First Estimates

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```
library ( dplyr )
# library ( plyr )
library ( ggplot2 )

tempDir = "/scratch/genevol/users/lucas/"
saveDir = "/raid/genevol/users/lucas/heritability/plots/"
```

Introduction

Step 1

After the removal of monomorphisms, filtration of the desired samples and after obtaining the list of non-correlated snp's per chromosome (considering correlation value of $\sqrt{0.1}$), it is now desired to calculate the GRM matrix.

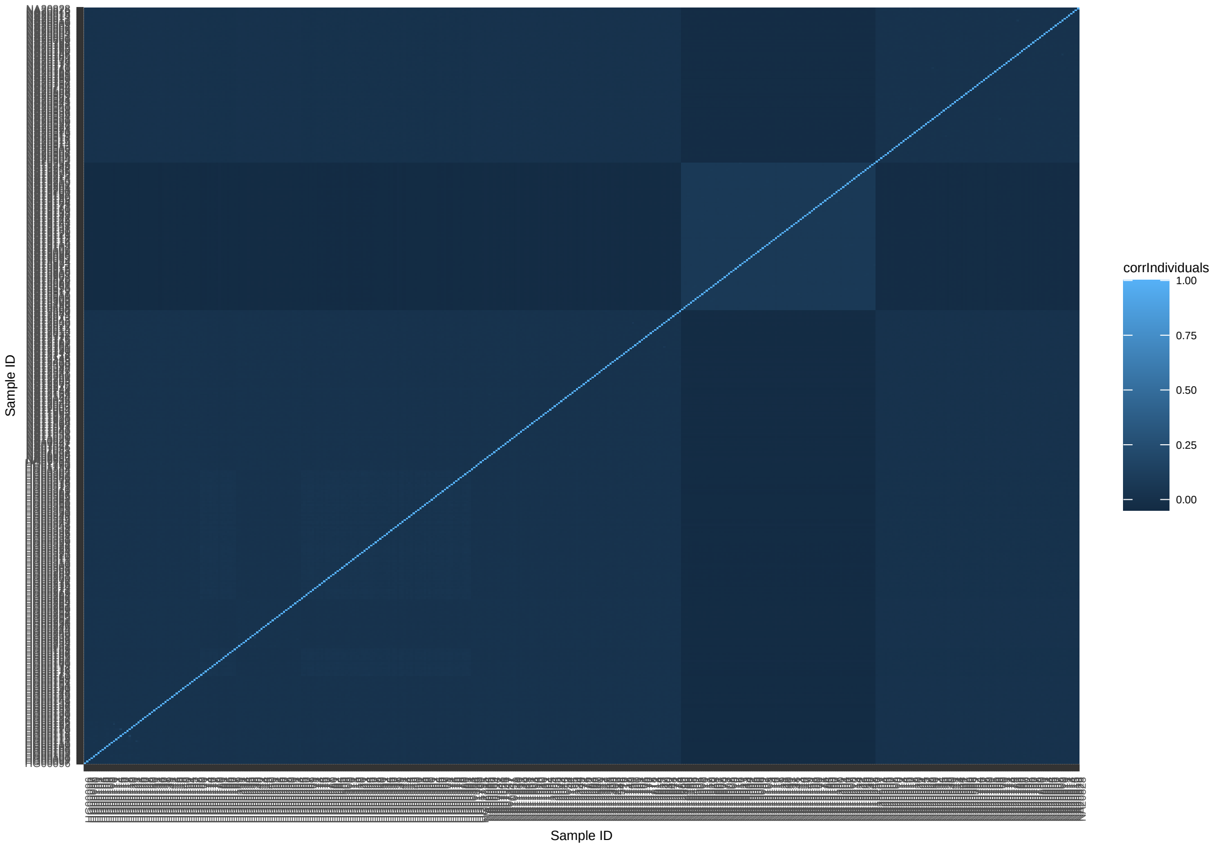
```
# Read file with all chromosomes
# allChrFile = SeqArray::seqOpen ( paste0 ( tempDir , "allChr.gds" ) )
# List of all genes of interest (after pruning)
listSnps = readRDS ( paste0 ( tempDir , "fullPrunedList.rds" ) )

