Using the UK Biobank as a global reference of worldwide populations: application to measuring ancestry diversity from GWAS summary statistics

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Abstract

The UK Biobank project is a prospective cohort study with deep genetic and phenotypic data collected on almost 500,000 individuals from across the United Kingdom. Within this dataset, we carefully define 21 distinct ancestry groups from all four corners of the world. These ancestry groups can serve as a global reference of worldwide populations, with a handful of applications. As an example application here, we use allele frequencies derived from these ancestry groups to effectively measure diversity from summary statistics of any genetic dataset. Measuring genetic diversity is an important problem because increasing genetic diversity is key to making new genetic discoveries, while also being a major source of confounding to be aware of in genetics studies.

Several projects have focused on providing genetic data from diverse populations, such as the HapMap project, the 1000 genomes project (1KG), the Simons genome diversity project, and the human genome diversity project (International HapMap 3 Consortium *et al.* 2010; 1000 Genomes Project Consortium *et al.* 2015; Mallick *et al.* 2016; Bergström *et al.* 2020). However, these datasets do not contain many individuals per population and therefore are not large enough for some purposes, such as accurately estimating allele frequencies for diverse worldwide populations. The UK Biobank (UKBB) project is a prospective cohort study with deep genetic and phenotypic data collected on almost 500,000 individuals from across the United Kingdom. Despite being a cohort from the UK, this dataset is so large that it includes individuals that were born in all four corners of the world. Here we carefully use information on self-reported ancestry, country of birth, and genetic similarity to define 21 distinct ancestry groups from the UK Biobank to be used as global reference populations. This includes nine groups with genetic ancestries from Europe, four from Africa, three from South Asia, three from East Asia, one from the Middle East, and one from South America (Table 1). The detailed procedure used to define these groups is presented in the Supplementary Materials.

As an example application of these groups, we propose to estimate global ancestry proportions from a cohort based on its allele frequencies only (i.e. summary statistics). Arriaga-MacKenzie *et al.* (2021) previously proposed method Summix, which finds the convex combination of ancestry proportions α_k (positive and sum to 1) which minimizes the following problem: $\sum_{j=1}^{M} \left(f_j^{(0)} - \sum_{k=1}^{K} \alpha_k f_j^{(k)} \right)^2$, where M is the number of variants, K the number of reference populations, $f_j^{(k)}$ is the frequency of variant j in population k, and $f_j^{(0)}$ is the frequency of variant j in the cohort of interest. In Arriaga-MacKenzie *et al.* (2021), they used the five continental 1KG populations as reference. Here we provide reference allele frequencies for 5,816,590 genetic variants across 21 diverse ancestry groups (which are later merged in 18 groups in table 1). Moreover, we rely on the projection of our reference allele frequencies onto the PCA (principal component analysis) space computed from the corresponding UKBB (and 1KG) individuals. This is described in more details in the Supplementary Materials. Finding the ancestry proportions in the PCA space (rather than using the allele frequencies directly) provides more power to distinguish between close populations. This enables us to use more reference populations (18) in order to get a more fine-grained measure of genetic diversity. We implement this method in function `snp_ancestry_summary` in our R package bigsnpr (Privé *et al.* 2018), relying on R package quadprog (Turlach *et al.* 2019) for solving this quadratic programming optimization problem.

We download several GWAS summary statistics for which allele frequencies are reported, and apply this method to them. We first apply function `snp_ancestry_summary` to more homogeneous samples as an empirical validation; when applying it to the Biobank Japan (Japanese cohort), FinnGen (Finnish), a Peruvian cohort, a Qatari cohort and Sub-Saharan African cohort, the ancestry proportions obtained match expectations (Table 1). When comparing our estimates with reported ancestries for more diverse cohorts, for example PAGE is composed of 44.6% Hispanic-Latinos, 34.7% African-Americans, 9.4% Asians, 7.9% Native Hawaiians and 3.4% of some other ancestries (self-reported), whereas our estimates are of 25.4% South American, 22.6% European (including 15.8% from South-West Europe), 34.1% African, 2.7% South Asian, 10.6% East Asian, and 4.6% Filipino. GWAS summary statistics from either European ancestries or more diverse ancestries all have a substantial proportion estimated from European ancestry groups, while ancestries from other continents are still largely underrepresented (Table 1).

