Supplement for “Rare variation facilitates inferences of fine-scale population structure in humans”

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Supplementary Text

1. Assessing the robustness of Cluster 1

To verify that the rare variant clustering is not a result of a technical artifact, we performed additional analyses. The entire data set was subject to extensive filtering to remove potential biases\(^1\). Furthermore, we ensured that Cluster 1 individuals came from both from sequencing centers (UW and Broad), both GAII and HiSeq 2000 platforms, and from all four exome targets. In addition, Cluster 1 individuals were distributed across a wide range of the ESP cohorts. Thus, Cluster 1 individuals are derived from multiple U.S. cities and are not correlated with any identifiable technical covariates.

2. European Samples Procrustes Analysis

We predicted the geographic origin of a subset of Cluster 1 samples using Procrustes analysis\(^6\). This analysis uses single value decomposition (SVD) between different axes, in our case principal component coordinates and longitude/latitude to obtain the best transformation of the first to the second coordinates. From the SVD trained on data with both sets of coordinates, we can make a prediction from one set (PCs) to the other (geography). To calculate the PCA, we used the HDGP European samples (N=134), excluding the Basque, and the 26 Cluster 1 individuals genotyped with an Illumina 1M chip. After filtering for LD and a minor allele frequency <5%, we were left with 188,034 SNPs. Using EIGENSTRAT\(^7\) we calculated the first two principal components for this data set (including the Cluster 1 samples). We then input PC1 and PC2 along with longitude/latitude from the HGDP samples and calculated the projection. We then modified the code of Wang et al. to use these same values to make a prediction for Cluster 1, which is shown in Figure 2A.
References used in Supplement

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**Supplementary Figures**

**Figure S1**
The same analysis as Figure 1C but with $N_B = 10,000$ (i.e., no bottleneck). We compared the expected information gain for common (blue) and rare (red) variants as a function of population separation time. In black is the ratio of rare to common information gain. No significant difference is observed with these results and those of Figure 1C.
Figure S2
This is an inset of Supplementary Figure S1 for the time to separation of 0 to 20KYA. Comparable to Figure 1D, but without a bottleneck in the demographic scenario.
Figure S3
Principle component analysis of European Americans of the ESP, and the HapMap CEU (Utah residents of Northern and Western European ancestry) and TSI (Tuscans from Italy) populations. ESP samples Cluster 1, Cluster 2, and Cluster 3 are defined in Figure 2B.
**Figure S4**
Using the PC values generated in the analyses of Figures 2A and 2B, but combined to compare PC1 of the common and rare. In red is the estimated linear regression between the two sets of values.
**Figure S5**
Using the PC values generated in the analyses of Figures 2A and 2B, but combined to compare PC2 of the common and rare. In blue is the estimated linear regression between the two sets of values.
Figure S6
Principal component analysis consisting of only common variation (MAF > 0.1) of ESP European Americans and displaying PC1 and 4. Cluster 1, Cluster 2, and Cluster 3 are defined in Figure 2B.
Figure S7
Same principal component analysis as Supplementary Figure S6, but displaying PC1 and 2.
**Figure S8**
Principal component analysis consisting of only rare variation (MAF < 0.005) of ESP European Americans. Cluster 1, Cluster 2, and Cluster 3 are defined in Figure 2B.
Figure S9
Same principal component analysis as displayed in Figure 3B, but displaying only the Jewish population samples. Cluster 1 is in red and other Jewish samples are presented in purple.
Figure S10

Full FRAPPE analysis of subset presented in Figure 4A. Continental labels indicate the overall pattern with a labeling focus on European admixed Jewish populations including Cluster 1.
Supplementary Tables

Table S1
A comparison of information gain (IG) for the common and rare variation. R/C is the ratio of expected rare to common IG. See Figure S1 for various groupings. Rare is defined as ≤ 0.5% and common as ≥50%.