# GRM - calculated as defined in CGTA
# grm_obj = SNPRelate::snpgdsGRM( allChrFile , snp.id = listGenes , method = "GCTA")

# Estimating through "gaston" package
altReadSnps = gaston::read.vcf( paste0 ( tempDir , "allChr.vcf.gz" ) )
```

```
## ped stats and snps stats have been set.
## 'p' has been set.
## 'mu' and 'sigma' have been set.
```

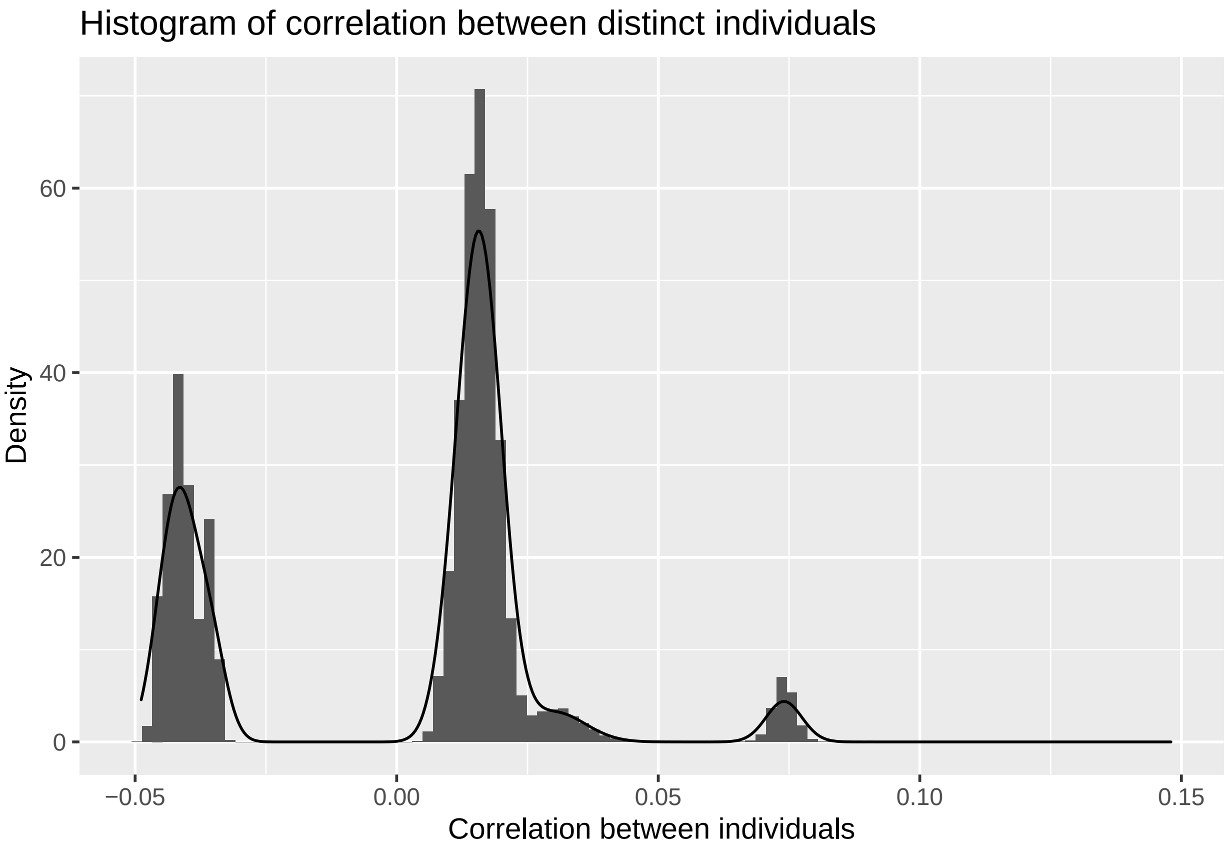
```
# setting "p" parameter - correction with mean "p" and std sqrt(2p(1-2p))
gaston::standardize( altReadSnps ) <- "p"
grm_matrix = gaston::as.matrix ( altReadSnps )
# grm_scaled = scale( grm_matrix , center = T , scale = T )
# grm_scaled = readRDS (paste0(tempDir , "scaledMatrixBk.rds"))


