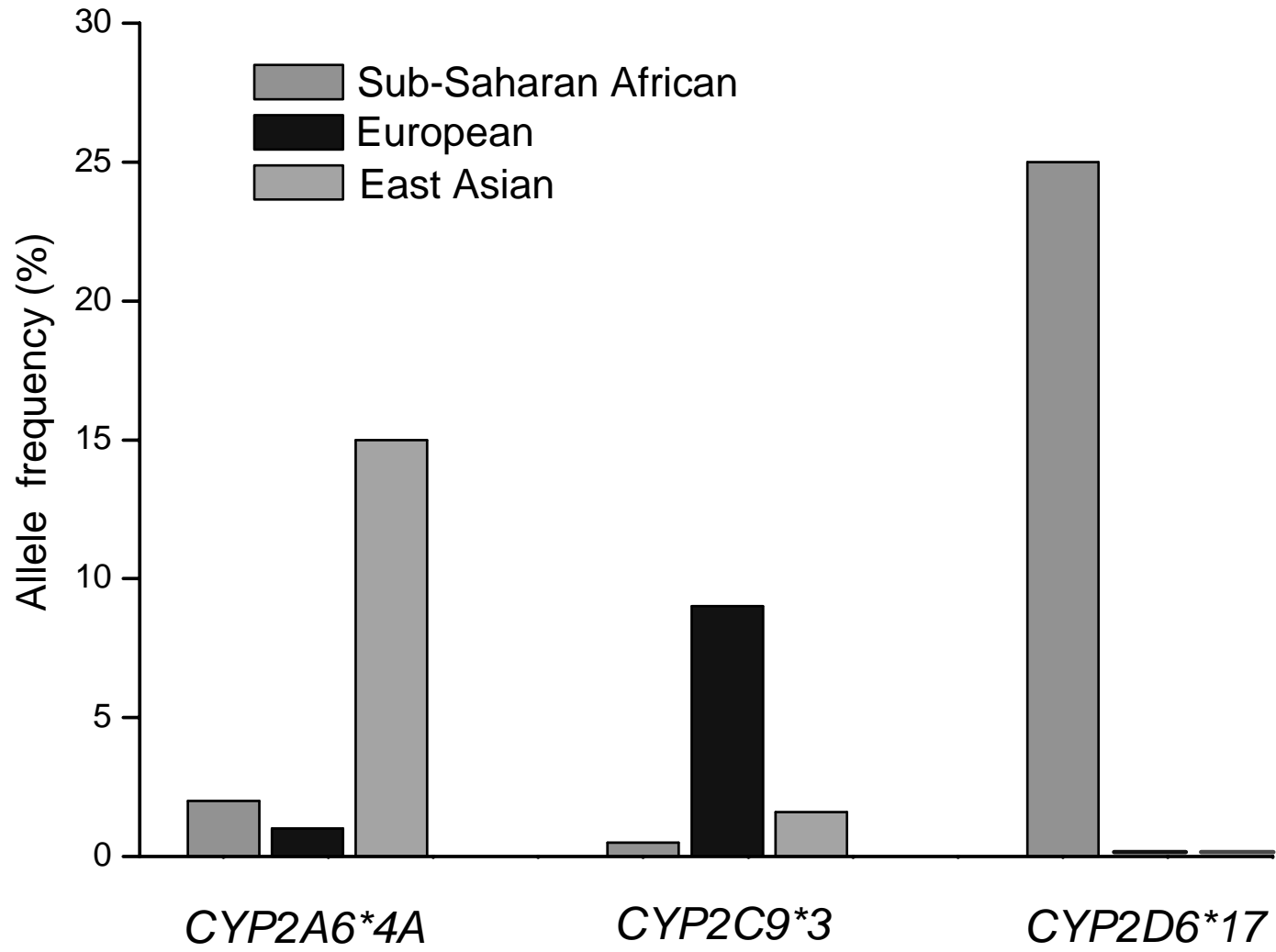


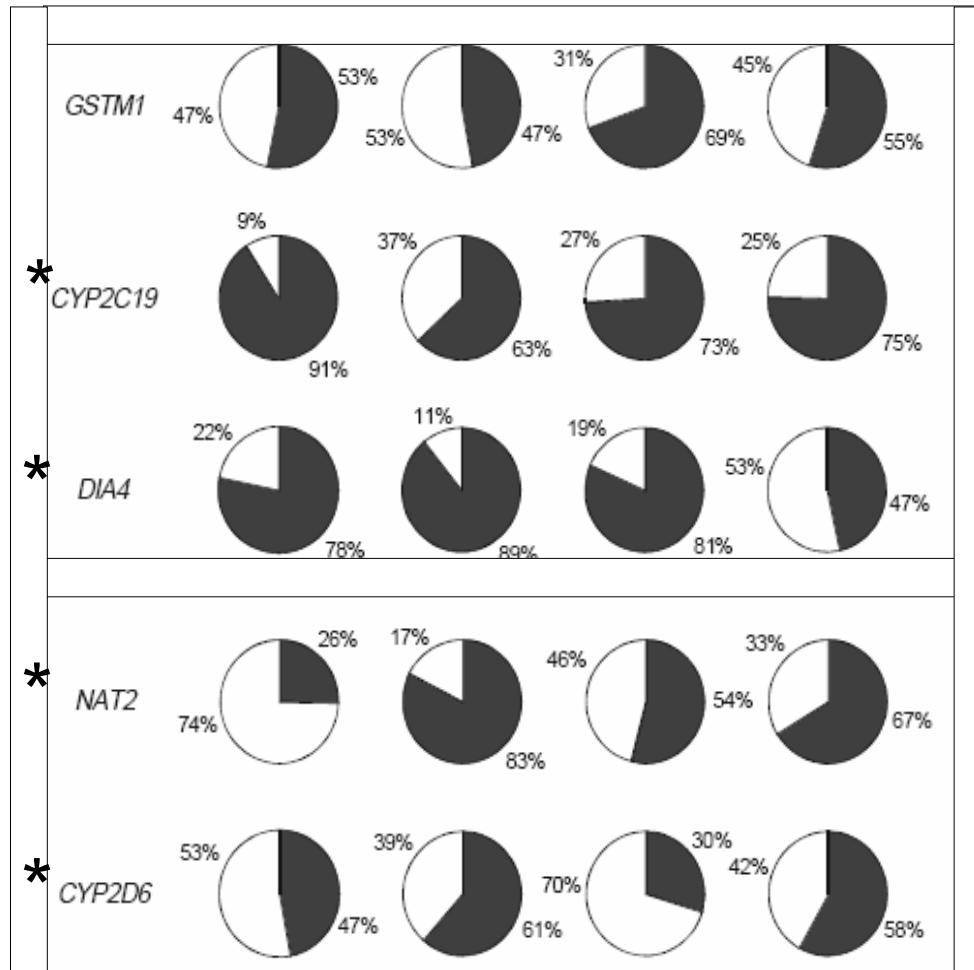
Table 2 • Proportion of membership of each sampled population in STRUCTURE-defined subclusters

Population	A	B	C	D
Bantu	0.04	0.02	0.93	0.02
Ashkenazi	0.96	0.01	0.01	0.02
Ethiopia	0.62	0.08	0.24	0.06
Norway	0.96	0.02	0.01	0.01
Armenia	0.90	0.04	0.02	0.05
China	0.09	0.05	0.01	0.84
Papua New Guinea	0.02	0.95	0.01	0.02
Afro-Caribbean	0.21	0.03	0.73	0.03

