

Germline Analysis of Tumor Immune Signatures in TCGA

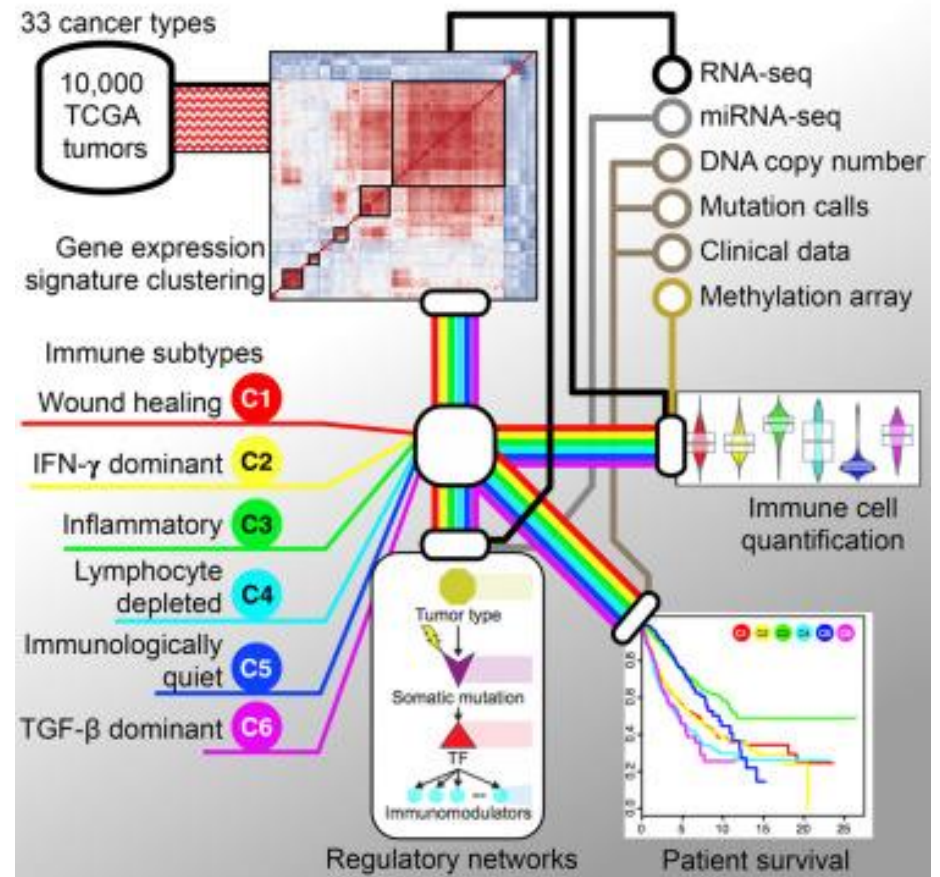
TCGA Germline Pan Immune WG

Co-Chairs Elad Ziv, Davide Bedognetti

The Immune Landscape of Cancer

Used gene expression, methylation array data, DNA copy number and mutation data from 10,000+ tumors from 33 cancer types

Identified 6 major immune subtypes

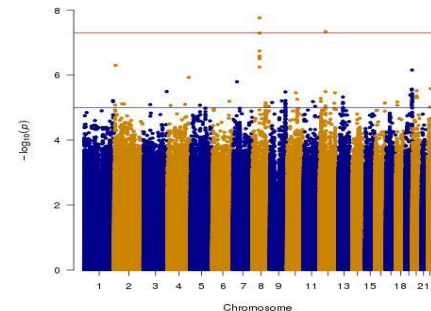
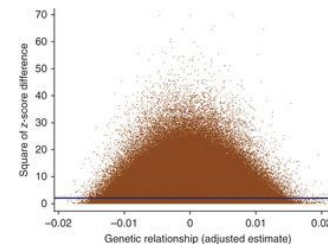
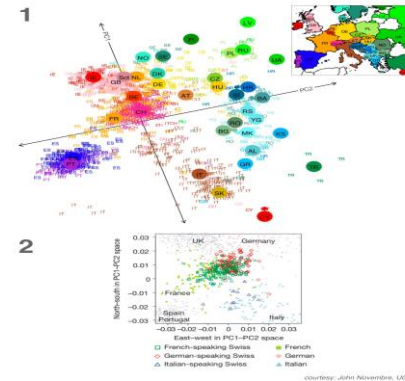


Approach

1: Genetic ancestry analysis (PCA of germline genetics). Determine continental genetic ancestry/admixture of each individual. Correlate with tumor immune response.

2: Heritability analysis. Estimate genetic relatedness of each pair. Determine whether genetic relatedness is correlated with phenotypic relatedness.

3: GWAS: impute genotypes (using Hap Ref Consortium) and perform GWAS for immune phenotypes, adjusting for PC's. Prioritize more heritable phenotypes.



Germline Genetic Approaches

Approaches

Common
variants

Single Variant
Association:
GWAS

eQTL Based
Association
TWAS

Mixed models
Heritability

Rare
variants

Variance-
component
Tests (SKAT)

Burden
Tests

Data

Affy 6.0
GWAS +
Imputation

Whole
exome seq

Single
variants

Gene based
tests

Multi-
gene/
Multi locus

Samples

CANCER	Freq.	Percent
ACC	86	0.9
BLCA	393	4.2
BRCA	1,038	11.2
CESC	285	3.1
CHOL	43	0.5
COAD	389	4.2
ESCA	123	1.3
GBM	487	5.3
HNSC	530	5.7
KICH	9	0.1
KIRC	116	1.3
KIRP	236	2.5
LGG	519	5.6
LIHC	337	3.6
LUAD	431	4.6
LUSC	333	3.6
MESO	86	0.9
OV	448	4.8
PAAD	149	1.6
PCPG	183	2.0
PRAD	474	5.1
READ	131	1.4
SARC	238	2.6
SKCM	470	5.1
STAD	365	3.9
TGCT	155	1.7
THCA	449	4.8
UCEC	499	5.4
UCS	42	0.5
UVM	80	0.9
TOTAL	9124	100

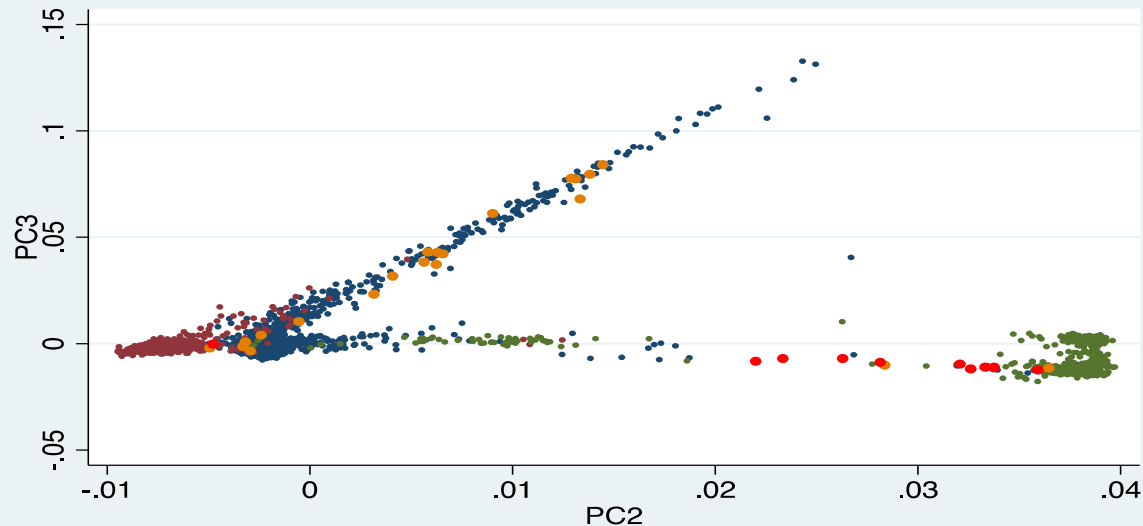
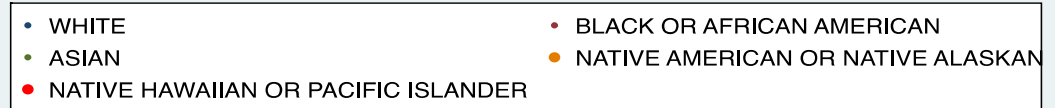
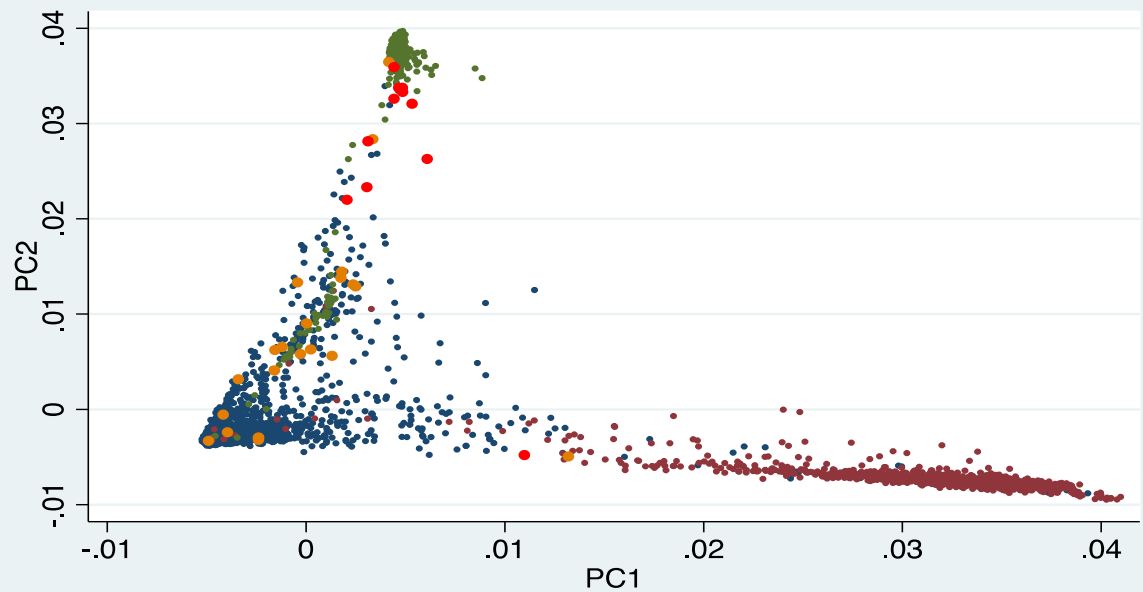
Genetic Ancestry Analysis