# manual_GRM = ( 1 / nrow ( grm_scaled ) ) * grm_scaled %*% t ( grm_scaled )
# GRM matrix calculation (GCTA)
grm_alt_p = gaston::GRM ( altReadSnps , which.snps = listSnps )
```

```
## Warning in which.snps & is.autosome(x@snps$chr): longer object length is not a
## multiple of shorter object length
```

```
# transform matrix into dataframe (3 columns - col1 = samples each row, col2 = samples each column ,  c
dfGrm = reshape2::melt(grm_alt_p)

# indexing with numeric values each sample (columns and rows)
# dfGrm$sampLines = rep ( seq ( 1 , nrow ( grm_alt_p ) ) , nrow ( grm_alt_p ) )
# dfGrm$sampCols = sort ( rep ( seq ( 1 , nrow ( grm_alt_p ) ) , nrow ( grm_alt_p ) ) )


# To calculate the correlation between individuals, the calculation A_ij/sqrt(A_ii)sqrt(A_jj) will be d
# dataframe with only diag. values
dfGrmDiag = dfGrm[ dfGrm$Var1 == dfGrm$Var2,]
# sqrt of those values
dfGrmDiag = dfGrmDiag %>% mutate ( sqrtVal = sqrt ( value ) , sqrtVal2 = sqrt ( value ) )

# merging each A_ii for each row and col
dfGrmM = merge ( dfGrm , dfGrmDiag[ ,c ( "sqrtVal" , "Var1" ) ] , on = c ( "Var1" ) )
dfGrmM2 = merge ( dfGrmM , dfGrmDiag[ ,c ( "sqrtVal2" , "Var2" ) ] , on = c ( "Var2" ) )

# Calculating A_ij/(sqrt(A_ii)sqrt(A_jj))
dfGrmFinal = dfGrmM2 %>% mutate ( corrIndividuals = value / ( sqrtVal * sqrtVal2 ) ) %>% arrange ( Var1

# plot heatmap - correlation between individuals
dfGrmFinal %>% ggplot( aes ( x = Var1 , y = Var2 , fill = corrIndividuals ) ) +
geom_tile() +
theme( axis.text.x = element_text(angle = 90, hjust = 1) , text = element_text (size = 5) ) +
labs ( x = "Sample ID" , y = "Sample ID" )
```



```
# It seems there are blocks with higher correlation between individuals between the samples

# Filter of all correlation values between individuals
dfUniqueCorr = dfGrmFinal %>% filter ( corrIndividuals < .9999 ) %>% distinct ( corrIndividuals , .keep

# Histogram and density of correlation values
dfUniqueCorr %>% ggplot ( aes ( x = corrIndividuals ) ) +
geom_histogram ( aes(y=..density..) , bins = 100 ) +
geom_density ( ) +
labs ( x = "Correlation between individuals" , y = "Density" , title = "Histogram of correlation betwee
```



```
# The correlation blocks are bolder in this plot

# Readind file with HLA expressions and ancestry information
hlaExp = readr::read_tsv("/raid/genevol/heritability/hla_expression.tsv")
```

```
## Parsed with column specification:
## cols(
##   subject_id = col_character(),
##   continental_pop = col_character(),
##   population = col_character(),
##   sex = col_character(),
##   gene_name = col_character(),
##   NumReads = col_double(),
##   TPM = col_double()
## )
```