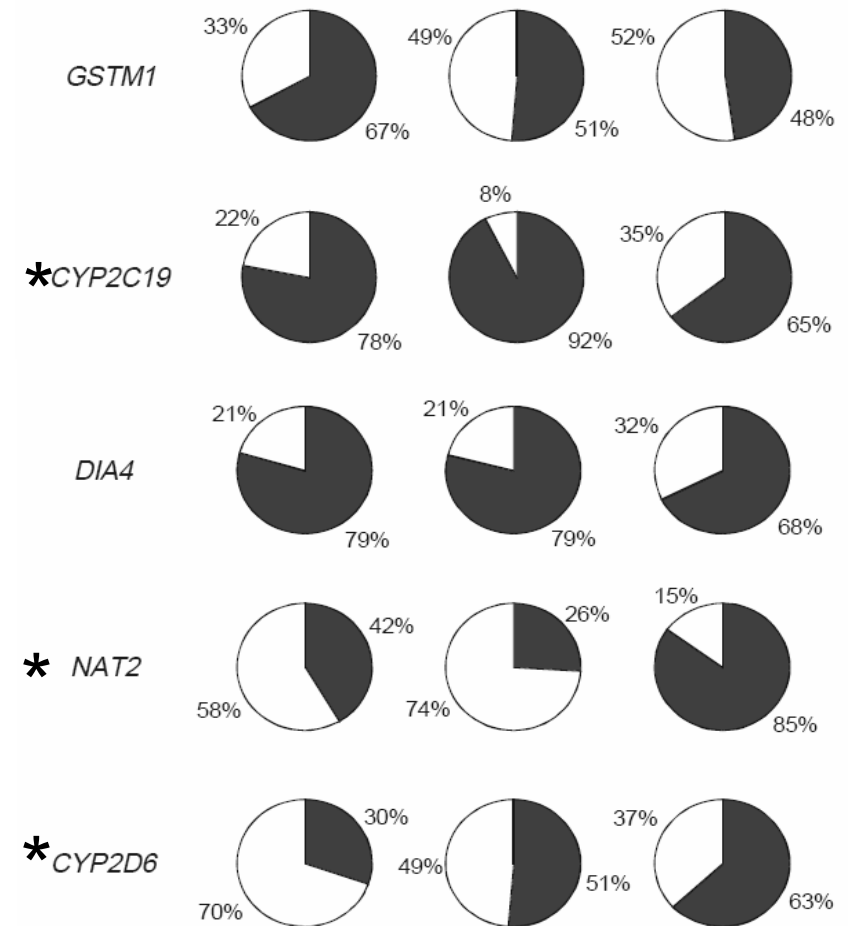
Wilson *et al.* Nat Genet. 2001

Allele frequencies at each of DME gene

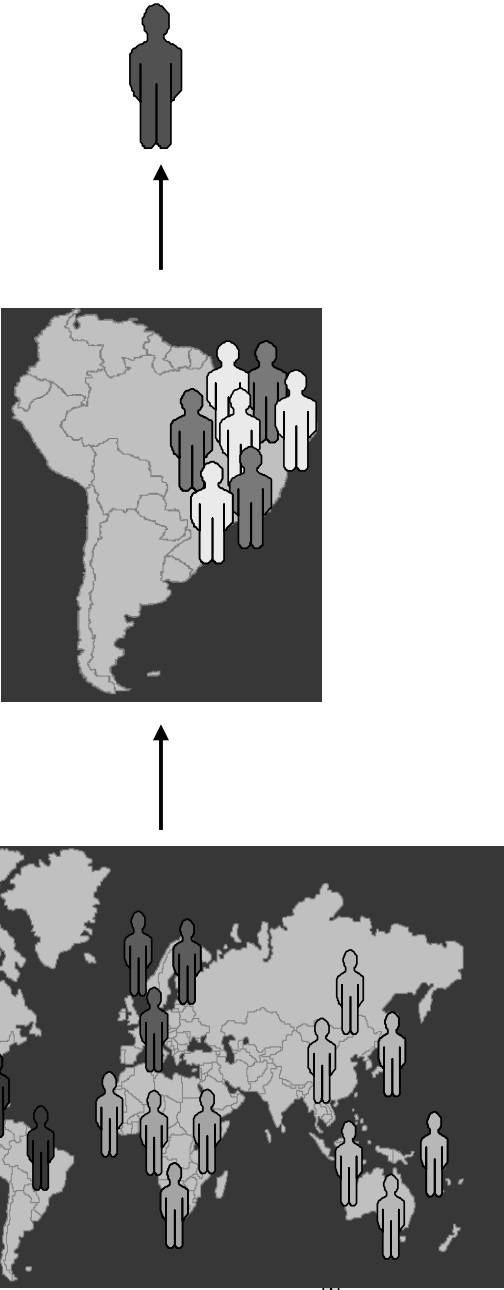
A. STRUCTURE-defined clusters



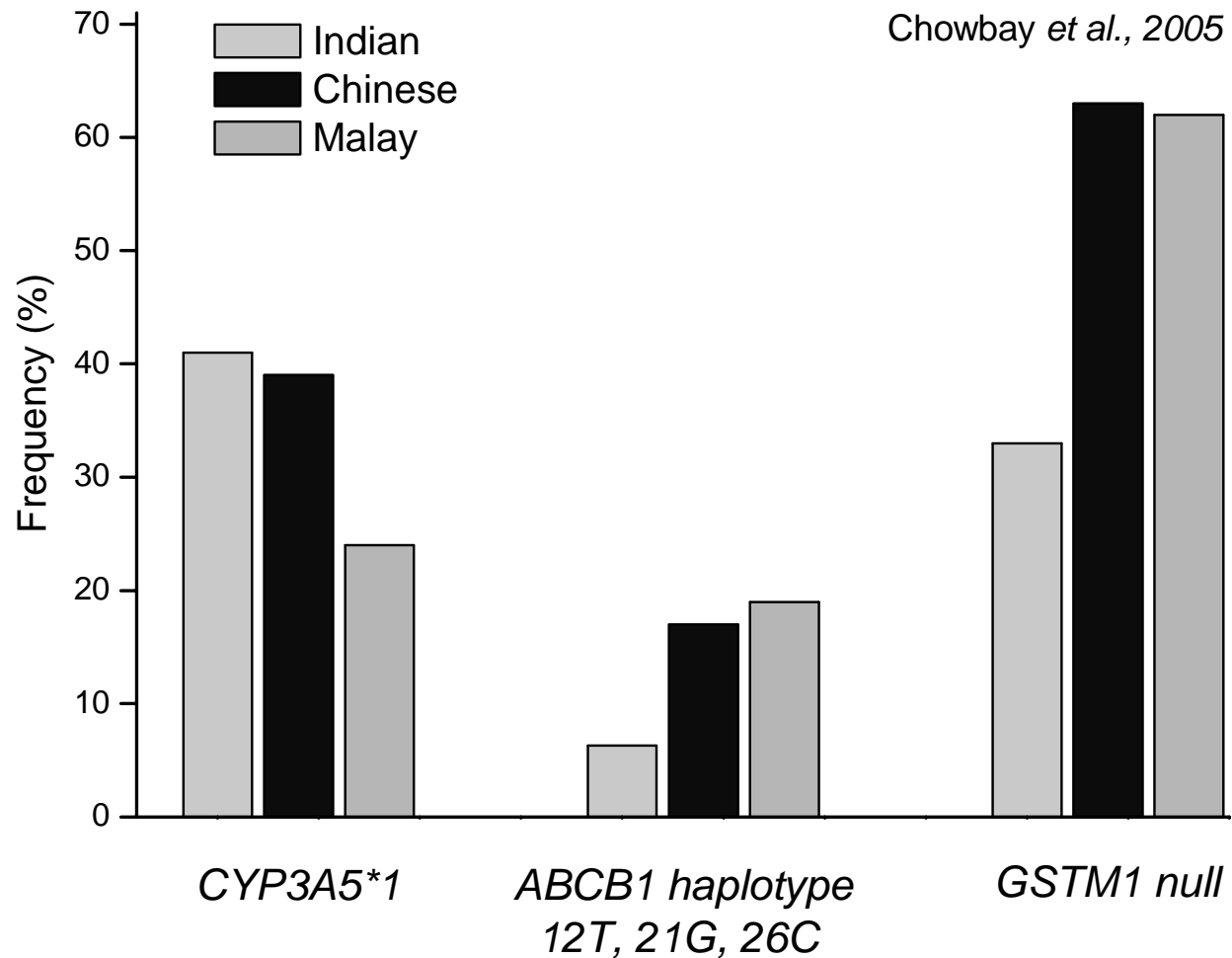
B. ETHNICALLY-labeled groups



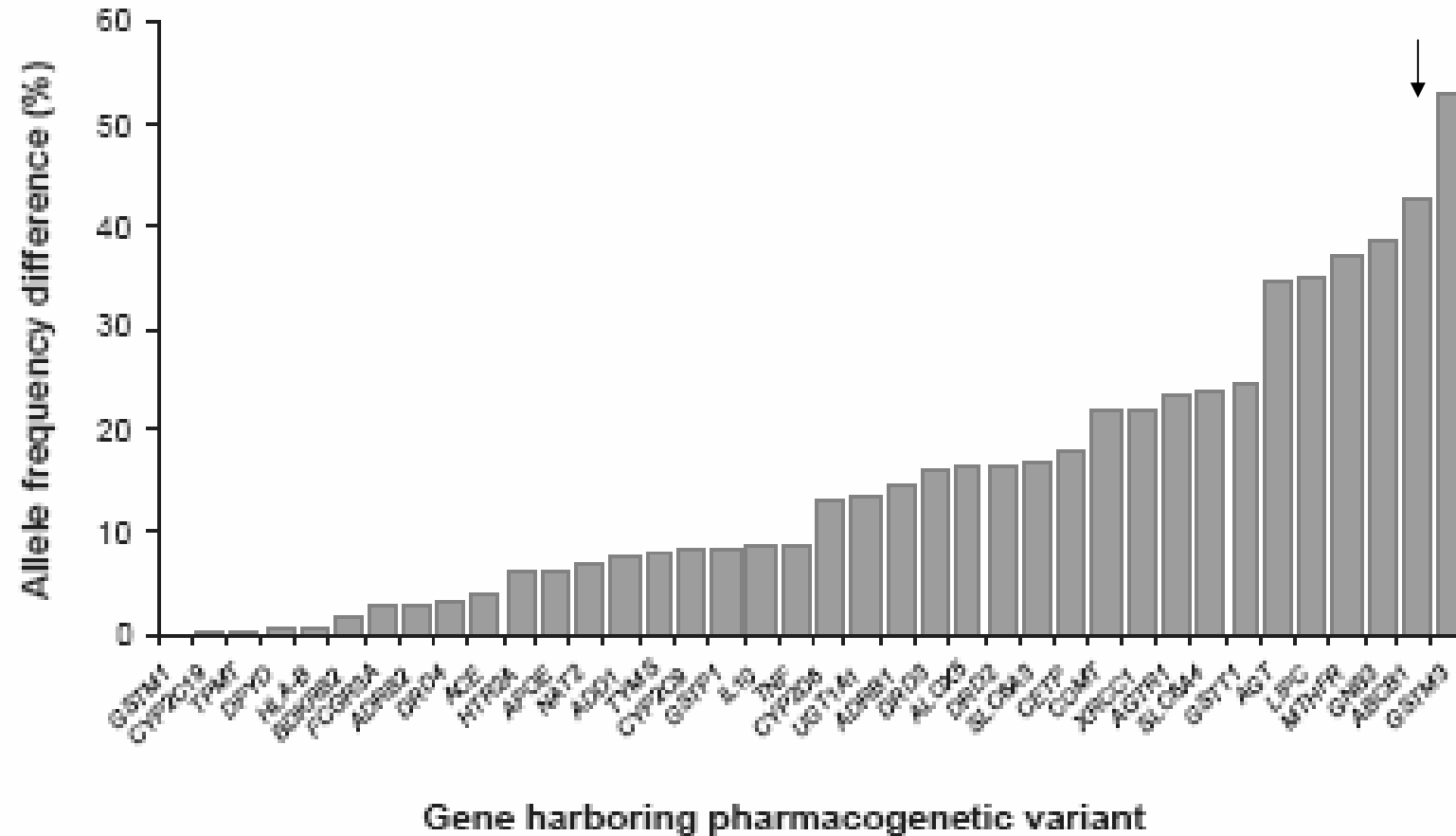
Stratification: subpopulations



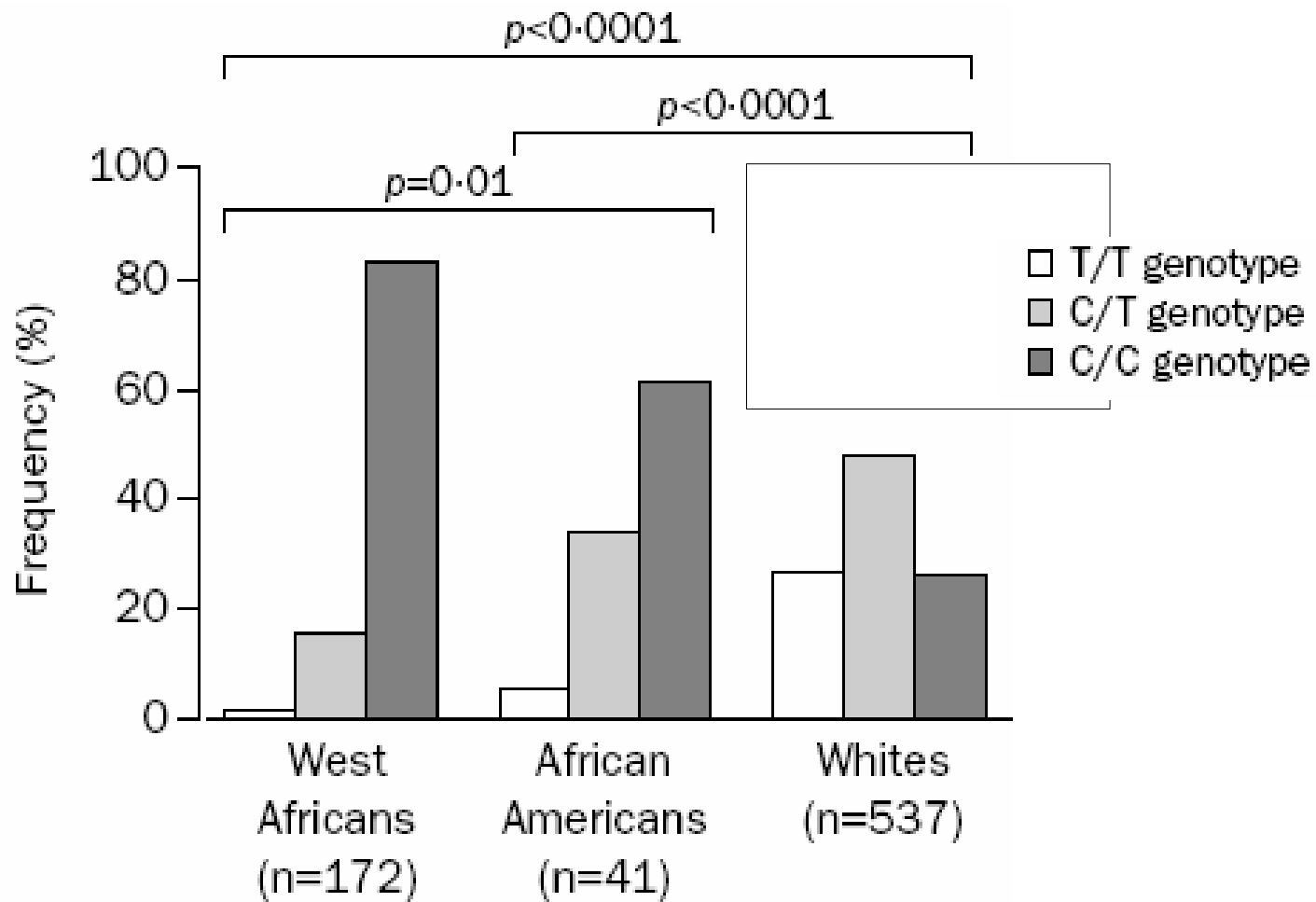
Population stratification in Singapore