PCA Results

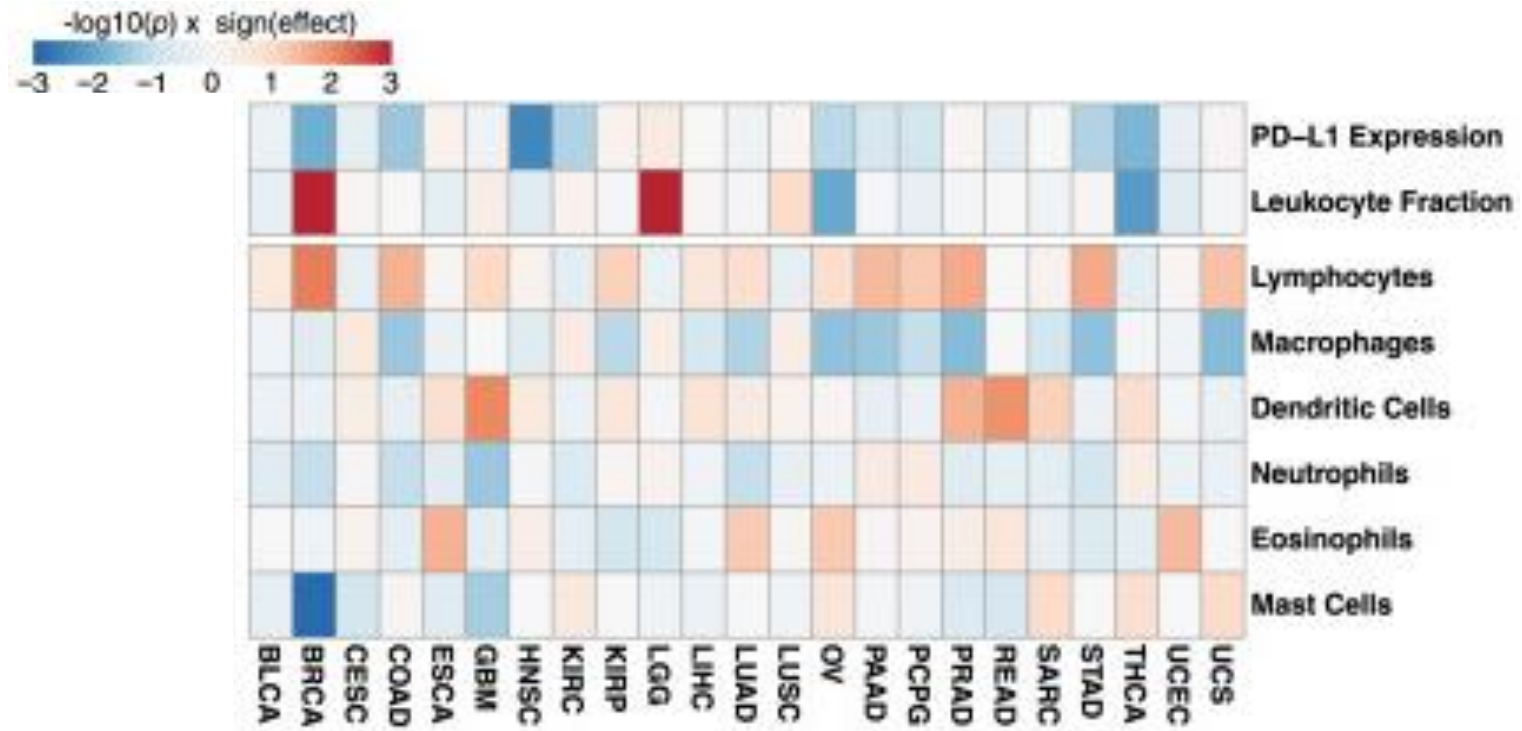
PC1: African vs. rest of populations

PC2: Asian, Native American and Pacific Islander vs. African and European

PC3: Native American (& Indigenous American components in Latinos) vs. other populations



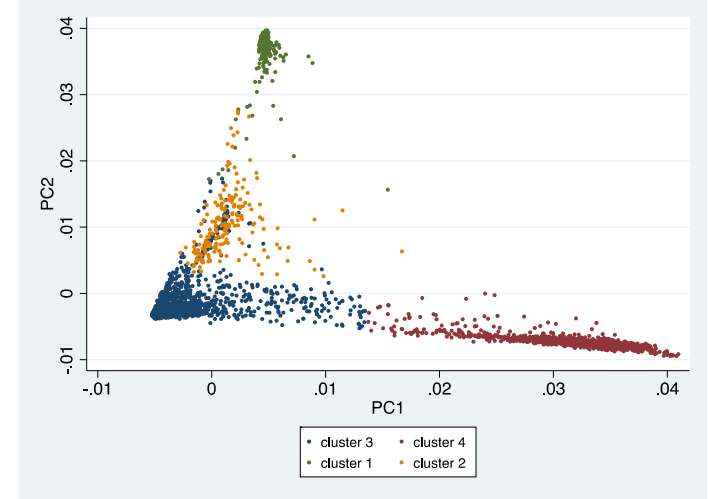
Associations between PC1 and Immune Signatures



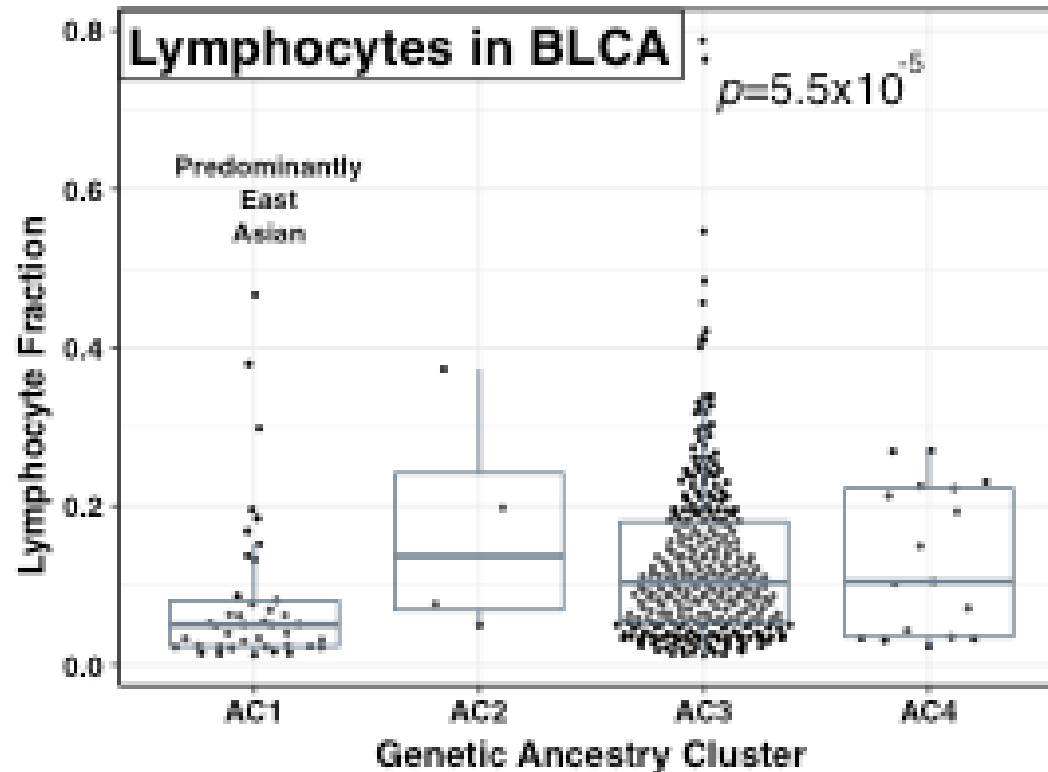
Linear regression models
immune signature $\sim$ genetic ancestry + cancer
type