```
# Ancestry of all samples
ancestry = unique ( hlaExp[ , c ( "subject_id" , "continental_pop" )] )

# Merging ancestry info with correlation dataframe
check = merge ( dfUniqueCorr , ancestry , by.x = c ( "Var1" ) , by.y = c ( "subject_id" ) )
check2 = merge ( check , ancestry , by.x = c ( "Var2" ) , by.y = c ( "subject_id" ) )

tableAncestry = unique ( check[,c("continental_pop" , "Var1")] ) %>% select ( continental_pop ) %>% tabl

knitr::kable( tableAncestry )
```

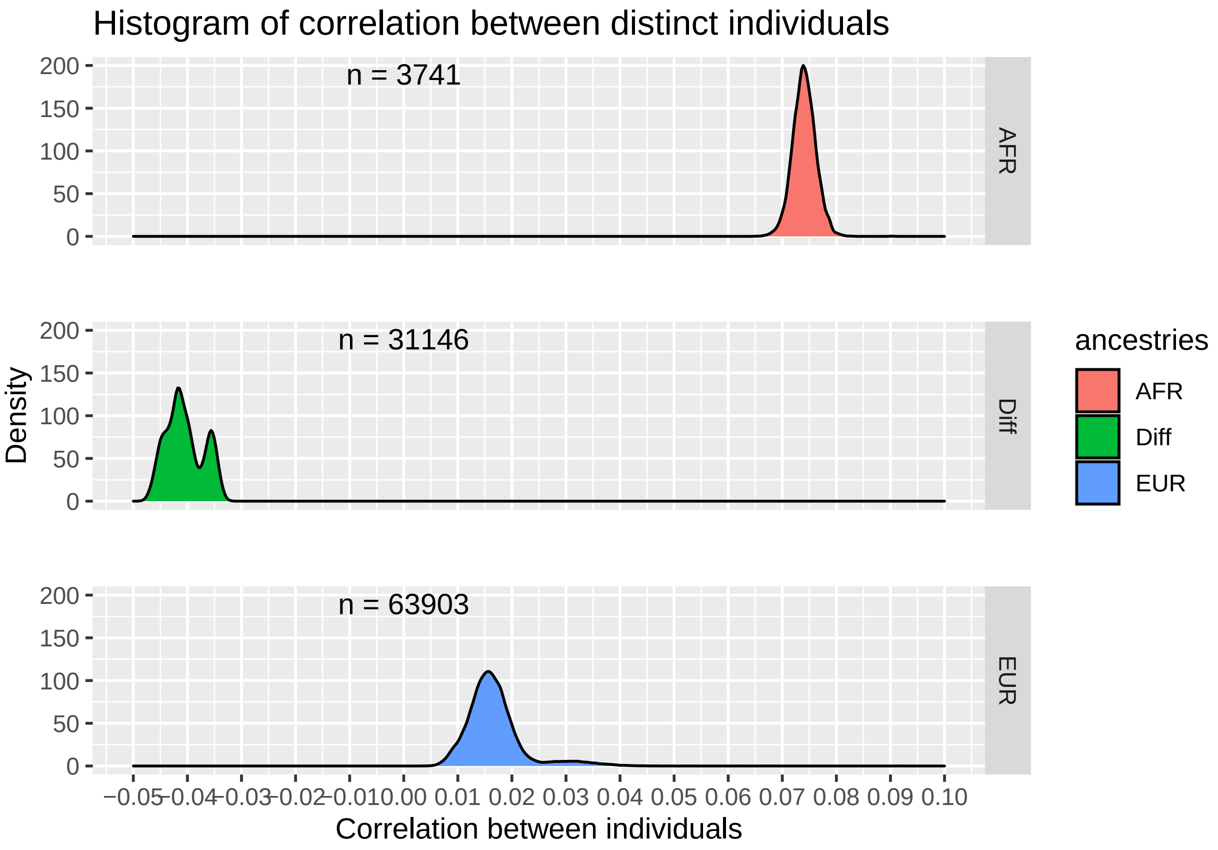
Ancestry	Freq	relFreq
AFR	87	19.59%
EUR	357	80.41%

