How molten is the pot? Analyzing self-reported and genetic ancestry of individuals and reproducing couples in the USA

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Introduction

The 2010 US Census showed that 15% of new US marriages occur between spouses of different ethnicities, a more than double increase over the previous two decades[1]. Further, although prior studies in personal genetics[2] have noted that self-reported ethnicity (SRE) is not fully concordant with genetic ancestry (GA), current medical genetics guidelines are based around SRE[3]. We sought to characterize the diversity of a population seeking carrier screening by exploring the discordance between SRE and GA. By analyzing current inter- and intra-ethnic mating patterns we sought to extrapolate the increase in diversity due to inter-ethnic coupling.

People of reproductive age are diverse in genetic ancestry within and across self-reporting categories
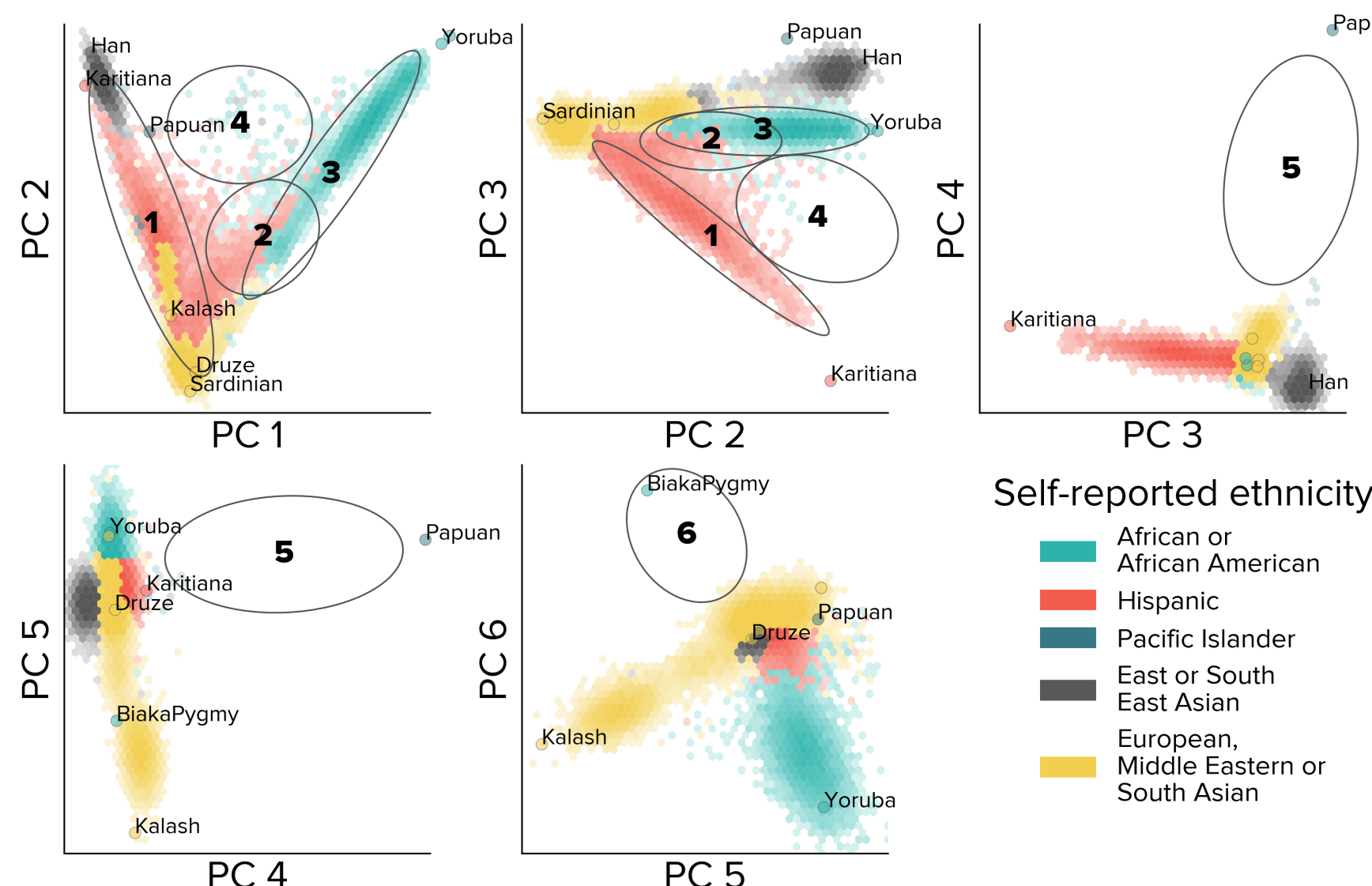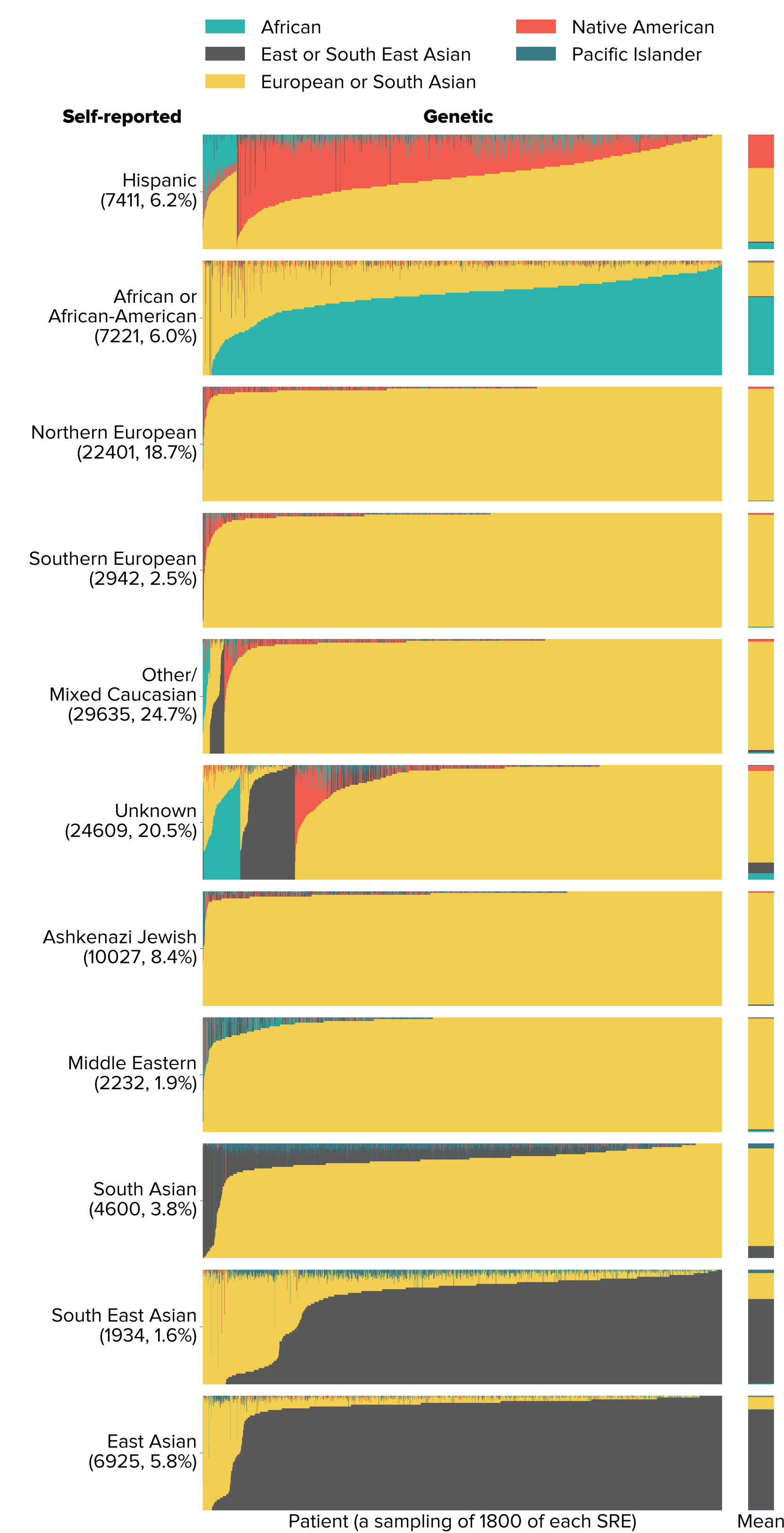

Methods

Deidentified data were drawn from individuals receiving carrier screening; all individuals self-reported ethnicity, including options for unknown and for mixed ethnicity. To evaluate discordance between SRE and GA, we adapted an existing ancestry analysis method[4,5,6] and analyzed data from 119,937 individuals who ordered our *Family Prep Screen* from 2014 to mid-2016, excluding patients from self-reporting groups with fewer than 500 patients. To evaluate mating patterns we analyzed the reports of 32,407 couples[7], having removed couples with at least one individual self-reporting as 'Unknown' or an ethnicity with less than 200 individuals. Forward trends were simulated holding male mating patterns constant and assuming every couple is equally likely to produce offspring.

