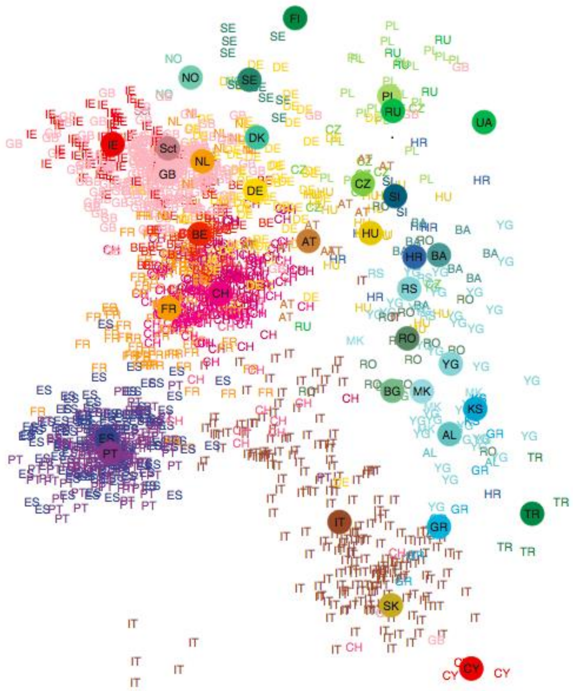
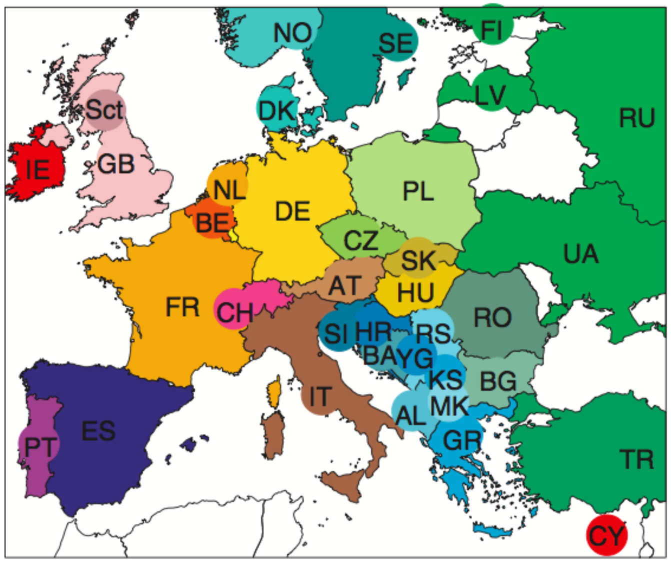




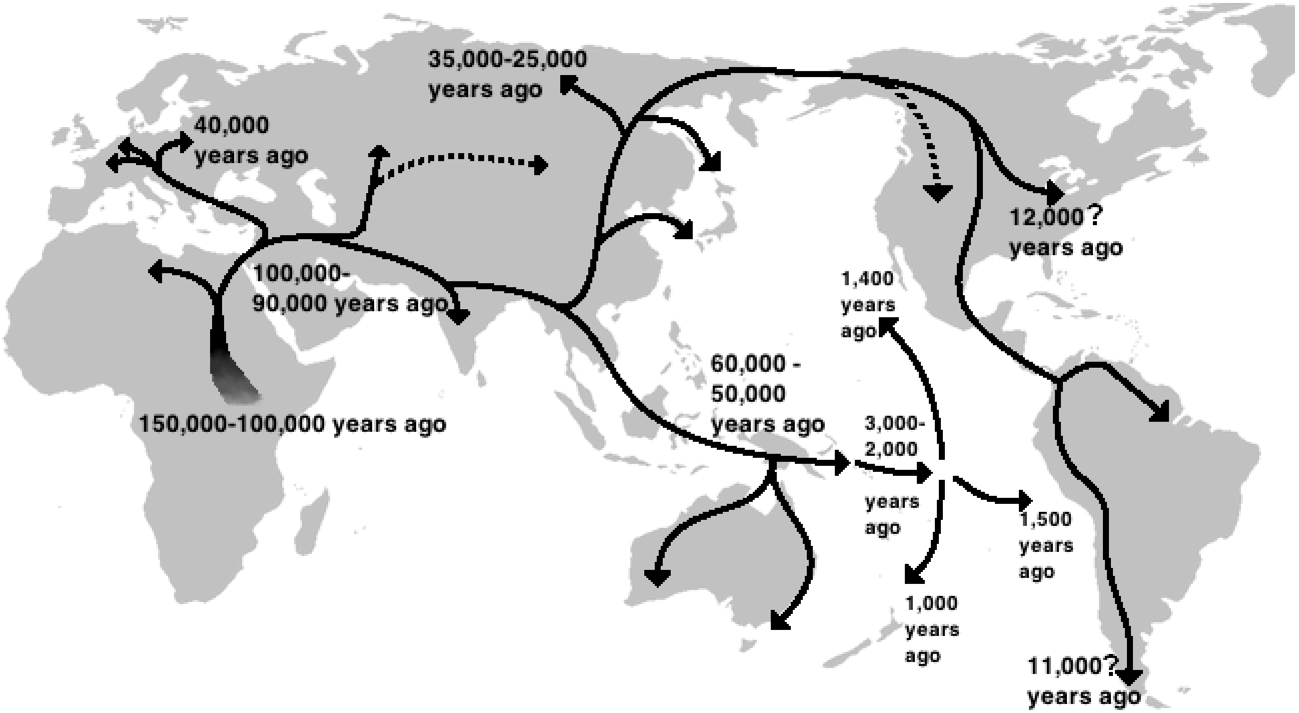
Population Stratification

Abdel Abdellaoui

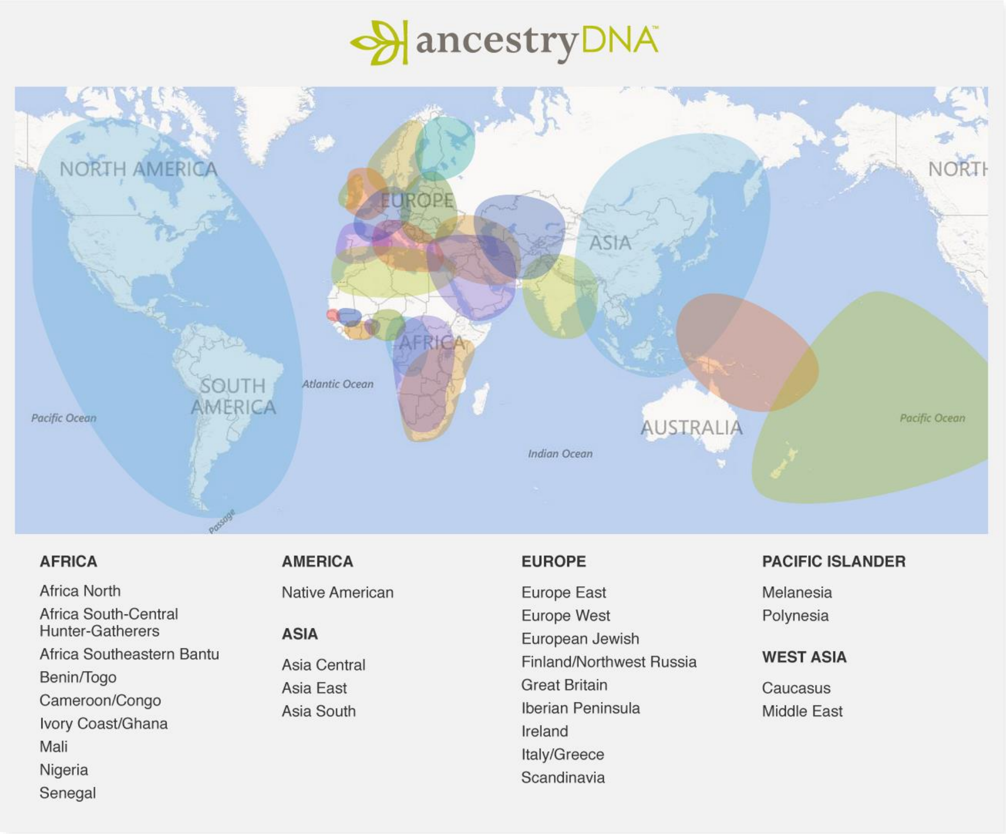
Department of Psychiatry, Amsterdam UMC, University of Amsterdam

Amsterdam UMC
Universitair Medische Centra

E-mail: a.abdellaoui@amsterdamumc.nl


35,000-25,000
years ago
40,000
years ago
12,000?
years ago
1,400
years
ago
100,000-
90,000 years ago
60,000 -
50,000
years ago
3,000-
2,000
years
ago
1,500
years
ago
150,000-100,000 years ago
1,000
years
ago
11,000?
years ago

Largest patterns of genetic variation = ancestry



AFRICA

Africa North
Africa South-Central Hunter-Gatherers
Africa Southeastern Bantu
Benin/Togo
Cameroon/Congo
Ivory Coast/Ghana
Mali
Nigeria
Senegal

AMERICA

Native American

ASIA

Asia Central
Asia East
Asia South

EUROPE

Europe East
Europe West
European Jewish
Finland/Northwest Russia
Great Britain
Iberian Peninsula
Ireland
Italy/Greece
Scandinavia

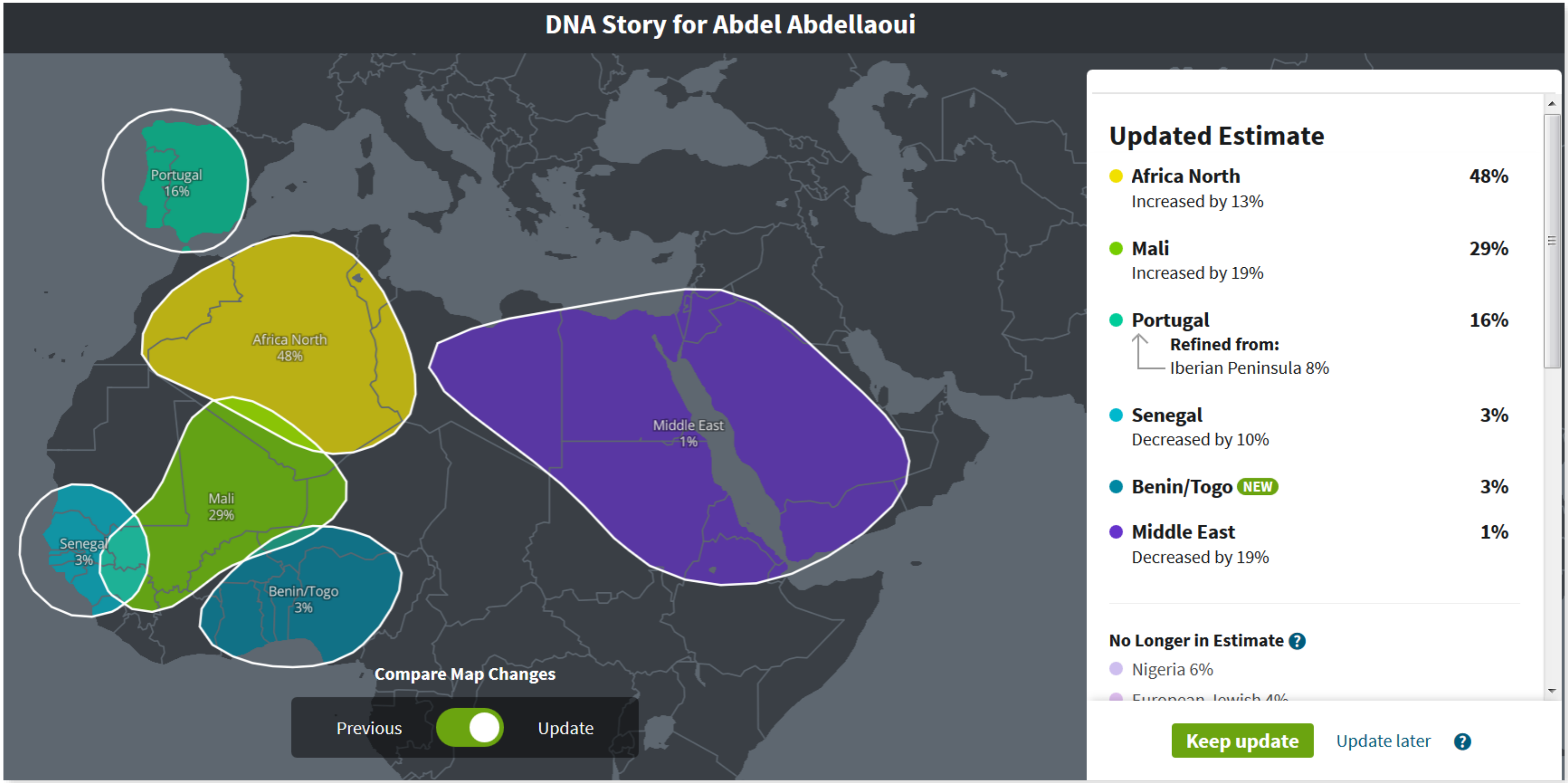
PACIFIC ISLANDER

Melanesia
Polynesia

WEST ASIA

Caucasus
Middle East

ancestryDNA™



DNA Story for Abdel Abdellaoui

Updated Estimate

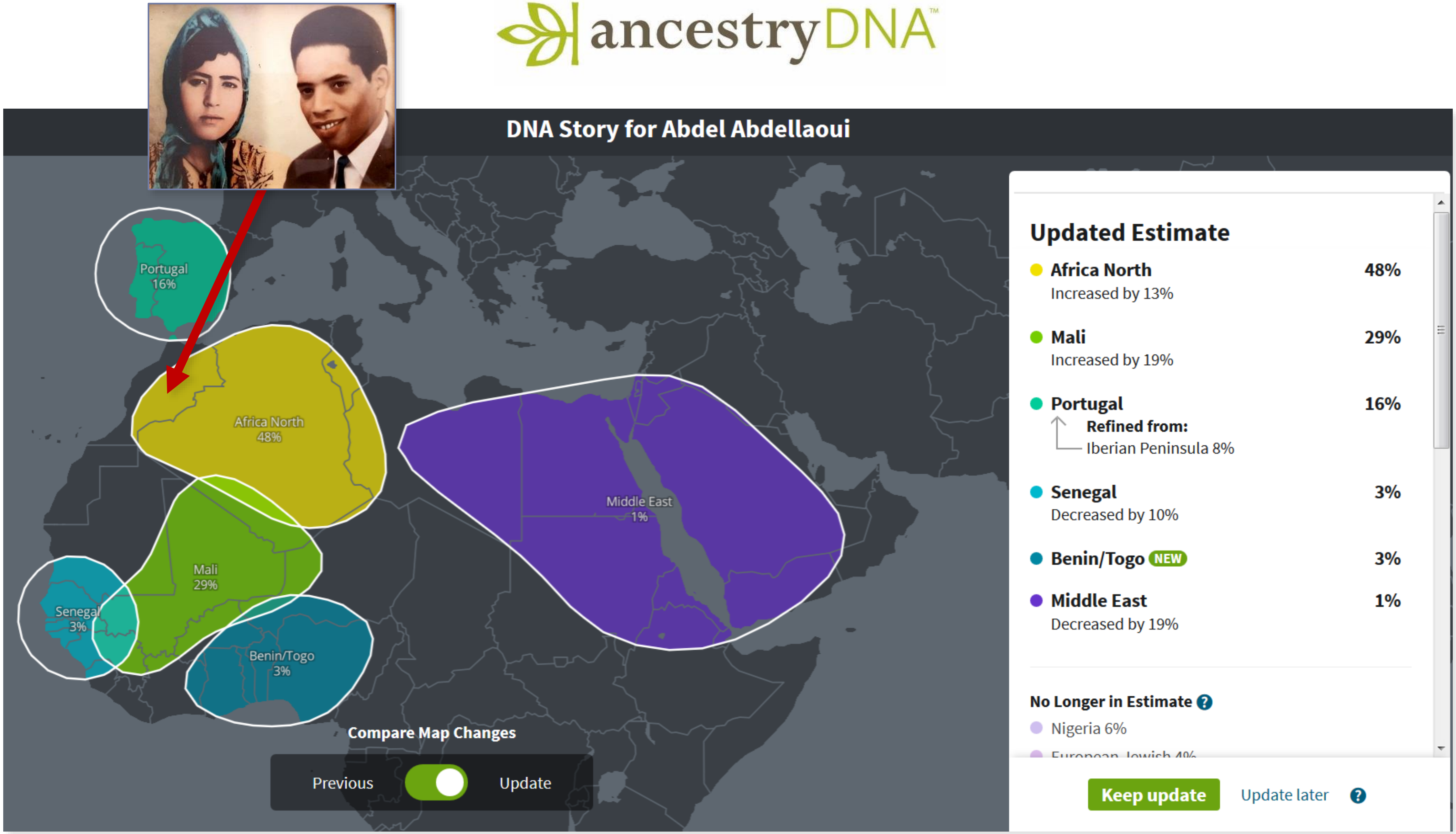
● **Africa North** Increased by 13%	**48%**
● **Mali** Increased by 19%	**29%**
● **Portugal** **Refined from:** Iberian Peninsula 8%	**16%**
● **Senegal** Decreased by 10%	**3%**
● **Benin/Togo** NEW	**3%**
● **Middle East** Decreased by 19%	**1%**

No Longer in Estimate ?

● Nigeria 6%

● European Jewish 4%

ancestryDNA™



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No Longer in Estimate

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- European Jewish 4%

88% of GWAS participants is of European descent

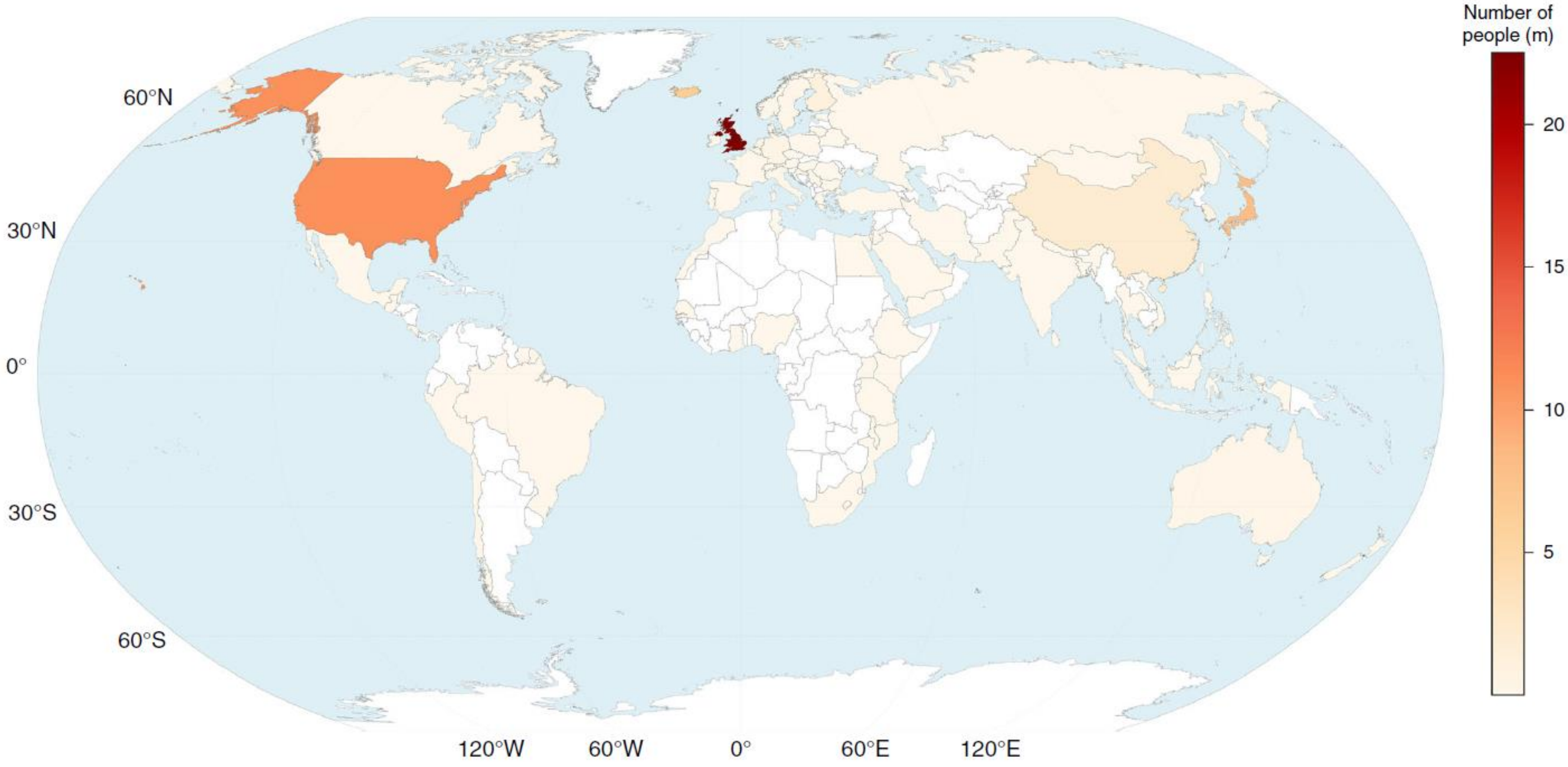

Fig. 3 A Choropleth Map of the Concentration of GWAS Participant Recruitment. A choropleth map (Robinson projection) detailing the geographic recruitment of GWAS participants. Source: NHGRI-EBI GWAS Catalog, Natural Earth (v4.0.0) and the CIA World Factbook. Replication material provides a per-capita population adjusted version

A scientometric review of genome-wide association studies
(Mills & Rahal, 2019)

Population stratification

- Population stratification = a systematic difference in allele frequencies between (sub)populations due to different ancestry.

- Can cause false positives if the trait values also differ between the (sub)populations.

Population stratification: chopstick example

Sample 1 Americans: χ^2=0, *p*=1			
	Use of chopsticks		
	Yes	No	Total
Allele 1	320	320	640
Allele 2	80	80	160
Total	400	400	800

Sample 2 Chinese: χ^2=0, *p*=1			
	Use of chopsticks		
	Yes	No	Total
Allele 1	320	20	340
Allele 2	320	20	340
Total	640	40	680

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There is a clear difference between Americans and Chinese in proportion of “cases” and “controls”

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Sample 1 + 2 = Americans + Chinese: χ^2=34.2, *p*=4.9 × 10^{-9}			
	Use of chopsticks		
	Yes	No	Total
Allele 1	640	340	980
Allele 2	400	100	500
Total	1040	440	1480

Dealing with population stratification in GWAS

Ways to deal with population stratification:

- Genomic Control (GC)
- Principal Component Analysis
- Within Family Association
- Mixed Linear Modeling

- Admixture Modeling

Dealing with population stratification in GWAS

Ways to deal with population stratification:

- Genomic Control (GC)
- Principal Component Analysis

→ This talk

- Within Family Association → Next session (Dorret Boomsma)
- Mixed Linear Modeling → Yesterday (Wei Zhou)

- Admixture Modeling → Tomorrow (Poster Session: Timothy Thornton)

Dealing with population stratification in GWAS

Ways to deal with population stratification:

- Genomic Control (GC)
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- Within Family Association
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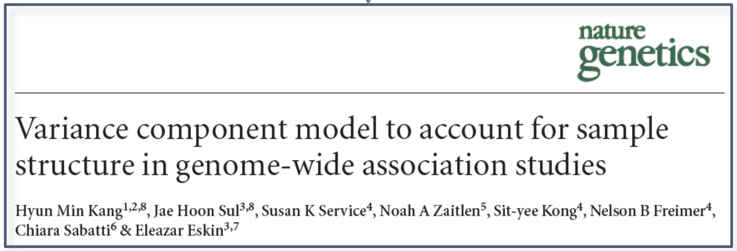
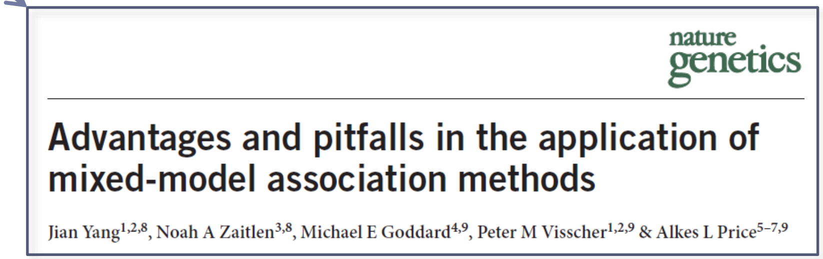


nature genetics

Variance component model to account for sample structure in genome-wide association studies

Hyun Min Kang[1,2,8], Jae Hoon Sul[3,8], Susan K Service[4], Noah A Zaitlen[5], Sit-yee Kong[4], Nelson B Freimer[4], Chiara Sabatti[6] & Eleazar Eskin[3,7]



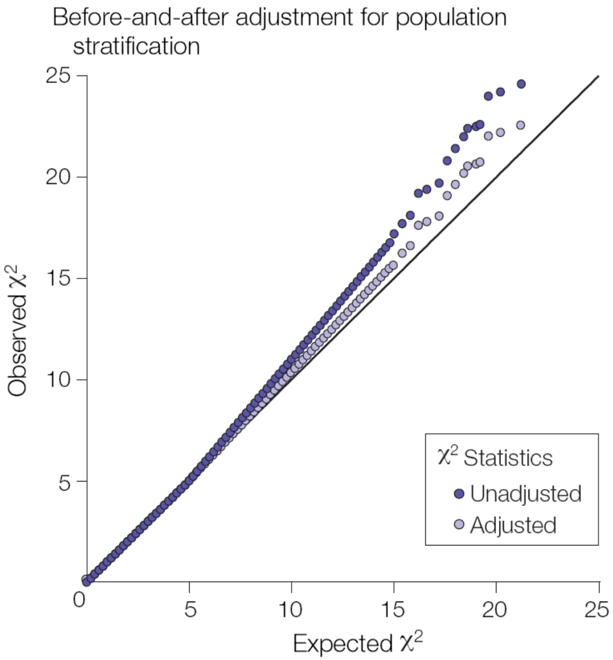
nature genetics

Advantages and pitfalls in the application of mixed-model association methods

Jian Yang[1,2,8], Noah A Zaitlen[3,8], Michael E Goddard[4,9], Peter M Visscher[1,2,9] & Alkes L Price[5–7,9]

Genomic Control (GC)

- Population stratification can result in higher test statistics (= lower *p*-values)
- The genomic control method estimates the factor with which the test statistics are inflated due to population stratification → λ
- Dividing by λ cancels this effect out for all SNPs:
  - Unadjusted: $\lambda\chi^2$
  - Adjusted: χ^2



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- **λ** is measured by dividing the **median** of the distribution of the chi-square statistics from the **actual tests** by the **median** of the chi-square distribution **under the null**.

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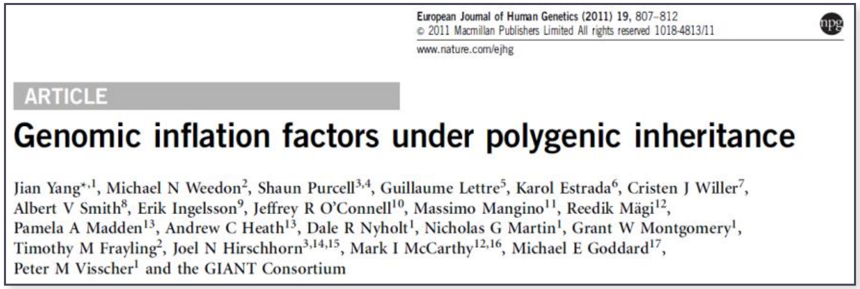
- GC is too conservative if the trait is **highly polygenic** (i.e. the median test statistic does not represent the null distribution).