Differences in the frequency of pharmacogenetically-relevant alleles between Caucasian Americans and African Americans



Goldstein & Hirschhorn, *Nat Genet* 2004



Schaeffeler *et al.*, Lancet 2001

ADMIXTURE IN NORTH AMERICAN POPULATIONS

European-Americans <5% of non-European alleles

African-Americans 19 -26% of European alleles
E. Parra, 1998; Dextro-Bisol et al., 1999

Hispanics

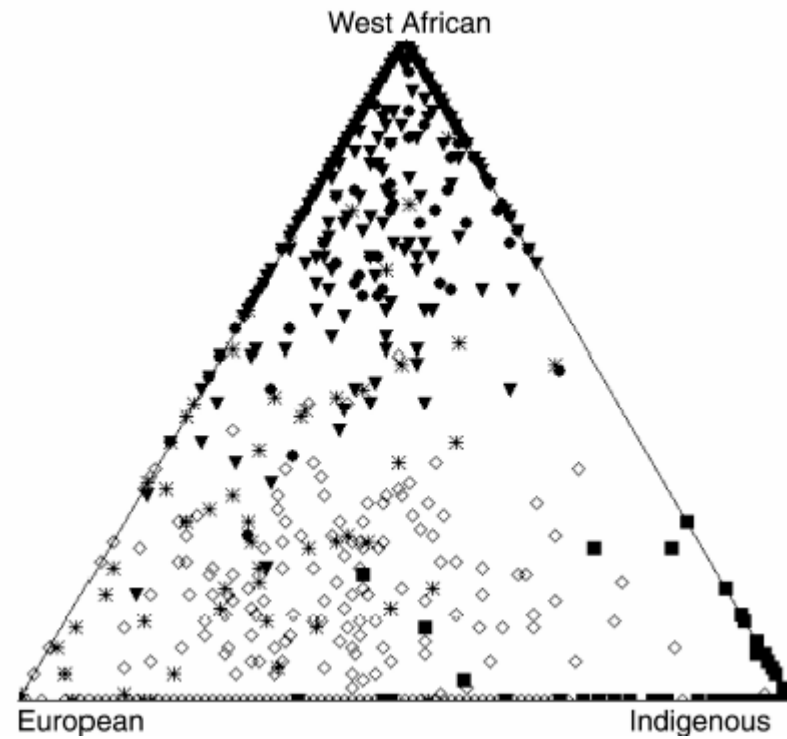
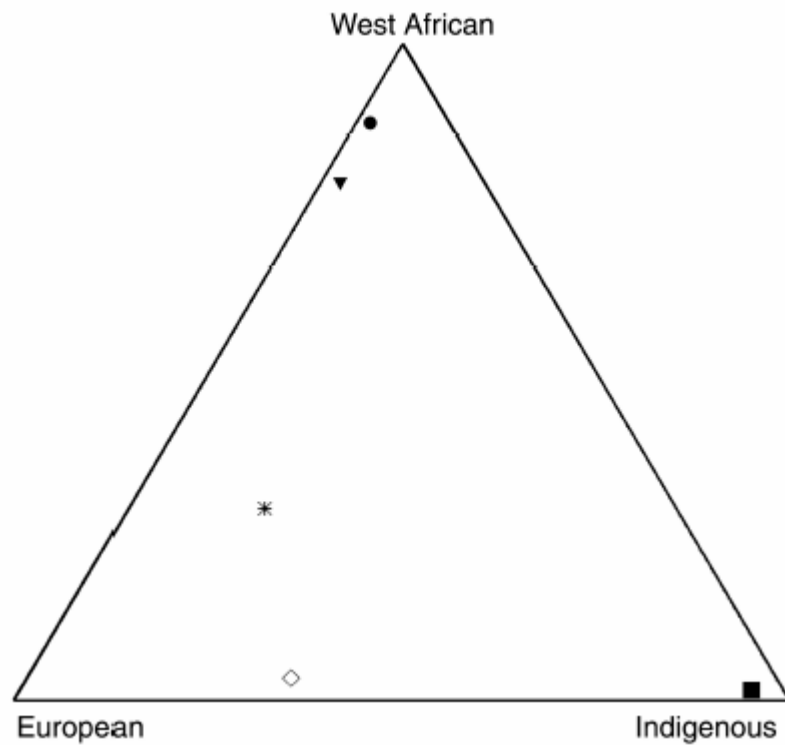
➤ Native Amer. 36 - 68% (west) 0 - 21% (east)