Patients self-reporting as Hispanic have diverse genetic ancestry within subgroups
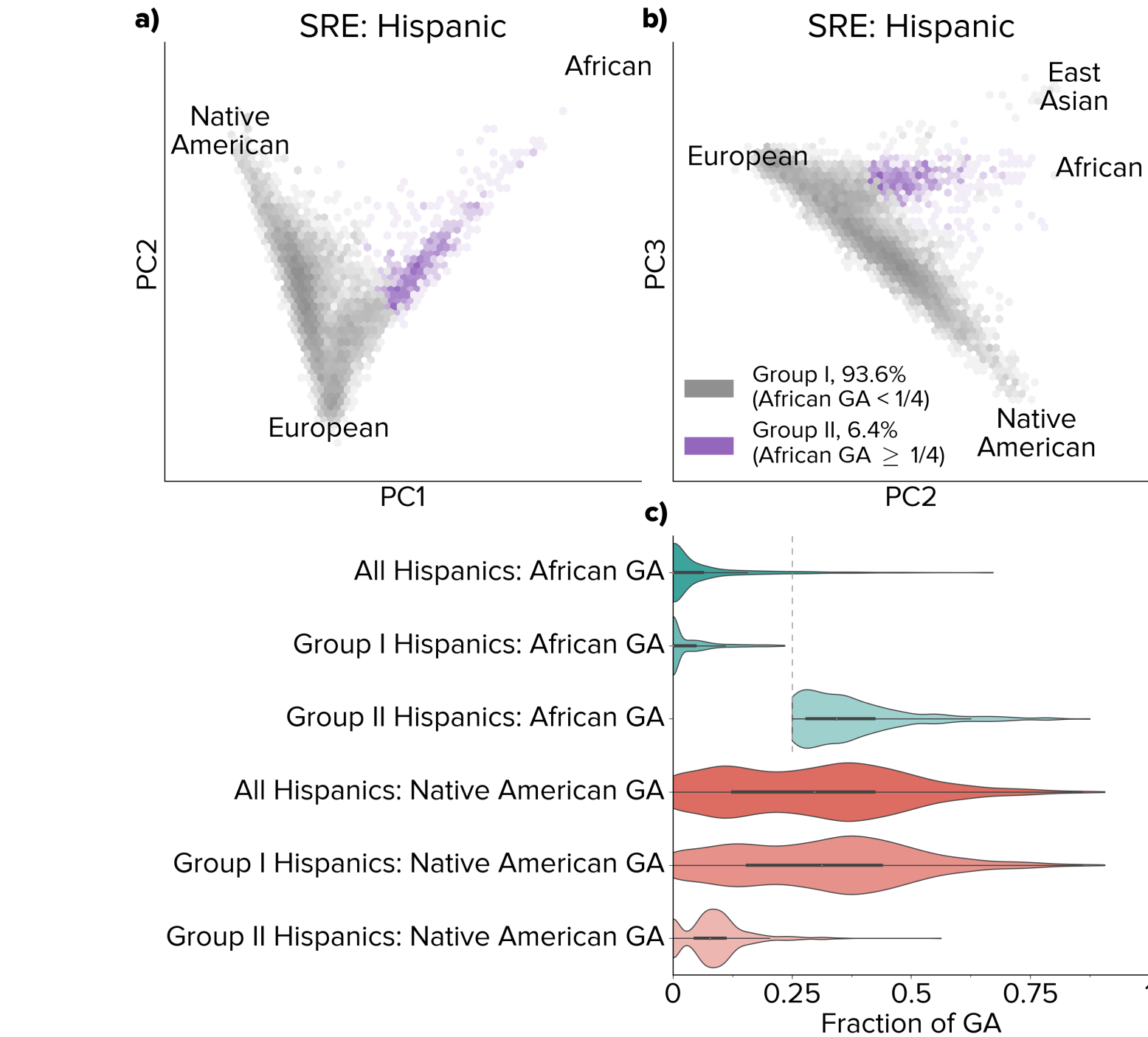
Patients from several self-reporting groups have Ashkenazi Jewish ancestry
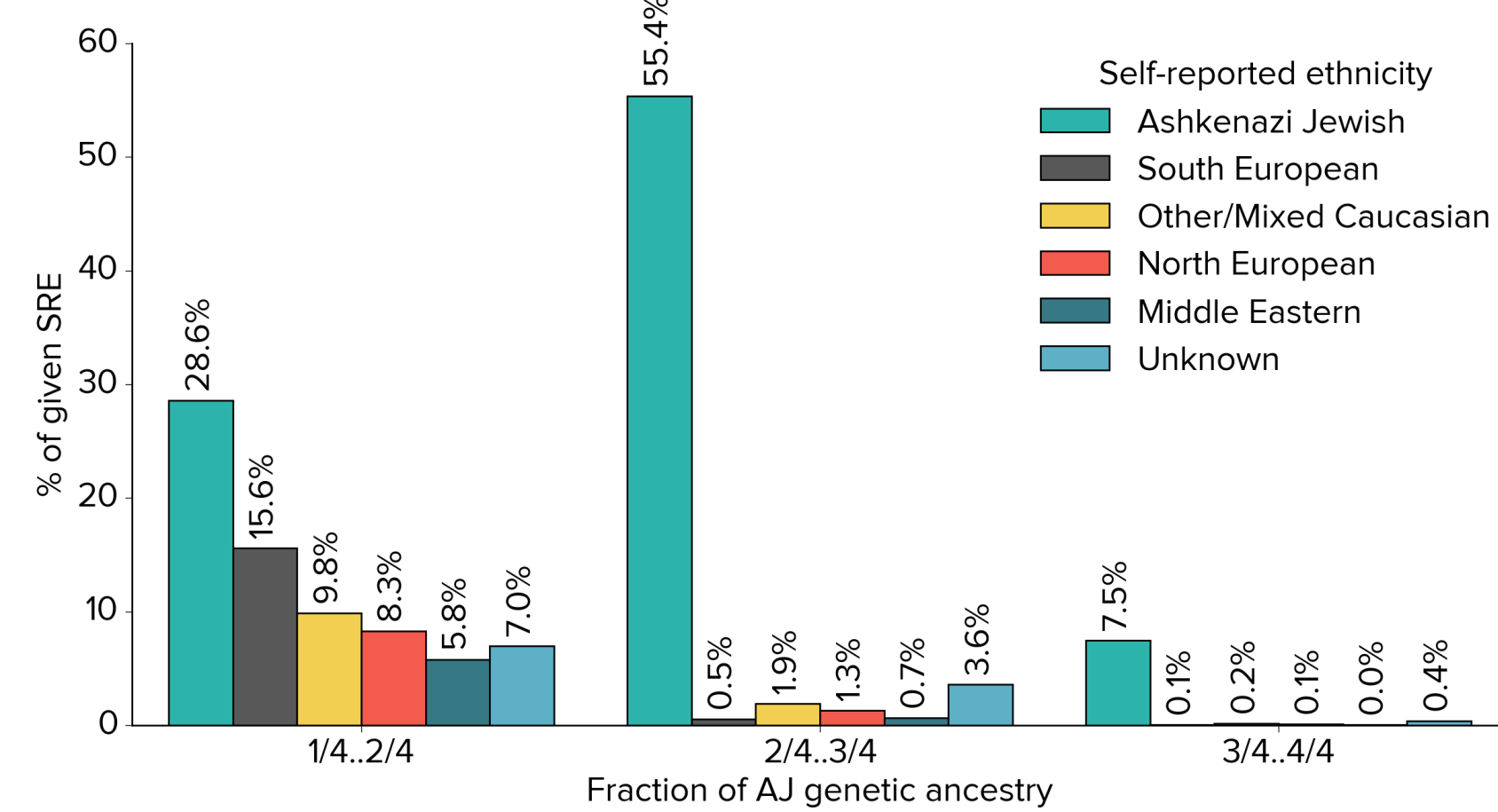
Current genetic screening guidelines from ACOG and ACMG recommend ethnicity-based panels, the biggest of which is for the Ashkenazi Jewish (AJ)[3]. We observed that 6.5% (Middle Easterners)—16% (South Europeans) of largely European-descent patients who did not self-report as AJ were predicted to have at least 25% AJ genetic ancestry.

Left column: Top: Stacked barplots of genetic ancestry fractions. Bottom: Principal component analysis. The intensity of each hexagonal bin indicates the number of patients. Color indicates the most represented SRE. Relevant reference populations are annotated. Diverse ancestry is observed in the Hispanic (1: the Native American-European cline, 2: the African-European cline where Hispanics are observed) and African American populations (3: the African-European cline where African Americans are observed), though 3-way admixture (4) is