European Journal of Human Genetics (2011) 19, 807–812
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www.nature.com/ejhg

ARTICLE

Genomic inflation factors under polygenic inheritance

Jian Yang*[,1], Michael N Weedon[2], Shaun Purcell[3,4], Guillaume Lettre[5], Karol Estrada[6], Cristen J Willer[7], Albert V Smith[8], Erik Ingelsson[9], Jeffrey R O'Connell[10], Massimo Mangino[11], Reedik Mägi[12], Pamela A Madden[13], Andrew C Heath[13], Dale R Nyholt[1], Nicholas G Martin[1], Grant W Montgomery[1], Timothy M Frayling[2], Joel N Hirschhorn[3,14,15], Mark I McCarthy[12,16], Michael E Goddard[17], Peter M Visscher[1] and the GIANT Consortium

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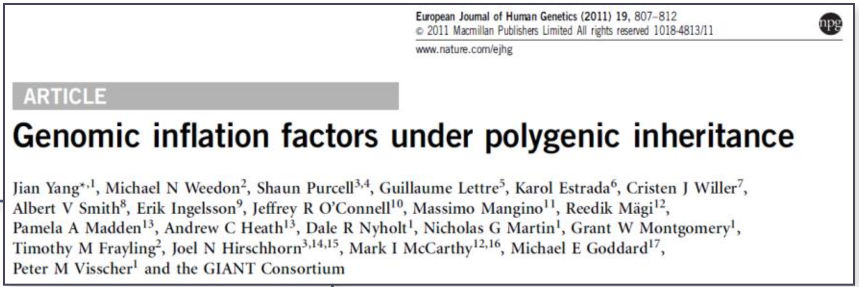
- Then, GC applies its correction by dividing the actual association test chi-square statistic results by this λ, thus making these results appropriately more pessimistic.
- GC is too conservative if the trait is **highly polygenic** (i.e. the median test statistic does not represent the null distribution).
- **LD Score regression** can be used to estimate a more powerful and accurate correction factor than GC.



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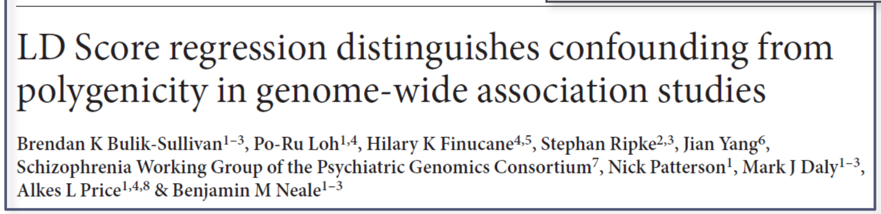
nature genetics



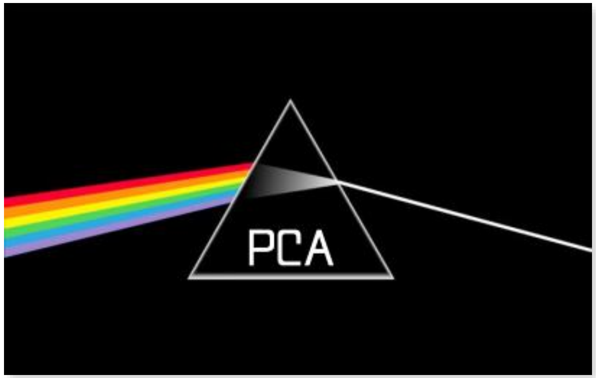
LD Score regression distinguishes confounding from polygenicity in genome-wide association studies

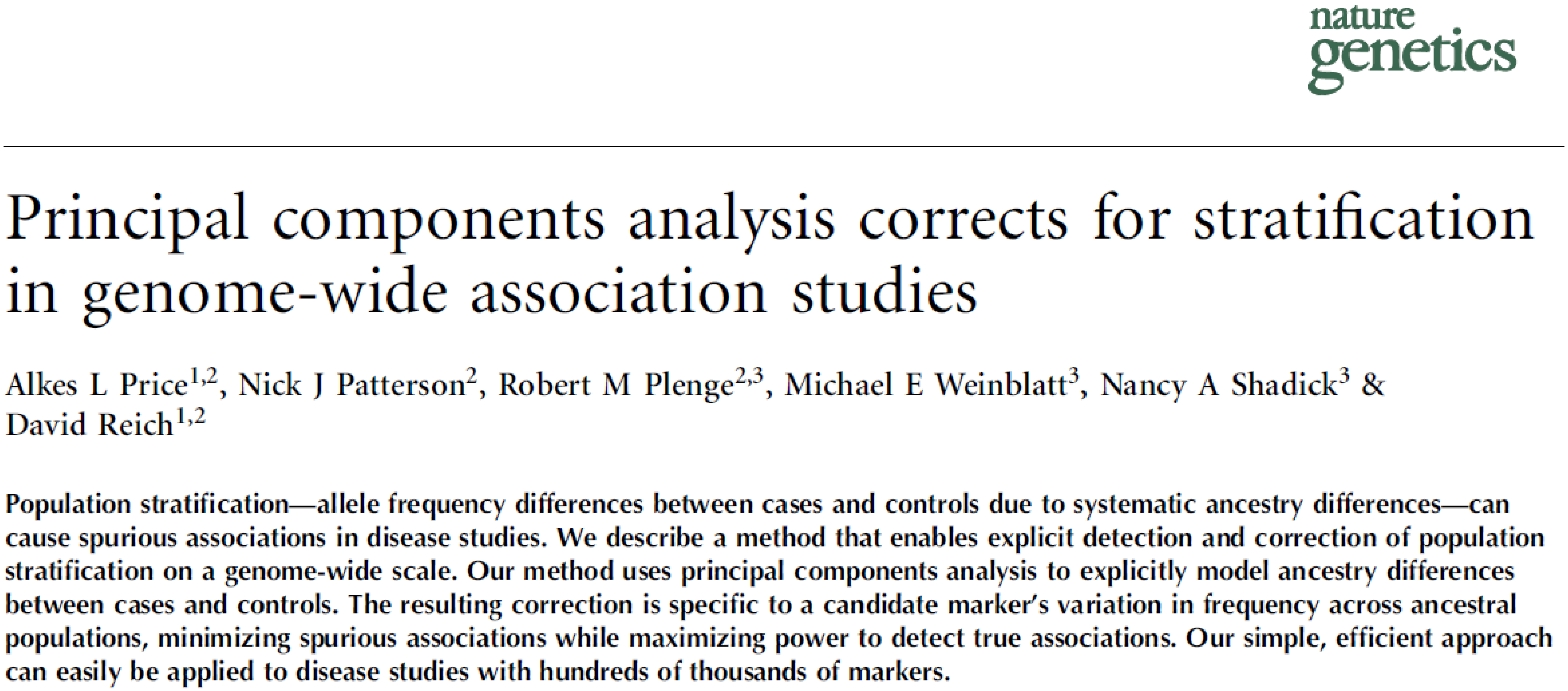
Brendan K Bulik-Sullivan[1–3], Po-Ru Loh[1,4], Hilary K Finucane[4,5], Stephan Ripke[2,3], Jian Yang[6], Schizophrenia Working Group of the Psychiatric Genomics Consortium[7], Nick Patterson[1], Mark J Daly[1–3], Alkes L Price[1,4,8] & Benjamin M Neale[1–3]

Principal Component Analysis (PCA)

Principal Component Analysis (PCA)

- PCA is a statistical method for exploring large number of measurements (e.g., SNPs) by reducing the measurements to fewer principal components (PCs) that explain the main patterns of variation:
  - The first PC is the mathematical combination of measurements that accounts for the largest amount of variability in the data.
  - The second PC (uncorrelated with the first) accounts for the second largest amount of variability.
  - Etc...





nature genetics

Principal components analysis corrects for stratification in genome-wide association studies

Alkes L Price[1,2], Nick J Patterson[2], Robert M Plenge[2,3], Michael E Weinblatt[3], Nancy A Shadick[3] & David Reich[1,2]

Population stratification—allele frequency differences between cases and controls due to systematic ancestry differences—can cause spurious associations in disease studies. We describe a method that enables explicit detection and correction of population stratification on a genome-wide scale. Our method uses principal components analysis to explicitly model ancestry differences between cases and controls. The resulting correction is specific to a candidate marker's variation in frequency across ancestral populations, minimizing spurious associations while maximizing power to detect true associations. Our simple, efficient approach can easily be applied to disease studies with hundreds of thousands of markers.

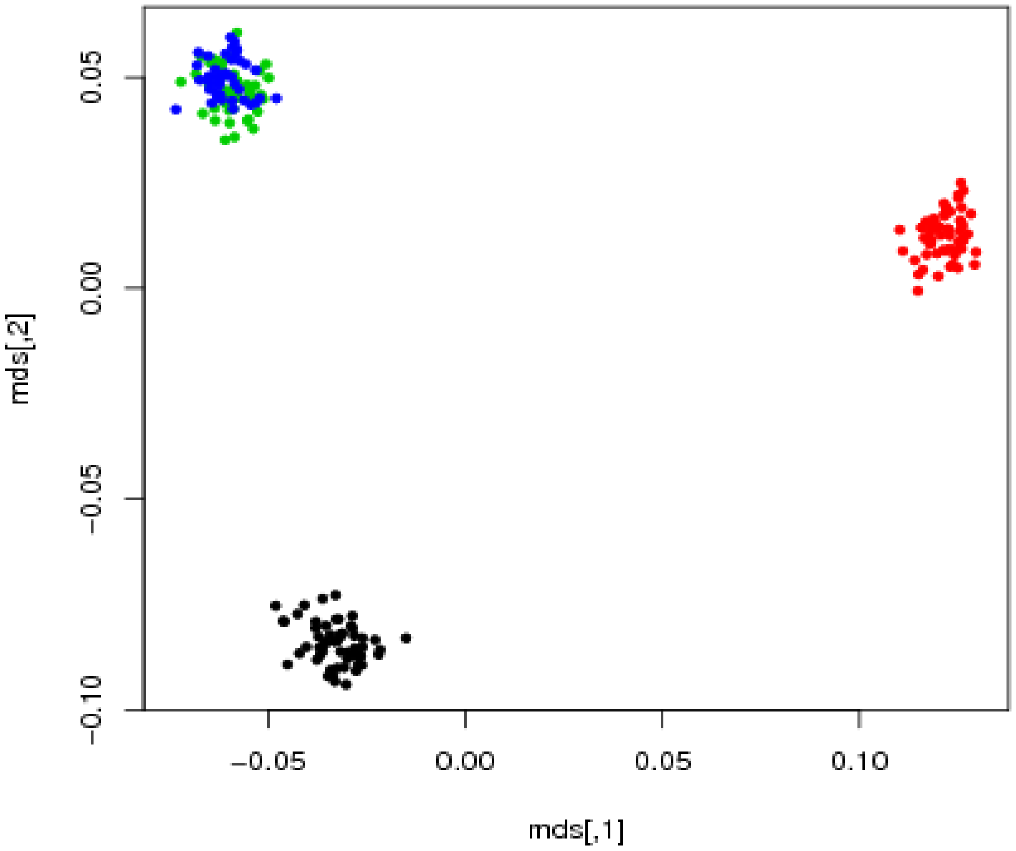
Principal Component Analysis (PCA)

CEPH/European

Yoruba

Han Chinese

Japanese



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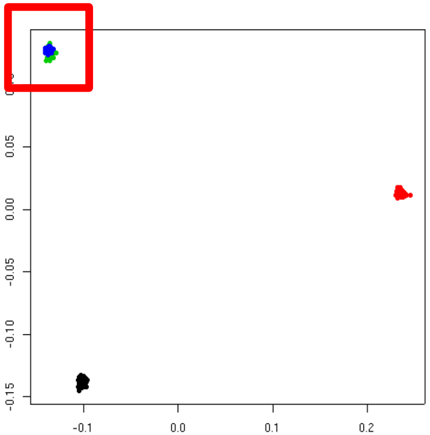
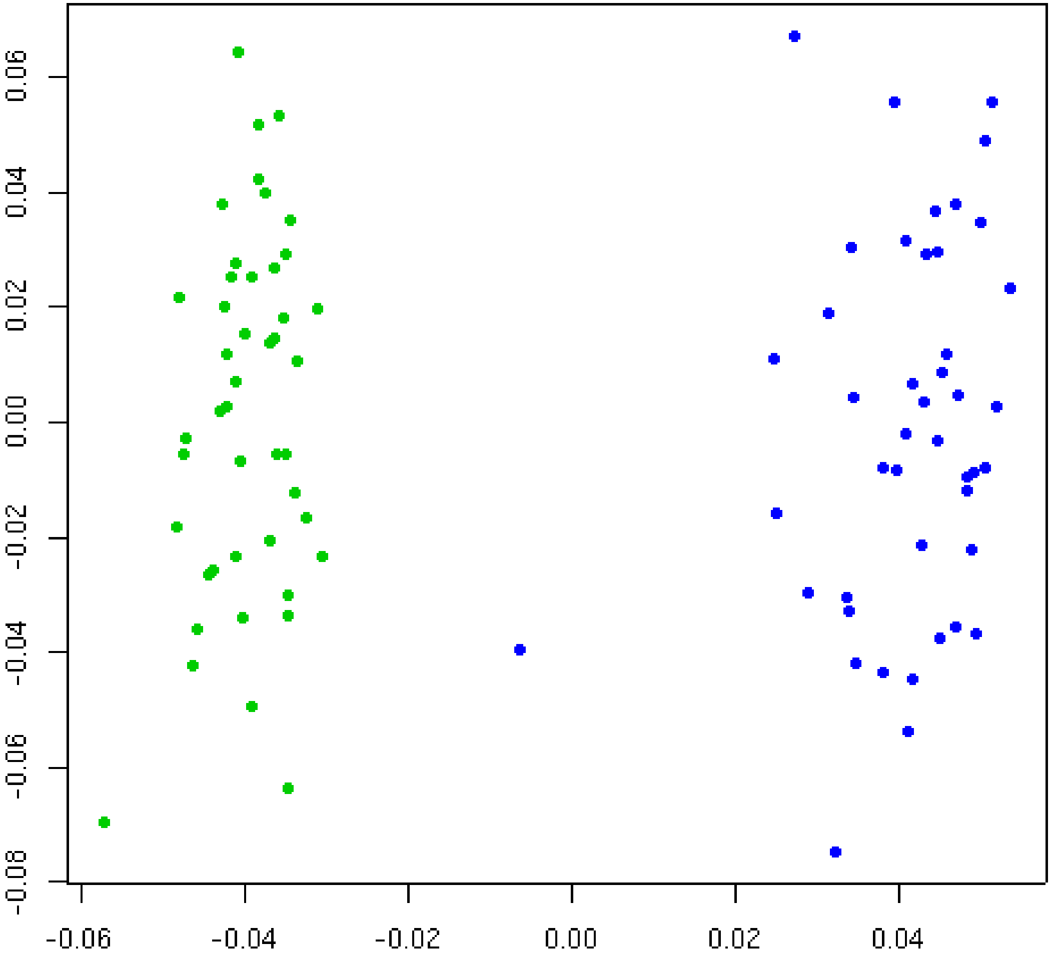
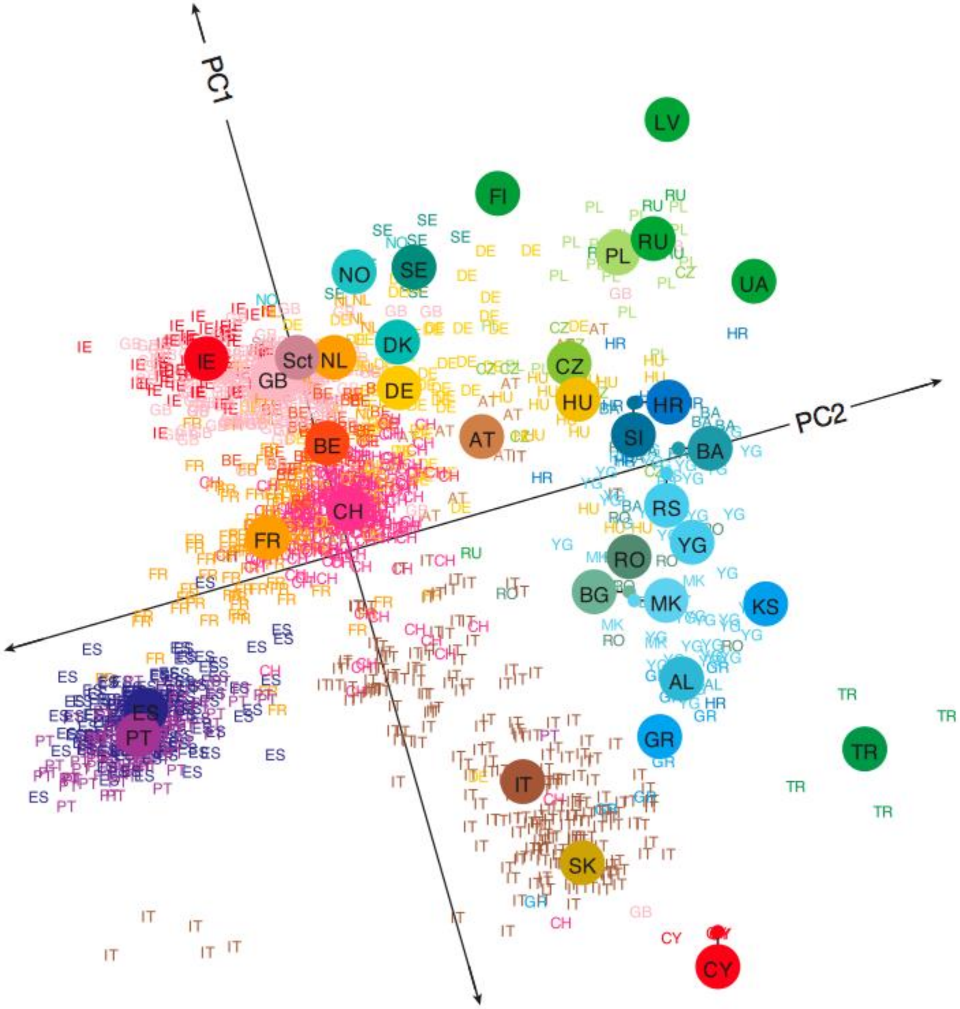


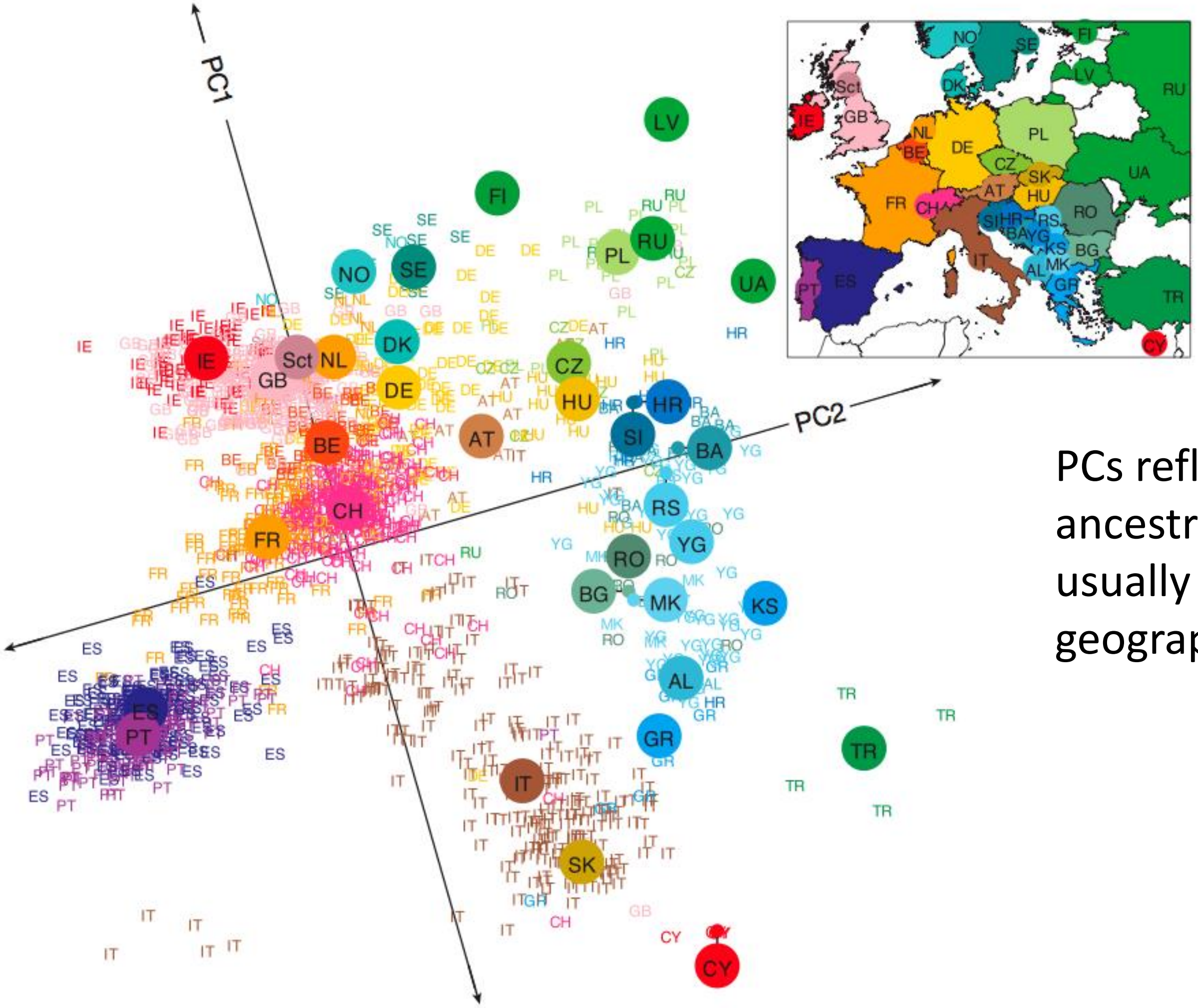


Fine-scale genetic variation



Genes mirror geography within Europe (Novembre et al, 2008)

Fine-scale genetic variation reflects geography

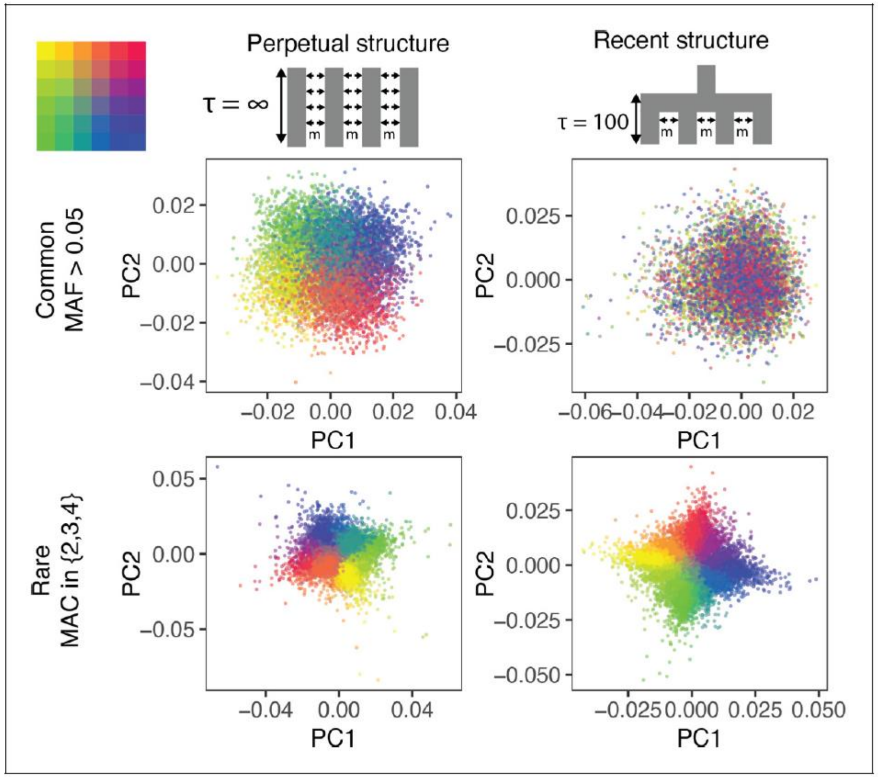


PCs reflecting ancestry differences usually correlate with geography.

Genes mirror geography within Europe (Novembre et al, 2008)

Some caveats

- PCA informs about population structures at different times, depending on allele frequency (rare variant => more recent history)
- Rare variant stratification (i.e., more recent history) can be missed



eLife

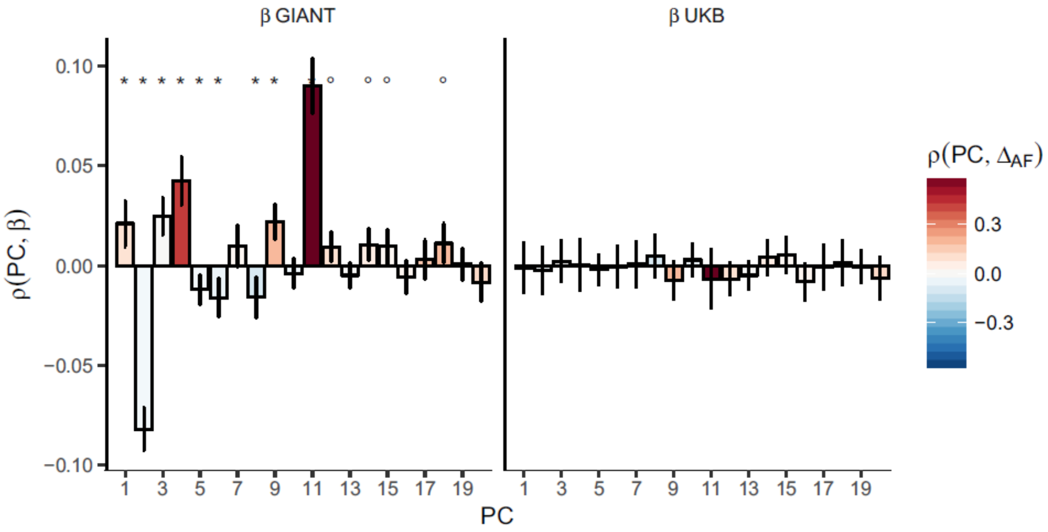
RESEARCH ARTICLE

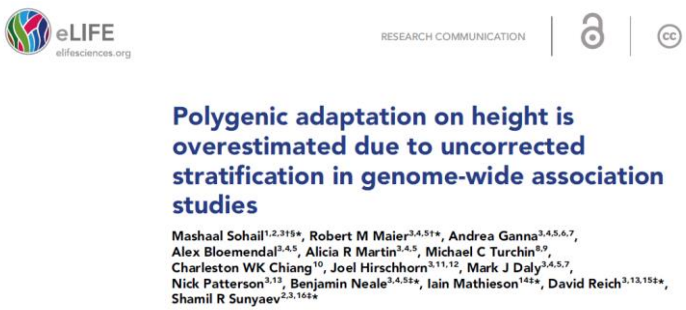
Demographic history mediates the effect of stratification on polygenic scores

Arslan A Zaidi*, Iain Mathieson*

Some caveats

- PCA informs about population structures at different times, depending on allele frequency (rare variant => more recent history)
- Rare variant stratification (i.e., more recent history) can be missed
- Effectiveness of PCA depends on sample size (large sample => better correction for stratification)

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elifesciences.org
RESEARCH COMMUNICATION

Polygenic adaptation on height is overestimated due to uncorrected stratification in genome-wide association studies

Mashaal Sohail[1,2,3†§*], Robert M Maier[3,4,5†*], Andrea Ganna[3,4,5,6,7], Alex Bloemendal[3,4,5], Alicia R Martin[3,4,5], Michael C Turchin[8,9], Charleston WK Chiang[10], Joel Hirschhorn[3,11,12], Mark J Daly[3,4,5,7], Nick Patterson[3,13], Benjamin Neale[3,4,5‡*], Iain Mathieson[14‡*], David Reich[3,13,15‡*], Shamil R Sunyaev[2,3,16‡*]

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- PCA informs about population structures at different times, depending on allele frequency (rare variant => more recent history)
- Rare variant stratification (i.e., more recent history) can be missed
- Effectiveness of PCA depends on sample size (large sample => better correction for stratification)
- PCA is not a magic ancestry-capturing method. It captures large patterns of variation (so also quality differences or large regions of LD)

Copy and unzip files needed for practical

- Open terminal: Applications Menu -> Terminal Emulator
- First run this in your terminal:

```
cp -r /home/abdel/PCA_practical .
cd PCA_practical
unzip dutch_1kG.zip
```