➤ African 0 - 17%

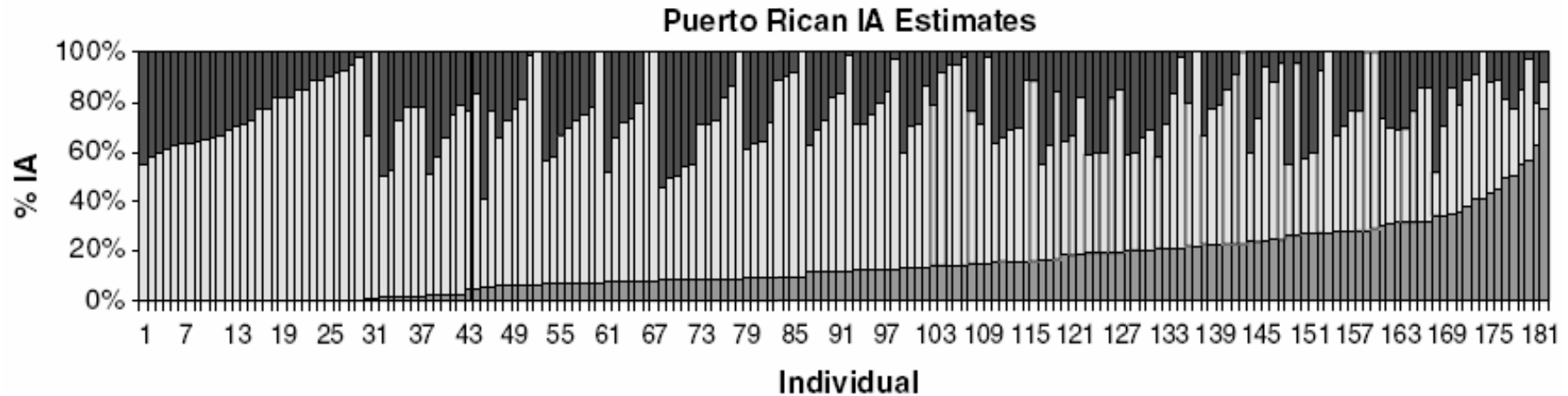
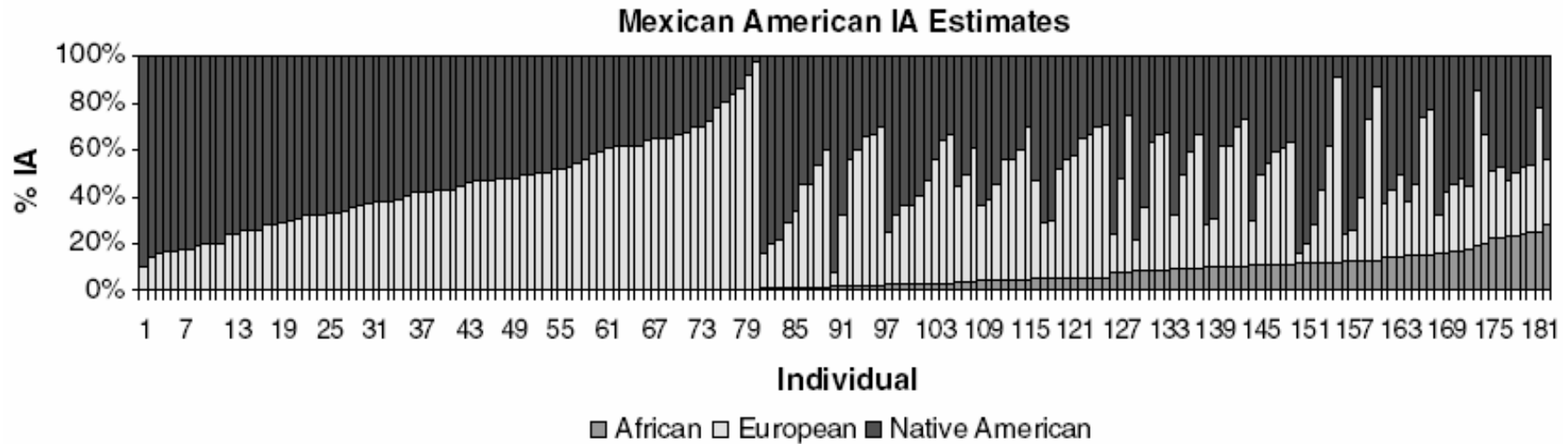
Bertoni *et al.*, 2003

- African-Caribbeans
- ▼ African-Americans
- * Puerto Ricans
- ◇ Hispanics
- Mexicans