not common. No evidence of significant Pacific Islander ancestry (would be in area 5). African ancestry in self-reporting African Americans is not considerably derived from the BiAka and Mbuti pygmy or San populations (would be in area 6).

REFERENCES **1.** Wang et al. Pew Research Center. The Rise of Intermarriage **2.** Bryc, K, et al. (2015). The genetic ancestry of African Americans, Latinos, and European Americans across the United States. American Journal of Human Genetics, 96(1), 37–53. **3.** Gross, S. J., et al. (2008). Carrier screening in individuals of Ashkenazi Jewish descent for the Professional Practice and Guidelines Committee. Genetics in Medicine, 10(1), 54–56. **4.** Wang, C., et al. (2015). Improved Ancestry Estimation for both Genotyping and Sequencing Data using Projection Procrustes Analysis and Genotype Imputation. The American Journal of Human Genetics, 926–937. **5.** Li, JZ, et al. (2008). Worldwide human relationships inferred from genome-wide patterns of variation. Science, 319(5866), 1100–4. **6.** Bray SM, et al. (2010). Signatures of founder effects, admixture, and selection in the Ashkenazi Jewish population. Proc Natl Acad Sci USA 107(37):16222-7. **7.** Haque, I. S., Lazarin, G. A., Kang, H. P., Evans, E. A., Goldberg, J. D., & Wapner, R. J. (2016). Modeled Fetal Risk of Genetic Diseases Identified by Expanded Carrier Screening. JAMA, 316(7), 734. http://doi.org/10.1001/jama.2016.11139

Results

Diversity in the US population is characterized by diversity in genetic ancestry and rise in exogamy. Admixture is observed within and across ethnicities, particularly in Hispanics and African Americans. Ethnicity can sometimes be mis- or un-reported, which has implications for screening guidelines and genetic counselling. Low levels of unreported Ashkenazi Jewish ancestry were observed in Europeans as well as patients who did not report their ethnicity. In our cohort, 17.2% chose reproductive partners of a different ethnic background, but with significant non-uniformity across different sexes. Our data is consistent with the intermarriage trend among newly married couples in the US population and we extrapolate that intermarriage rates in 2060 will approach 40%.