```
# Approximately 20% of the 444 individuals are African, while the other 80% are European



# Checking the amount of comparisons between individuals with same ancestry and different ones
checkFin = check2 %>% mutate ( ancestries = ifelse ( continental_pop.x == continental_pop.y , continenta


tableComparisons = table ( checkFin$ancestries ) %>% as.data.frame() %>% mutate ( freqRel = Freq/ sum (

knitr::kable ( tableComparisons )
```

Ancestry	NumComparisons	freqRel
AFR	3741	0.0378682
Diff	31146	0.3152748
EUR	63903	0.6468570

```
numComparisons = plyr::ddply(.data=checkFin,
                 "ancestries",
                 summarize,
                 n=paste("n =", length(corrIndividuals)))

checkFin %>% ggplot ( aes ( x = corrIndividuals , fill =  ancestries ) ) +
    geom_density ( ) +
    facet_grid ( ancestries~. ) +
    theme(panel.spacing = unit (2, "lines") ) +
    labs ( x = "Correlation between individuals" , y = "Density" , title = "Histogram of correlation be
  geom_text(data=numComparisons, aes(x=0, y=190, label=n),
                    colour="black", inherit.aes=FALSE, parse=FALSE) +
  scale_x_continuous ( breaks = seq ( from = -0.05 , to = 0.1 , by = 0.01 ) , limits = c( -0.05 , 0.1 )
```

```
## Warning: Removed 2 rows containing non-finite values (stat_density).
```

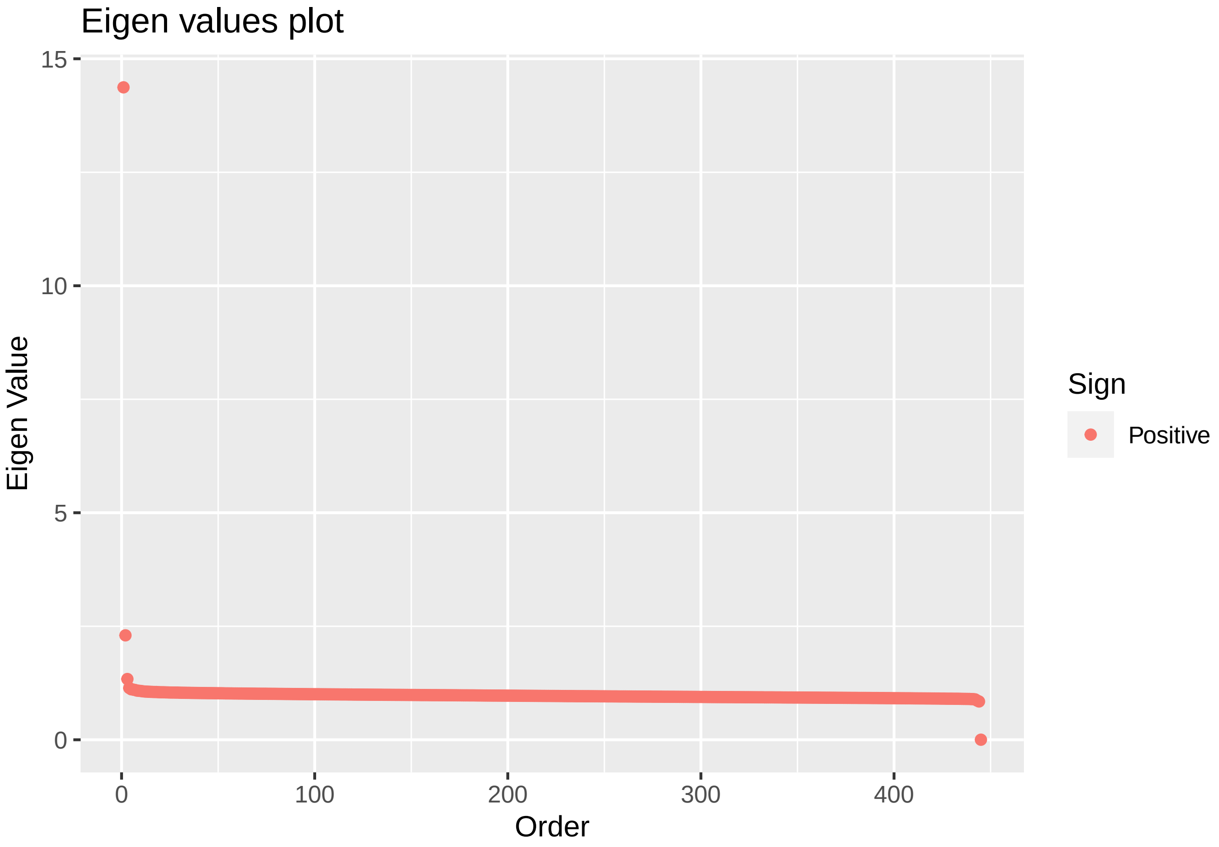