- command.txt contains all the remaining commands we are going to run in the terminal (which are also on the slides abdel_pop_strat_boulder_2023.pdf)

Overview practical

- Analyses are based on the paper "*Population Structure, Migration, and Diversifying Selection in the Netherlands*" (Abdellaoui et al, 2013)

Analyses:

- Run PCA on 1000 Genomes, and project PCs on Dutch individuals
  - Goal: identify Dutch individuals with non-European ancestry and exclude
- Run PCA on remaining Dutch individuals
  - Goal: obtain PCs reflecting Dutch ancestry differences

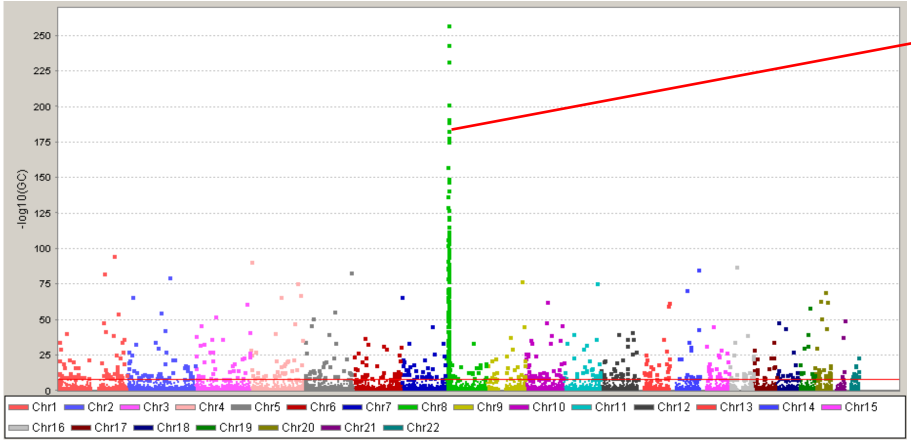
- Software used:
  - Eigenstrat -> http://genepath.med.harvard.edu/~reich/Software.htm
  - Plink -> http://pngu.mgh.harvard.edu/~purcell/plink
  - R -> http://www.r-project.org/

Description of the data

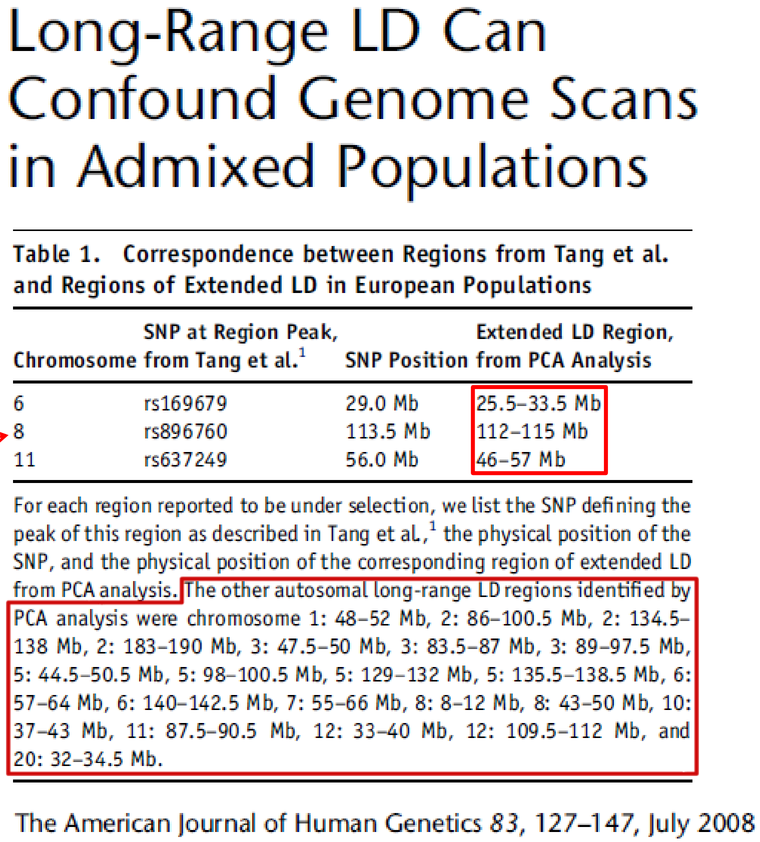
- Individuals:
  - 171 Dutch individuals from the Netherlands Twin Registry (NTR)
  - 221 from 1000 Genomes (Europeans, Africans, and Asians)
    - If you’re interested in the 1000 Genomes dataset in plink format (~16 million SNPs): e-mail a.abdellaoui@amsterdamumc.nl
- SNPs:
  - 113,164 SNPs (from Affy 6.0 chip)
  - Quality Control (done in Plink):
    - MAF > .05
    - HWE *p* > .001
    - SNP missingness < .05 (individual missingness < .02)
    - Excluded long-range LD regions
    - LD Pruned

Why exclude long-range LD regions?

- Elevated levels of LD can be overrepresented in PCs, deluding the genome-wide patterns that reflect the subtle ancestry differences.



GWAS on PC: PC reflects variation at chr8 inversion



Long-Range LD Can Confound Genome Scans in Admixed Populations

Table 1. Correspondence between Regions from Tang et al. and Regions of Extended LD in European Populations

Chromosome	SNP at Region Peak, from Tang et al.[1]	SNP Position	Extended LD Region, from PCA Analysis
6	rs169679	29.0 Mb	25.5–33.5 Mb
8	rs896760	113.5 Mb	112–115 Mb
11	rs637249	56.0 Mb	46–57 Mb

For each region reported to be under selection, we list the SNP defining the peak of this region as described in Tang et al.,[1] the physical position of the SNP, and the physical position of the corresponding region of extended LD from PCA analysis. The other autosomal long-range LD regions identified by PCA analysis were chromosome 1: 48–52 Mb, 2: 86–100.5 Mb, 2: 134.5–138 Mb, 2: 183–190 Mb, 3: 47.5–50 Mb, 3: 83.5–87 Mb, 3: 89–97.5 Mb, 5: 44.5–50.5 Mb, 5: 98–100.5 Mb, 5: 129–132 Mb, 5: 135.5–138.5 Mb, 6: 57–64 Mb, 6: 140–142.5 Mb, 7: 55–66 Mb, 8: 8–12 Mb, 8: 43–50 Mb, 10: 37–43 Mb, 11: 87.5–90.5 Mb, 12: 33–40 Mb, 12: 109.5–112 Mb, and 20: 32–34.5 Mb.

The American Journal of Human Genetics *83*, 127–147, July 2008

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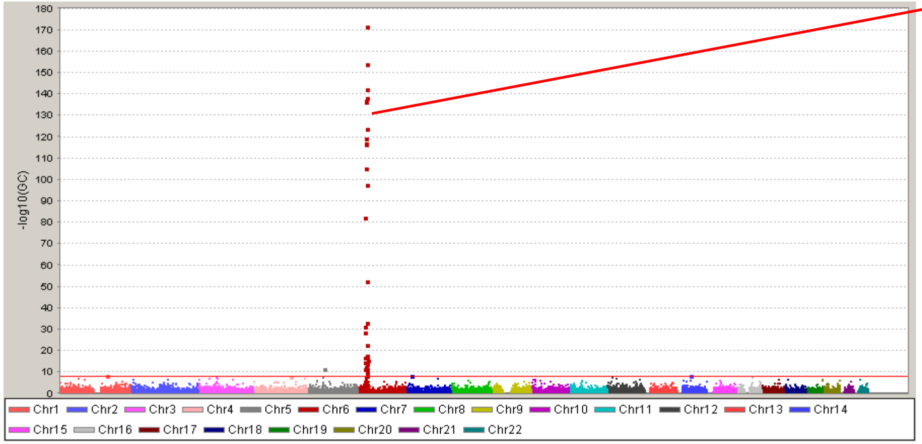
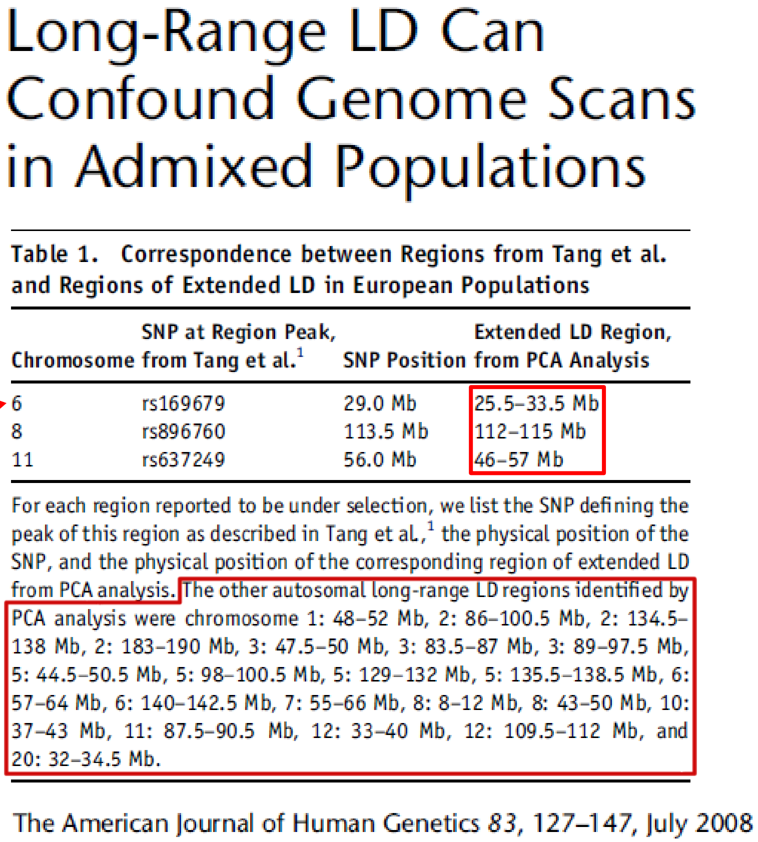


GWAS on PC: PC reflects variation at MHC region (chr 6)



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The American Journal of Human Genetics *83*, 127–147, July 2008

Why also prune for LD?

- From EIGENSTRAT paper *Principal components analysis corrects for stratification in genome-wide association studies (Price et al, 2006)*:

“Strong LD at a given locus which affects many markers could result in an axis of variation which corresponds to genetic variation specifically at that locus, rather than to genome-wide ancestry. Nonetheless, **we recommend inferring population structure using all markers. This recommendation is based on an analysis of HapMap data which suggests that these potential problems will not affect results in practice.**”

Why also prune for LD?

- PCA was conducted on three sets of SNPs varying in LD on 1000 Genomes populations and Dutch subjects separately
- PCs were identical for 1000 Genomes across the 3 SNP sets. For the Dutch dataset, there were big differences:

SNP set used for PCA	Nr. of SNPs for PCA	Correlations between PCs and North-South gradient (N = 3363)		Correlations between PCs and East-West gradient (N = 3363)		λ for GWASs on height including the North-South PC as a covariate
		Pearson Correlation	Difference test	Pearson Correlation	Difference test	
SNP set 1: All SNPs that passed QC	499,849	$r_{\text{PC2},\updownarrow}$= .428	-	$r_{\text{PC8},\leftrightarrow}$= .205	-	1.03937
SNP set 2: SNP set 1 without the 24 long-range LD regions	487,672	$r_{\text{PC1},\updownarrow}$= .574	$p = 3.9*10^{-46}$ (versus SNP set 1)	$r_{\text{PC3},\leftrightarrow}$= .260	$p = 4.2*10^{-10}$ (versus SNP set 1)	1.03092
SNP set 3: SNP set 2 with genome-wide LD based SNP pruning	130,248	$r_{\text{PC1},\updownarrow}$=.588	$p = 1.9*10^{-4}$ (versus SNP set 2)	$r_{\text{PC2},\leftrightarrow}$=.369	$p = 3.5*10^{-21}$ (versus SNP set 2)	1.02961

- Conclusion: minimizing LD is necessary for more homogeneous datasets (i.e., datasets with subjects from a single population)

Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

Files needed for EIGENSTRAT

- Input files: three files containing information about SNPs and samples (.ped, .map, .fam)
- Parameter file: file containing parameters for the PCA

EIGENSTRAT input files are in plink format

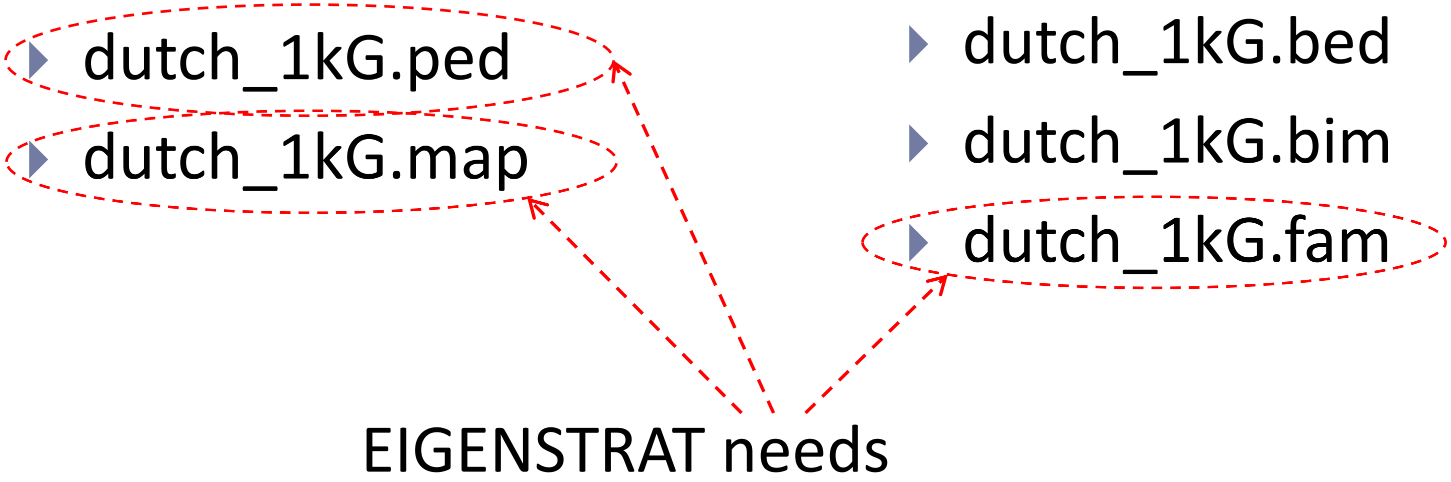
Plink ped files (--recode)

- dutch_1kG.ped
- dutch_1kG.map

Plink binary files (--make-bed)

- dutch_1kG.bed
- dutch_1kG.bim
- dutch_1kG.fam

EIGENSTRAT input files are in plink format



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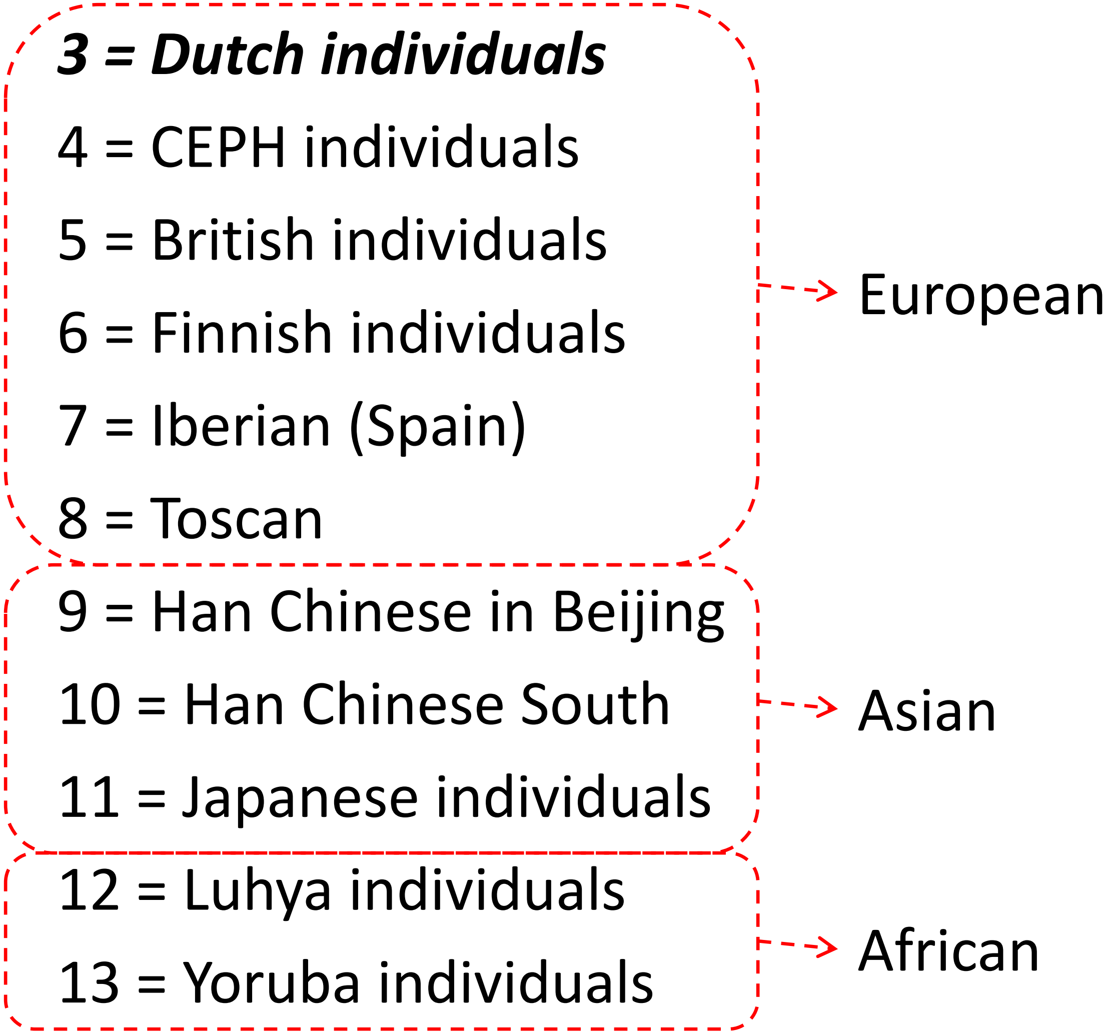
Plink binary files (--make-bed)

- dutch_1kG.bed
- dutch_1kG.bim
- dutch_1kG.fam

EIGENSTRAT needs

Values in the phenotype column (column 6) of .fam file:



3 = Dutch individuals

4 = CEPH individuals

5 = British individuals

6 = Finnish individuals

7 = Iberian (Spain)

8 = Toscan

→ European

9 = Han Chinese in Beijing

10 = Han Chinese South

11 = Japanese individuals

→ Asian

12 = Luhya individuals

13 = Yoruba individuals

→ African

Parameter file (.par)

- The .par file will have the following lines:

genotypename: **dutch_1kG.ped** -> *input genotype file*

snpname: **dutch_1kG.map** -> *input snp file*

indivname: **dutch_1kG.fam** -> *input individual file*

evecoutname: **dutch_1kG.evec** -> *output file of PCs*

evaloutname: **dutch_1kG.eval** -> *output file of all eigenvalues*

numoutevec: **10** -> *number of PCs to output*

numoutlieriter: **0** -> *maximum number of outlier removal iterations (0 turns it off)*

poplistname: **poplist_1kG.txt** -> *file containing population value of individuals (If wishing to infer PCs using only individuals from a subset of populations, and then project to individuals from all other populations; will be used to detect individuals of non-European descent)*

snpweightoutname: **dutch_1kG.snpweight** -> *output file with SNP weightings of each PC*

Parameter file (.par)

- Let’s make the .par file. Run the following commands:

```
echo "genotypename: dutch_1kG.ped" >> dutch_1kG.par
echo "snpname: dutch_1kG.map" >> dutch_1kG.par
echo "indivname: dutch_1kG.fam" >> dutch_1kG.par
echo "evecoutname: dutch_1kG.evec" >> dutch_1kG.par
echo "evaloutname: dutch_1kG.eval" >> dutch_1kG.par
echo "numoutevec: 10" >> dutch_1kG.par
echo "numoutlieriter: 0" >> dutch_1kG.par
echo "poplistname: poplist_1kG.txt" >> dutch_1kG.par
echo "snpweightoutname: dutch_1kG.snpweight" >> dutch_1kG.par
```

- We need to make the poplistname file (poplist_1kG.txt), containing the population values of the 1000 Genomes populations (4-13). Run the following command:

```
shopt -s xpg_echo
echo "4\n5\n6\n7\n8\n9\n10\n11\n12\n13" > poplist_1kG.txt
```

We're ready to run EIGENSTRAT

- Run this command:

```
smartpca -p dutch_1kG.par > dutch_1kG.log
```

Let’s look at the PCs in R

- First, let's make the file readable for R:

```
sed 's/:/ /g' dutch_1kG.evec > dutch_1kG.R.evec
```

- Run R script to make plot and identify outliers:

```
R CMD BATCH outliers.R
```

Let’s look at the PCs in R

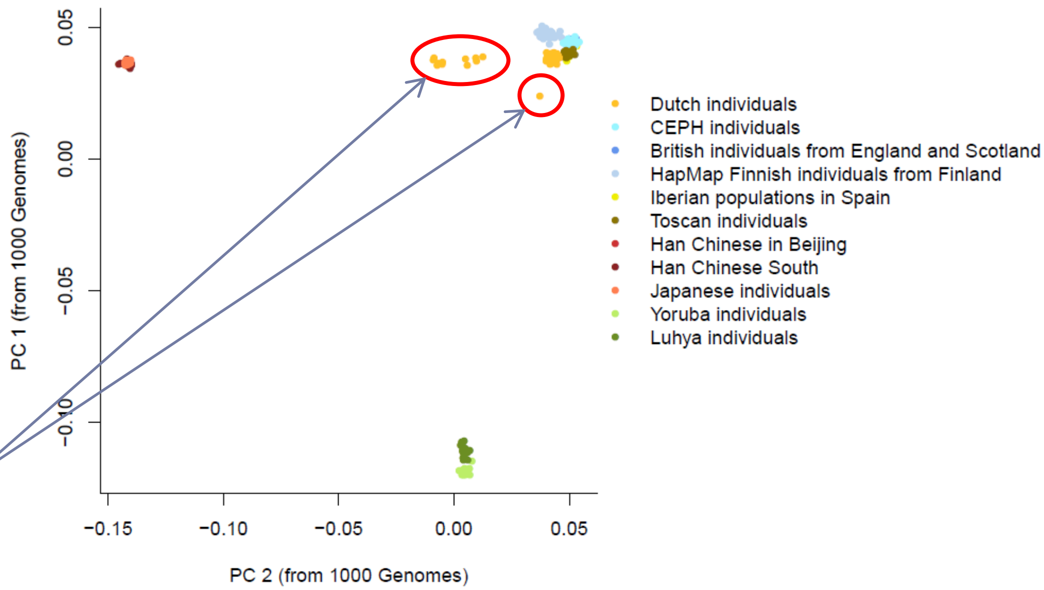
- First, let's make the file readable for R:

```
sed 's/:/ /g' dutch_1kG.evec > dutch_1kG.R.evec
```

- Run R script to make plot and identify outliers:

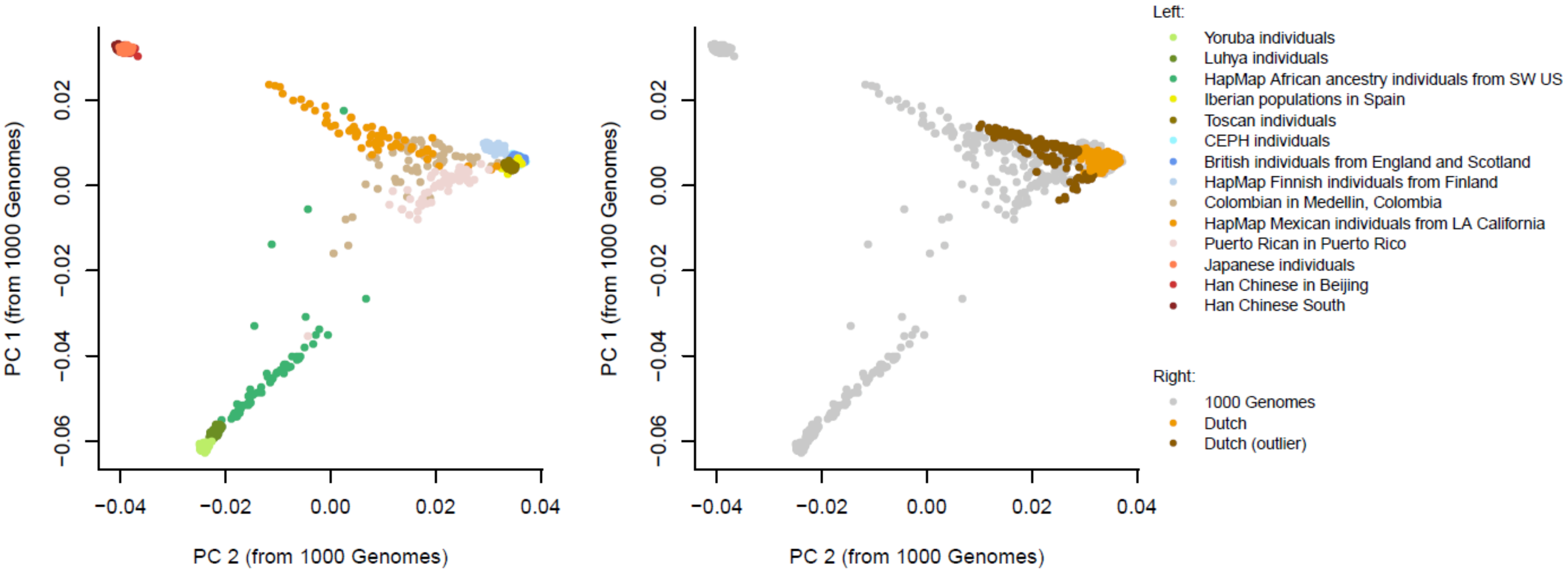
```
R CMD BATCH outliers.R
```

- What does the R script do? (open outliers.R)
  - Read in EIGENSTRAT file
  - Plot PC1 & PC2
  - Write IDs to file of Dutch individuals scoring higher than maximum European or lower than minimum European scores on PC1 or PC2 (to outliers.txt)



Identifying Dutch with non-European ancestry

- PCs were calculated using a set of 1014 unrelated individuals from 1000 Genomes, and were then projected on ~7500 Dutch individuals.
- 258 individuals were excluded. Parental birth place was available for 132 of these individuals, of which 55.3% had at least one parent born outside of the Netherlands (as opposed to 4% of the rest of the individuals).



Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

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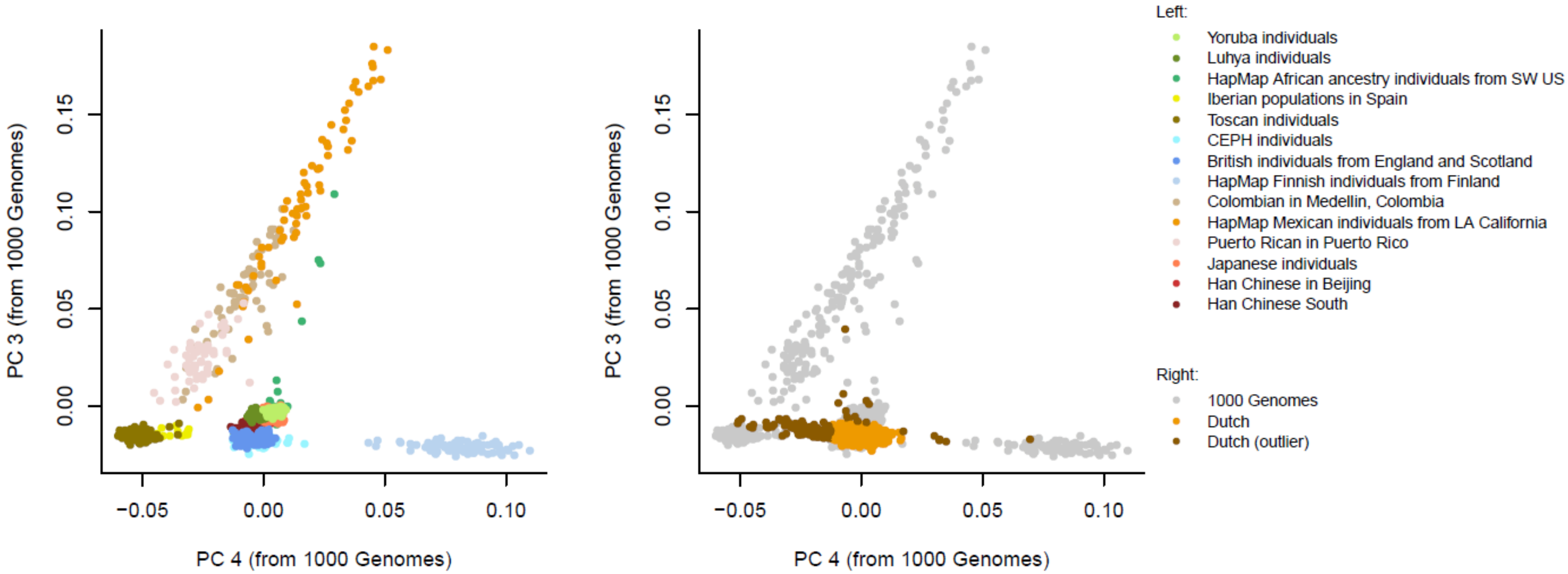

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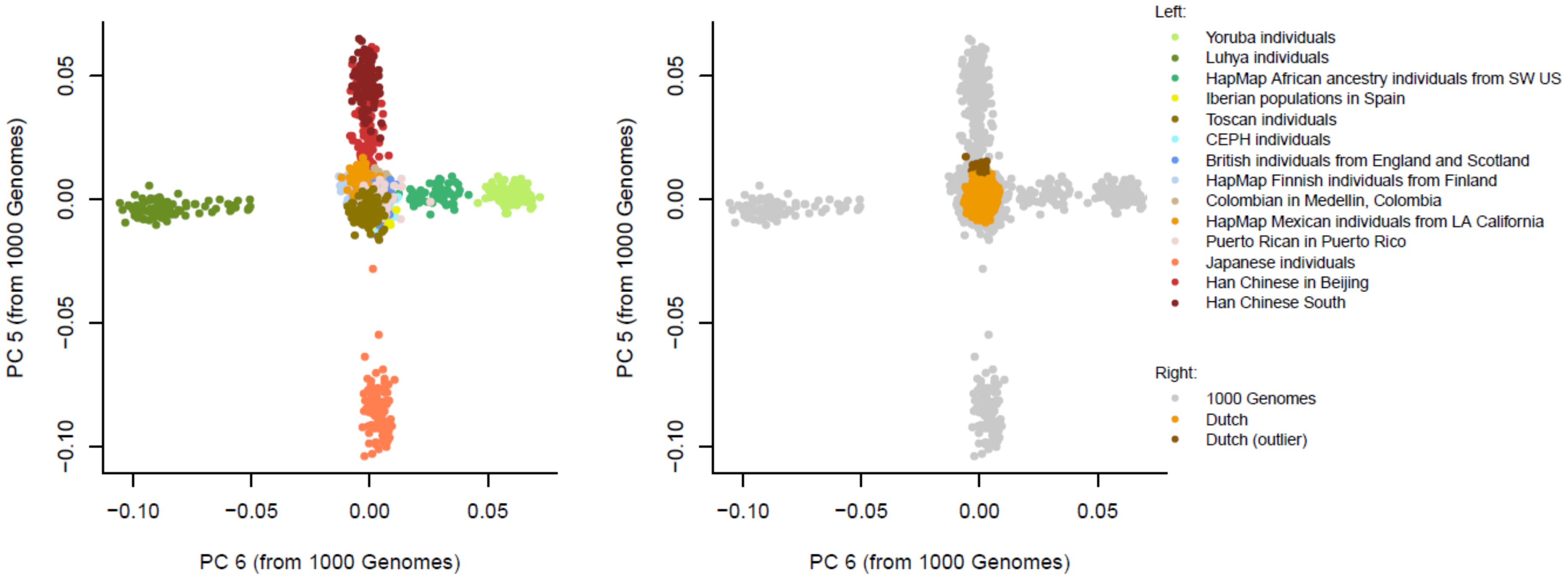


Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

Exclude Dutch individuals with non-European ancestry and 1000 Genomes

```
awk '$6>3{print $1,$2}' dutch_1kG.fam > 1kG.ids
cat outliers.txt 1kG.ids > remove_outliers.ids

plink --bfile dutch_1kG --remove remove_outliers.ids --make-bed --out dutch
plink --bfile dutch --recode --out dutch
```

Parameter file (.par)

- Let’s make the .par file. Run the following commands:

```
echo "genotypename: dutch.ped" >> dutch.par
echo "snpname: dutch.map" >> dutch.par
echo "indivname: dutch.fam" >> dutch.par
echo "evecoutname: dutch.evec" >> dutch.par
echo "evaloutname: dutch.eval" >> dutch.par
echo "numoutevec: 10" >> dutch.par
echo "numoutlieriter: 0" >> dutch.par
echo "poplistname: poplist_NL.txt" >> dutch.par
echo "snpweightoutname: dutch.snpweight" >> dutch.par
```

- We also need to make the poplistname file (poplist_NL.txt). Run the following command:

```
echo "3" > poplist_NL.txt
```

We're ready to run the 2nd round of EIGENSTRAT!

- Run this command:

```
smartpca -p dutch.par > dutch.log
```

Let’s plot the first two PCs in R

- First, let's make the file readable for R:

```
sed 's/:/ /g' dutch.evec > dutch.R.evec
```

- Run R script to make plot :

```
R CMD BATCH plot_NL.R
```

Let’s plot the first two PCs in R

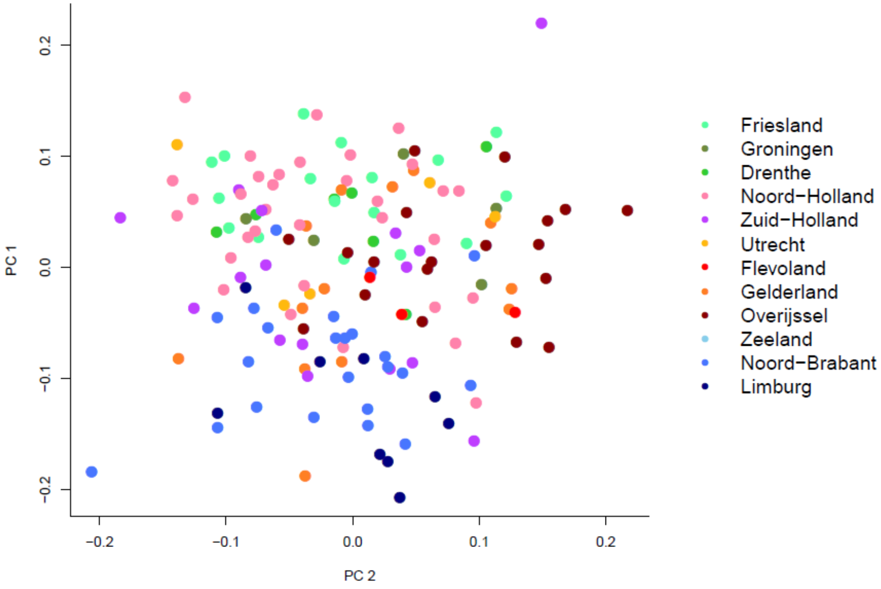
- First, let's make the file readable for R:

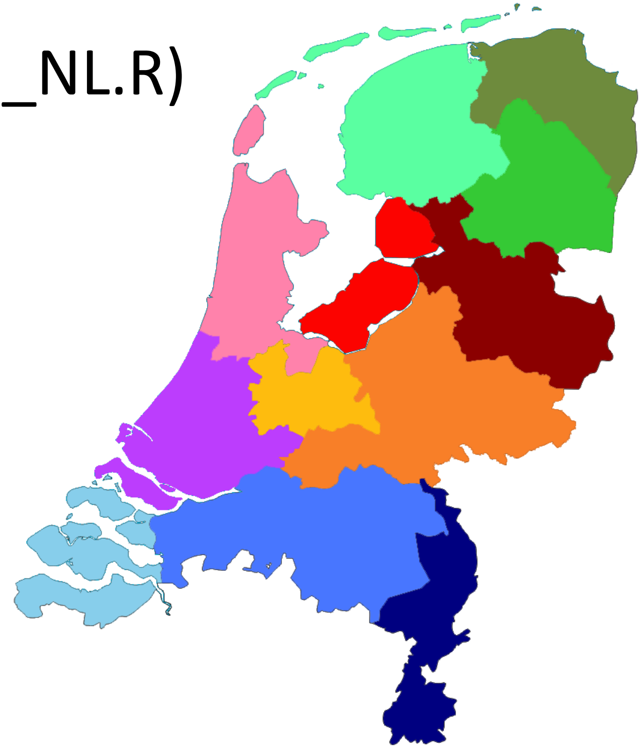
```
sed 's/:/ /g' dutch.evec > dutch.R.evec
```

- Run R script to make plot :

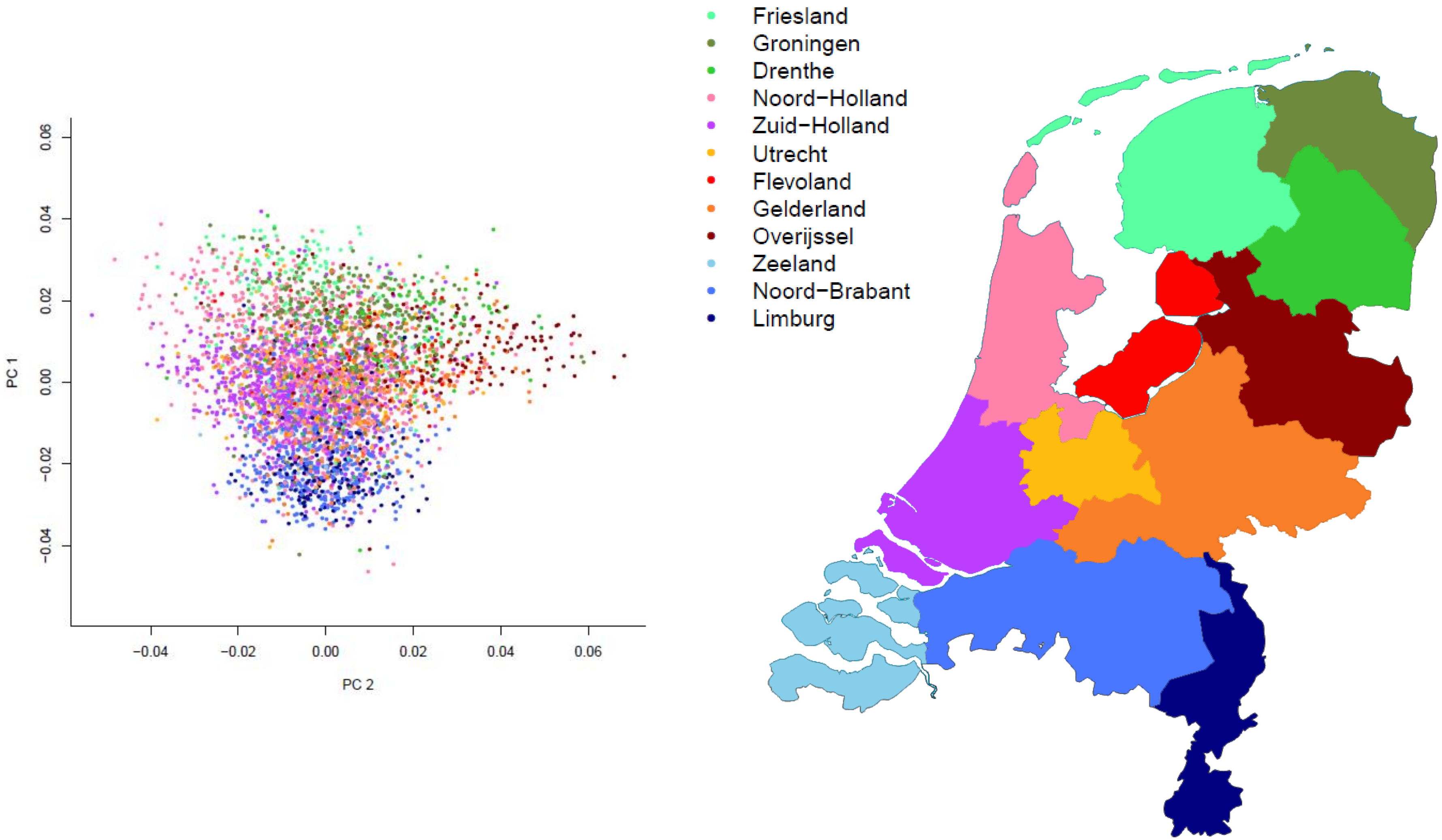
```
R CMD BATCH plot_NL.R
```

- What does the R script do? (open plot_NL.R)





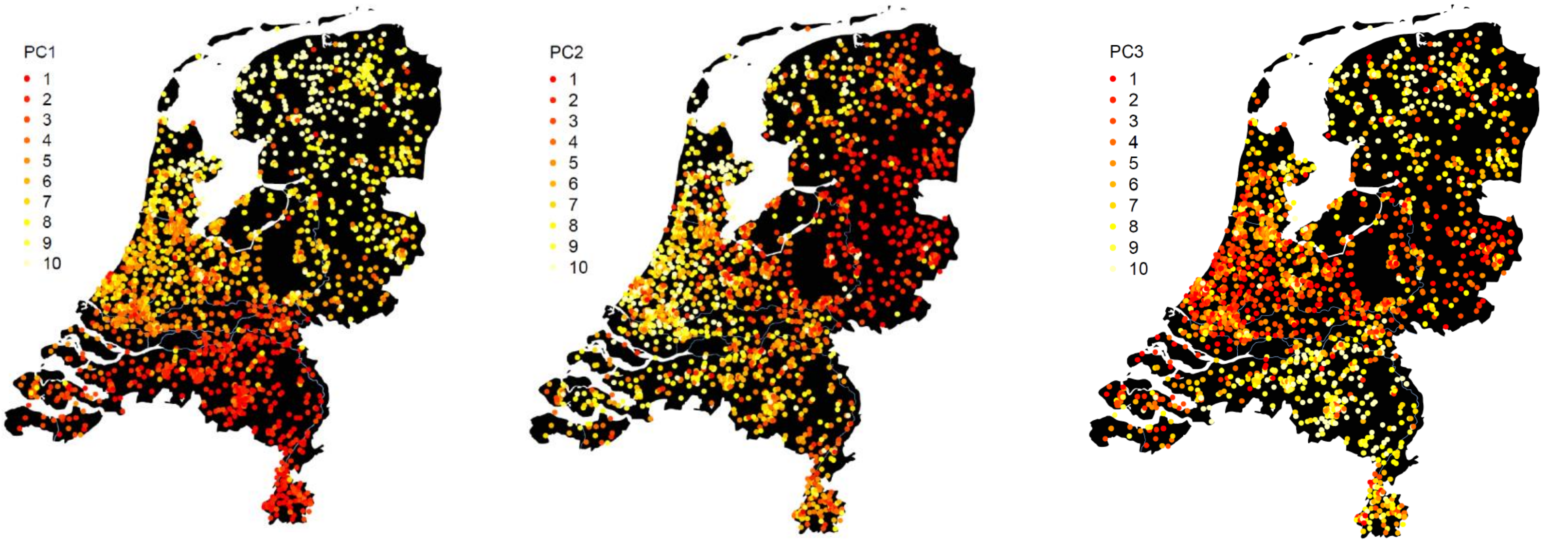
Same plot, with N=4,441



Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

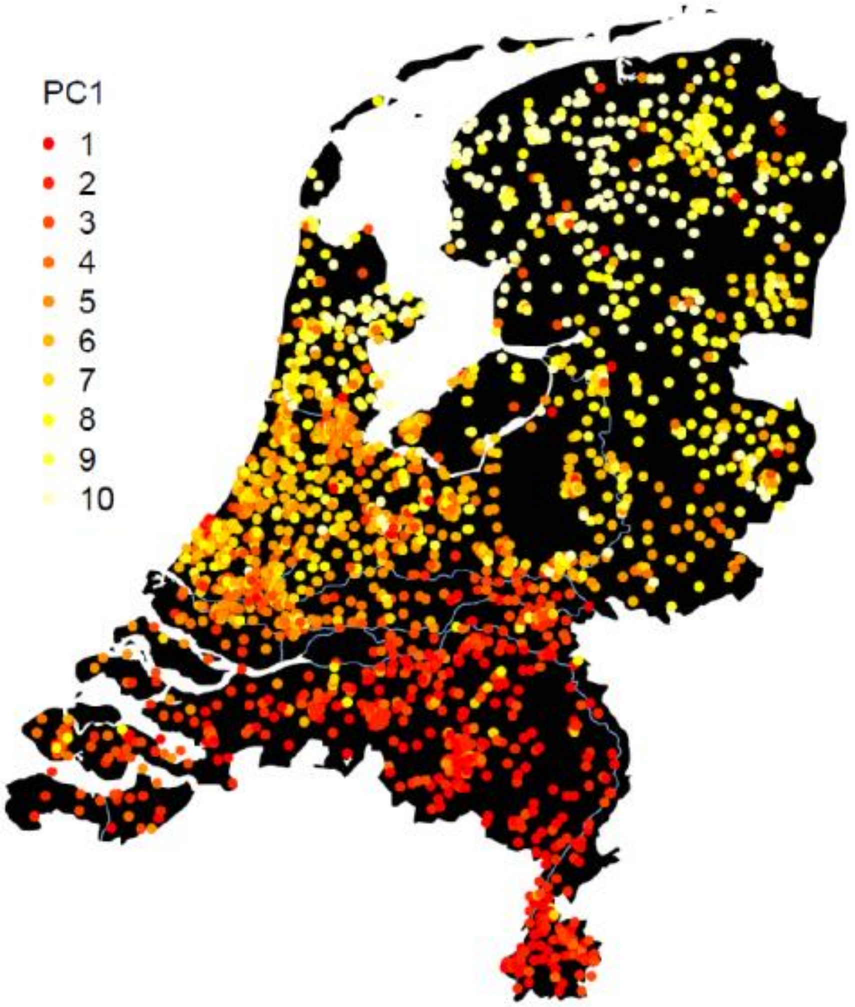
PC1, PC2, and PC3

- The color of the dots represent the mean PC value per postal code (based on current living address of the 4,441 subjects).

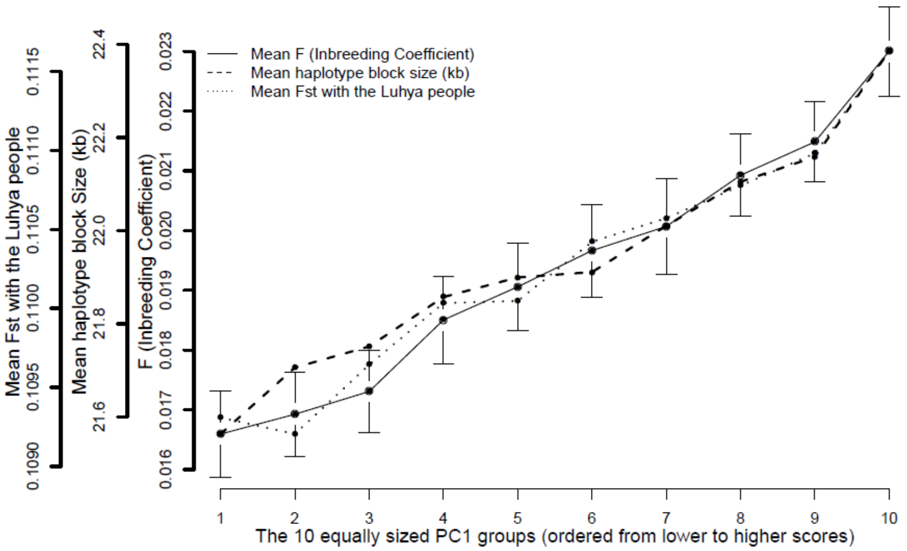


Population Structure, Migration, and Diversifying Selection in the Netherlands
(Abdellaoui et al, 2013)

PC1 (N=4,441)



- Correlates .656 with European North-South PC.
- Serial founder effect? (correlation with F: .245)
- Spouse correlation = .555

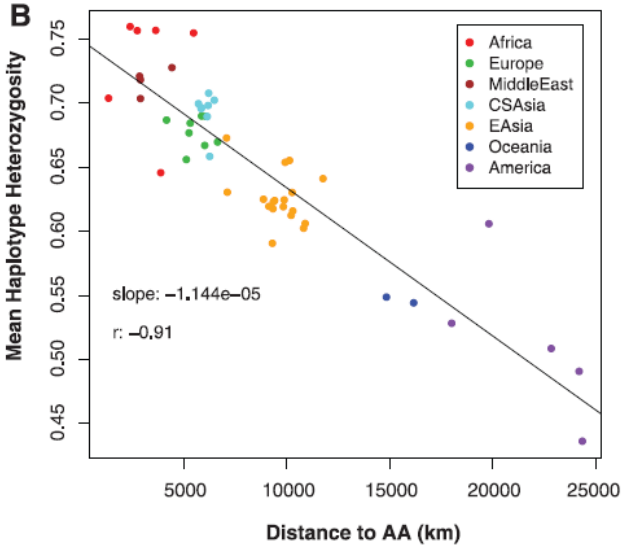


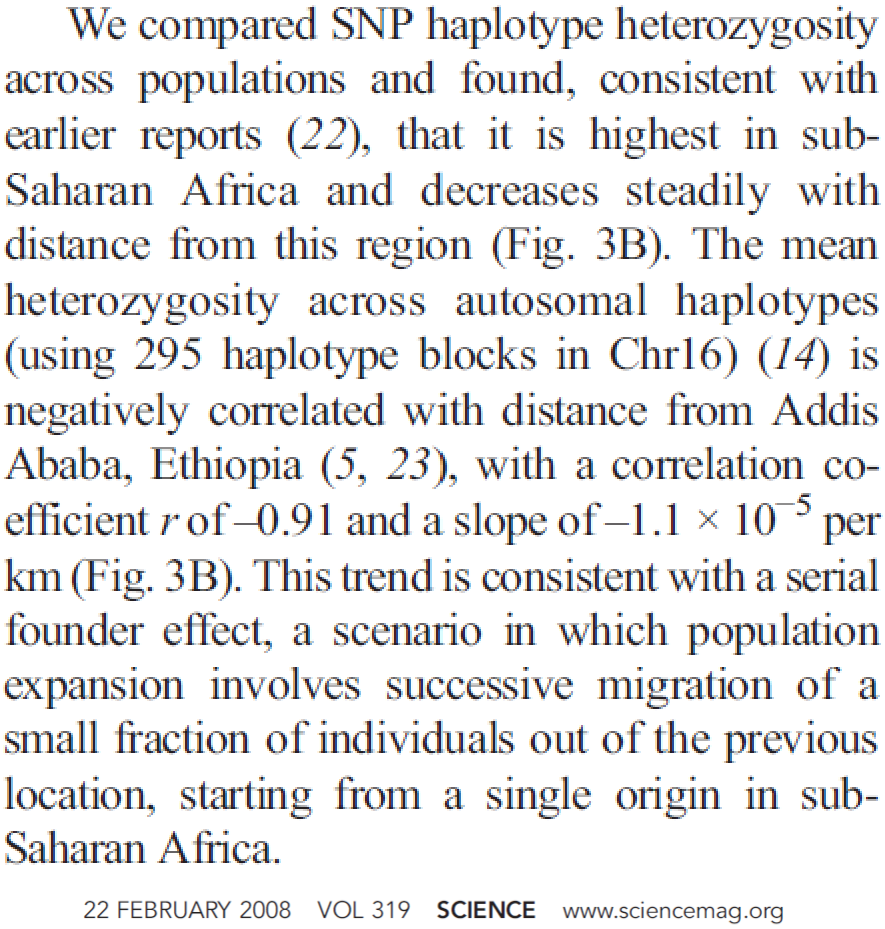
Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

Serial founder effect: heterozygosity decreases (F increases) as you move away from Addis Ababa, Ethopia

Worldwide Human Relationships Inferred from Genome-Wide Patterns of Variation

Jun Z. Li,[1,2]*† Devin M. Absher,[1,2]* Hua Tang,[1] Audrey M. Southwick,[1,2] Amanda M. Casto,[1] Sohini Ramachandran,[4] Howard M. Cann,[5] Gregory S. Barsh,[1,3] Marcus Feldman,[4]‡ Luigi L. Cavalli-Sforza,[1]‡ Richard M. Myers[1,2]‡





We compared SNP haplotype heterozygosity across populations and found, consistent with earlier reports (*22*), that it is highest in sub-Saharan Africa and decreases steadily with distance from this region (Fig. 3B). The mean heterozygosity across autosomal haplotypes (using 295 haplotype blocks in Chr16) (*14*) is negatively correlated with distance from Addis Ababa, Ethiopia (*5*, *23*), with a correlation coefficient r of -0.91 and a slope of -1.1×10^{-5} per km (Fig. 3B). This trend is consistent with a serial founder effect, a scenario in which population expansion involves successive migration of a small fraction of individuals out of the previous location, starting from a single origin in sub-Saharan Africa.