Ancestry group	N	BBJ	FinnGen	Perú	Qatar	Africa	GERA	PAGE	BrCa	PrCa	CAD	body fat	covid	eczema	epilepsy	urate
Africa (West)	735					30	1.9	27.7	0.3	0.3	2.2	0.7	4	0.2	0.7	2.2
Africa (South)	449					70	0.9	5.9	0.2		1.2	0.3	1.2	0.5	0.3	3.5
Africa (East)	276				13						0.1		0.3			1.9
Africa (North)	268				22			0.5					0.1			
Middle East	523				64.6							0.2				1.3
Ashkenazi	1975						4.4	0.5	0.2	1.8	0.4	0.8	0.4	0.6	1.8	
Italy	345						4.6		3.1	1.2	9.7	5.5			3.4	0.8
Europe (East)	667						10.5		6.9	11.3	10.5	11.4	13.2	11.7	13.9	10.8
Finland	143 (+ 99)		100				2.4	0.7	9.7	13	5.9	8.8	14.8	12.8	6.5	2
Europe (North West)	4416						59.9	5.6	68.5	64.5	51.8	59.8	61.4	70.9	68	46
Europe (South West)	603						3.5	15.8	4.7	4.5				2.1	2.1	
South America	473 (+ 84)			100			4.6	25.4	1.5	0.8	1.6	0.4	1.8	0.5		
Sri Lanka	372				0.4		0.4		3.4	1.7	4.7	4.2	1.8			1.9
Pakistan	400							1.1			7	4				
Bangladesh	223 (+ 86)							1.6								
Asia (East)	961						3.5	1.2	1.2	0.7	2.5	1.2	0.1	0.1	3.1	
Japan	240 (+ 104)	100					2.2	9.4	0.4		2.4	2.8	0.7	0.7	0.3	29.8
Philippines	295						1.5	4.6					0.2			

Table 1: Reference populations with their size (N), and corresponding ancestry proportions (in %) from several GWAS datasets. Note that "Ireland", "United Kingdom" and "Scandinavia" are merged as a single "Europe (North West)" group. Similarly, "Europe (North East)" and "Europe (South East)" are merged as a single "Europe (East)" group. Citations for the allele frequencies used: the Biobank Japan (BBJ, Sakaue *et al.* (2021)), FinnGen (`https://r5.finngen.fi/`), GWAS in Peruvians (Asgari *et al.* 2020), GWAS in Qataris (Thareja *et al.* 2021), GWAS in Sub-Saharan Africans (Africa, Chen *et al.* (2019)), GERA (Hoffmann *et al.* 2018), PAGE (Wojcik *et al.* 2019), breast cancer (BrCa, Michailidou *et al.* (2017)), prostate cancer (PrCa, Schumacher *et al.* (2018)), coronary artery disease (CAD, Nikpay *et al.* (2015)), body fat percentage (Lu *et al.* 2016), COVID-19 (The COVID-19 Host Genetics Initiative and Ganna 2021), eczema (Paternoster *et al.* 2015), epilepsy (The International League Against Epilepsy Consortium on Complex Epilepsies 2018), and serum urate (Tin *et al.* 2019). Several of these GWAS summary statistics have been downloaded through the NHGRI-EBI GWAS Catalog (MacArthur *et al.* 2017).

Here we identify an unprecedentedly large and diverse set of ancestry groups within a single cohort, the UK Biobank. Using allele frequencies derived from these ancestry groups (and the individual-level data for computing the PCs), we show how to effectively measure diversity from GWAS summary statistics reporting allele frequencies. Measuring genetic diversity is an important problem because increasing genetic diversity is key to making new genetic discoveries, while also being a major source of confounding to be aware of in genetics studies. Our work has limitations though. First, it is not fully clear whether we can capture any ancestry, e.g. Native Hawaiians in the PAGE study; it seems that they are partly captured by the "Philippines" ancestry group we define. Second, with the 21 ancestry groups we define, we think we are capturing a large proportion of the genetic diversity in Europe, but we may still be missing more fine-grained diversity in other continents. Third, when we use the allele frequencies reported in the GWAS summary statistics, it is not clear whether they were computed from all individuals (i.e. before performing any quality control and filtering), and, for meta-analyses of binary traits, whether they were computed as a weighted average of total or effective sample sizes. Despite these limitations, we envision that the ancestry groups we define here will have many useful applications. The presented method that uses these groups could e.g. be used to automatically report ancestry proportions in the GWAS Catalog (MacArthur *et al.* 2017). These ancestry groups could also be used for assigning ancestry in other cohorts using the PC projection from this study (Privé *et al.* 2021), assessing portability of polygenic scores (Privé *et al.* 2021), or deriving linkage disequilibrium (LD) references matching GWAS summary statistics from diverse ancestries.

Software and code availability

The newest version of R package bigsnpr can be installed from GitHub (see `https://github.com/privefl/bigsnpr`). Refer to the help page of function `snp_ancestry_summary` for how to use it. The set of reference allele frequencies for 5,816,590 genetic variants across 21 diverse ancestry groups defined here can be downloaded at `https://figshare.com/ndownloader/files/31620968` and PC loadings for all variants across 16 PCs at `https://figshare.com/ndownloader/files/31620953`. All code used for this paper is available at `https://github.com/privefl/freq-ancestry/tree/main/code`. We have extensively used R packages bigstatsr and bigsnpr (Privé *et al.* 2018) for analyzing large genetic data, packages from the future framework (Bengtsson 2021) for easy scheduling and parallelization of analyses on the HPC cluster, and packages from the tidyverse suite (Wickham *et al.* 2019) for shaping and visualizing results.

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Declaration of Interests

The author declares no competing interests.

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