$\beta > 0$ higher with African ancestry

Associations between PC2 and Immune Signatures



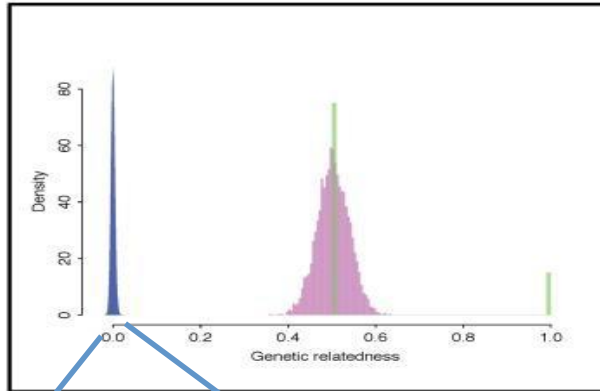
H



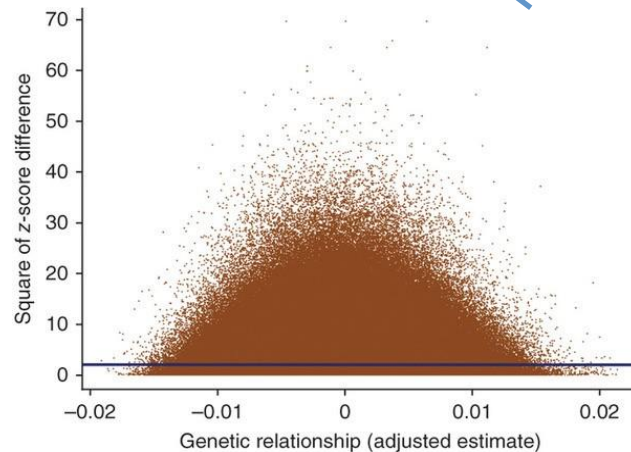
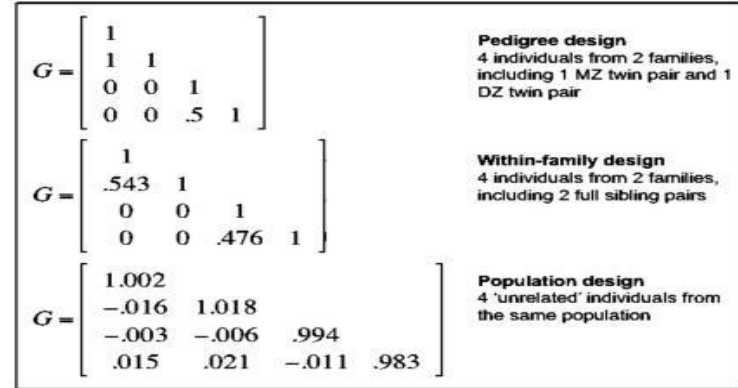
Heritability Analysis

Heritability from GWAS Data

A



B



Intuition: relationship of genotypic relatedness and phenotypic relatedness is a function of overall variance explained by genetic factors

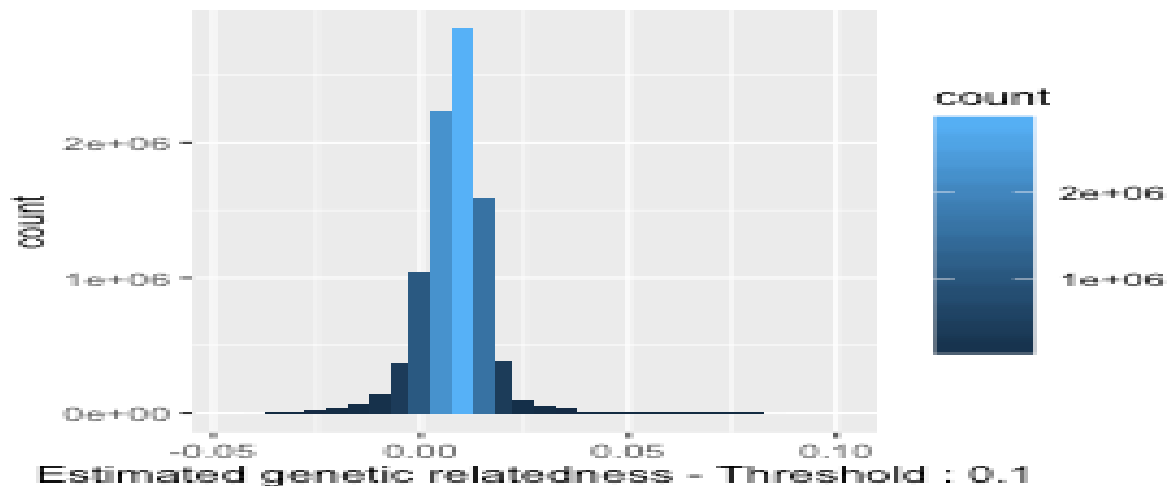
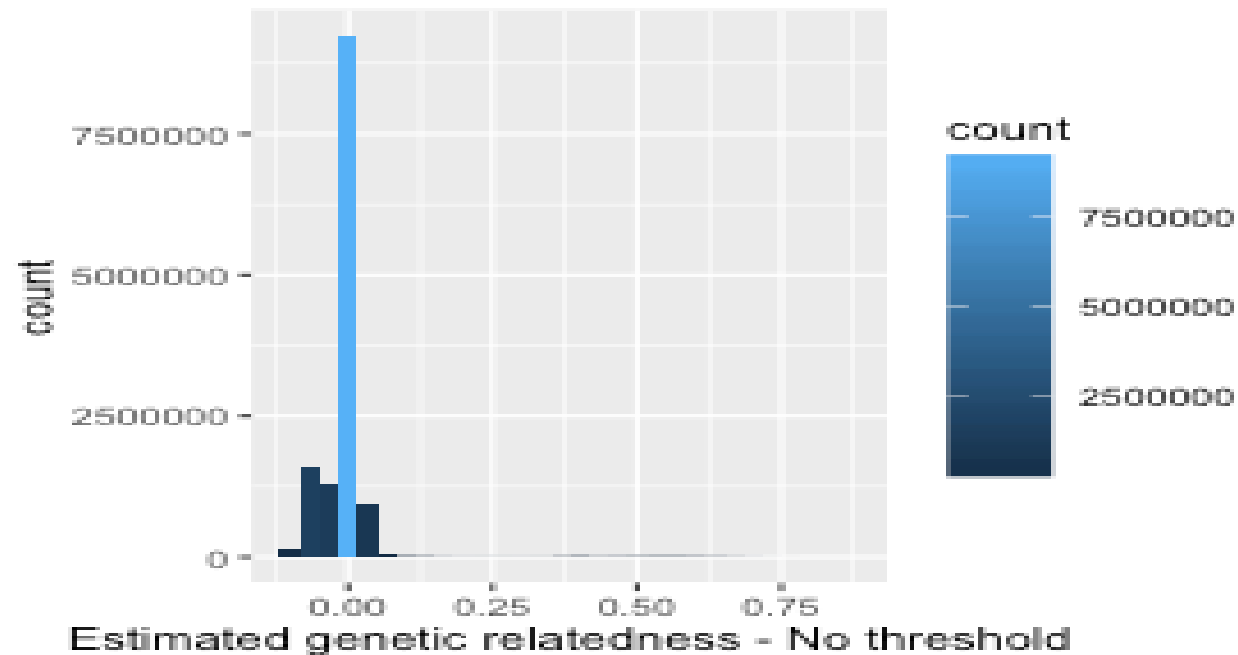
Use linear mixed models