```
# display individuals with correlation greater than 10% in the sample
listGreatCorr = checkFin[ ( checkFin$corrIndividuals > .1 ) & ( checkFin$corrIndividuals < .999 ) , ] %

knitr::kable(listGreatCorr)
```

Var2	Var1	value	sqrtVal	sqrtVal2	corrIndividuals	continental_pop.x	continental_pop.y	ancestries
HG00120	HG00116	0.0900913	0.7819197	0.7784466	0.1480103	EUR	EUR	EUR
HG00240	HG00238	0.0785526	0.7790548	0.7979290	0.1263654	EUR	EUR	EUR

```
correlationMatrix = reshape2::dcast(dfGrmFinal, Var1~Var2 , value.var = "corrIndividuals")
rownames ( correlationMatrix ) = correlationMatrix$Var1
correlationMatrix$Var1 = NULL


eigenValuesGrm = eigen ( correlationMatrix )
dfEigen = eigenValuesGrm$values %>%
as.data.frame ( ) %>%
mutate ( order = 1:445 ) %>%
rename ( "Value" = '.' ) %>%
mutate ( neg = ifelse ( Value < 0 , "Negative" , "Positive" ) )
```

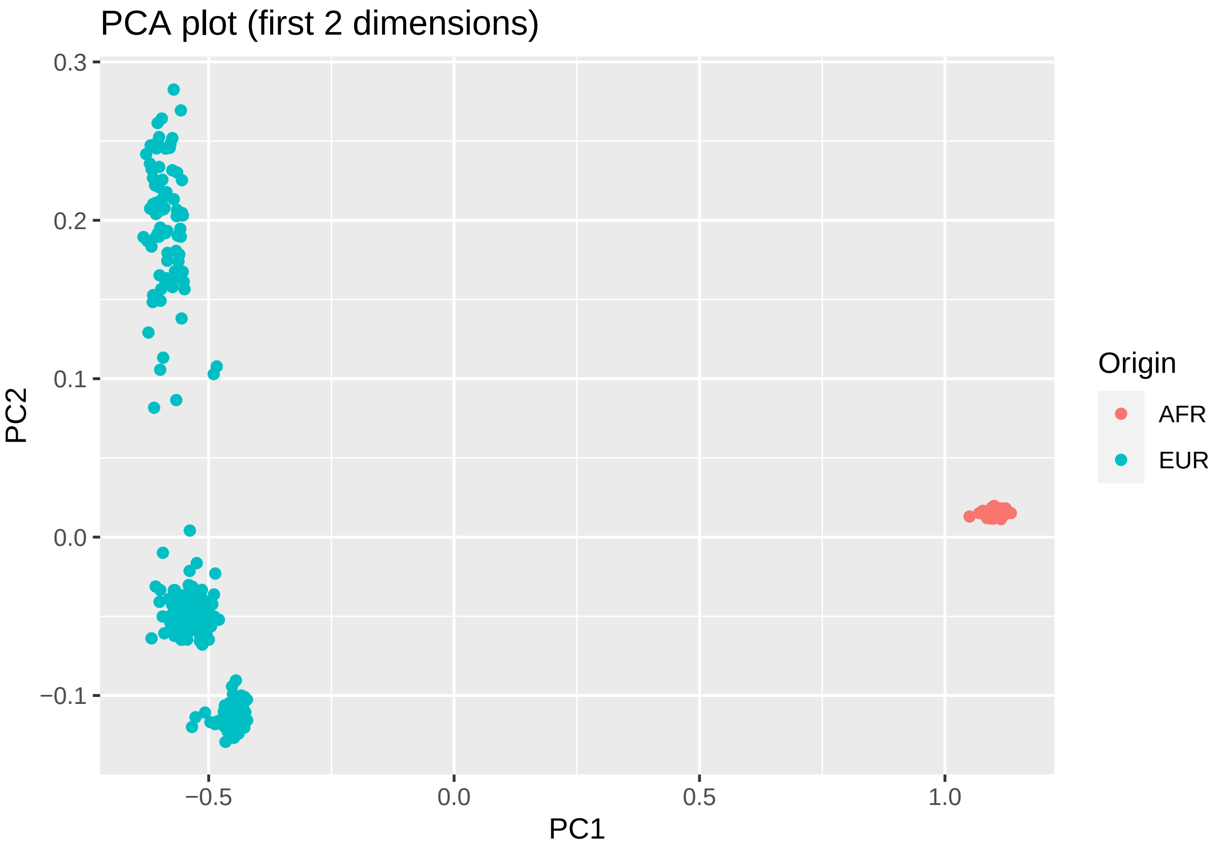
```
dfEigen %>% ggplot ( aes ( x = order , y = Value , colour = neg )  ) +
geom_point ( ) +
labs ( x = "Order" , y = "Eigen Value" , title = "Eigen values plot" , colour = "Sign" )
```



```
expressionInterest = hlaExp %>% filter ( subject_id %in% colnames ( correlationMatrix ) )

mainInfo = expressionInterest %>% distinct( subject_id , continental_pop ,population )