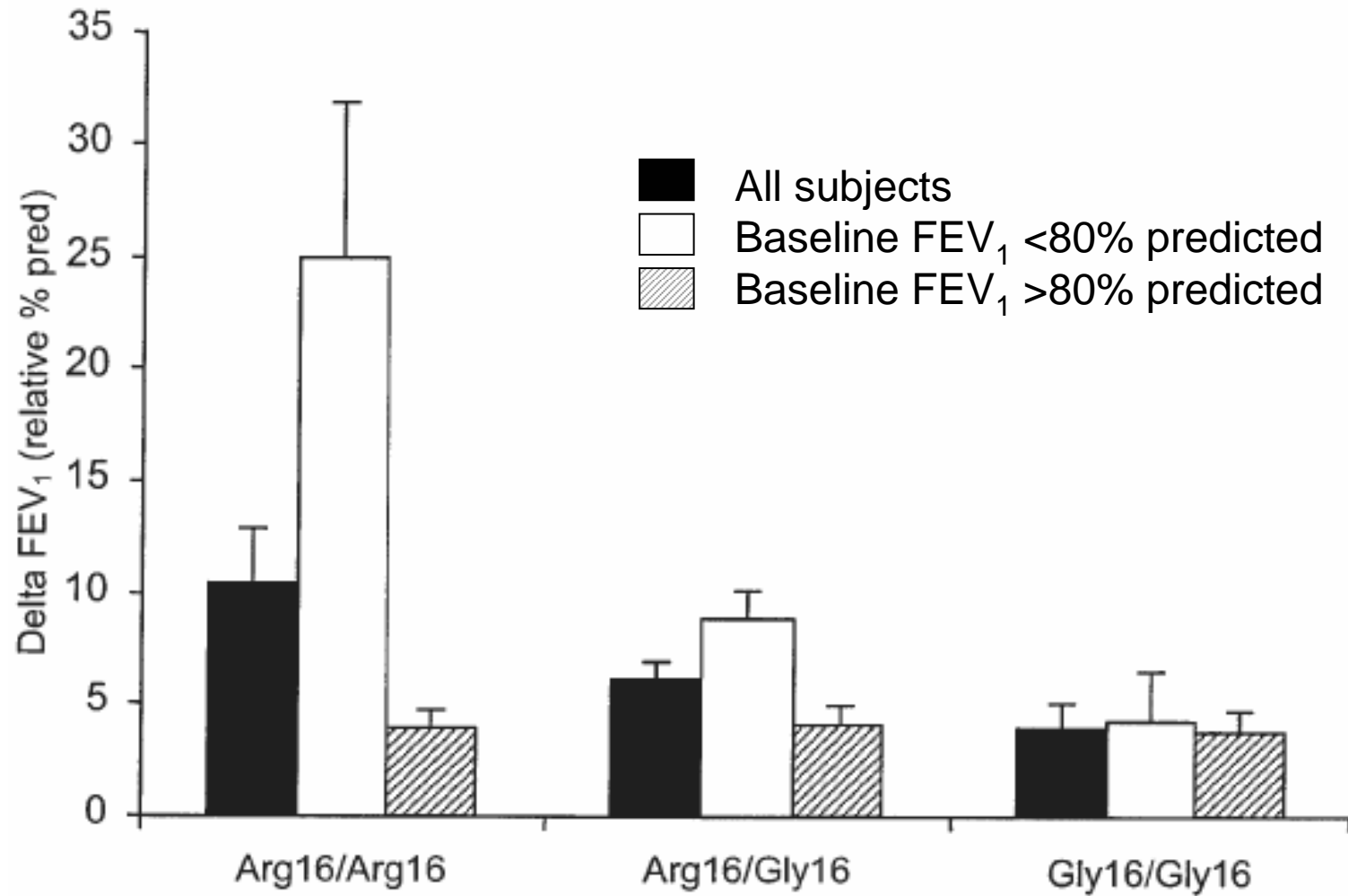
E. Parra *et al.*, Nat Genet 2004



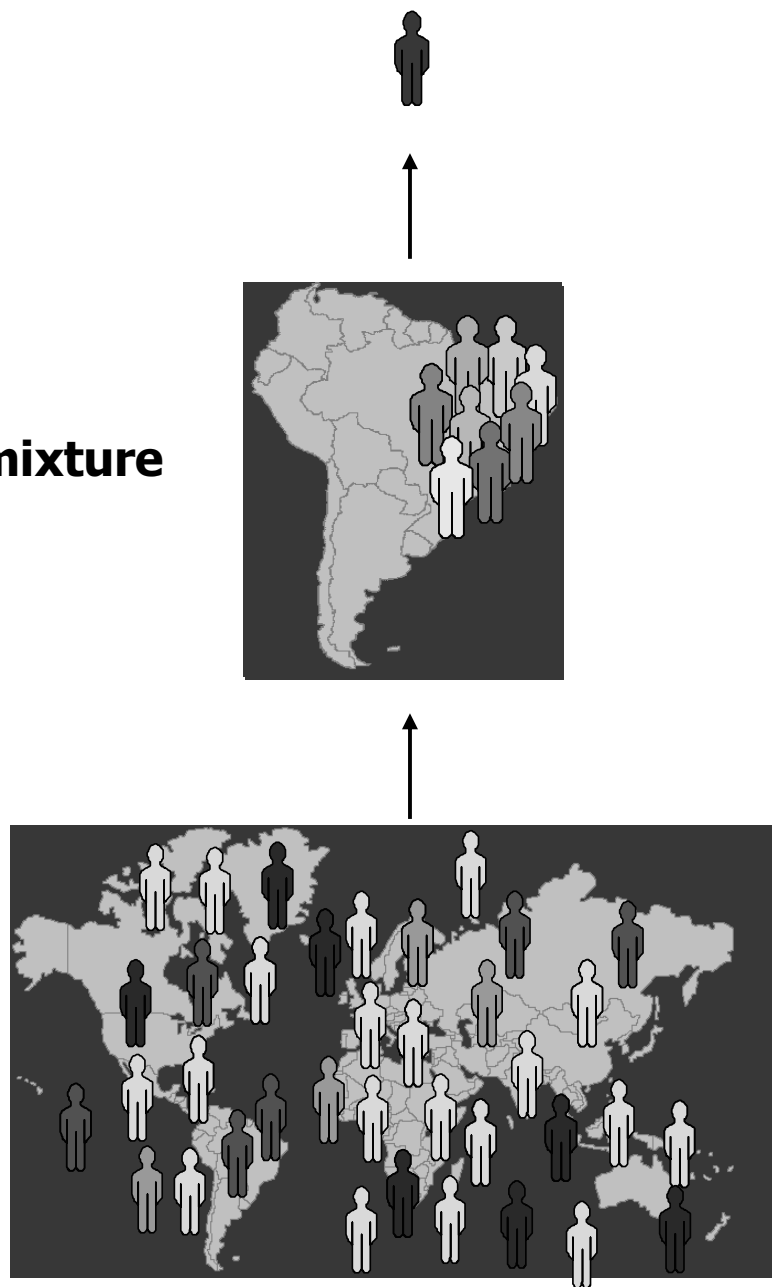
Genetic admixture in Mexican-American and Puerto Rican



Influence of codon 16 genotypes in β_2 AR on the responsiveness to albuterol in Puerto Rican subjects with asthma



Stratification: Admixture

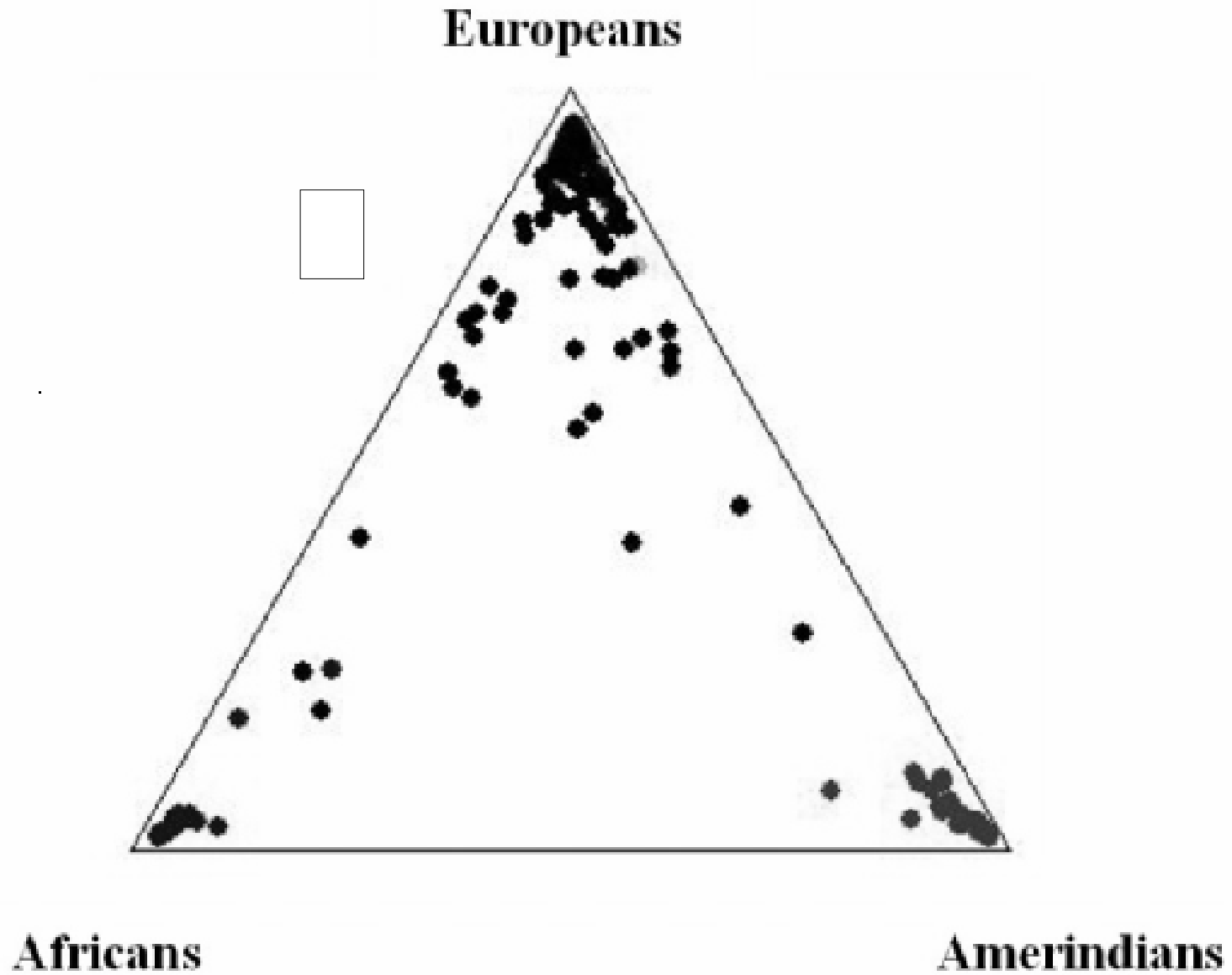




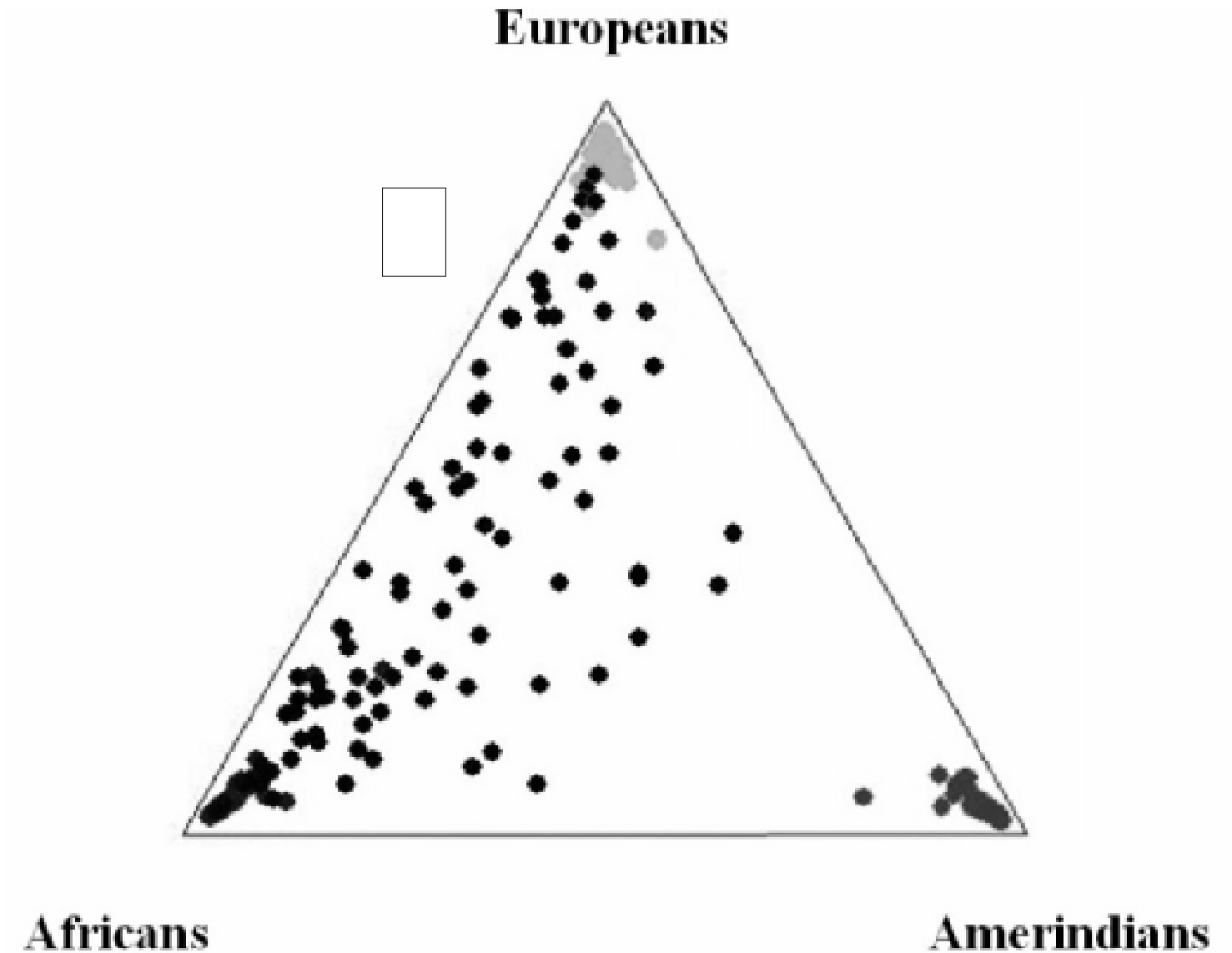
Tarsila do Amaral
Operários, 1933

"... The combinations of marriage (in Brazil) between white, indian and black are so manifold that the nuances of flesh color are countless."