Calculate genetic relatedness matrix

Determine correlation between genotypic relatedness and phenotypic distance

Yang et al *Nat Genetics* 2010

Distribution of Genetic Relatedness TCGA



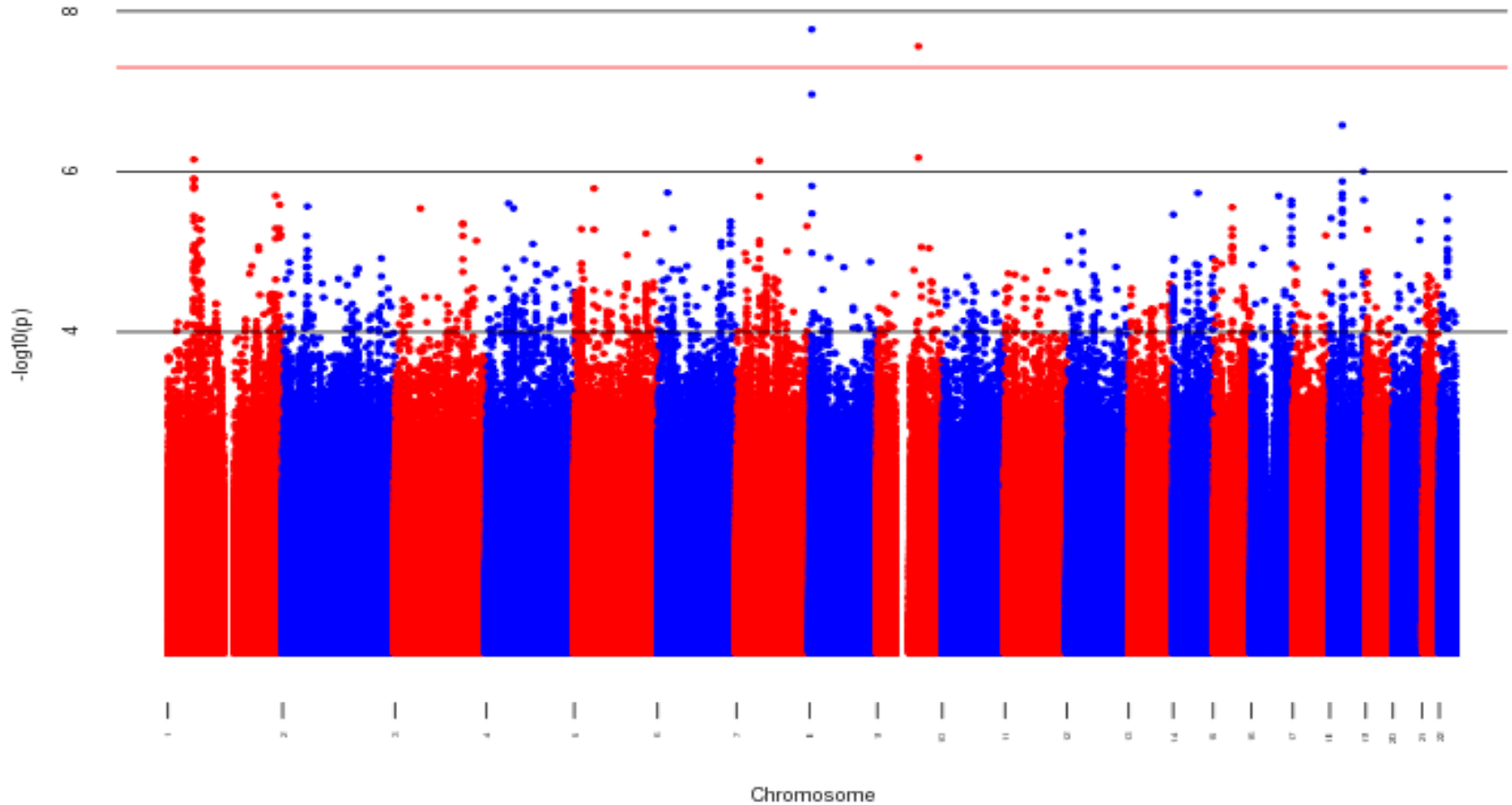
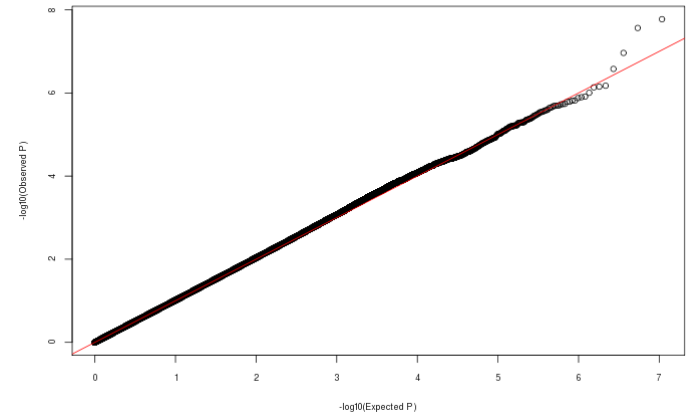
On ~4000 Caucasian ancestry samples

Heritability for Immune Signatures in Breast Cancer

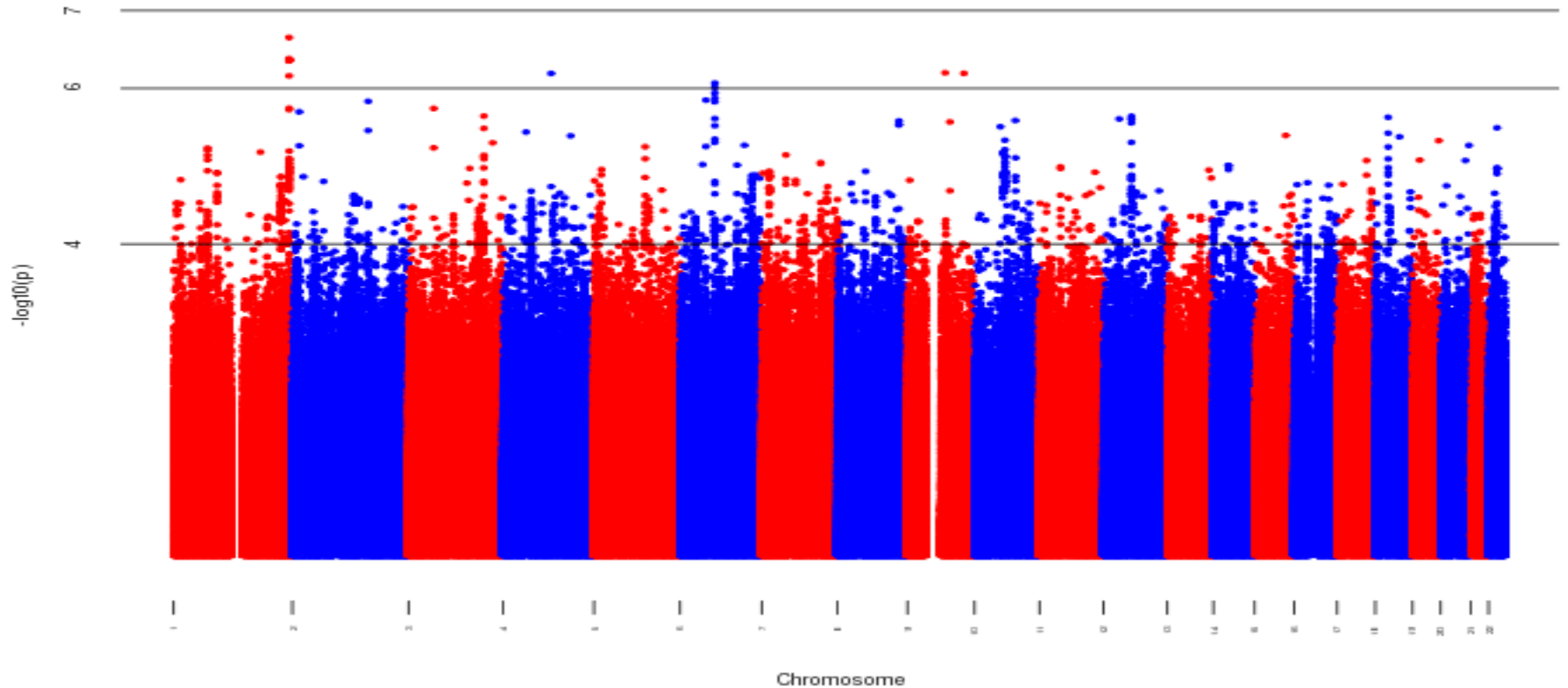
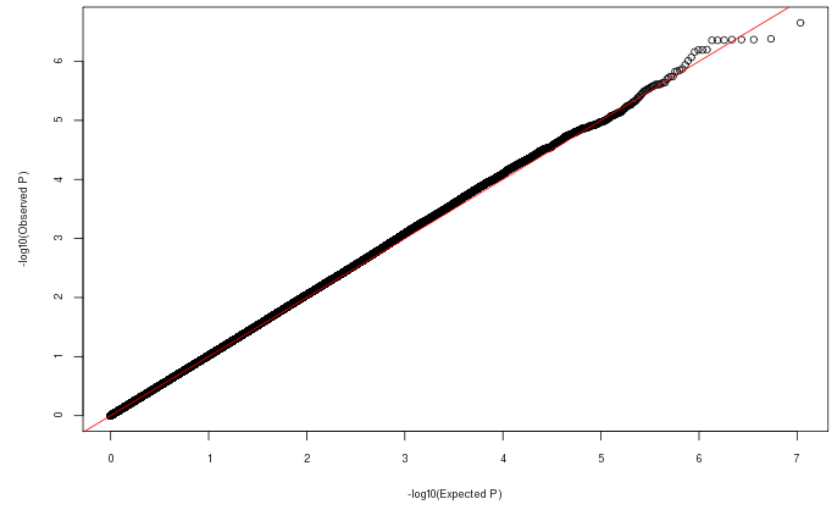
Signature	h^2	SE	P value
NHI Gene	0.54	0.19	<0.01
PDL1_data	0.44	0.19	0.01
Buck14	0.31	0.17	0.02
TGFB_PCA	0.26	0.17	0.05
B Cell PCA	0.24	0.17	0.07
CD8_PCA	0.18	0.17	0.13
T Cell PCA	0.11	0.16	0.27