| Group1      | Group2     | IG Rare | IG Common | R/C |
|-------------|------------|---------|-----------|-----|
| EA          | AA         | 5.01x10^{-4} | 0.027     | 0.019 |
| Cluster 3   | AA         | 5.04x10^{-4} | 0.027     | 0.018 |
| Cluster 3   | Cluster 1  | 1.44x10^{-4} | 4.66x10^{-4} | 0.309 |
| Cluster 3   | Cluster 2  | 2.36x10^{-5} | 8.15x10^{-5} | 0.289 |
| Cluster 3   | Cluster 1/Cluster 2 | 1.05x10^{-4} | 4.61x10^{-4} | 0.325 |
| Cluster 1   | Cluster 2  | 1.18x10^{-3} | 1.47x10^{-3} | 0.805 |

Table S2
Ne = 10000
Gen = 25 (years)
S1 = 2*500 or 2*1000
S2 = 2*500 or 2*1000
N0 = 2,000,000
B = 0.1 or 1 (bottleneck)
t_e = T_e/(4*Ne*Gen)
t_s = T_s/(4*Ne*Gen)
alpha = log(N0/(B*Ne))/t_e
theta = 4*Ne*1.5*10^{-8}*223800 # 4Ne*Mu*length so that length*100(reps) ~= full exome of ESP intersect
REP=100 for the Information Theory simulations and “22500 –s 1” for the FRAPPE simulations.

With growth:
msms -N Ne -ms (S1+S2) REP -t 134.28 -I 2 S1 S2 0 -ej t_e 2 1 -eN t_e 1 -G alpha -n 1 N0/Ne -n 2 N0/Ne

Without growth (Te = 0):
msms -N Ne -ms (S1+S2) 100 -t 134.28 -I 2 S1 S2 0 -ej t_e 2 1 -n 1 1 -n 2 1
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HeartGO:

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**ESP Groups**

\textsuperscript{1}Anthropometry Project Team, \textsuperscript{2}Blood Count/Hematology Project Team, \textsuperscript{3}Blood Pressure Project Team, \textsuperscript{4}Data Flow Working Group, \textsuperscript{5}Early MI Project Team, \textsuperscript{6}ELSI Working Group, \textsuperscript{7}Executive Committee, \textsuperscript{8}Family Study Project Team, \textsuperscript{9}Lipids Project Team, \textsuperscript{10}Lung Project Team, \textsuperscript{11}Personal Genomics Project Team, \textsuperscript{12}Phenotype and Harmonization Working Group, \textsuperscript{13}Population Genetics and Statistical Analysis Working Group, \textsuperscript{14}Publications and Presentations Working Group, \textsuperscript{15}Quantitative Analysis Ad Hoc Task Group, \textsuperscript{16}Sequencing and Genotyping Working Group, \textsuperscript{17}Steering Committee, \textsuperscript{18}Stroke Project Team, \textsuperscript{19}Structural Variation Working Group, \textsuperscript{20}Subclinical/Quantitative Project Team

**ESP Cohorts**

\textsuperscript{21}Acute Lung Injury (ALI), \textsuperscript{22}Atherosclerosis Risk in Communities (ARIC), \textsuperscript{23}Cardiovascular Health Study (CHS), \textsuperscript{24}Chronic Obstructive Pulmonary Disease (COPDGene), \textsuperscript{25}Coronary Artery Risk Development in Young Adults (CARDIA), \textsuperscript{26}Cystic Fibrosis (CF), \textsuperscript{27}Early Pseudomonas Infection Control (EPIC), \textsuperscript{28}Framingham Heart Study (FHS), \textsuperscript{29}Jackson Heart Study (JHS), \textsuperscript{30}Lung Health Study (LHS), \textsuperscript{31}Multi-Ethnic Study of Atherosclerosis (MESA), \textsuperscript{32}Pulmonary Arterial Hypertension (PAH), \textsuperscript{33}Severe Asthma Research Program (SARP), \textsuperscript{34}Women's Health Initiative (WHI)