Gobineau, French Minister, Rio de Janeiro, 1869



200 SELF-DECLARED **WHITE** BRAZILIANS - (Pena *et al.*, 2005)



100 SELF-DECLARED **BLACK** BRAZILIANS - (Pena *et al.*, 2005)

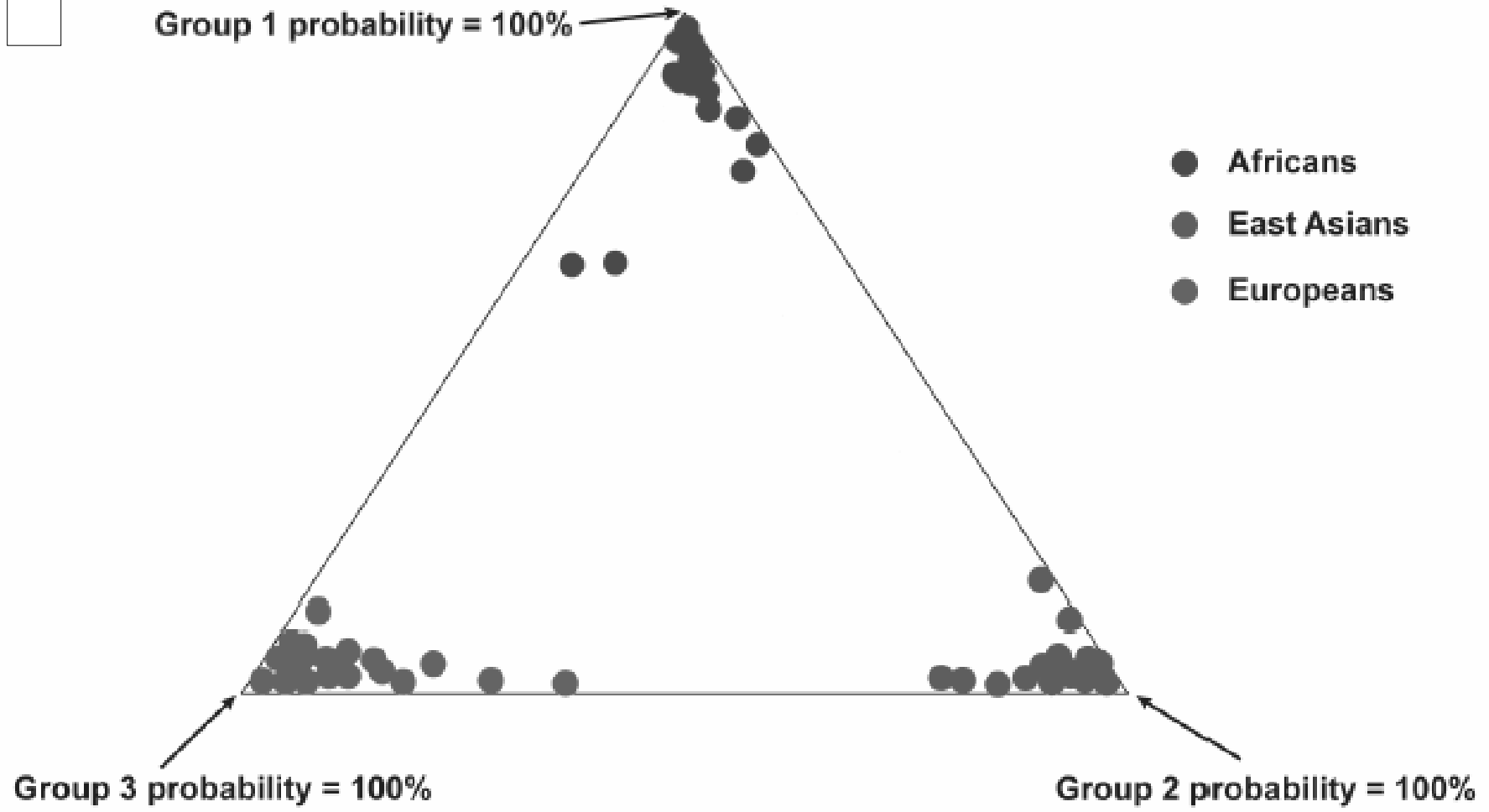
DISTRIBUTION OF *TPMT* VARIANT ALLELES ^a

Population group	<i>TPMT</i> *3A	<i>TPMT</i> *3C
European	2.4 – 5.7	0.2 - 0.8
African		
West-African ^b	0	5.4 – 7.6
North-American		
European-American	3.2	0.2
African-American	0.8	2.4
South American		
White Brazilian	1.8	1.8
Non-white Brazilian ^c	2.0	2.5
Argentinian	3.1	0

^a Percent of total *TPMT* alleles;

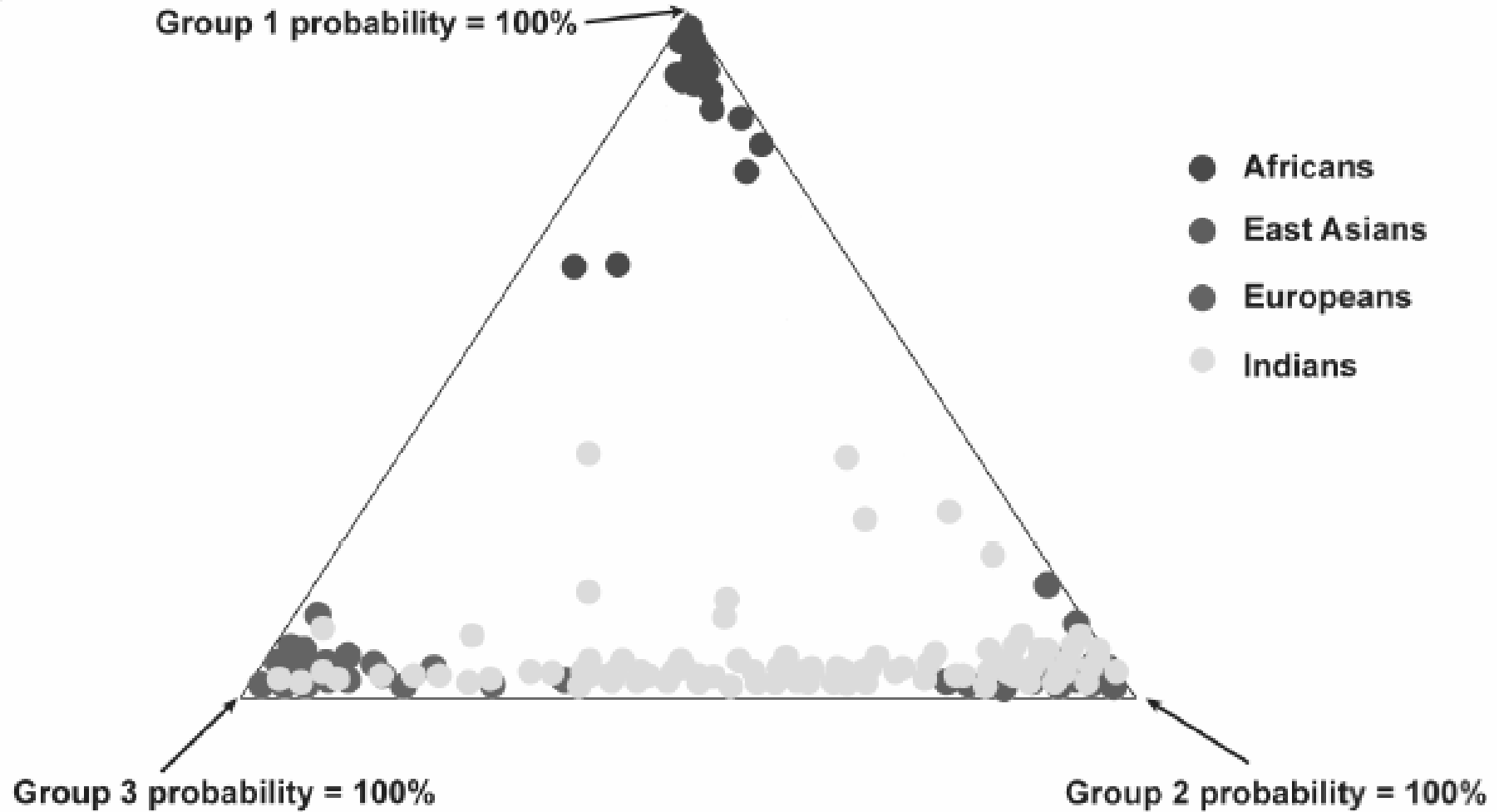
^b Kenyans and Ghanians; ^c blacks and “ethnically-admixed”.