Genome Wide Association(GWAS) For Immune Cell Infiltrates

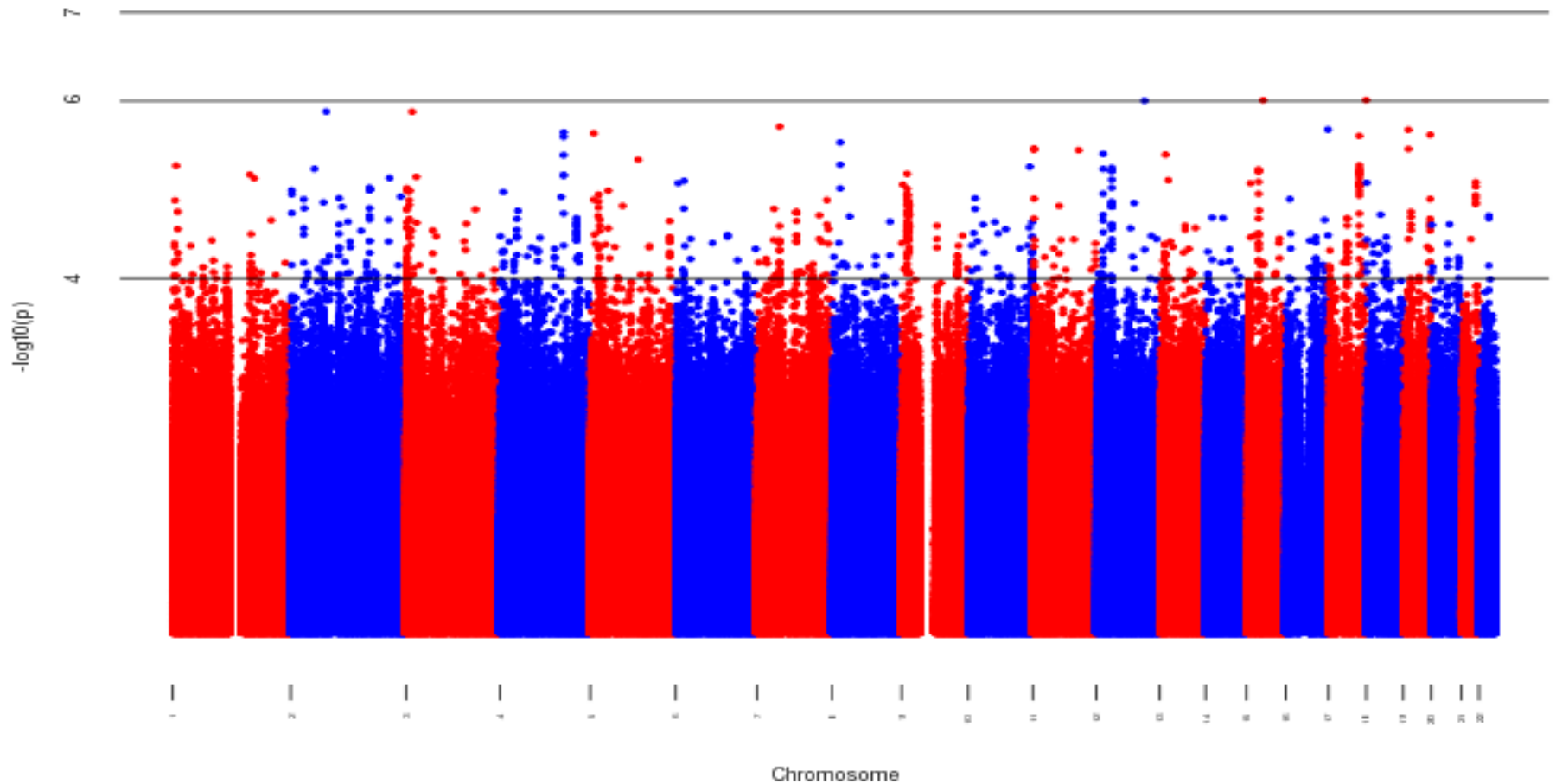
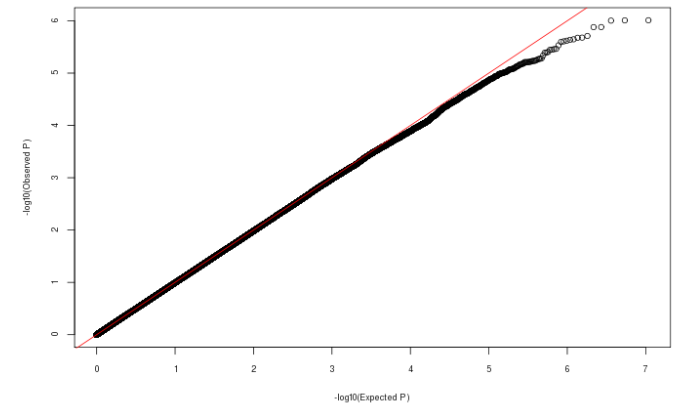
GWAS Results: Lymphocytes



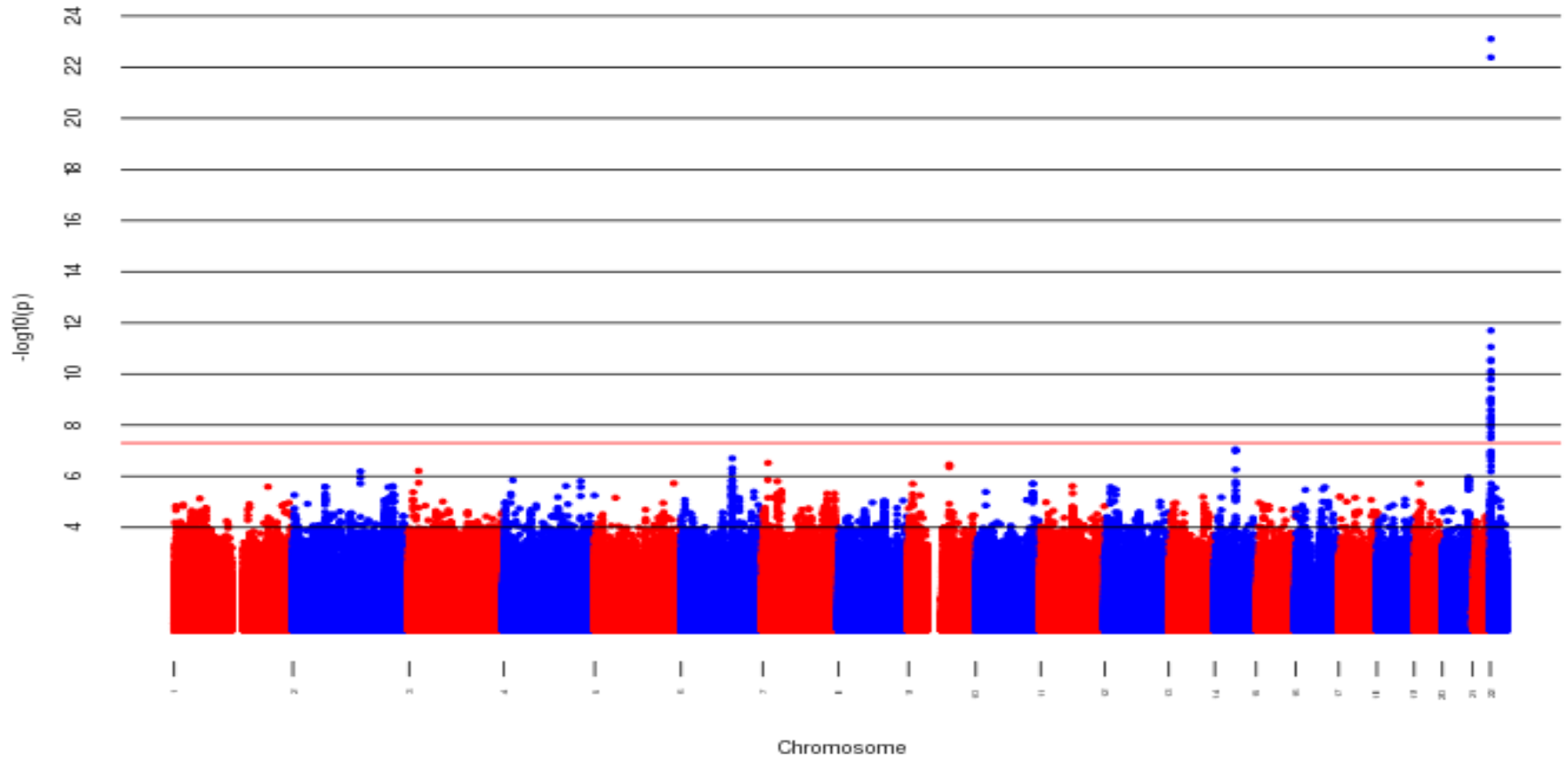
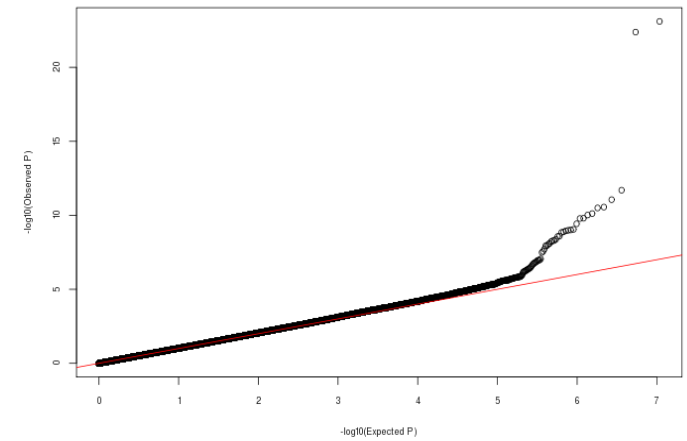
GWAS Results: Macrophages