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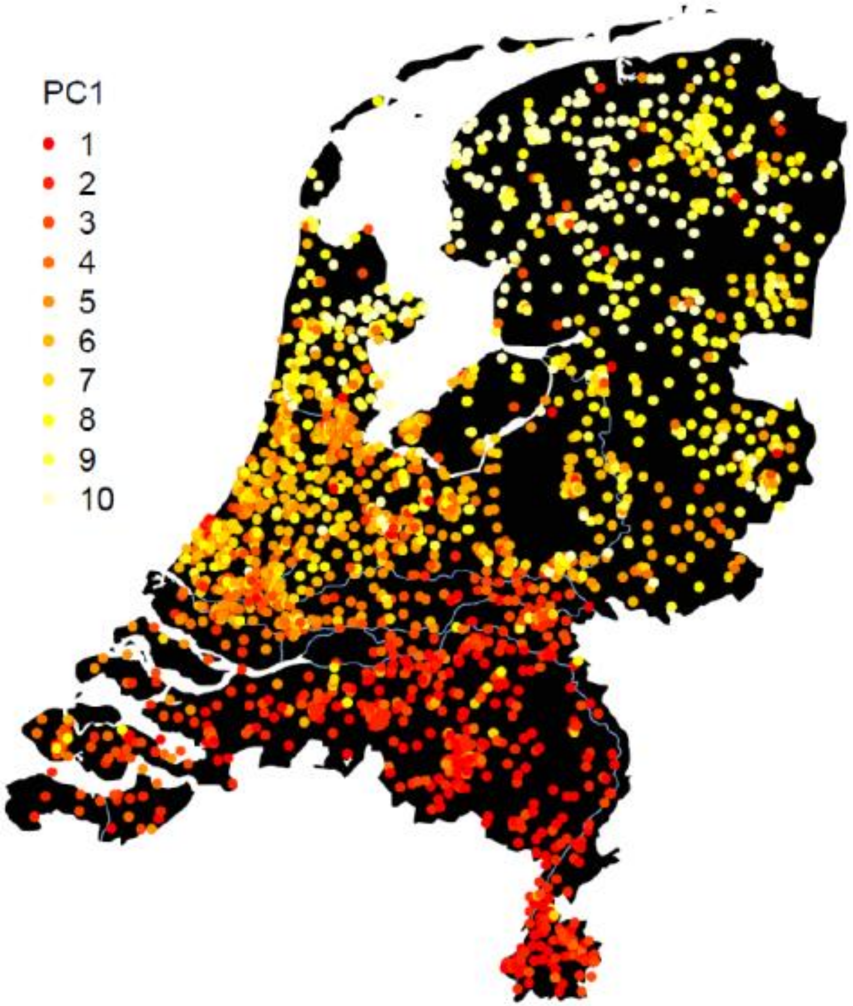
- Genome-wide homozygosity (F) can be computed in plink with *--het*

Height

- Northern Dutch are known to be taller on average than the Dutch from the Southern parts of the Netherlands. Also within Europe, Northern Europeans are taller on average than Southern Europeans.
- In our sample, height does not correlate very high with the North-South gradient of the current living address:
  - males: r = .055, p = .032; females: r = .066, p = .001
- Height however correlates higher and more significantly with the North-South PC:
  - males: r = .178, $p = 3\times10^{-12}$; females: r = .166, $p = 1\times10^{-18}$

PC1 (N=4,441)



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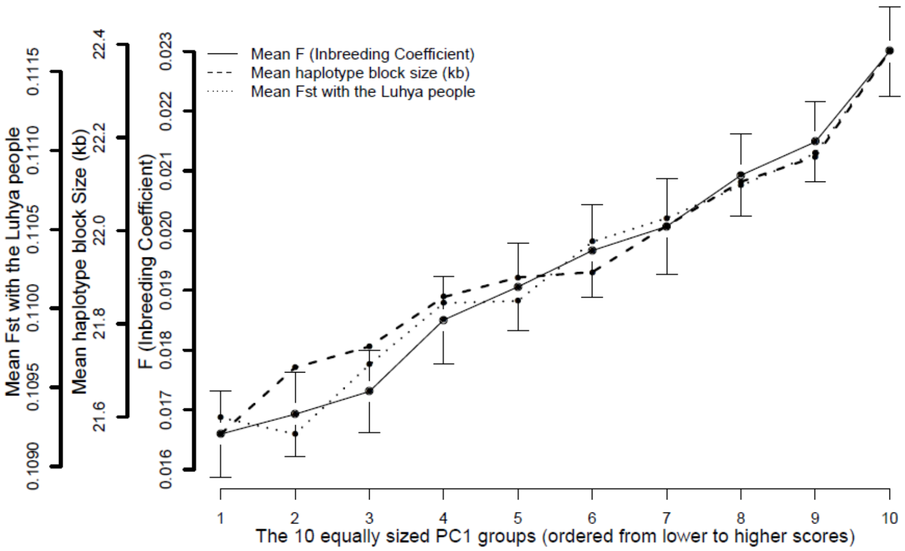
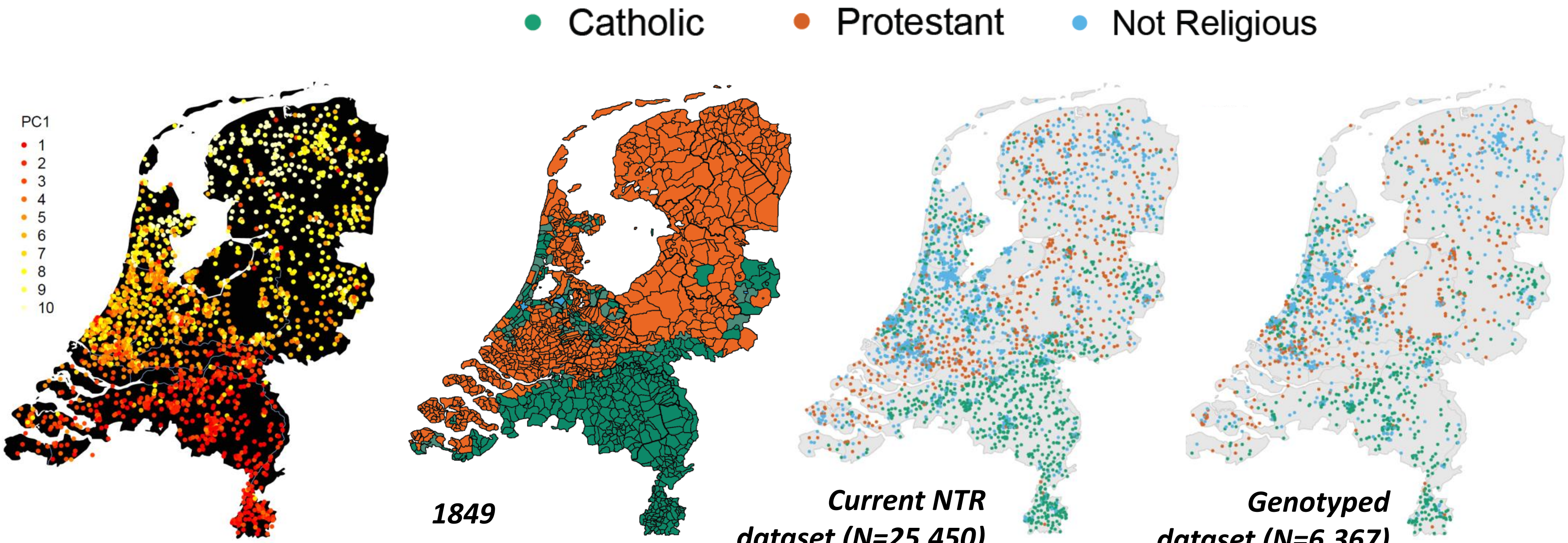


Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

Religion in the Netherlands

- The Netherlands had a long history (>400 years) of societal segregation and assortment based on religious affiliation.
  - Spouse correlation for religion in current dataset = .728 (p < .001)
- This may have increased parental relatedness among religious people.



1849

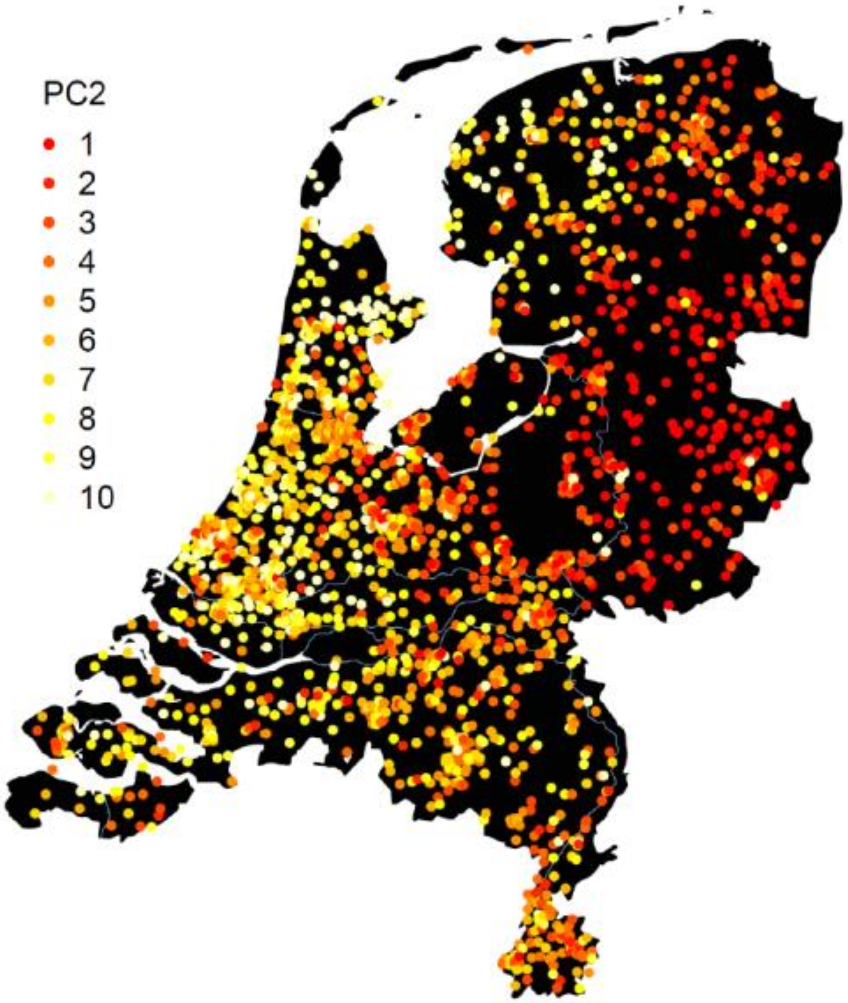
Current NTR dataset (N=25,450)

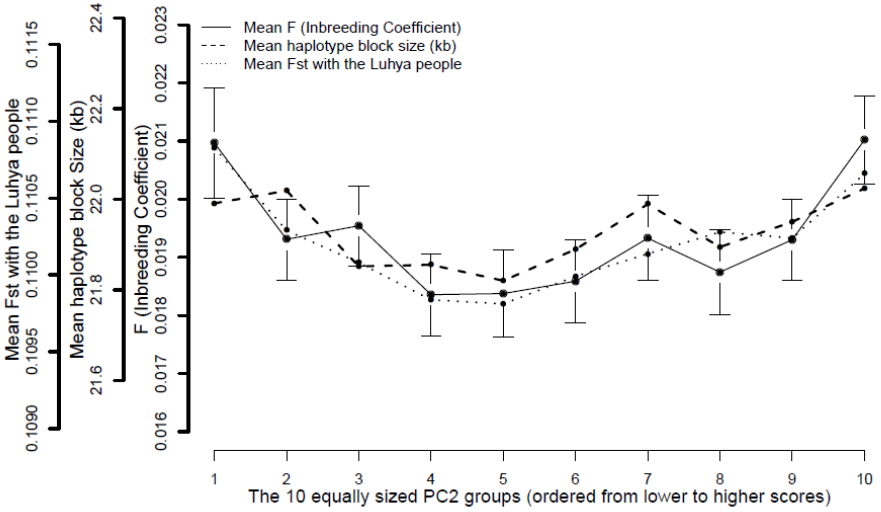
Genotyped dataset (N=6,367)

Association between autozygosity and major depression: Stratification due to religious assortment (Abdellaoui et al, 2013)

PC2 (N=4,441)

- Spouse correlation = .164





Population Structure, Migration, and Diversifying Selection in the Netherlands
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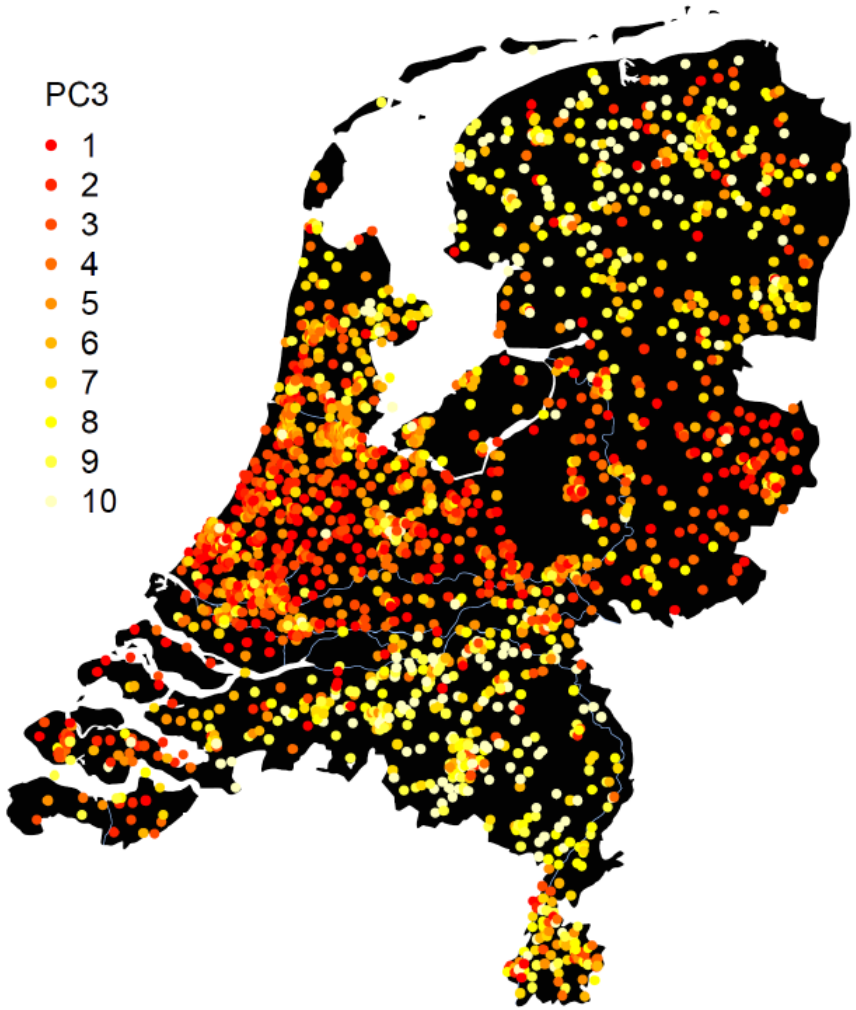
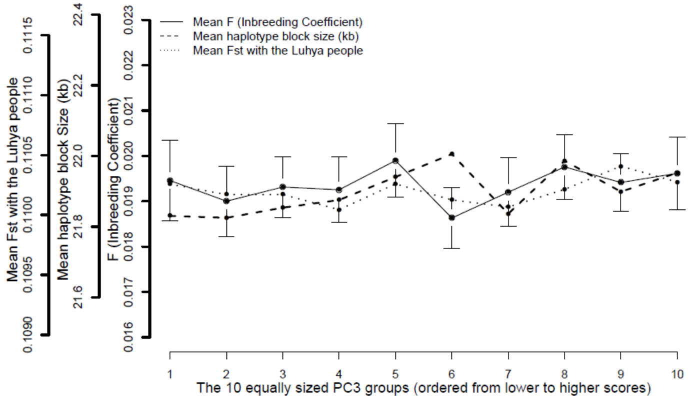
PC3 (N=4,441)

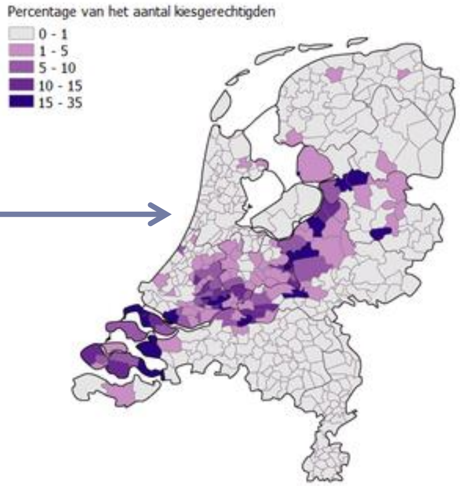


- Was only observed with minimized LD
- Spouse correlation = .174



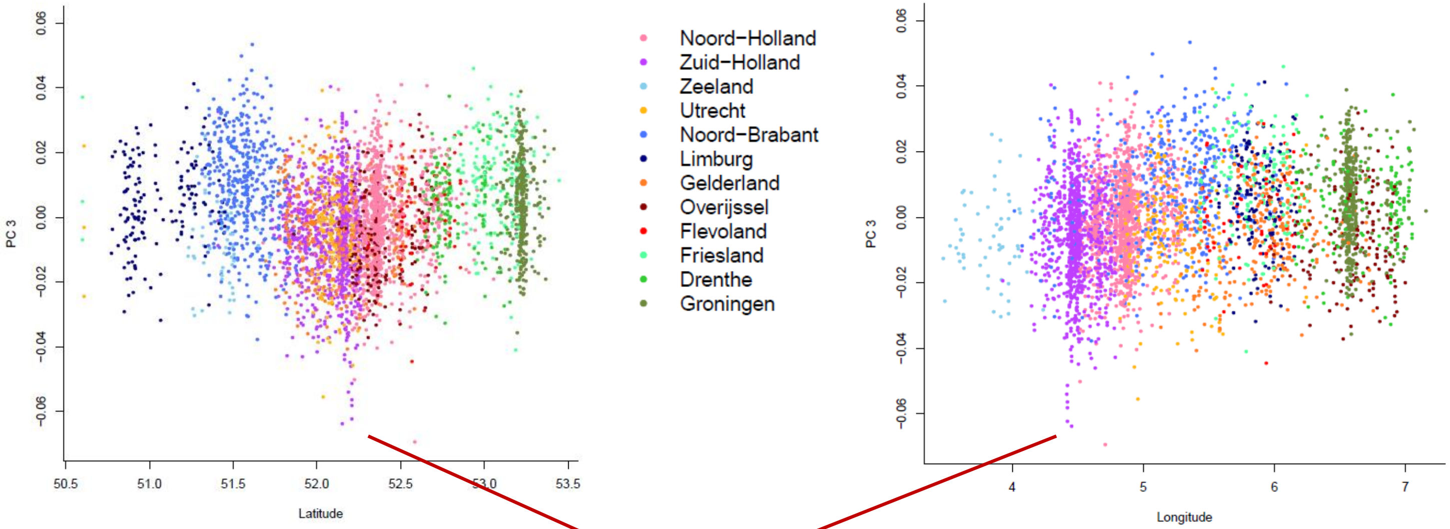
- Bible belt?

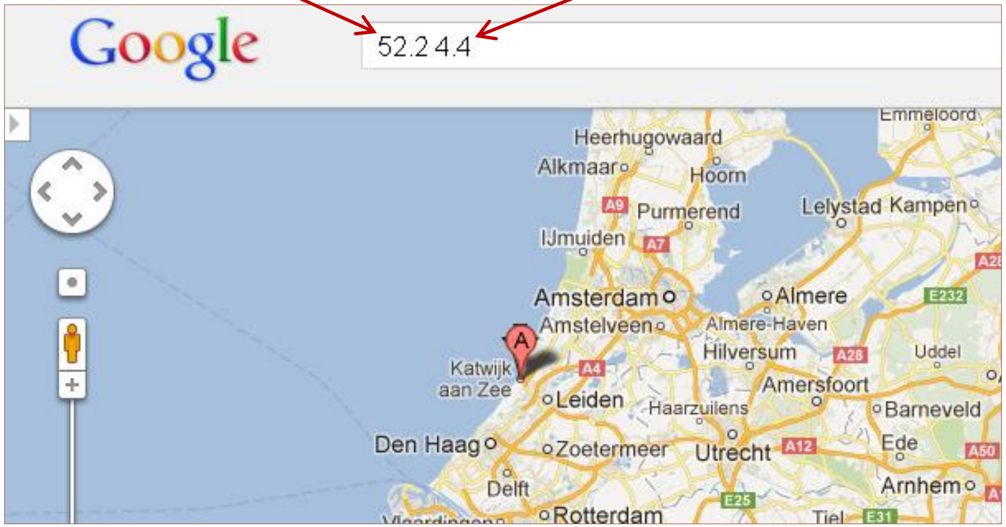
Votes for conservative Christian party (SGP) →



Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

PC3 (N=4,441)

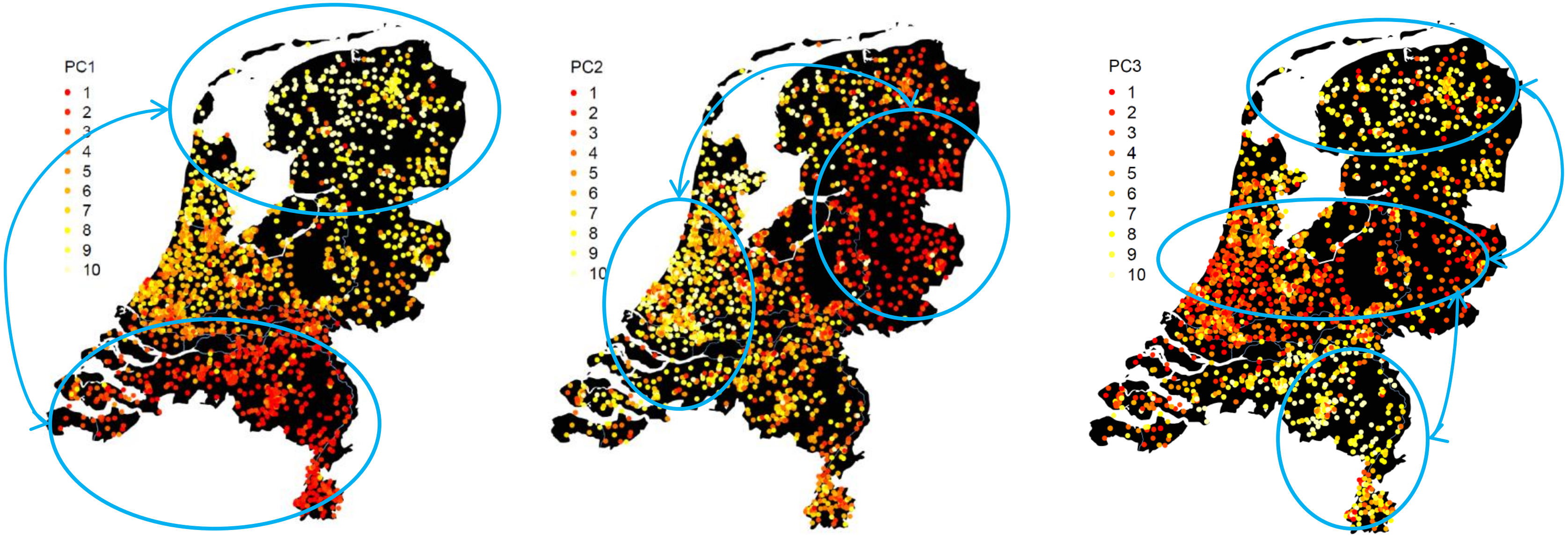




52.2 4.4

Natural selection vs genetic drift

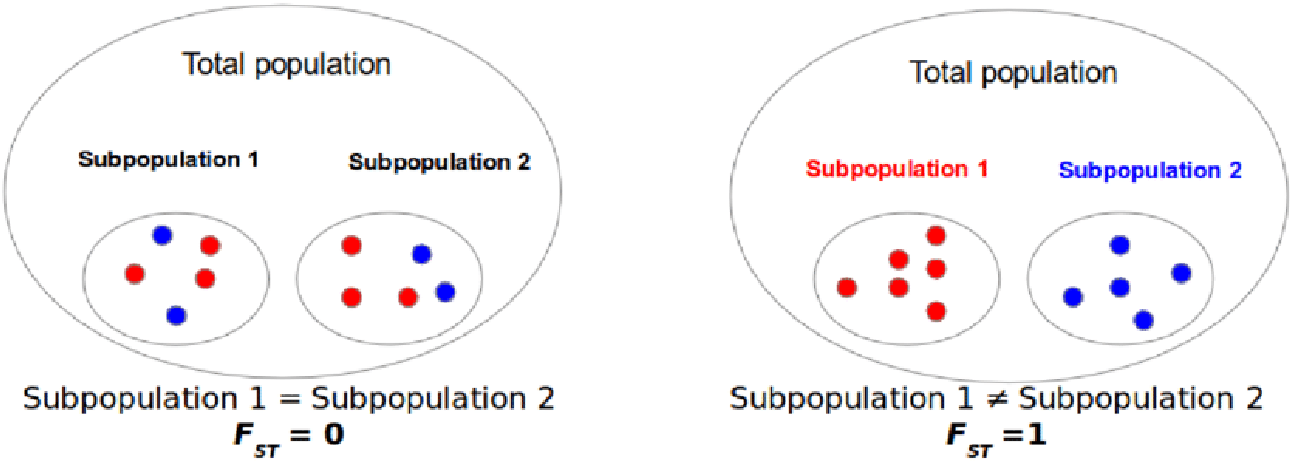
- The 1000 individuals with the lowest PC score were compared with the 1000 individuals with the highest PC score
- Using the 500 000 SNPs it is estimated what the expected divergence is under genetic drift
- For each SNP we then compute whether the divergence is significantly greater than expected under genetic drift (i.e., whether they are under selection)



Population Structure, Migration, and Diversifying Selection in the Netherlands
(Abdellaoui et al, 2013)

Using PCs and F_{st} to identify loci under selection

- Bayescan 2.1 was used to calculate F_{st} values for all SNPs and identify outliers with a Bayesian approach
- F_{st}‘s were computed between top 1000 and bottom 1000 individuals for each ancestry-informative PC



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- F_{st} is then decomposed into 2 components:
  - population-specific component (β), shared by all loci
  - locus-specific component (α), shared by both populations
- If α is significantly different from 0, the locus may have been under selection:
  - α > 0 = diversifying selection
  - α < 0 = balancing selection (power to detect this is weak)
- Significance is based on FDR corrected q-value (< .05)

Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

Using PCs and F_{st} to identify loci under selection: results

- 499,849 SNPs in total (51.4% within genes):
  - PC1 (North-South): 273 significant SNPs (59% within 88 genes)
  - PC2 (East-West): 172 significant SNPs (58.1% within 55 genes)
  - PC3 (Middle-Band): 100 significant SNPs (75% within 41 genes)

- Several of the genes with significant SNPs have been observed to be strongly differentiated within Europe in previous studies:
  - *LCT* (PC1), *HERC2* (PC1), *CADPS* (PC1), *IRF1* (PC1), *SLC44A5* (PC1), *R3HDM1* (PC1), *ACOXL* (PC3), and *BTBD9* (PC3)

HERC2 & eye color

- Highest F_{st} observed in PC1 for SNP in HERC2 gene (rs8039195). Strongly associated with eye color in several GWASs ($p = 7.8 \times 10^{-112}$ in current dataset).

HERC2 & eye color

- Highest F_{st} observed in PC1 for SNP in HERC2 gene (rs8039195). Strongly associated with eye color in several GWASs (p = 7.8 × 10^{-112} in current dataset).
- F_{st}'s were calculated for 3495 SNPs in and around HERC2 between Northern European populations (British and Finnish) and Southern European populations (Iberian and Toscan) from 1000 Genomes.

Population	rs8039195 (HERC2)		
	CC	CT	TT
Finnish	.0	6.5	93.5
Northern Dutch	.4	13.1	86.5
British	1.2	21.4	77.4
Southern Dutch	2.3	23.9	73.7
Iberian	.0	50.0	50.0
Toscan	16.8	42.1	41.1

Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

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Iberian	.0	50.0	50.0
Toscan	16.8	42.1	41.1

- Of the SNPs genotyped in the Dutch, rs8039195 had the highest F_{st}.

Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

HERC2 & eye color

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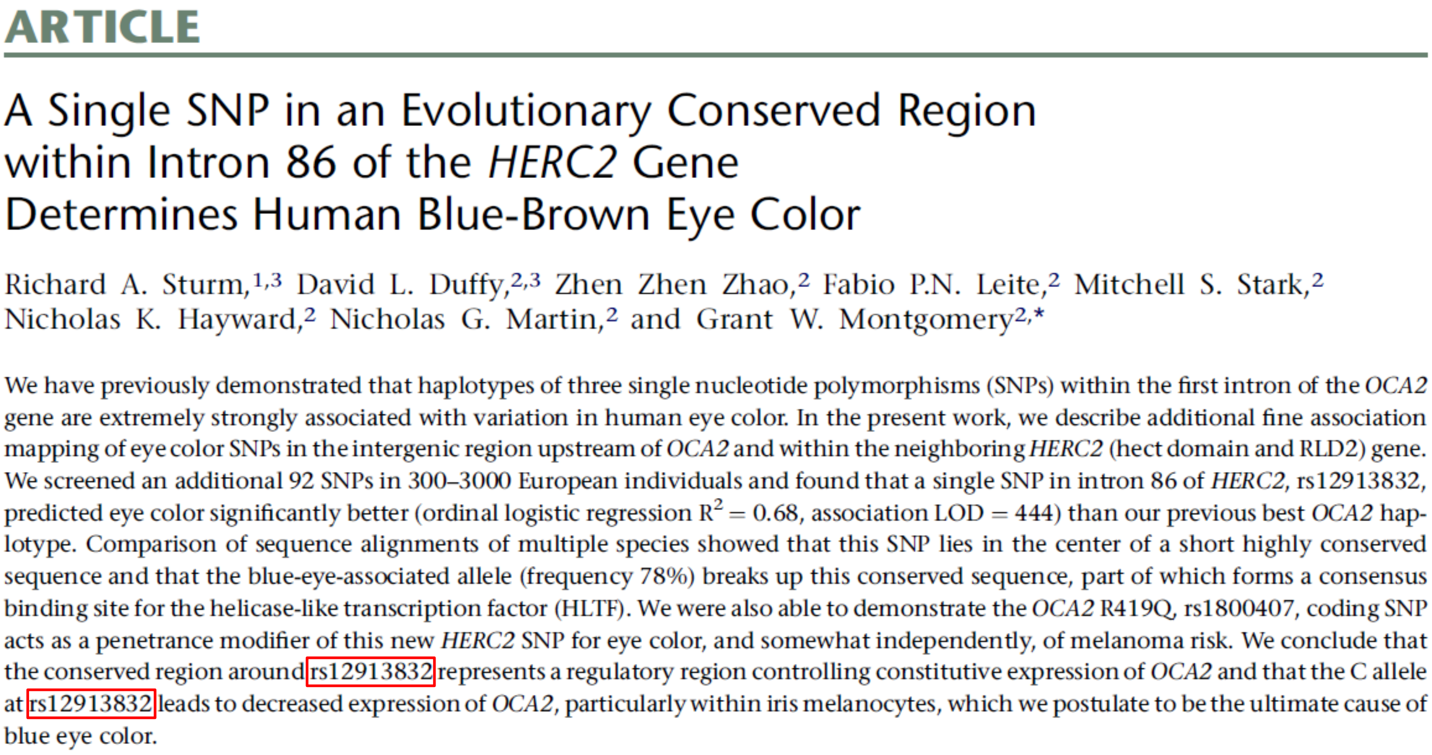
Iberian	.0	50.0	50.0
Toscan	16.8	42.1	41.1

- Of the SNPs genotyped in the Dutch, rs8039195 had the highest F_{st}.
- Of all 3495 SNPs, highest F_{st} was observed for rs12913832 (LD with rs8039195: $r^2 = .394$, $D' = .993$), the SNP with the largest effect on human blue/brown eye color.