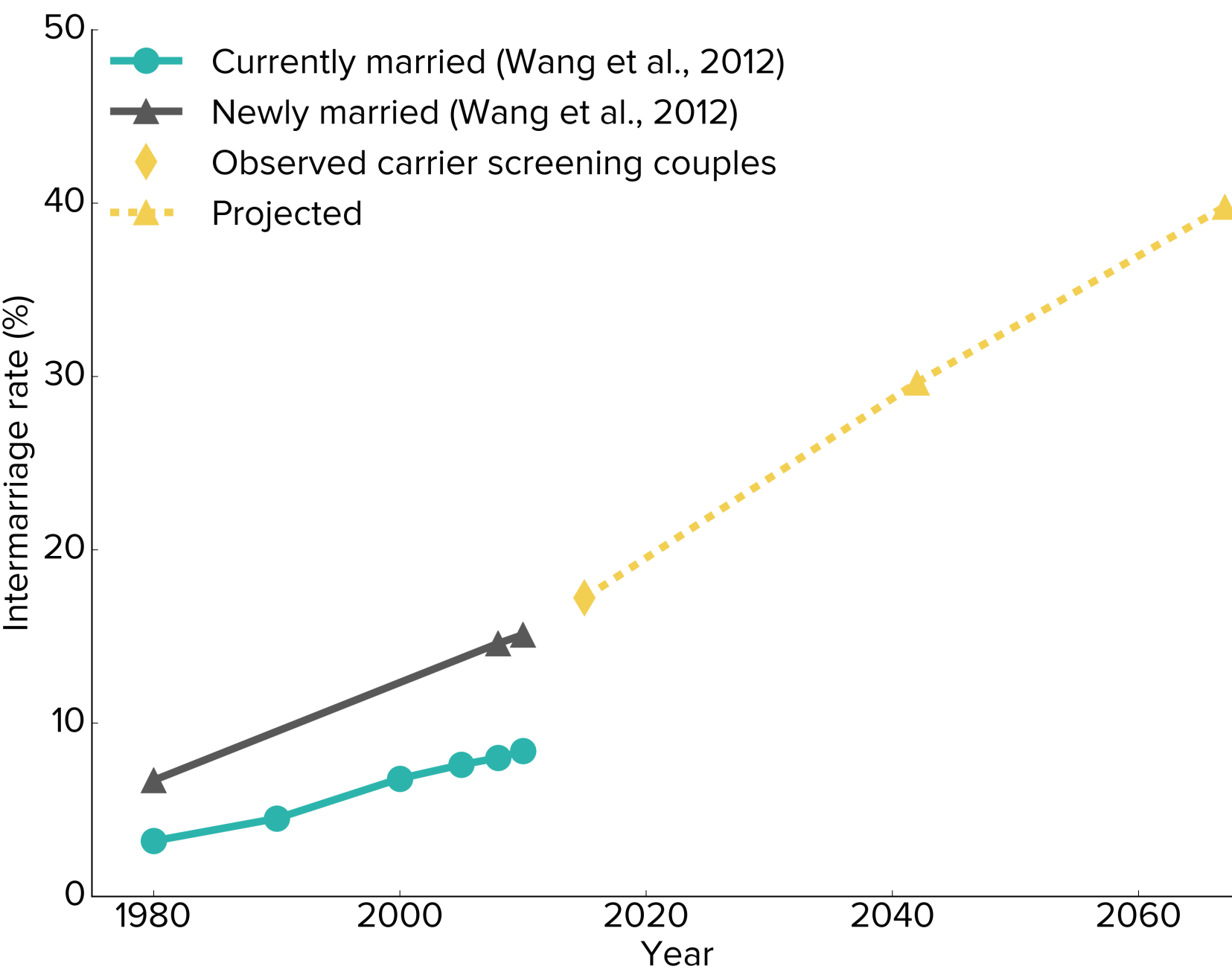### While most partners are chosen within an ethnic group, there is significant exogamy
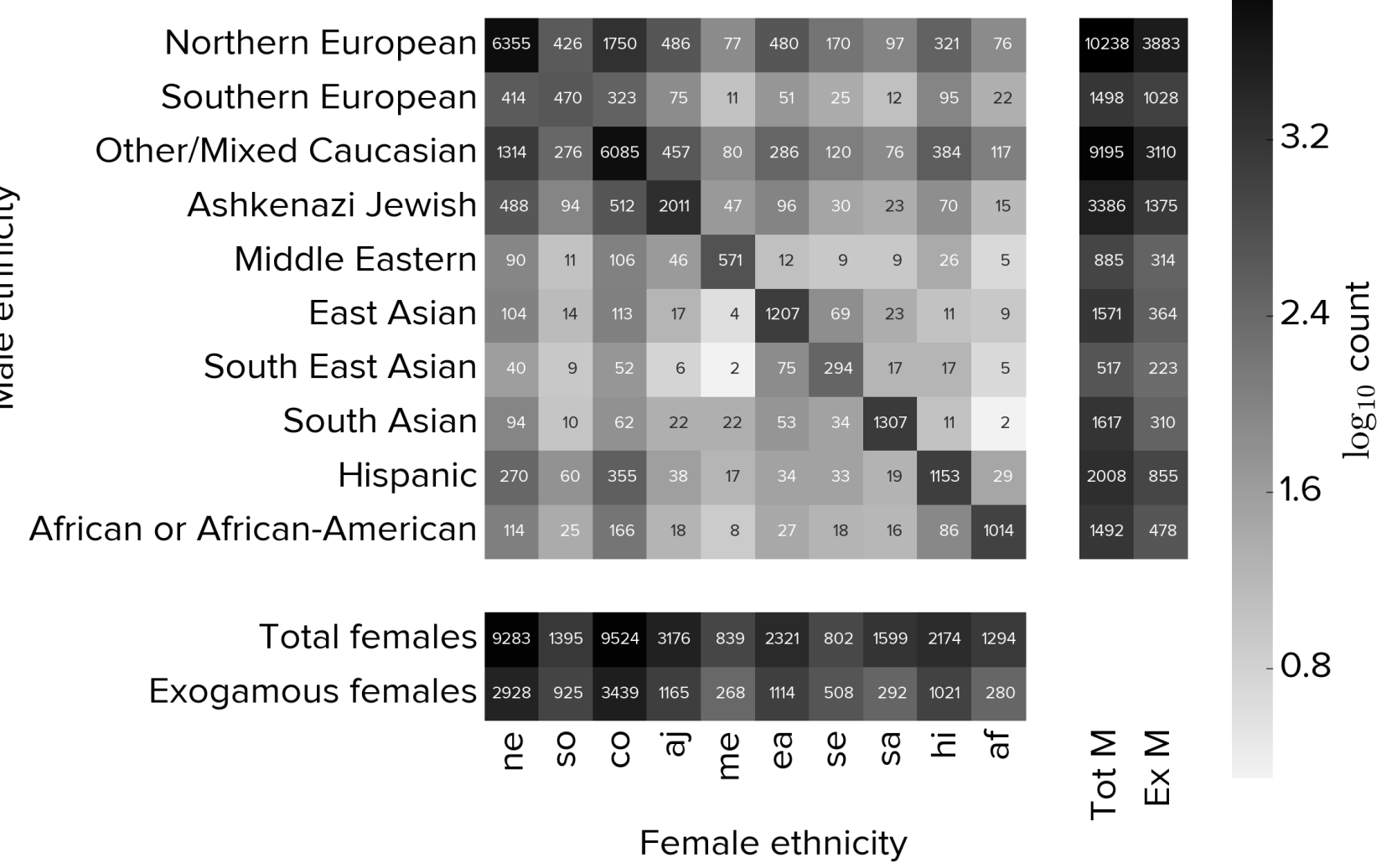
Sex biases in exogamy patterns go both ways
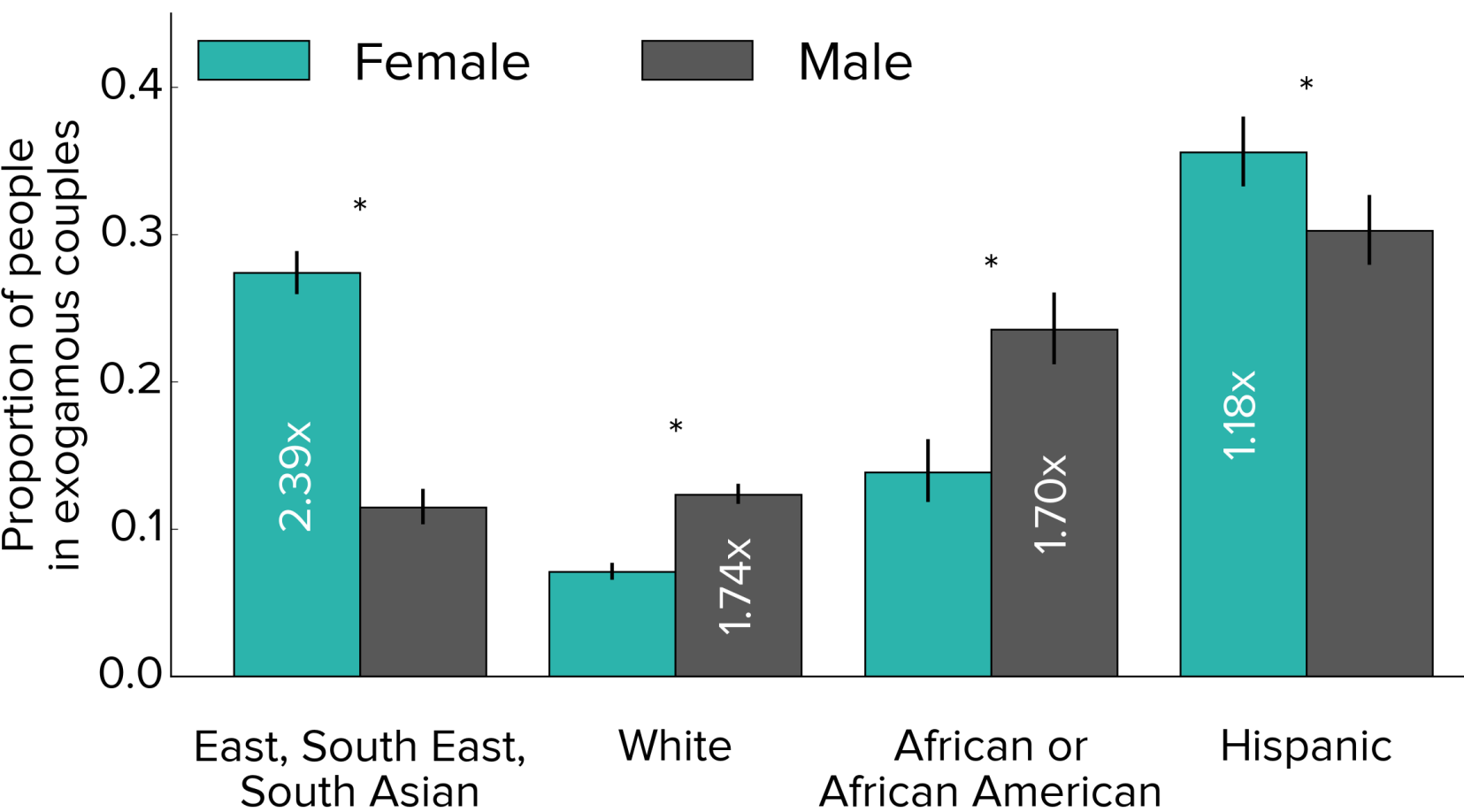
All shown sex biases in exogamy significant at the 95% confidence level.

Intermarriage rates are expected to rise

Intermarriage rate with projected values simulated forward two generations assuming each generation is 27 years (typical range is 22-32yr)[3]. The "Other Mixed/Caucasian" was modeled as 94% White and 6% Mixed as supported by GA data. Male mating patterns were held constant, but no significant difference was seen when female mating patterns were held constant instead.