numEigen = 2
print ( paste0 ( "Total variation explained by the first ", numEigen , " eigen values: " , 100*round ( 
```

```
## [1] "Total variation explained by the first 2 eigen values: 3.75%"
```

```
vectors_ = eigenValuesGrm$vectors[,1:numEigen]
calcScores = as.matrix ( correlationMatrix , ncol = 445 )  %*% vectors_ %>%
  as.data.frame() %>%
  rename ( "PC1" = "V1" , "PC2" = "V2" ) %>%
  mutate ( subject_id = rownames ( correlationMatrix ) )
pcaPlot = merge ( mainInfo , calcScores )

pcaPlot %>% ggplot ( aes ( x = PC1 , y = PC2  , colour = continental_pop ) ) +
  geom_point ( ) +
  labs ( title = "PCA plot (first 2 dimensions)" , colour = "Origin" )
```



```
matrixModelReference = eigenValuesGrm$vectors %*% t ( eigenValuesGrm$vectors )
rownames ( matrixModelReference ) = rownames ( correlationMatrix )
colnames ( matrixModelReference ) = colnames ( correlationMatrix )

simpleModels = function ( exp_ , df ){

  dfFilter = df  %>% filter ( gene_name == exp_ )

  fixed0 = lm ( TPM ~ 1 , data = dfFilter )
  sum0 = summary ( fixed0 )
  fixedEffectSigma = sum0$sigma^2

  mixedModel = coxme::lmekin( dfFilter$TPM ~ 1 + (1|dfFilter$subject_id) , data=dfFilter, varlist=list(