GWAS Results: TH1

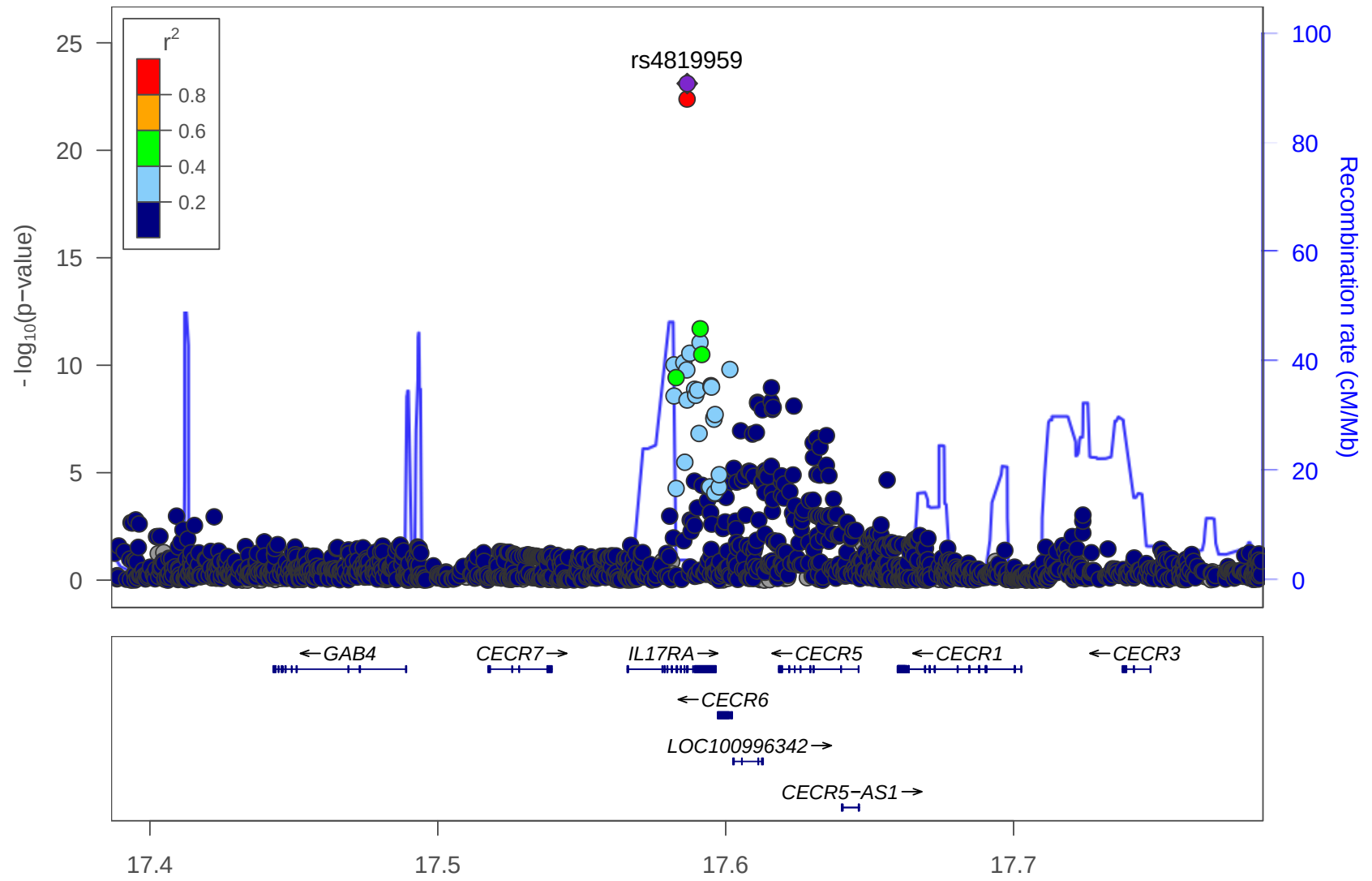


GWAS Results: TH17

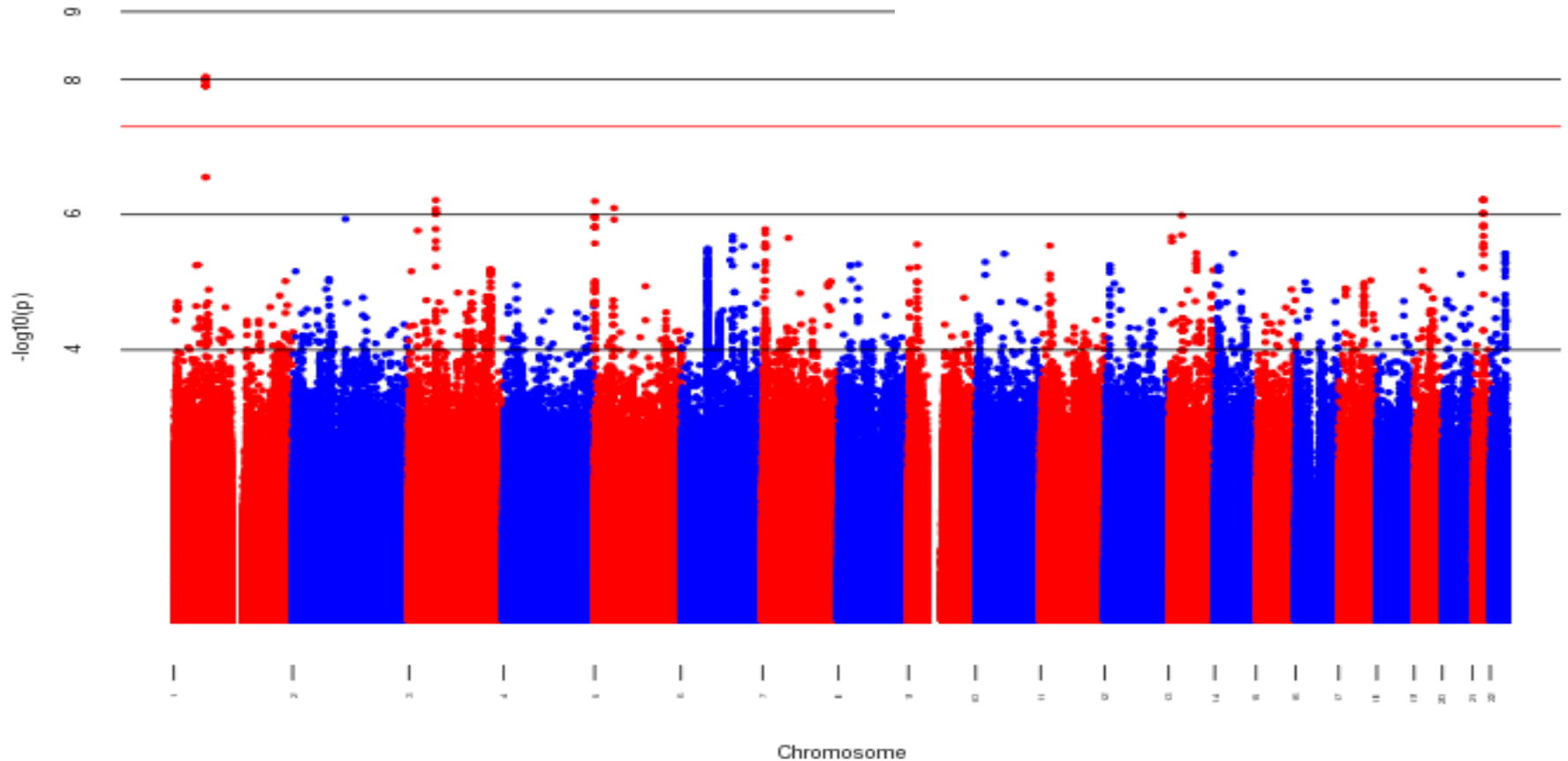
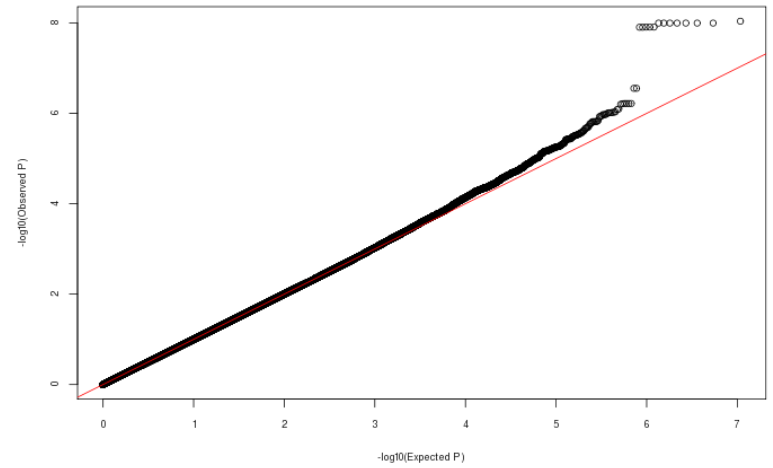