Population Structure, Migration, and Diversifying Selection in the Netherlands
(Abdellaoui et al, 2013)

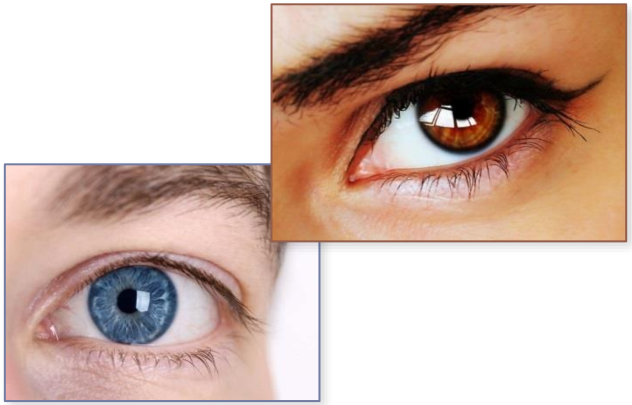


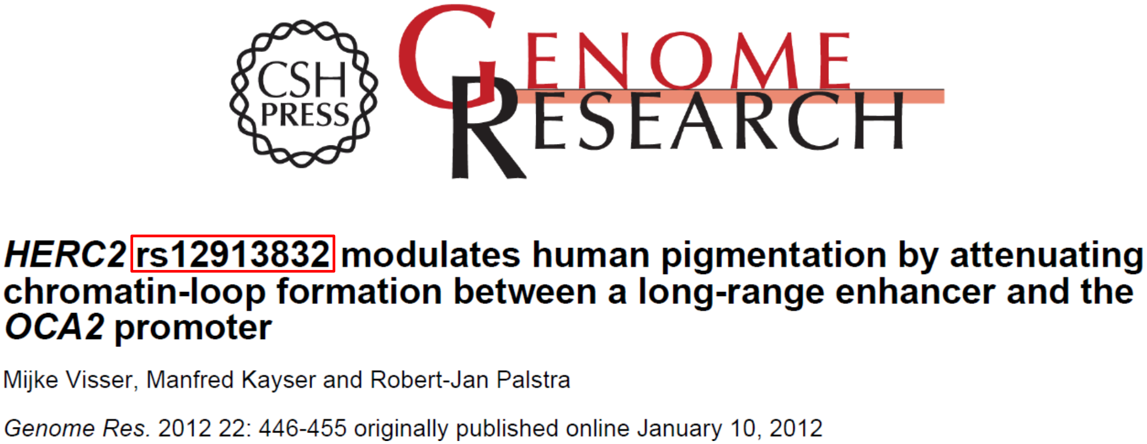
ARTICLE

A Single SNP in an Evolutionary Conserved Region within Intron 86 of the *HERC2* Gene Determines Human Blue-Brown Eye Color

Richard A. Sturm,[1,3] David L. Duffy,[2,3] Zhen Zhen Zhao,[2] Fabio P.N. Leite,[2] Mitchell S. Stark,[2] Nicholas K. Hayward,[2] Nicholas G. Martin,[2] and Grant W. Montgomery[2,*]

We have previously demonstrated that haplotypes of three single nucleotide polymorphisms (SNPs) within the first intron of the *OCA2* gene are extremely strongly associated with variation in human eye color. In the present work, we describe additional fine association mapping of eye color SNPs in the intergenic region upstream of *OCA2* and within the neighboring *HERC2* (hect domain and RLD2) gene. We screened an additional 92 SNPs in 300–3000 European individuals and found that a single SNP in intron 86 of *HERC2*, rs12913832, predicted eye color significantly better (ordinal logistic regression $R^2 = 0.68$, association LOD = 444) than our previous best *OCA2* haplotype. Comparison of sequence alignments of multiple species showed that this SNP lies in the center of a short highly conserved sequence and that the blue-eye-associated allele (frequency 78%) breaks up this conserved sequence, part of which forms a consensus binding site for the helicase-like transcription factor (HLTF). We were also able to demonstrate the *OCA2* R419Q, rs1800407, coding SNP acts as a penetrance modifier of this new *HERC2* SNP for eye color, and somewhat independently, of melanoma risk. We conclude that the conserved region around rs12913832 represents a regulatory region controlling constitutive expression of *OCA2* and that the C allele at rs12913832 leads to decreased expression of *OCA2*, particularly within iris melanocytes, which we postulate to be the ultimate cause of blue eye color.





CSH PRESS GENOME RESEARCH

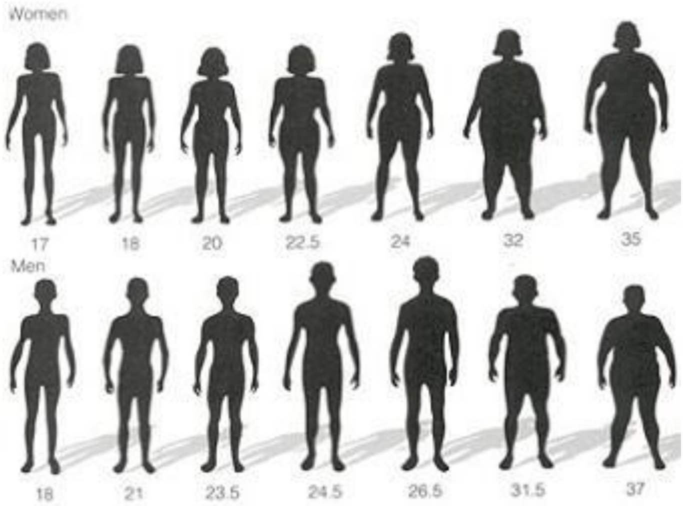
HERC2 rs12913832 modulates human pigmentation by attenuating chromatin-loop formation between a long-range enhancer and the *OCA2* promoter

Mijke Visser, Manfred Kayser and Robert-Jan Palstra

Genome Res. 2012 22: 446-455 originally published online January 10, 2012

Using PCs and F_{st} to identify loci under selection: results

- Other notable genes include:
  - FTO (PC1): has been associated with BMI and obesity many times.



Using PCs and F_{st} to identify loci under selection: results

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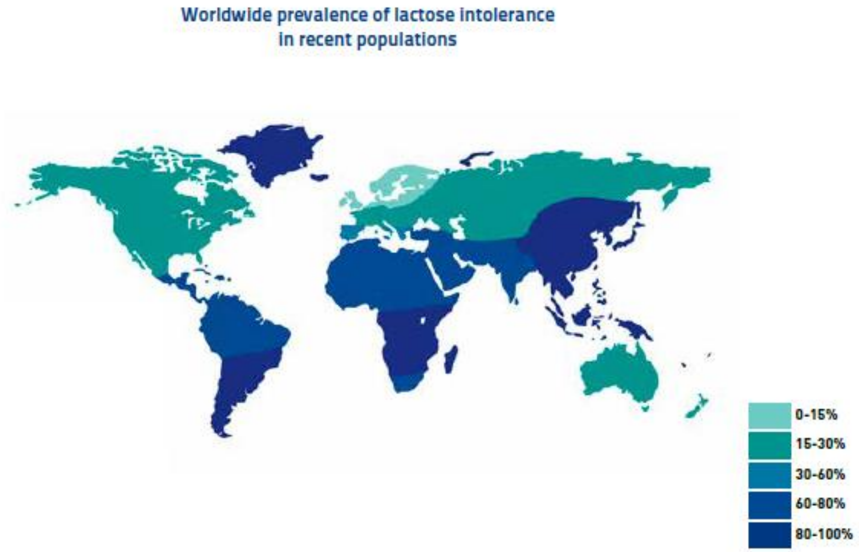
  - LCT (PC1): influences the ability to digest lactose into adulthood.


Worldwide prevalence of lactose intolerance in recent populations
0-15%
15-30%
30-60%
60-80%
80-100%

Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

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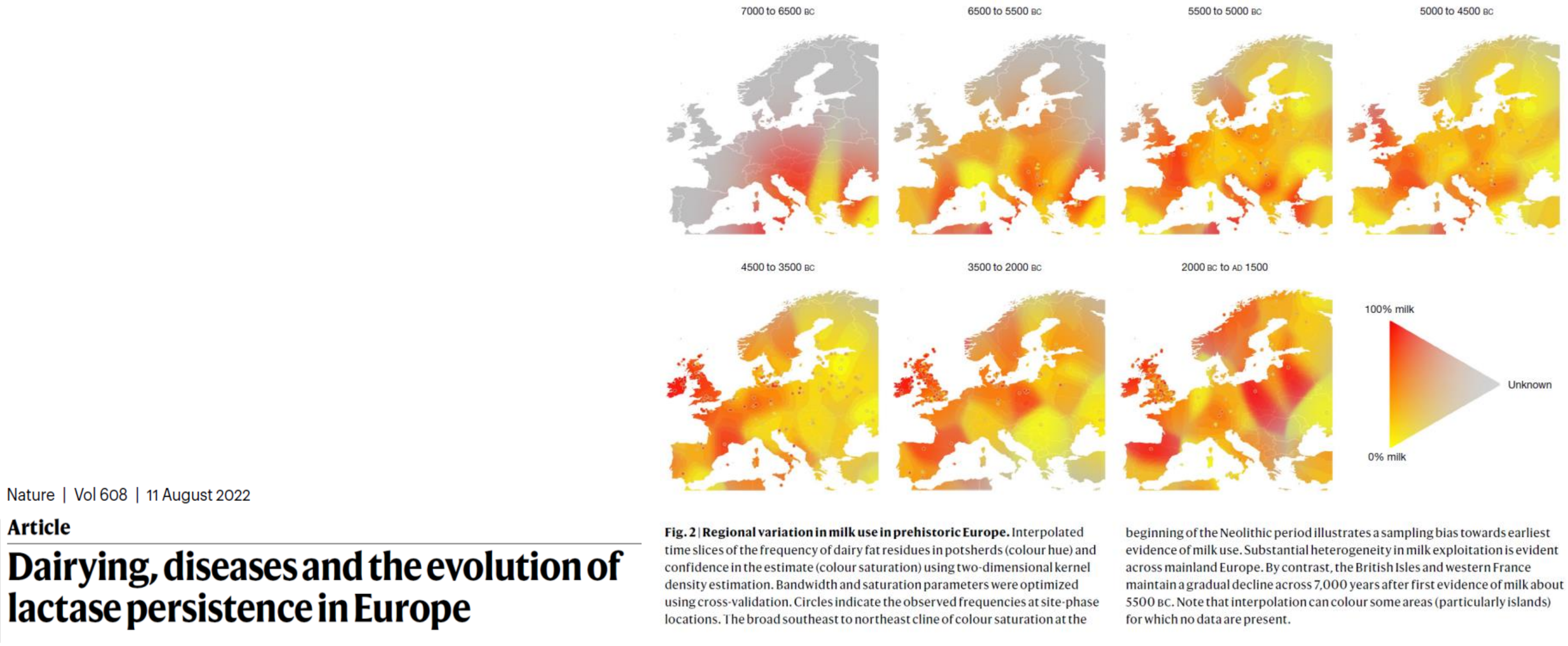

Nature | Vol 608 | 11 August 2022

Article

Dairying, diseases and the evolution of lactase persistence in Europe

Fig. 2 | Regional variation in milk use in prehistoric Europe. Interpolated time slices of the frequency of dairy fat residues in potsherds (colour hue) and confidence in the estimate (colour saturation) using two-dimensional kernel density estimation. Bandwidth and saturation parameters were optimized using cross-validation. Circles indicate the observed frequencies at site-phase locations. The broad southeast to northeast cline of colour saturation at the beginning of the Neolithic period illustrates a sampling bias towards earliest evidence of milk use. Substantial heterogeneity in milk exploitation is evident across mainland Europe. By contrast, the British Isles and western France maintain a gradual decline across 7,000 years after first evidence of milk about 5500 BC. Note that interpolation can colour some areas (particularly islands) for which no data are present.

Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

Using PCs and F_{st} to identify loci under selection: results

- Other notable genes include:
  - FTO (PC1): has been associated with BMI and obesity many times.
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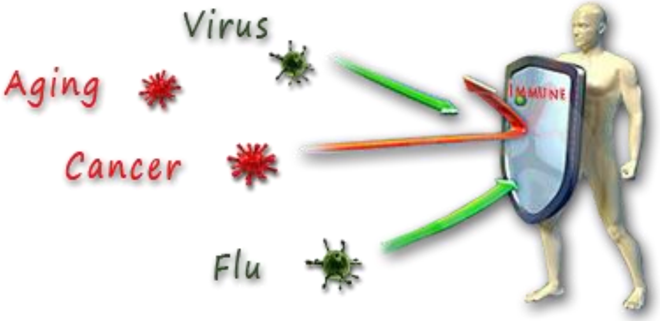
  - HCP5 (HLA Complex P5 gene) from the MHC region. One of two genes that appear in multiple PCs (PC1 & PC2), and plays a role in the immune system. Strong divergence of genes from the HLA complex has been observed in many human populations. Other immunity-related genes that showed significant signals of selection in this study as well as previous studies are: *IRF1* (PC1), *ACE* (PC1), *LRRC4C* (PC2), *PLCL1* (PC3), and *HSPD1* (PC3).



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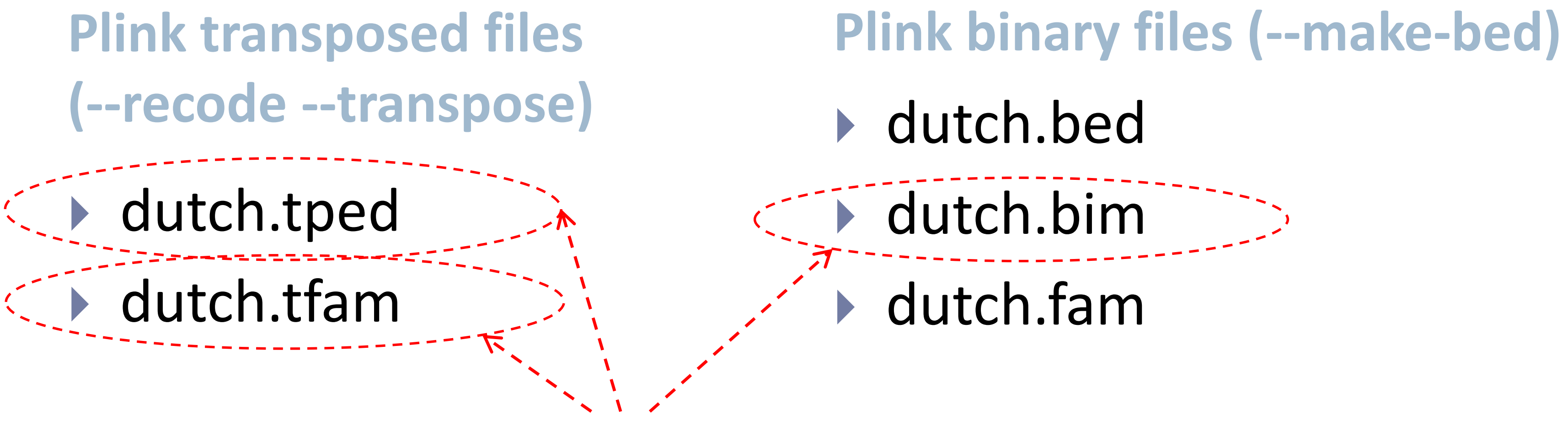
Bayescan can be found here: http://cmpg.unibe.ch/software/bayescan/

Population Structure, Migration, and Diversifying Selection in the Netherlands (Abdellaoui et al, 2013)

Converting plink files to Bayescan format with the script convert_to_bayescan.pl



Plink transposed files (--recode --transpose)

- dutch.tped
- dutch.tfam

Plink binary files (--make-bed)

- dutch.bed
- dutch.bim
- dutch.fam

convert_to_bayescan.pl needs

- The populations you want to compare have to be coded as 1 and 2 in the phenotype column (6th column) of the .tfam file.
- Use --pheno to update phenotypes : http://pngu.mgh.harvard.edu/~purcell/plink/data.shtml#pheno

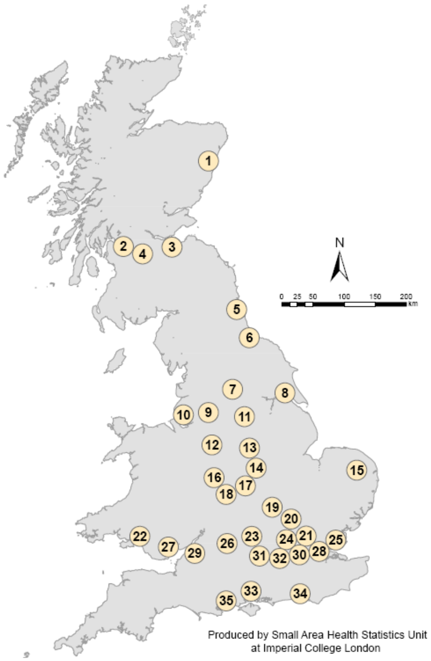
Usage:

```
 perl convert_to_bayescan.pl dutch dutch_outputfile
```

Geographic Distribution of Ancestry in UK Biobank

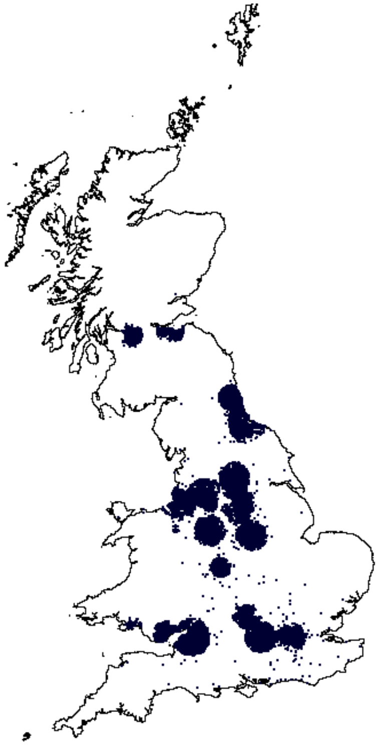
biobank uk

Improving the health of future generations

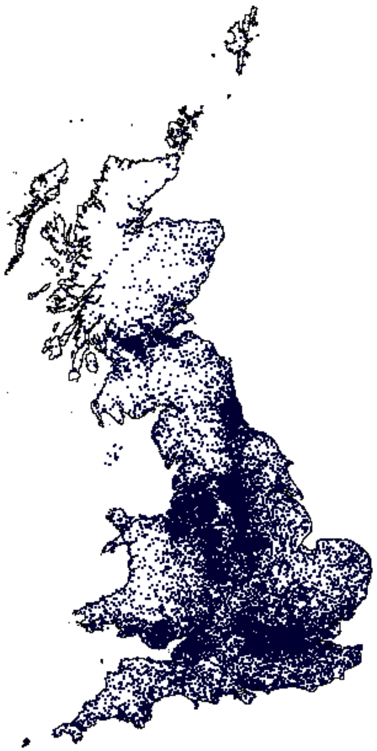


Produced by Small Area Health Statistics Unit
at Imperial College London

Assessment centers



Current living address



Place of birth

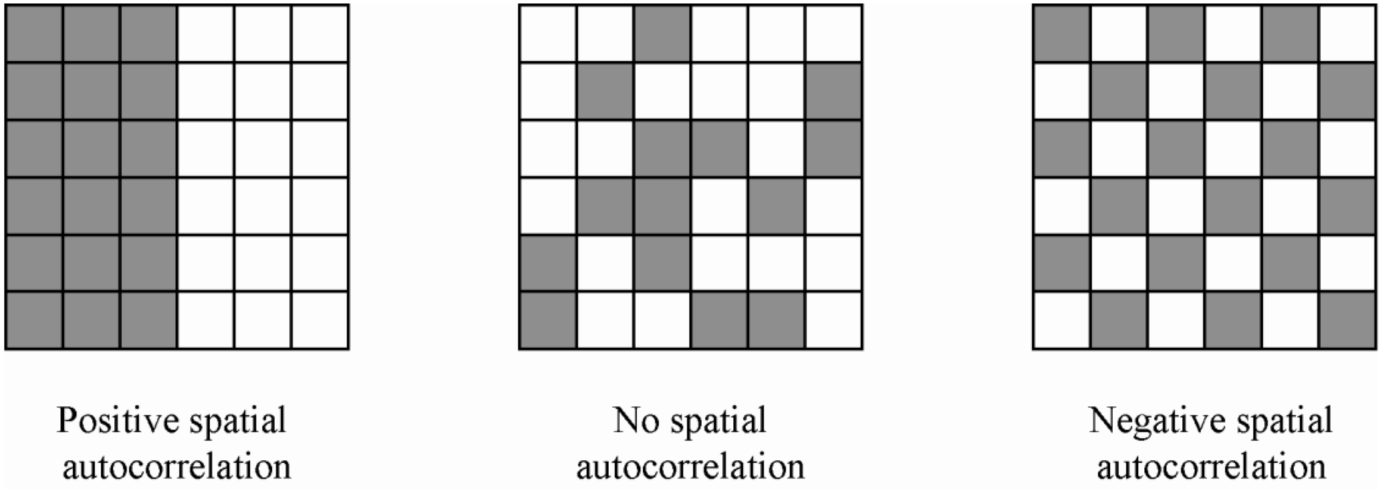
Moran’s *I*

A measure of spatial autocorrelation

Moran’s *I* = 1

Moran’s *I* = 0

Moran’s *I* = -1



Positive spatial autocorrelation

No spatial autocorrelation

Negative spatial autocorrelation

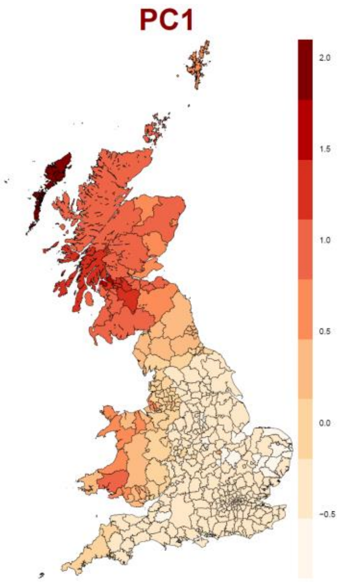
Clustered together

Spatially random

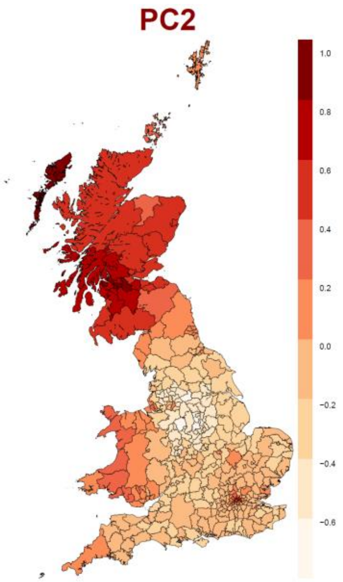
Dispersed

Ancestry differences in Great Britain

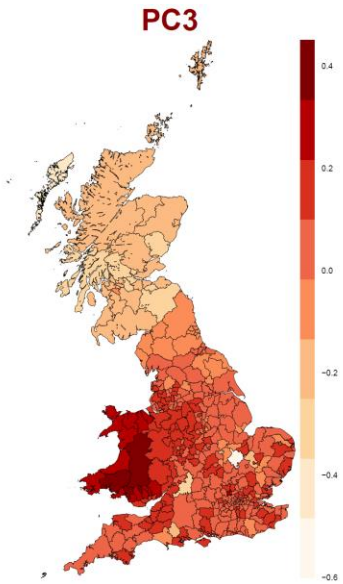
- Local authorities (378 areas) – evenly spaced cut-offs



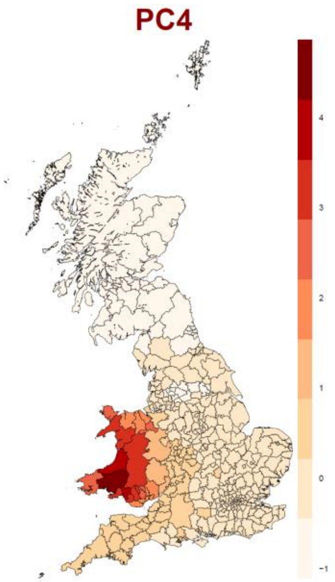
Moran's I = .77
$p < 10^{-4}$



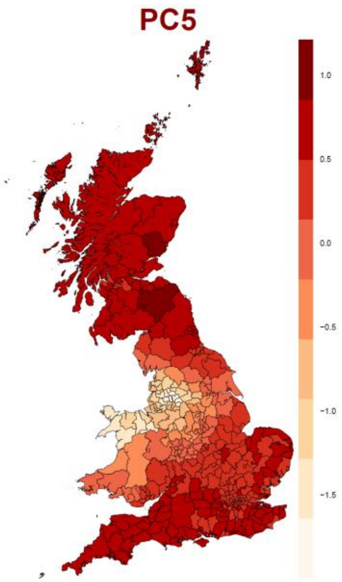
Moran's I = .83
$p < 10^{-4}$



Moran's I = .58
$p < 10^{-4}$



Moran's I = .84
$p < 10^{-4}$



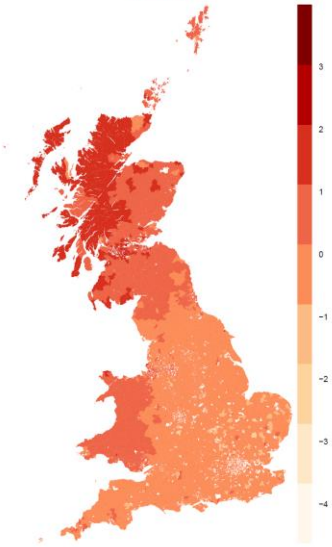
Moran's I = .93
$p < 10^{-4}$

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

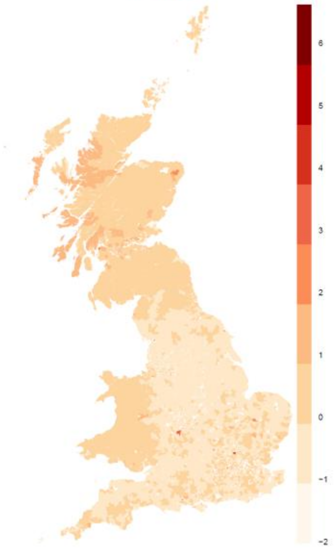
- MSOA: 8,436 areas – evenly spaced cut-offs