a

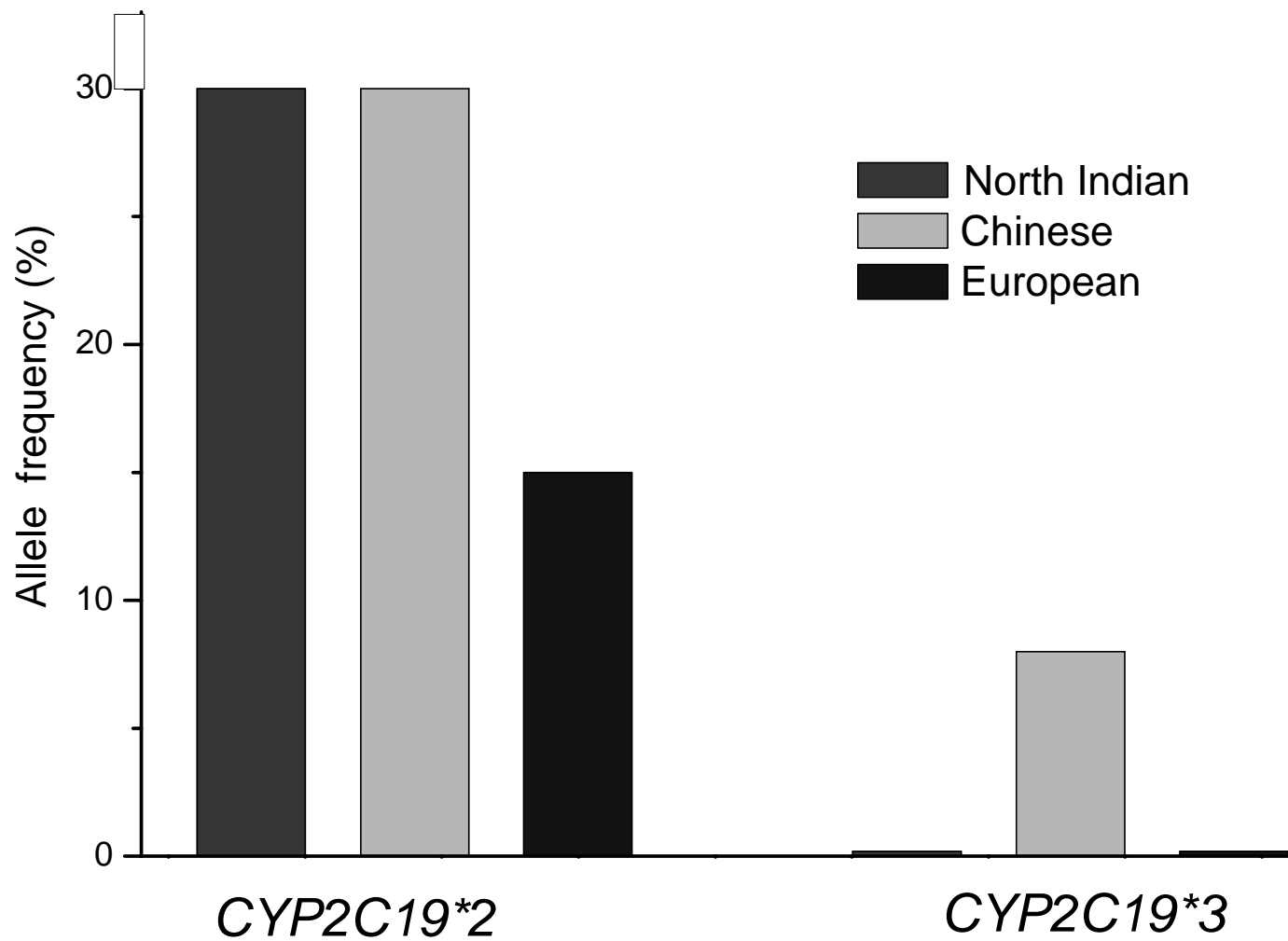


Jorde & Wooding, *Nat Genet* 2004, adapted from Bamshad *et al.*, *Am J Hum Genet* 2003

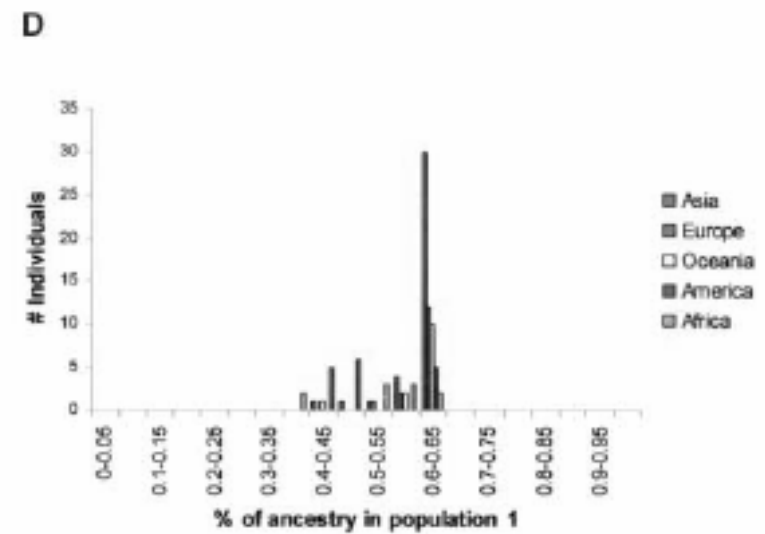
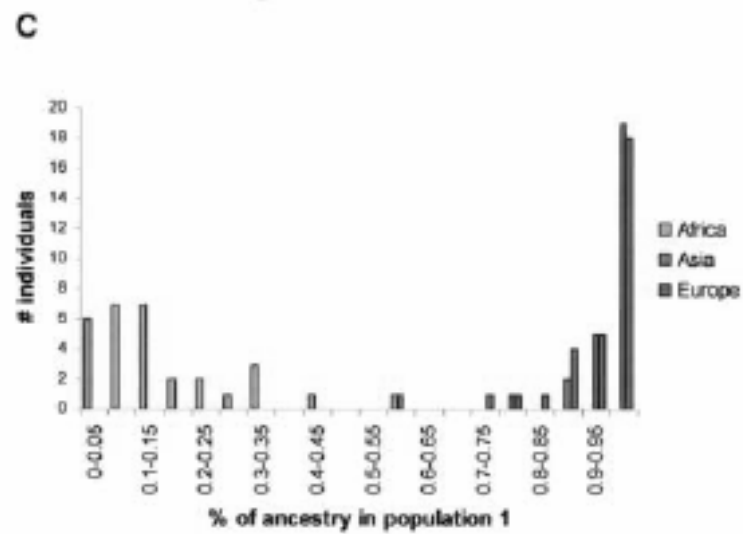
b



Jorde & Wooding, *Nat Genet* 2004, adapted from Bamshad *et al.*, *Am J Hum Genet* 2003



Lamba *et al.*, 1999; Xie *et al.*, 2001



Serre & Pääbo, 2004

Worldwide Gradients of Human Genetic Diversity

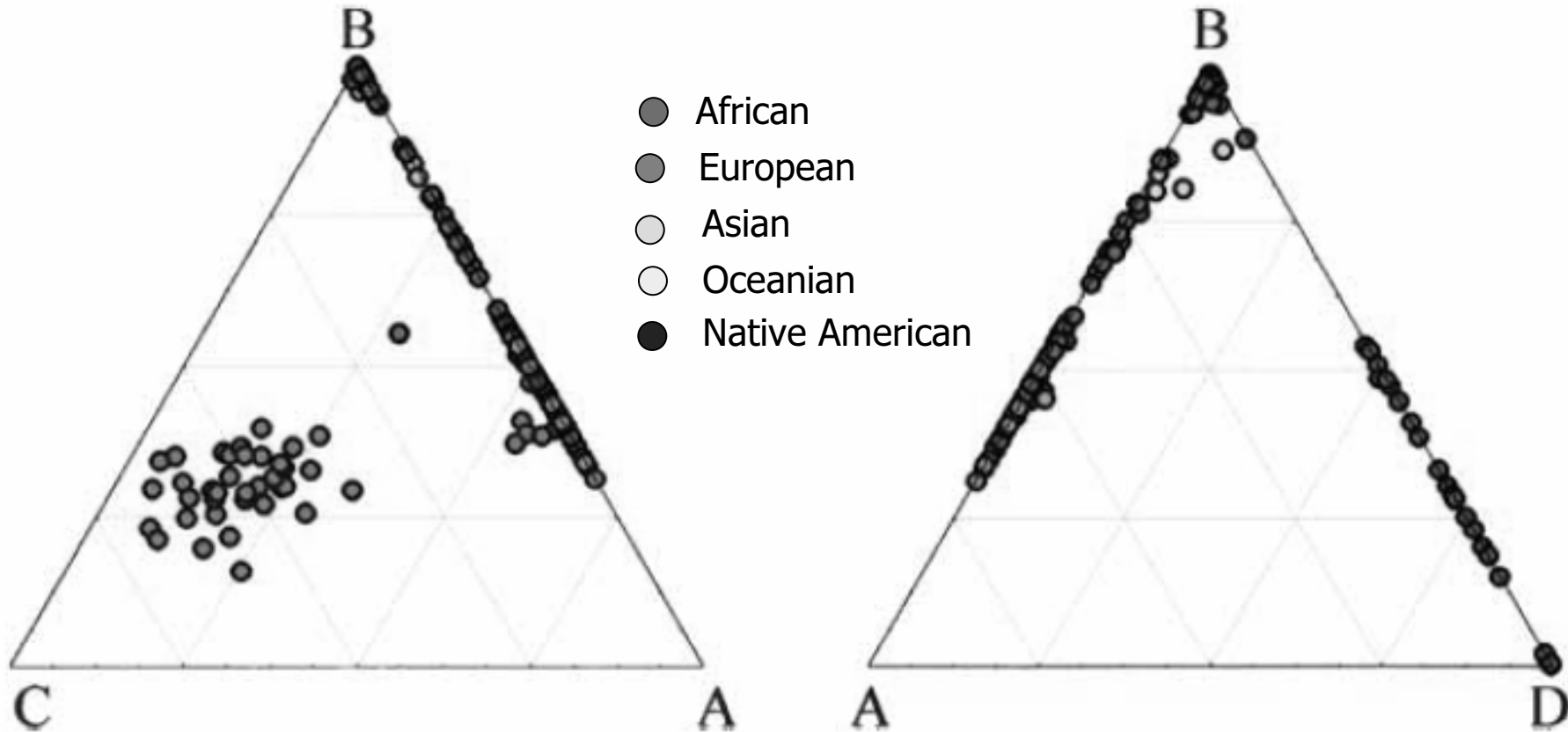


Figure 2 Assignment of 261 individuals from the CEPH diversity panel (Cann et al. 2002) according to their coefficients of ancestry of four inferred populations (A, B, C, and D).