Fine Mapping Results for TH17

Plotted SNPs

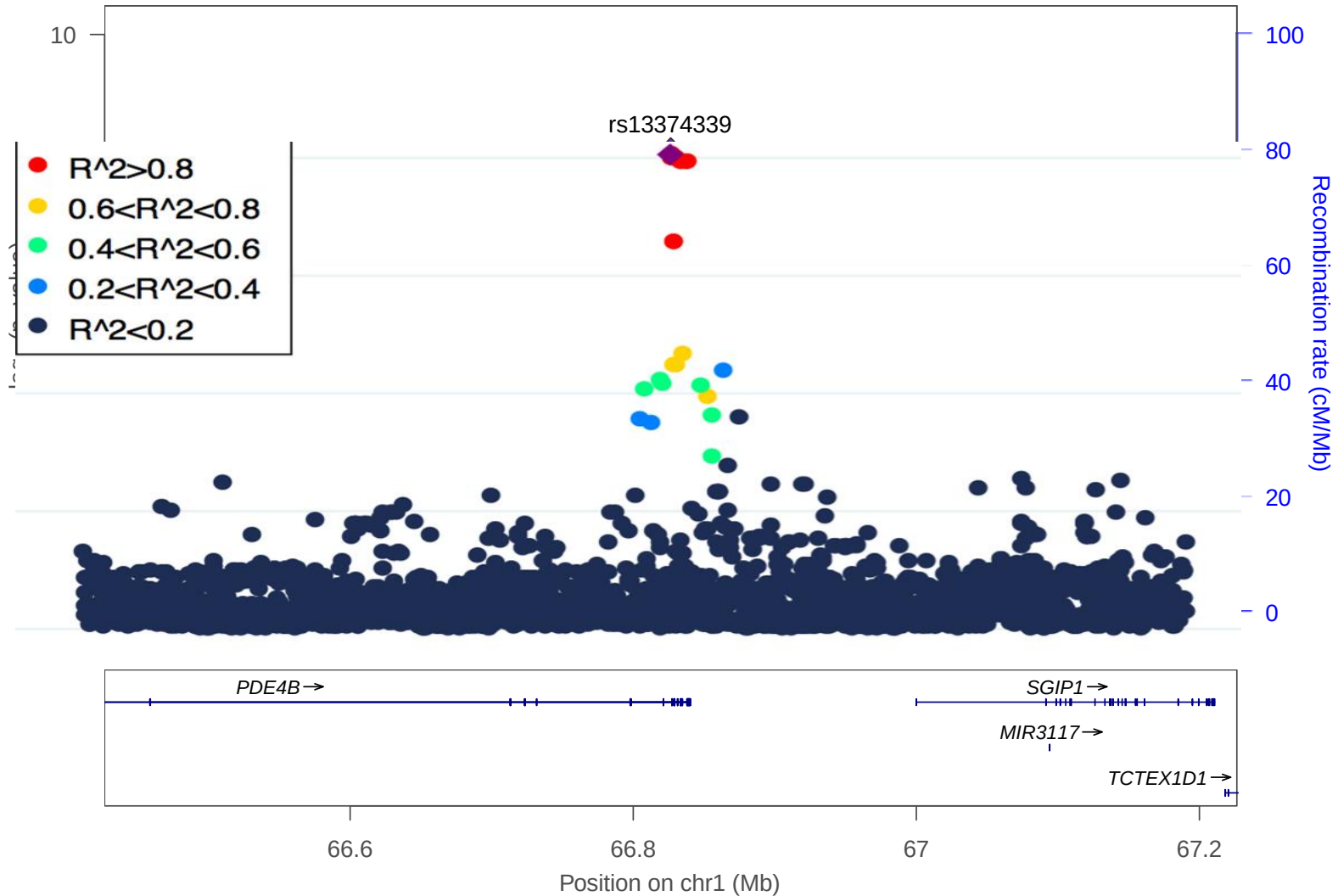


GWAS Results: TH2

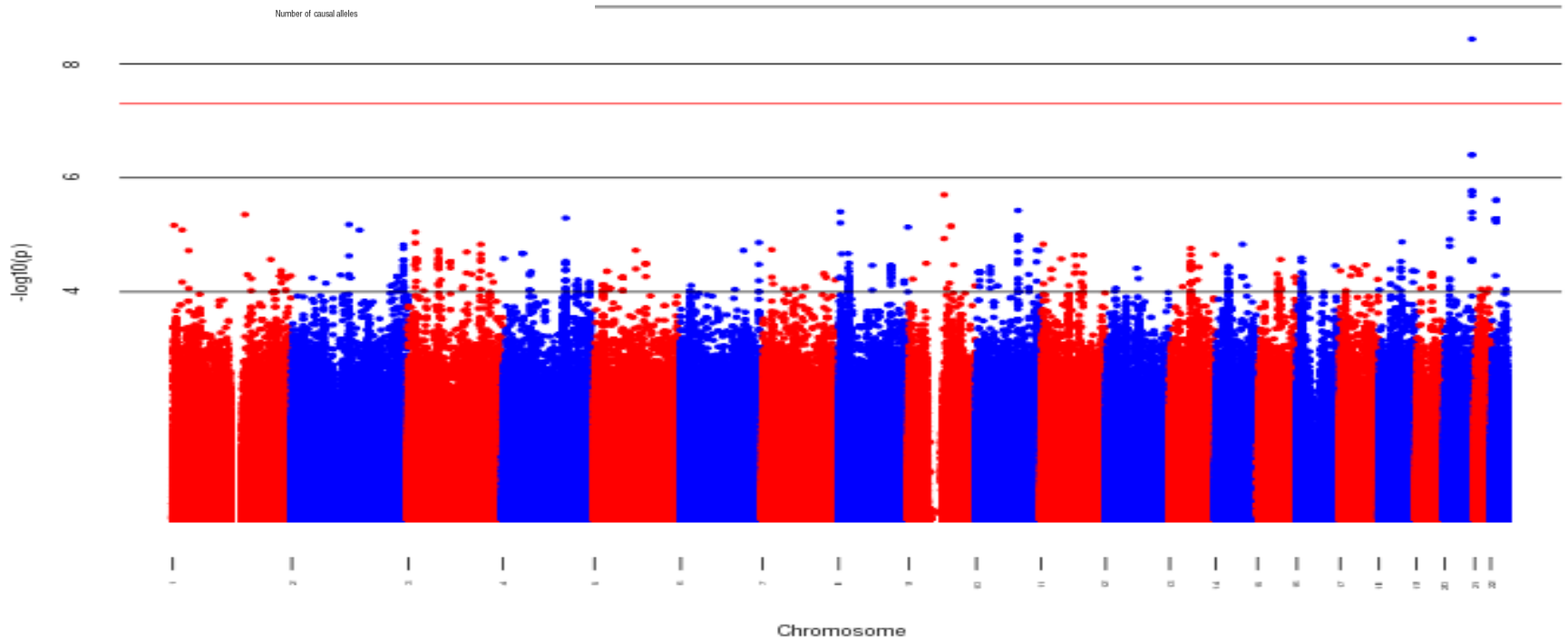
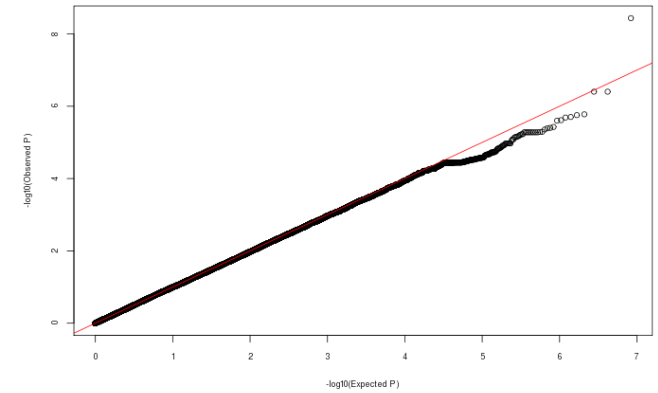
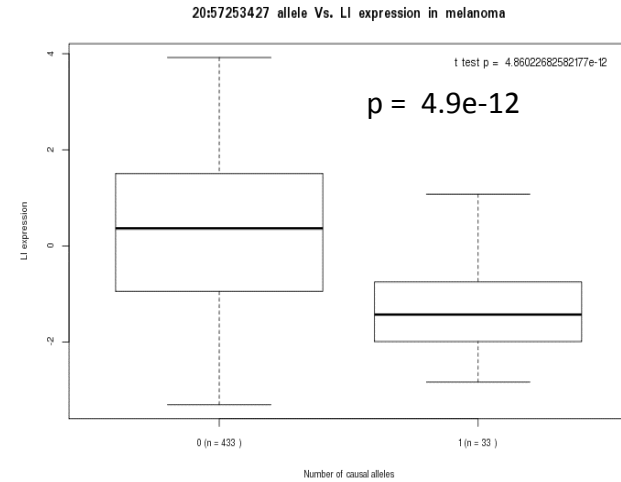