PC1



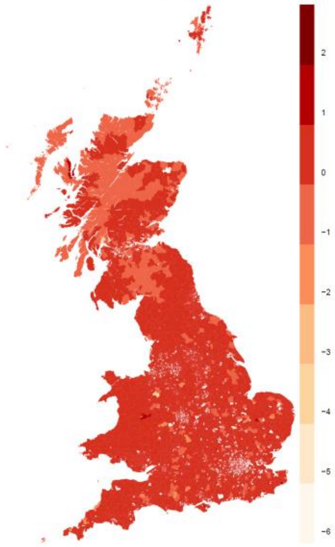
Moran's *I* = .77
$p < 10^{-4}$

PC2



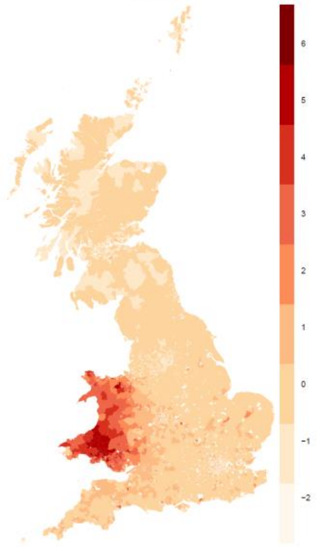
Moran's *I* = .83
$p < 10^{-4}$

PC3



Moran's *I* = .58
$p < 10^{-4}$

PC4



Moran's *I* = .84
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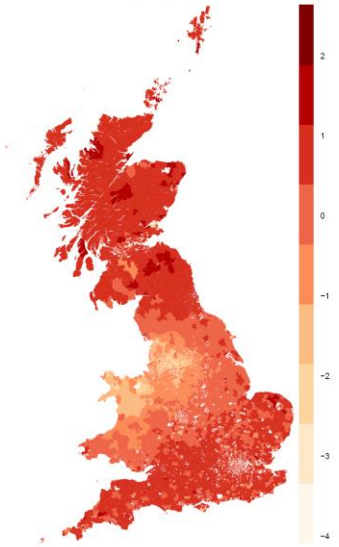
PC5



Moran's *I* = .93
$p < 10^{-4}$

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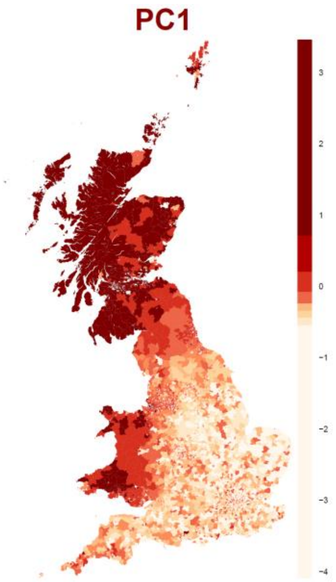
Ancestry differences in Great Britain

- MSOA: 8,436 areas – class-interval cut-offs



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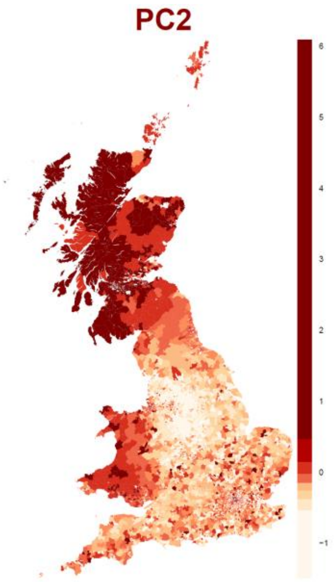
$p < 10^{-4}$



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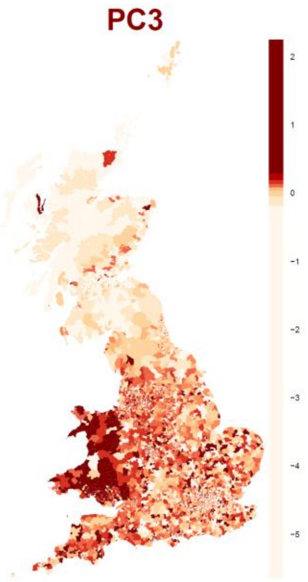
$p < 10^{-4}$



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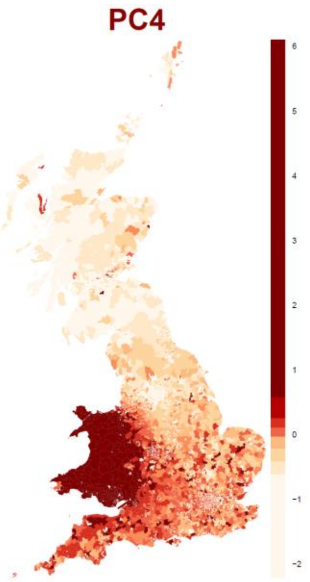

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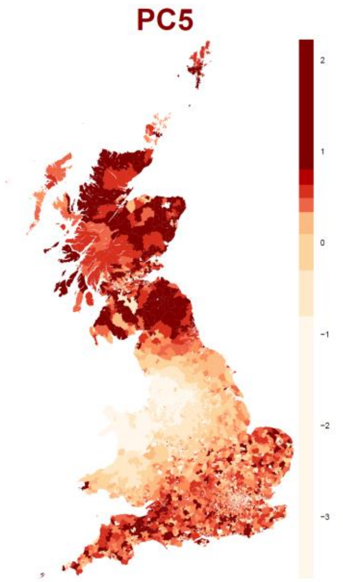

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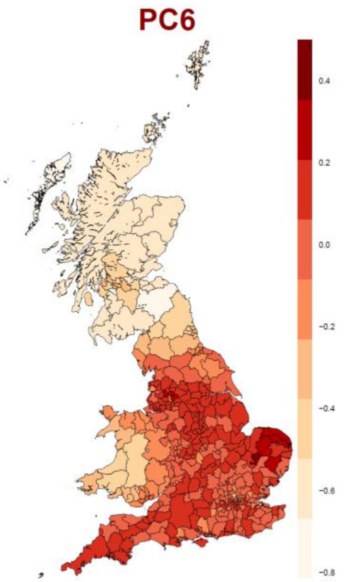
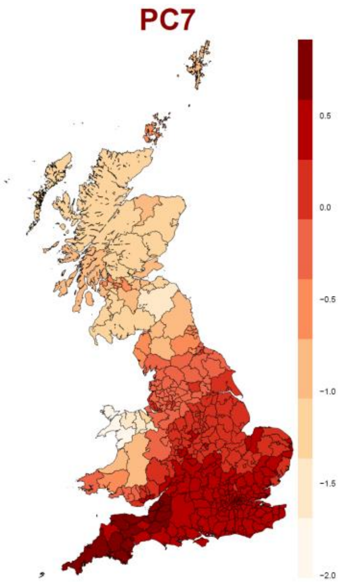
Ancestry differences in Great Britain

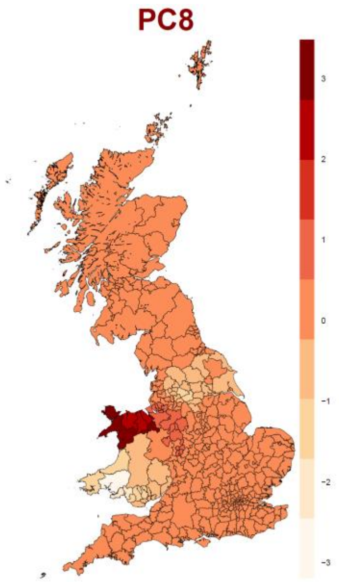
- Local authorities: 378 areas – evenly spaced cut-offs



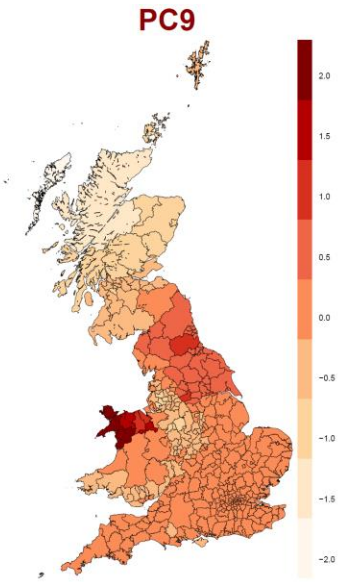
Moran's I = .70
$p < 10^{-4}$



Moran's I = .78
$p < 10^{-4}$



Moran's I = .61
$p < 10^{-4}$



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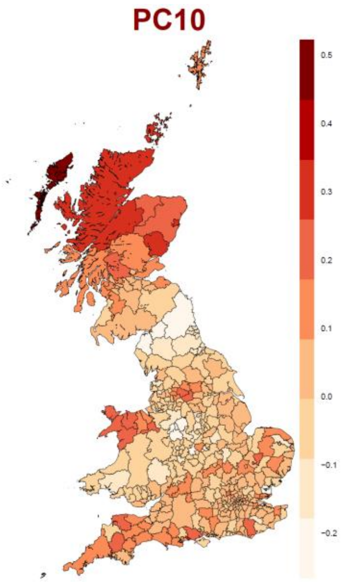
$p < 10^{-4}$



Moran's I = .43
$p < 10^{-4}$

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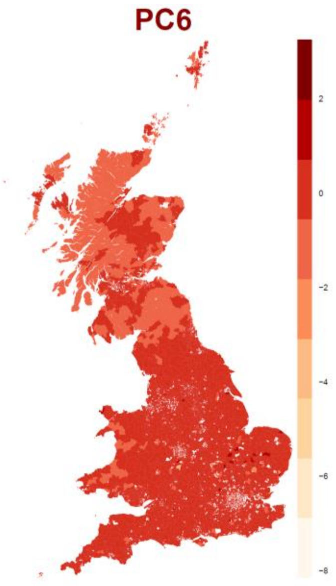
Ancestry differences in Great Britain

- MSOA: 8,436 areas – evenly spaced cut-offs



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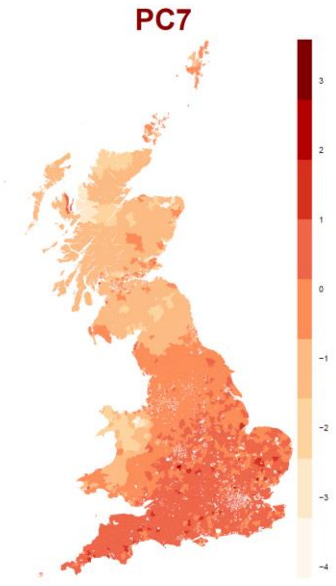
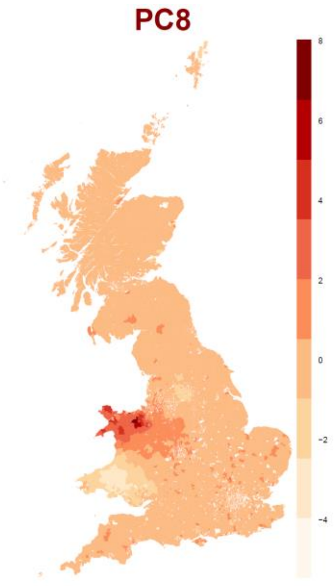
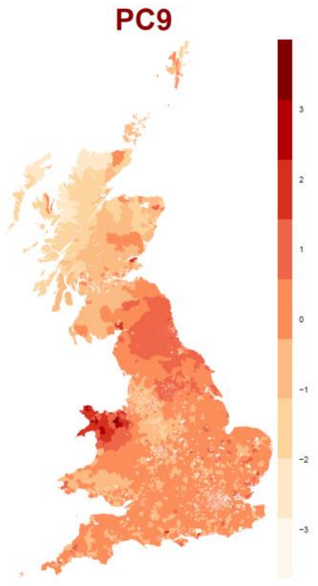
$p < 10^{-4}$



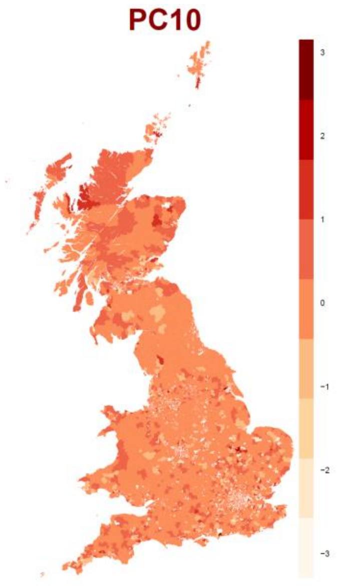
Moran's *I* = .78
$p < 10^{-4}$



Moran's *I* = .61
$p < 10^{-4}$



Moran's *I* = .61
$p < 10^{-4}$



Moran's *I* = .43
$p < 10^{-4}$

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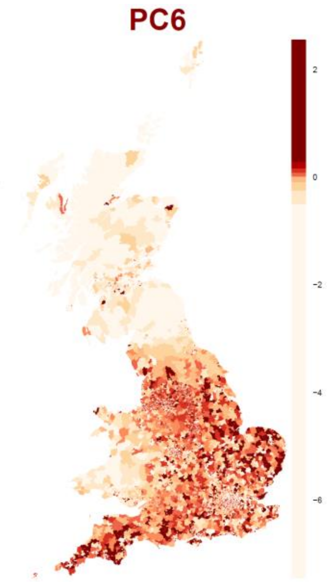
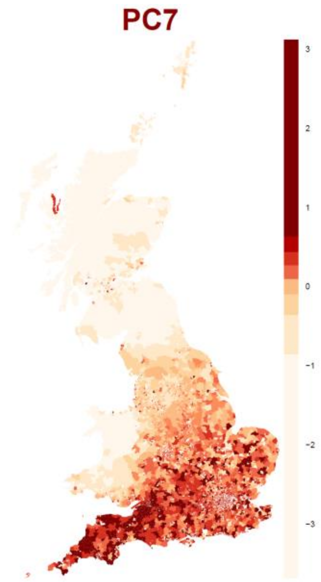
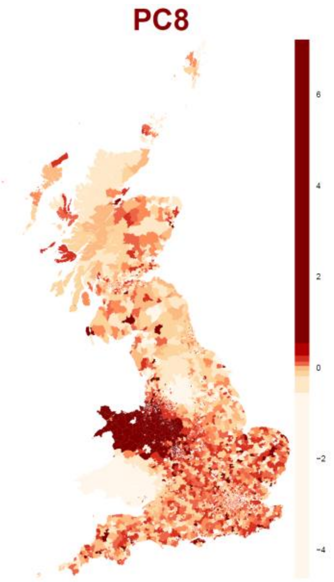


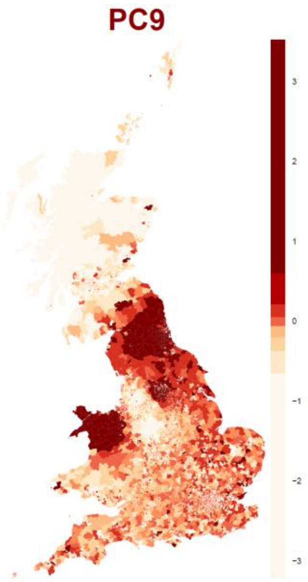
Moran's *I* = .70
***p* < 10^{-4}**



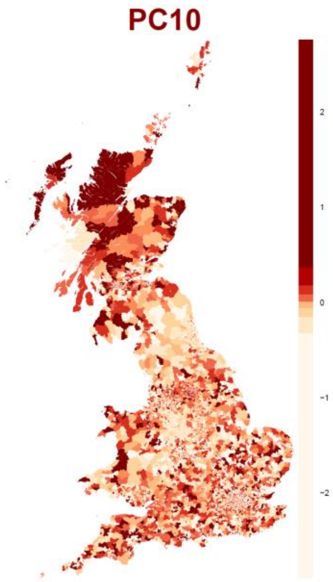
Moran's *I* = .78
***p* < 10^{-4}**



Moran's *I* = .61
***p* < 10^{-4}**



Moran's *I* = .61
***p* < 10^{-4}**



Moran's *I* = .43
***p* < 10^{-4}**

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

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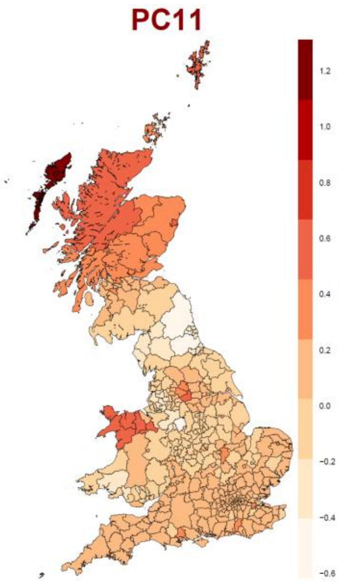
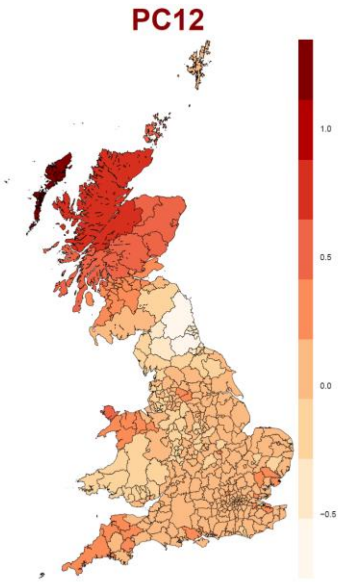
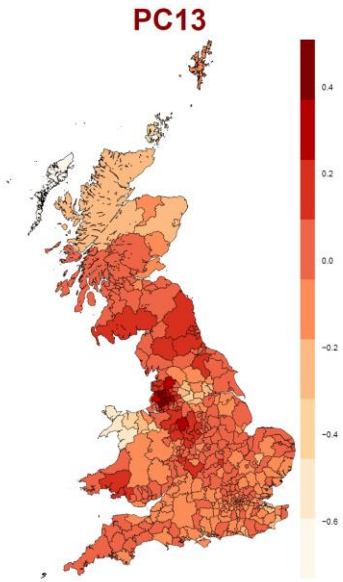


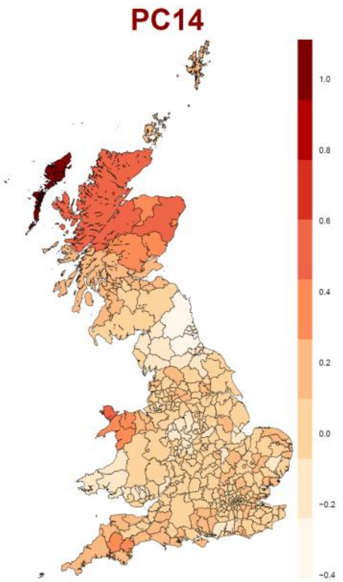
Moran's I = .57
$p < 10^{-4}$



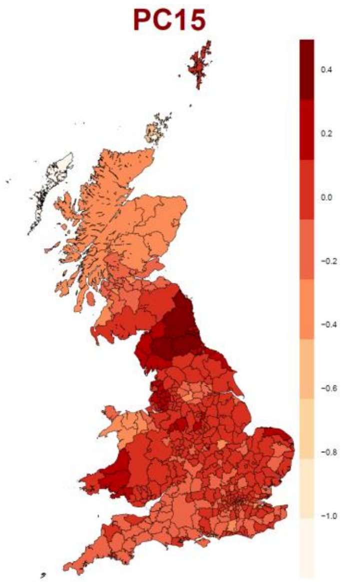
Moran's I = .60
$p < 10^{-4}$



Moran's I = .50
$p < 10^{-4}$



Moran's I = .47
$p < 10^{-4}$



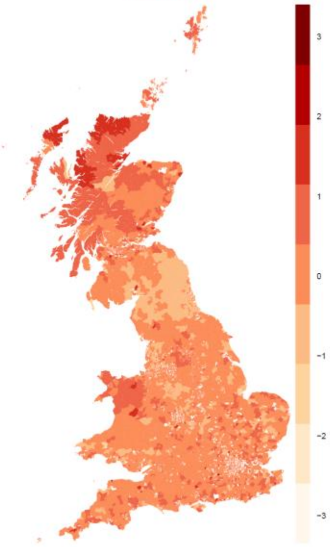
Moran's I = .49
$p < 10^{-4}$

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

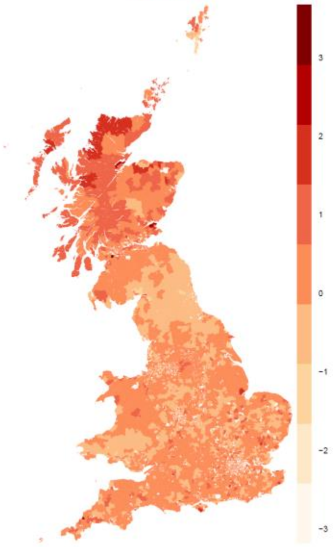
- MSOA: 8,436 areas – evenly spaced cut-offs

PC11



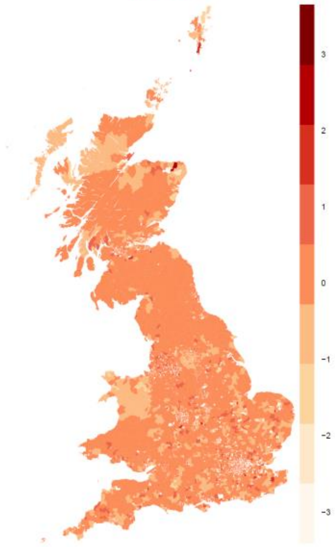
Moran's I = .57
$p < 10^{-4}$

PC12



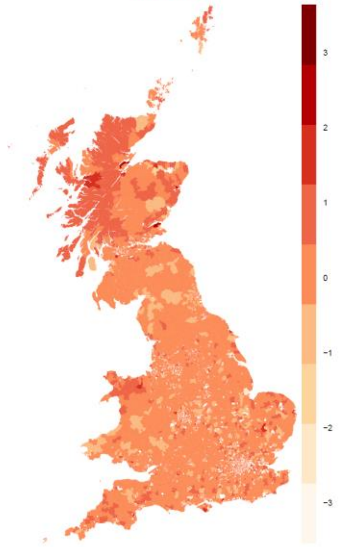
Moran's I = .60
$p < 10^{-4}$

PC13



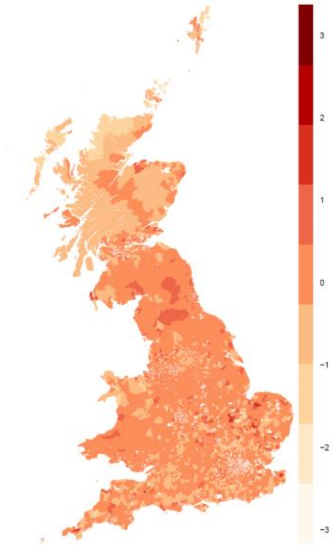
Moran's I = .50
$p < 10^{-4}$

PC14



Moran's I = .47
$p < 10^{-4}$

PC15



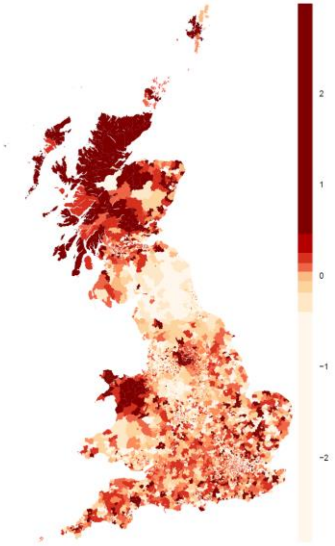
Moran's I = .49
$p < 10^{-4}$

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

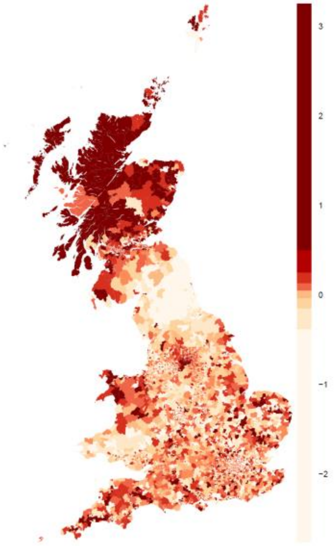
- MSOA: 8,436 areas – class-interval cut-offs

PC11



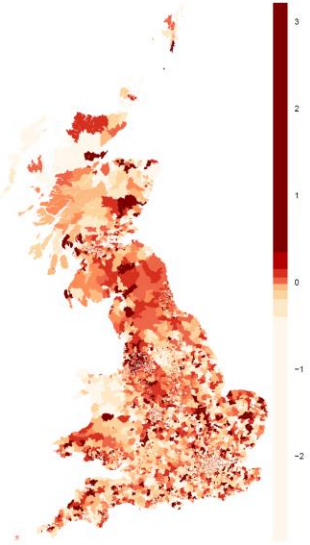
Moran's I = .57
***p* < 10^{-4}**

PC12



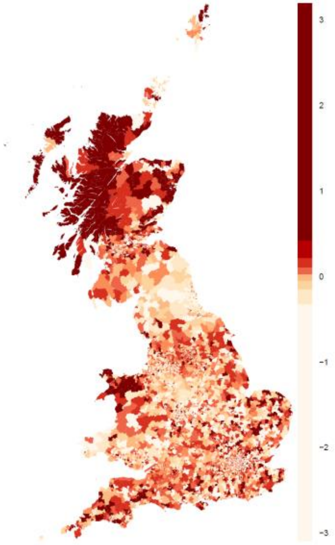
Moran's I = .60
***p* < 10^{-4}**

PC13



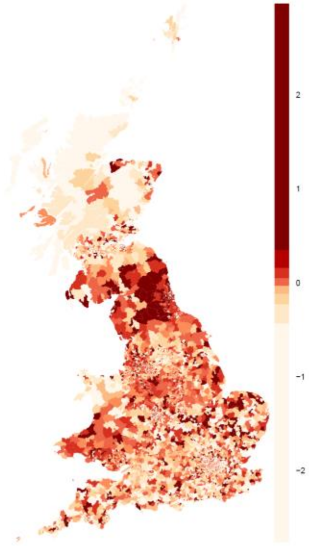
Moran's I = .50
***p* < 10^{-4}**

PC14



Moran's I = .47
***p* < 10^{-4}**

PC15



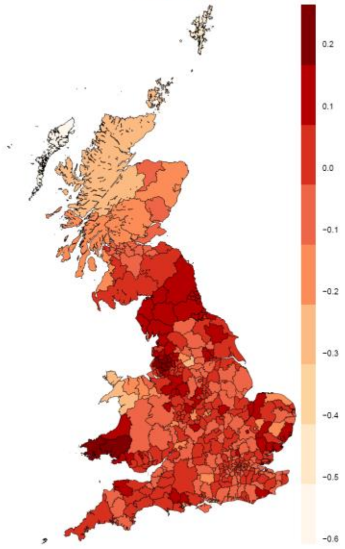
Moran's I = .49
***p* < 10^{-4}**

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

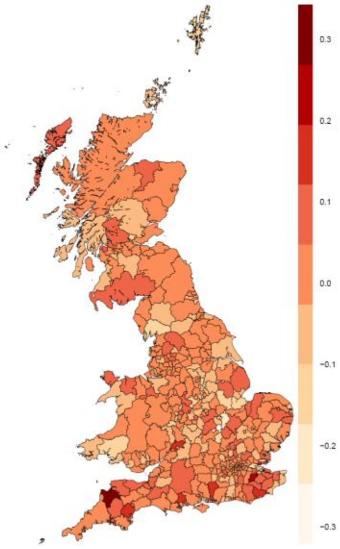
- Local authorities: 378 areas – evenly spaced cut-offs