Clines , not "Races"

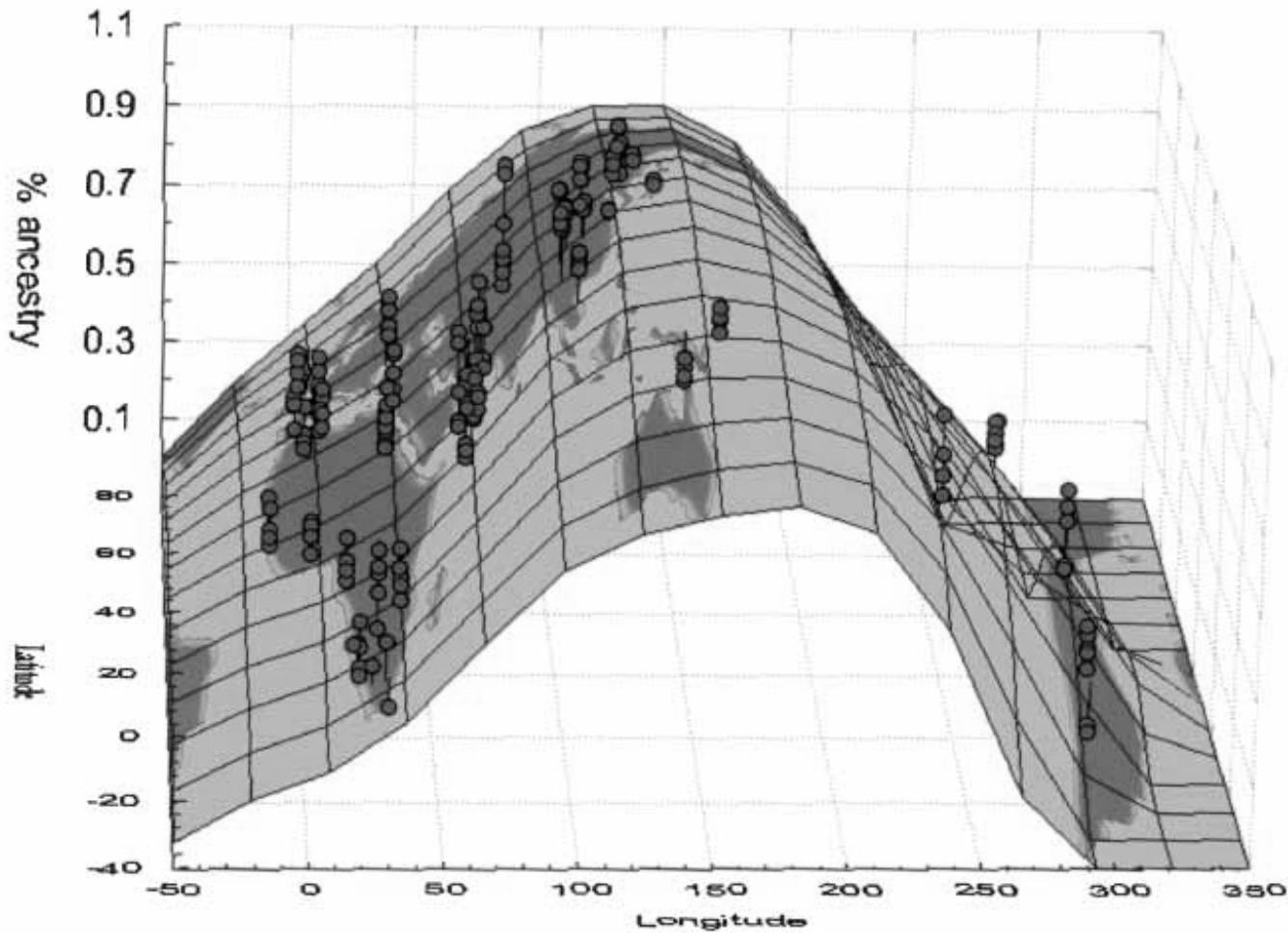
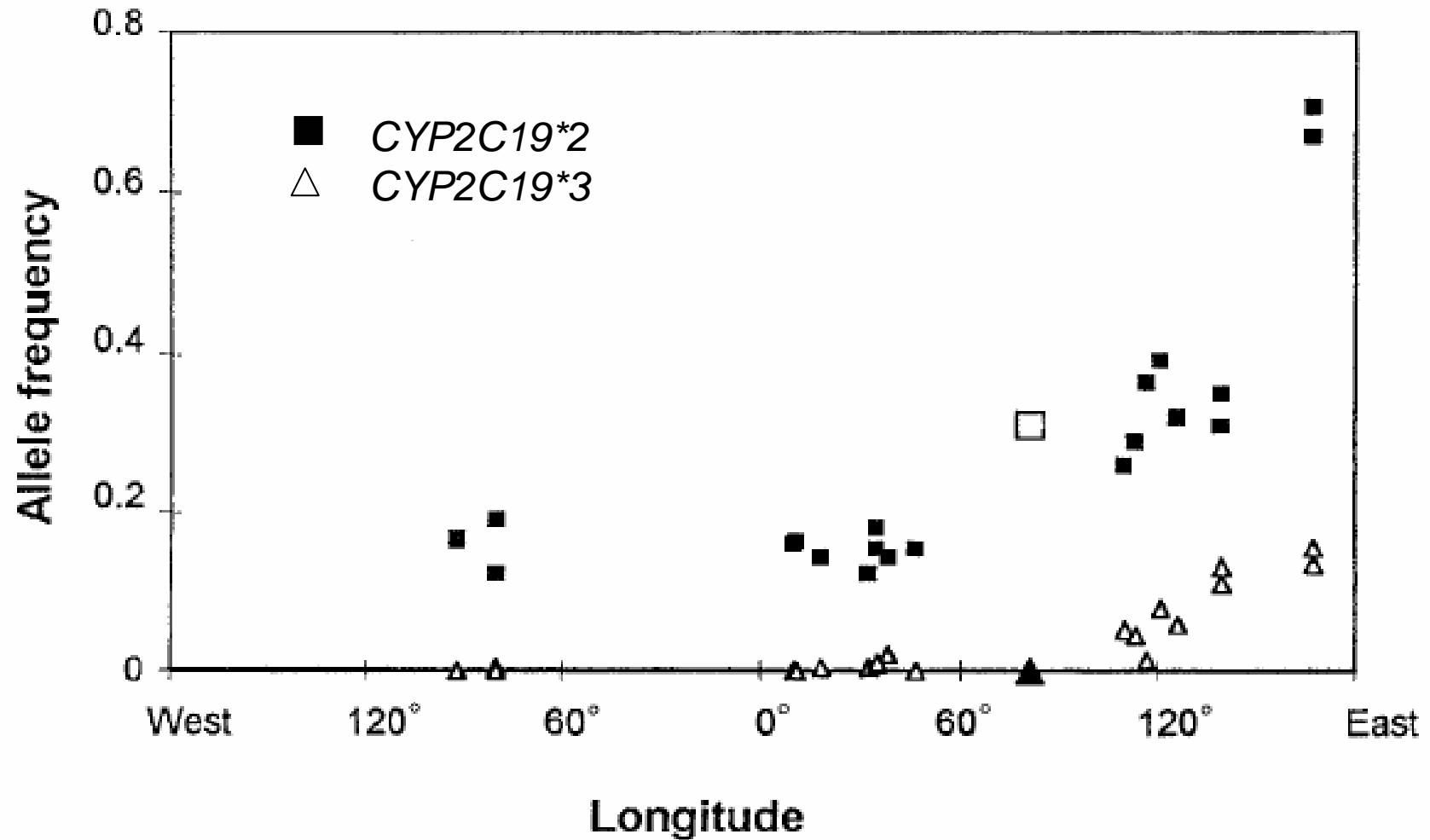


Figure 3 Geographic representation of the proportion of ancestry in inferred population B obtained by Structure. Red dots represent individuals defined by their longitude (x -axis), latitude (y -axis), and coefficient of ancestry (z -axis) in the inferred population B. The surface of the world was fitted to the xyz coordinates using a distance weighted least-squares smoothing method.

Worldwide gradients in *CYP2C19* variant allele frequency



Lamba *et al.* Clin Pharm Ther 2000

Control of Confounding of Genetic Associations in Stratified Populations

- **Genomic Control**

Independent marker loci used to adjust the distribution of a standard test statistic. Scaling factor λ . (Reich & Goldstein, 2001).

- **Structure Association**

Independent marker loci used to infer population stratification and adjust for population substructure and admixture.

- Bayesian MCMC methods: STRUCTURE (Pritchard *et al.*, 2000)
ADMIXMAP (Hoggart *et al.*, 2003)

- Frequentist (ML) methods: (Hanis *et al.*, 1991; Tang *et al.*, 2005)