  mixedEffectSigma = mixedModel$sigma^2
  sigmaA = as.numeric(mixedModel$vcoef)

  modelExpanded = coxme::lmekin( dfFilter$TPM ~ 1 + dfFilter$PC1 + dfFilter$PC2 + (1|dfFilter$subject_i

  mixedEffectSigmaExp <- modelExpanded$sigma^2
  sigmaAExp = as.numeric(modelExpanded$vcoef)

  return ( c ( exp_ , fixedEffectSigma , mixedEffectSigma , sigmaA , mixedEffectSigmaExp , sigmaAExp ) )

}

listNames = unique ( expressionInterest$gene_name )
```

```
modelDf = merge ( expressionInterest , calcScores )

requiredInfo = NULL
for ( name_ in listNames ){

  requiredInfo = rbind ( requiredInfo , simpleModels ( exp_ = name_ ,df = modelDf ) )

}

finalDf = requiredInfo %>% as.data.frame ( ) %>% rename ("Gene" = "V1" ,
                                                          "fixedSigma" = "V2" ,
                                                          "residualMixedSigma" = "V3" ,
                                                          "randomEffectSigma" = "V4",
                                                          "residualMixedSigmaExp" = "V5" ,
                                                          "randomEffectSigmaExp" = "V6") %>%
mutate ( fixedSigma = as.numeric ( as.character ( fixedSigma ) ) ,
    residualMixedSigma = as.numeric ( as.character (residualMixedSigma)) ,
    randomEffectSigma =  as.numeric ( as.character (randomEffectSigma)) ,
    residualMixedSigmaExp = as.numeric ( as.character (residualMixedSigmaExp)),
    randomEffectSigmaExp = as.numeric ( as.character (randomEffectSigmaExp))
    ) %>%
  mutate ( comparisonNull = residualMixedSigma/fixedSigma ,
           comparisonNullExp = residualMixedSigmaExp/fixedSigma ,
           hSimple = randomEffectSigma / ( randomEffectSigma + residualMixedSigma ) ,
           hExpanded = randomEffectSigmaExp / ( randomEffectSigmaExp + residualMixedSigmaExp ))

finalDf %>% knitr::kable()
```

Gene	fixedSigma	residualMixedSigma	randomEffectSigma	residualMixedSigmaExp	randomEffectSigmaExp	comparisonNull	comparisonNullExp	hSimple	hExpanded
HLA-A	180900.16	60164.54	120329.09	58425.98	116851.95	0.3325843	0.3229736	0.6666667	0.6666667
HLA-B	526383.05	175066.72	350133.45	170757.97	341515.94	0.3325843	0.3243987	0.6666667	0.6666667
HLA-C	127438.40	42384.01	84768.01	41334.90	82669.79	0.3325843	0.3243520	0.6666667	0.6666667
HLA-DPA1	31587.29	10505.43	21010.87	10167.96	20335.92	0.3325843	0.3219004	0.6666667	0.6666667
HLA-DPB1	37625.10	12513.52	25027.03	10931.32	21862.65	0.3325843	0.2905327	0.6666667	0.6666667
HLA-DQA1	51654.46	17179.46	34358.92	16230.64	32461.28	0.3325843	0.3142156	0.6666667	0.6666667
HLA-DQB1	38524.93	12812.79	25625.57	12706.63	25413.27	0.3325843	0.3298288	0.6666667	0.6666667

Gene	fixedSigma	residualMixedSigma	randomEffectSigma	residualMixedSigmaExp	randomEffectSigmaExp	comparisonNull	comparisonNullExp	hSimple	hExpanded
HLA-DRA	390199.51	129774.22	259548.45	125991.71	251983.42	0.3325843	0.3228905	0.6666667	0.6666667
HLA-DRB1	148507.21	49391.16	98782.32	41843.09	83686.19	0.3325843	0.2817580	0.6666667	0.6666667