PC16



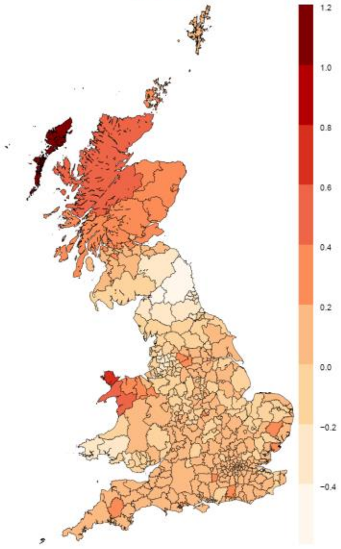
Moran's *I* = .30
***p* < 10^{-4}**

PC17



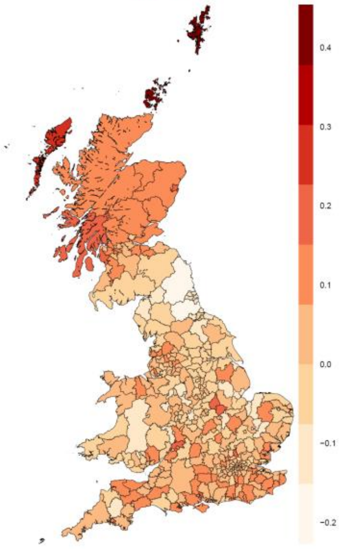
Moran's *I* = .10
p = .002

PC18



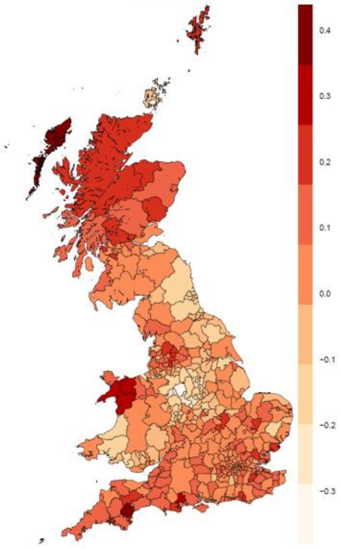
Moran's *I* = .53
***p* < 10^{-4}**

PC19



Moran's *I* = .25
***p* < 10^{-4}**

PC20



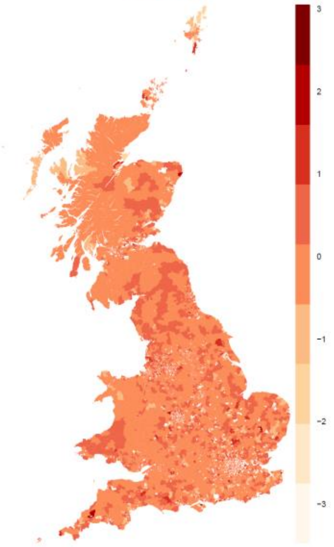
Moran's *I* = .56
***p* < 10^{-4}**

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

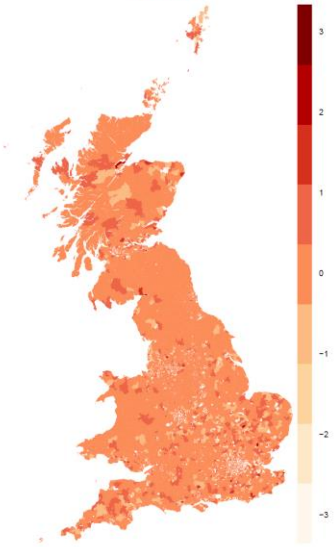
- MSOA: 8,436 areas – evenly spaced cut-offs

PC16



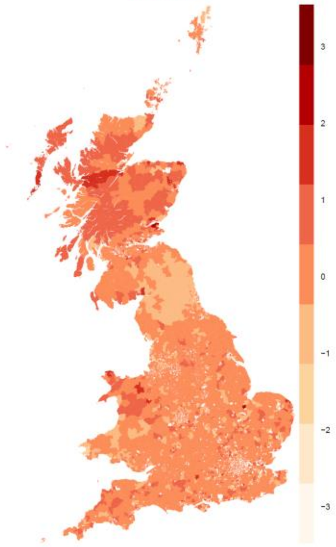
Moran's *I* = .30
$p < 10^{-4}$

PC17



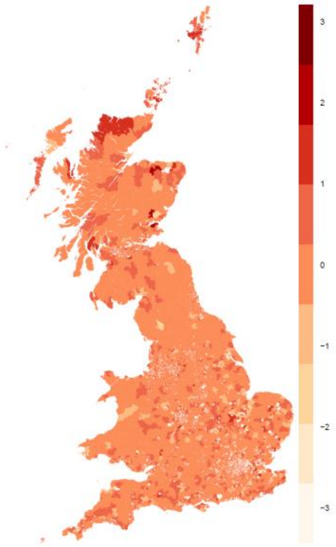
Moran's *I* = .10
$p = .002$

PC18



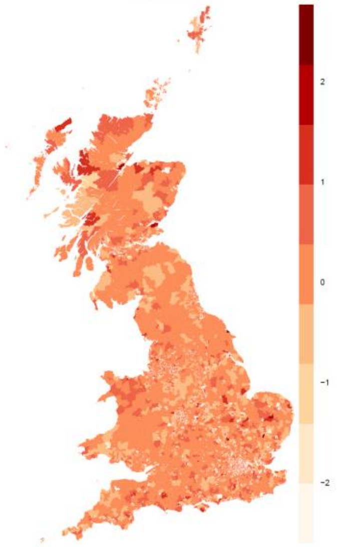
Moran's *I* = .53
$p < 10^{-4}$

PC19



Moran's *I* = .25
$p < 10^{-4}$

PC20



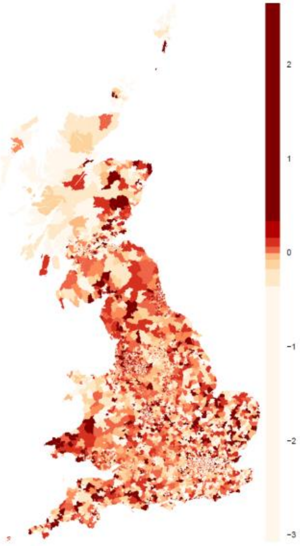
Moran's *I* = .56
$p < 10^{-4}$

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

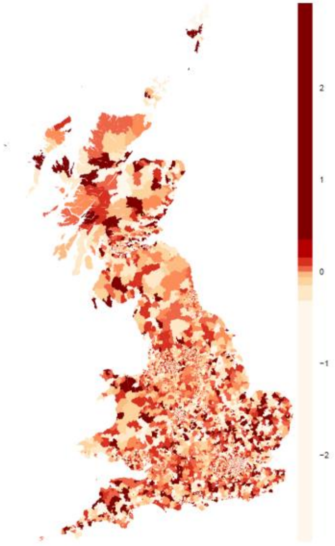
- MSOA: 8,436 areas – class-interval cut-offs

PC16



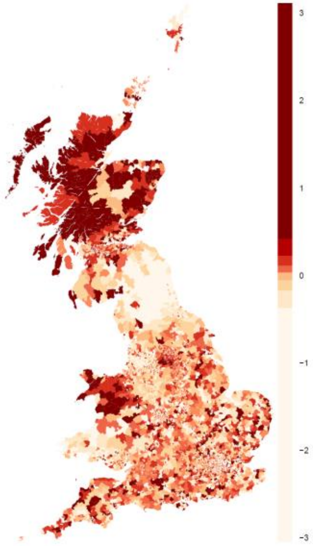
Moran's *I* = .30
$p < 10^{-4}$

PC17



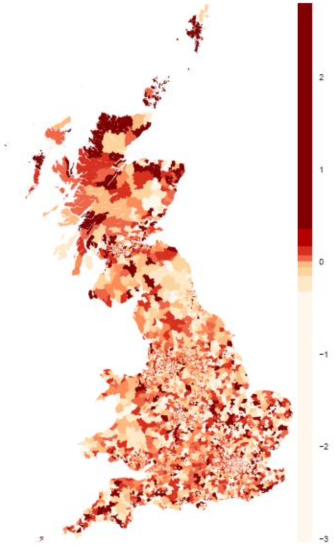
Moran's *I* = .10
p = .002

PC18



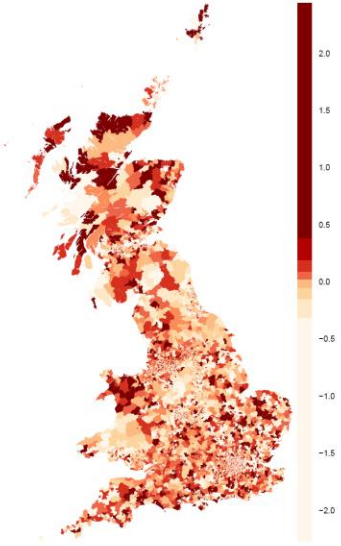
Moran's *I* = .53
$p < 10^{-4}$

PC19



Moran's *I* = .25
$p < 10^{-4}$

PC20



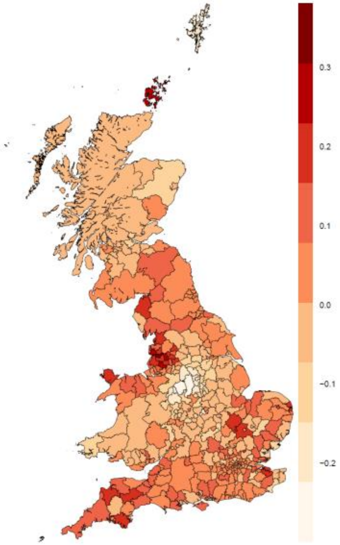
Moran's *I* = .56
$p < 10^{-4}$

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

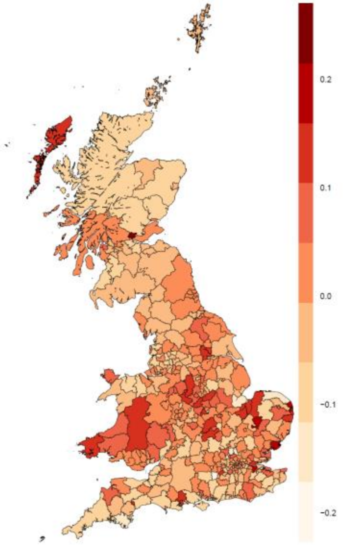
- Local authorities: 378 areas – evenly spaced cut-offs

PC21



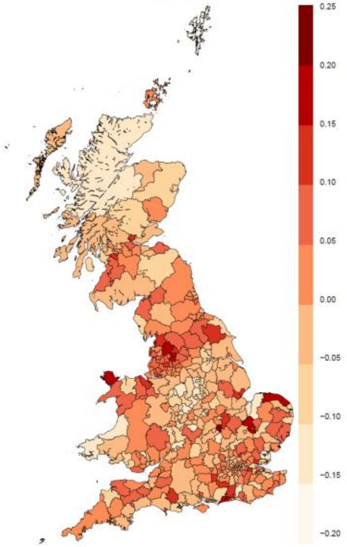
Moran's *I* = .51
***p* < 10^-4^**

PC22



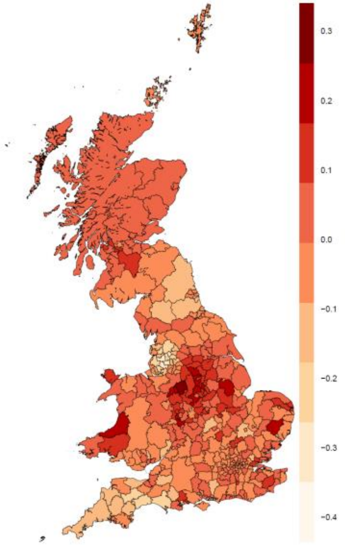
Moran's *I* = .11
***p* = 3 x 10^-4^**

PC23



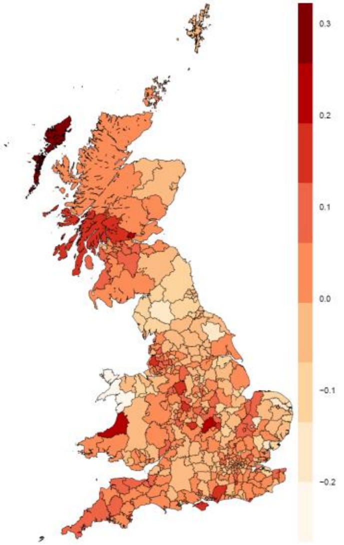
Moran's *I* = .22
***p* < 10^-4^**

PC24



Moran's *I* = .58
***p* < 10^-4^**

PC25



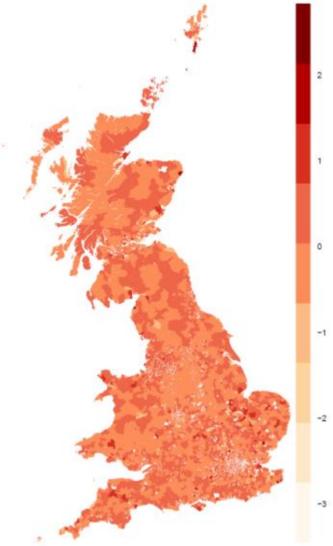
Moran's *I* = .23
***p* < 10^-4^**

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

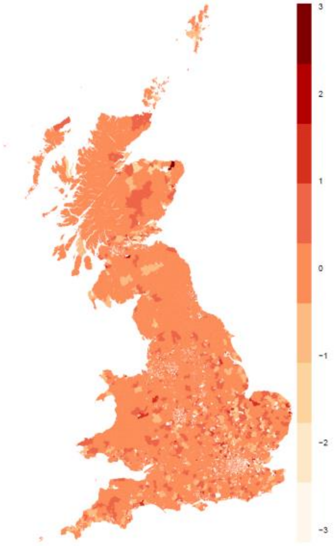
- MSOA: 8,436 areas – evenly spaced cut-offs

PC21



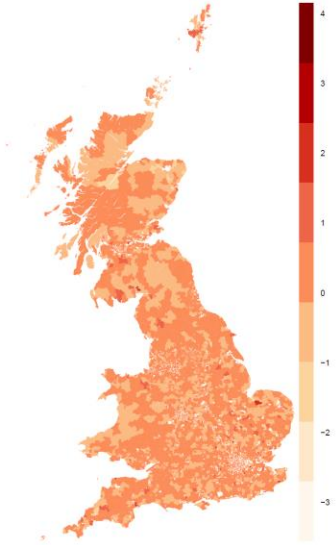
Moran's I = .51
$p < 10^{-4}$

PC22



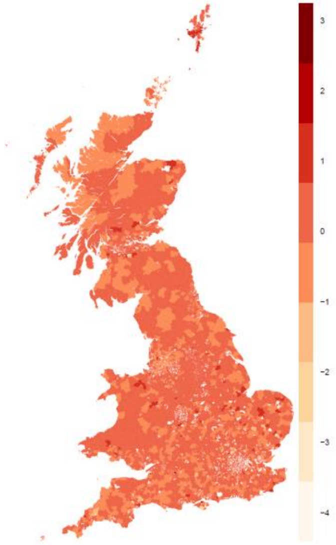
Moran's I = .11
$p = 3 \times 10^{-4}$

PC23



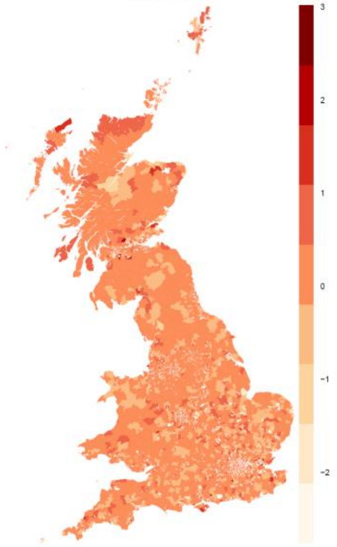
Moran's I = .22
$p < 10^{-4}$

PC24



Moran's I = .58
$p < 10^{-4}$

PC25



Moran's I = .23
$p < 10^{-4}$

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

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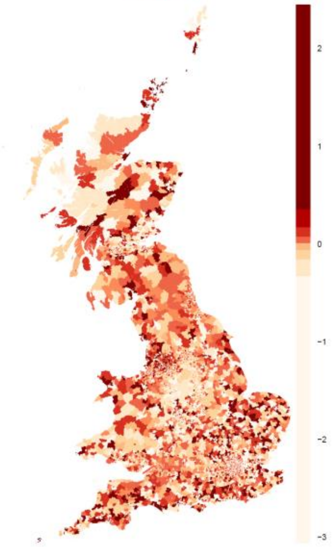
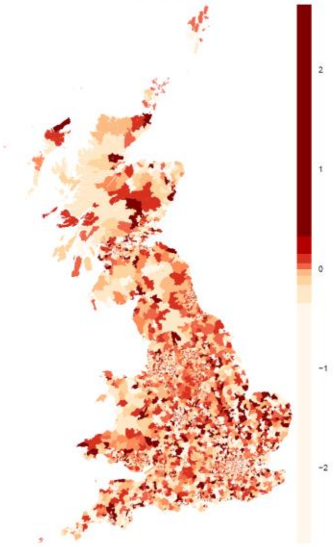
PC21



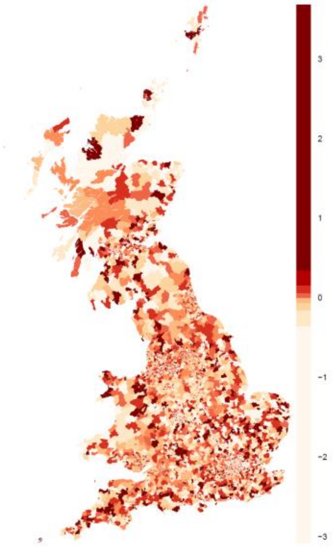
Moran's *I* = .51
***p* < 10^{-4}**

PC22



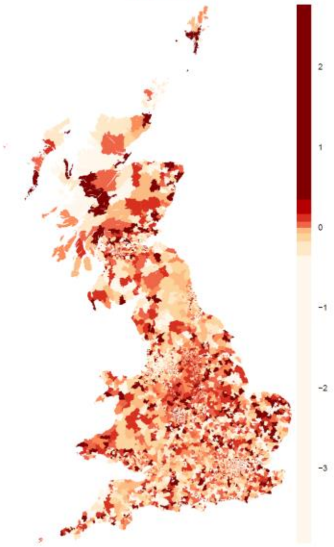
Moran's *I* = .11
***p* = 3 x 10^{-4}**

PC23



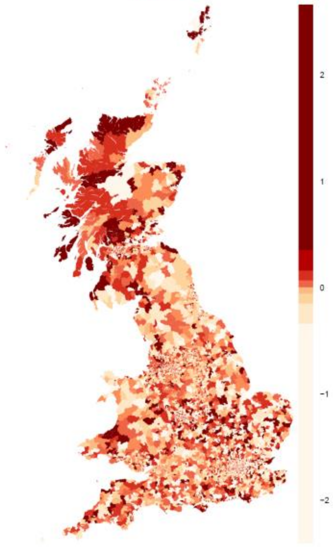
Moran's *I* = .22
***p* < 10^{-4}**

PC24



Moran's *I* = .58
***p* < 10^{-4}**

PC25

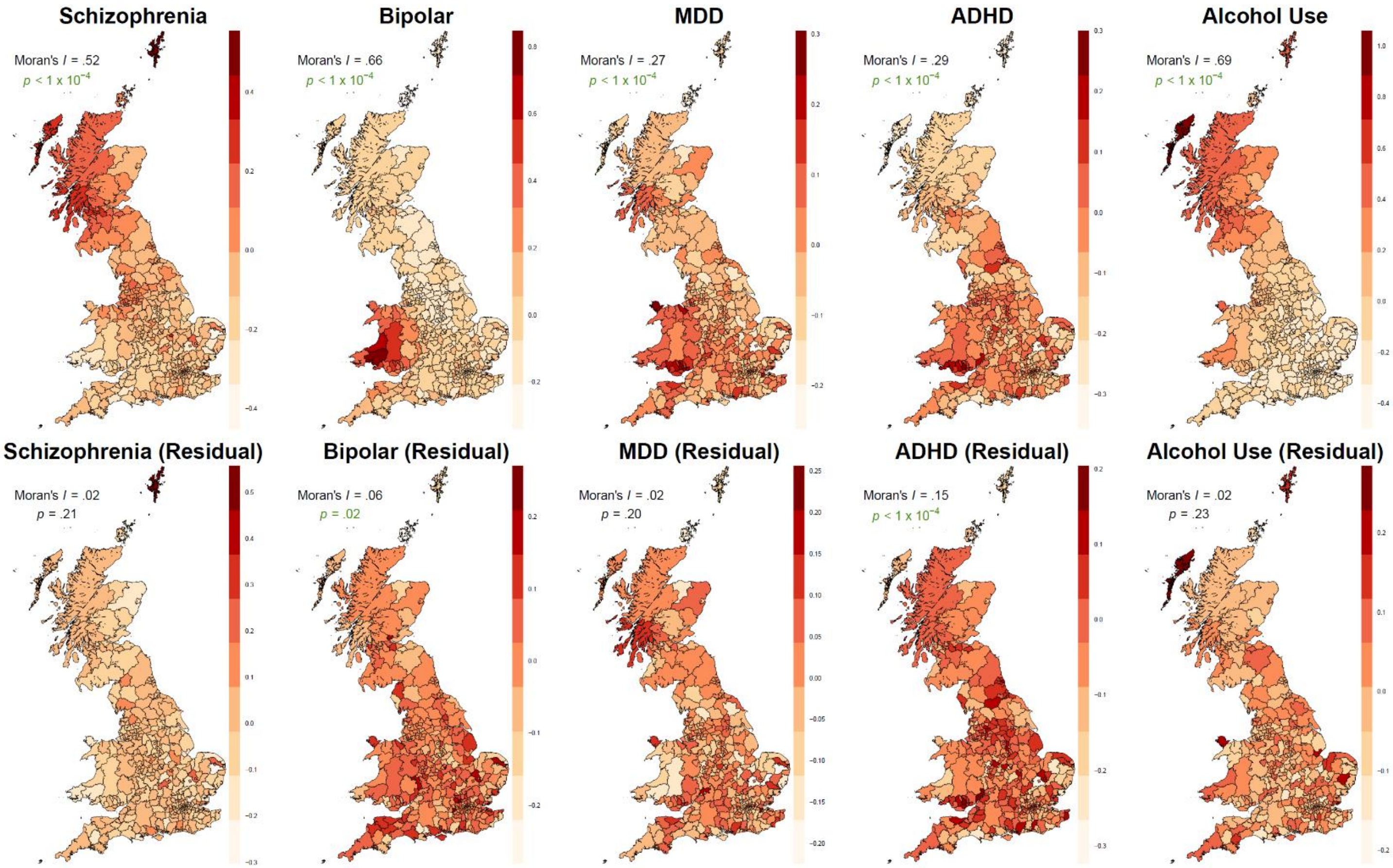


Moran's *I* = .23
***p* < 10^{-4}**

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

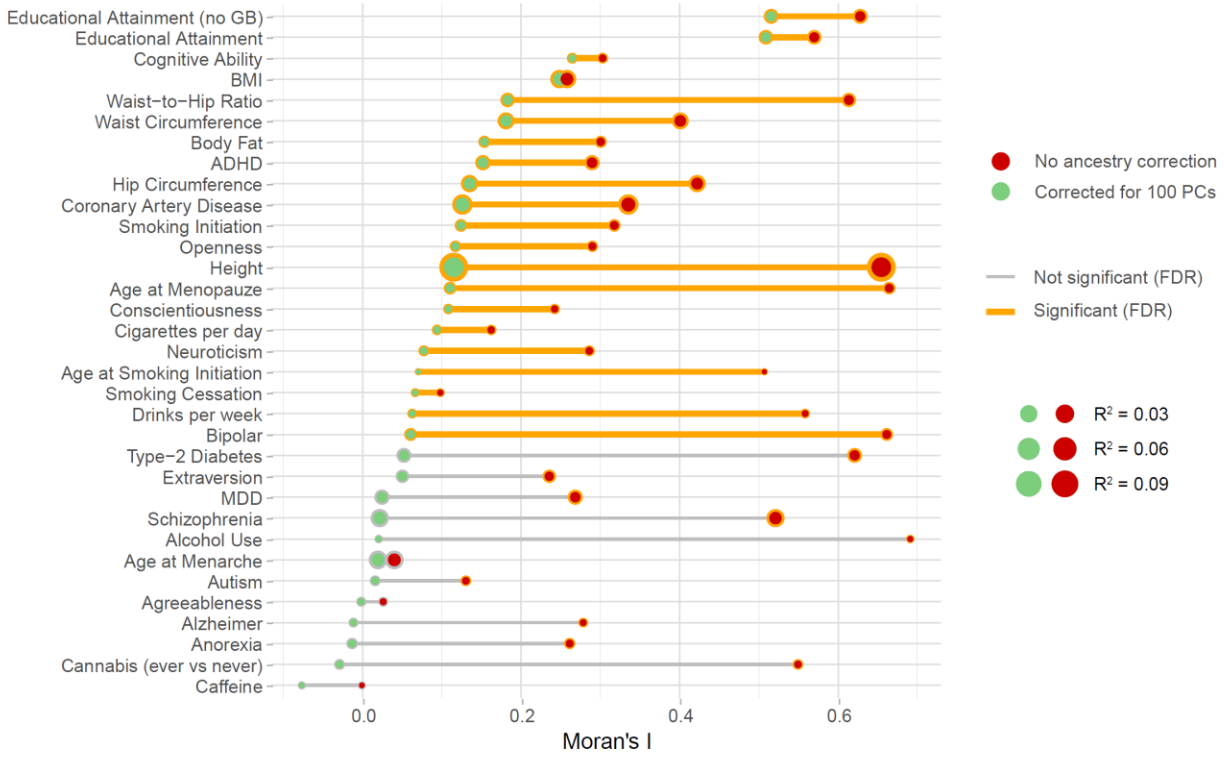
- Polygenic scores, before and after regressing out 100 PCs



Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

- Polygenic scores, before and after regressing out 100 PCs

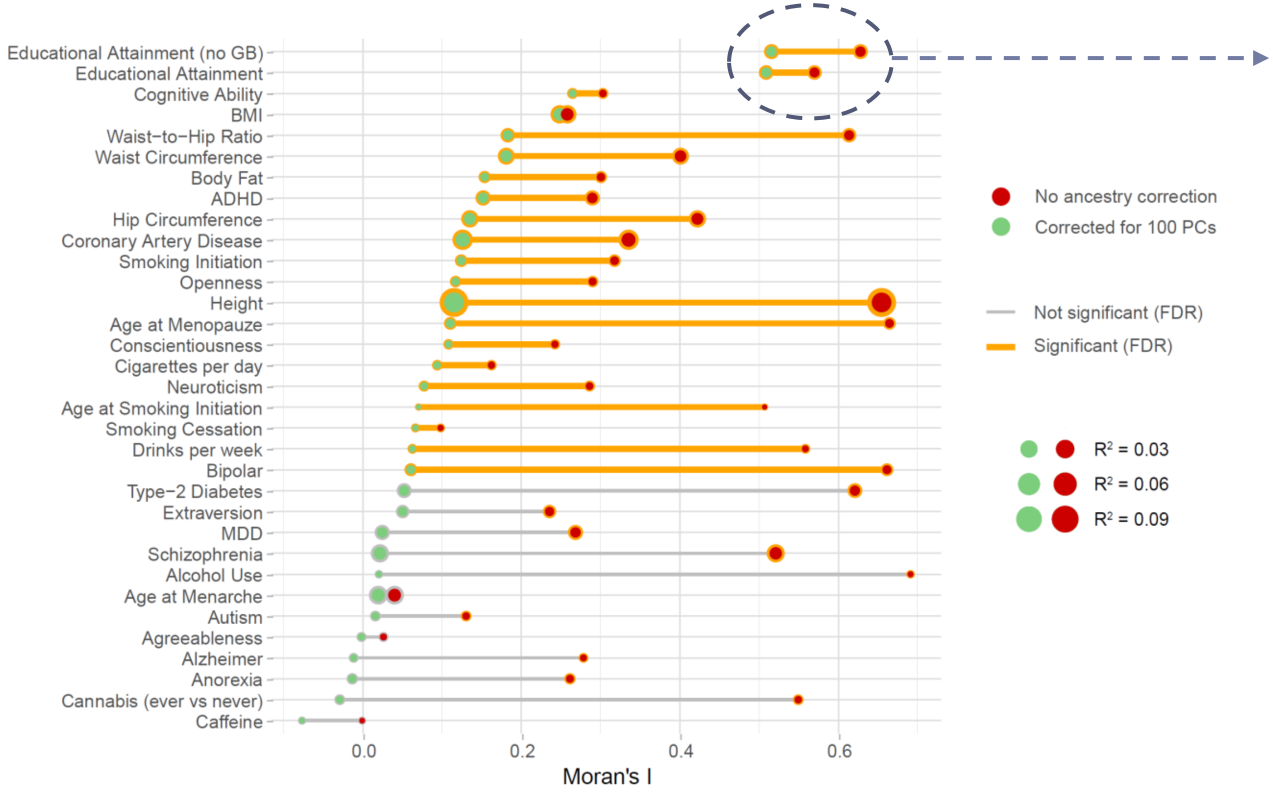


Moran’s I = measure for geographic clustering

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Ancestry differences in Great Britain

- Polygenic scores, before and after regressing out 100 PCs



More on this tomorrow at 8 AM (optional gene-environment correlations session)

Moran's I = measure for geographic clustering

Genetic Correlates of Social Stratification in Great Britain (Abdellaoui et al, 2019)

Next up:

Family-Based Association

with Dorret Boomsma & Mike Neale