Fine Mapping Results for TH2

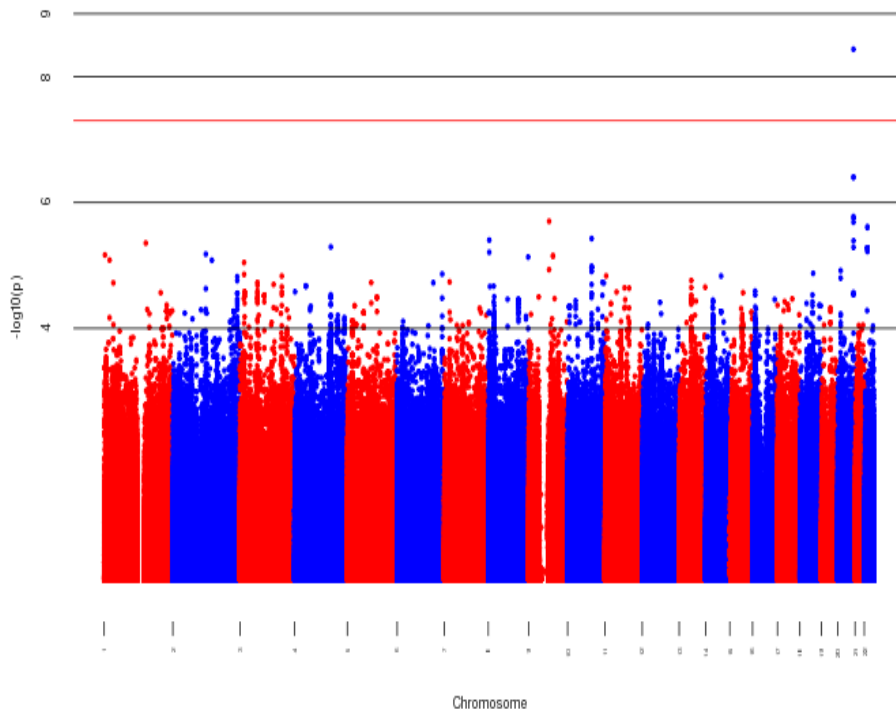
Plotted SNPs



GWAS for LI score (Lymphocytes) in Melanoma



Chrom20 locus is associated with multiple immune traits in melanoma and with immune response in other cancers

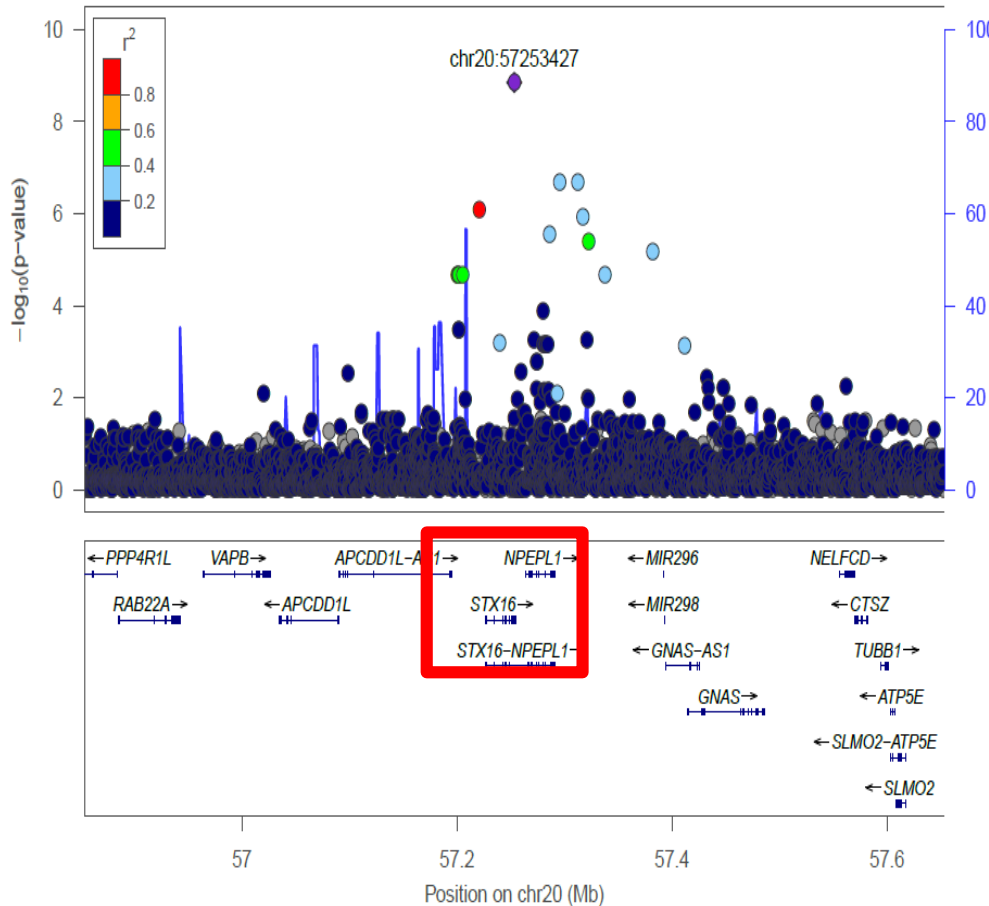


	P value
PD1	1.40E-09
PDL1	0.0001344
CTLA4P	0.03158
LI expression	3.66E-09
Module3_IFN_score	3.72E-05
TGFB_score_21050467 7	0.3377
CD103pos_CD103_neg_ratio_25446897	0.9133
CD8_CD68_ratio	3.01E-06
CSR_Activated_15701700	1.643E-01

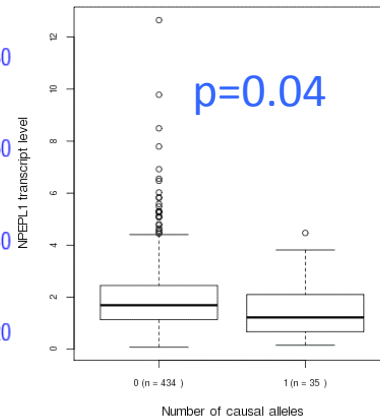
	P value
Bladder Ca	0.1635
Breast Ca	0.5041
Cervical Cancer	0.578
Colon Ca	0.1146
GBM	0.02411
Head and Neck	0.013
Renal Clear Cell	0.6314
Lung Adeno	0.7788
Lung Sq	0.9113
Prostate	0.8328

Analysis across all non-melanoma cancers $p=0.02$

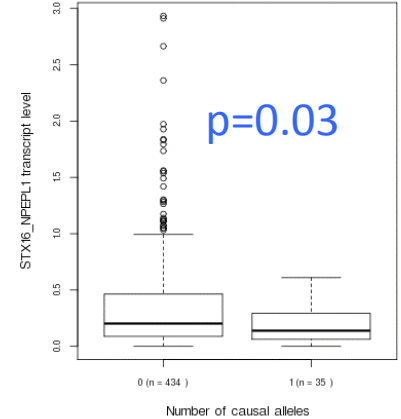
Fine Mapping and eQTL for LI in Melanoma



20:57253427 allele Vs. NPEPL1 transcript level



20:57253427 allele Vs. STX16_NPEPL1 transcript level

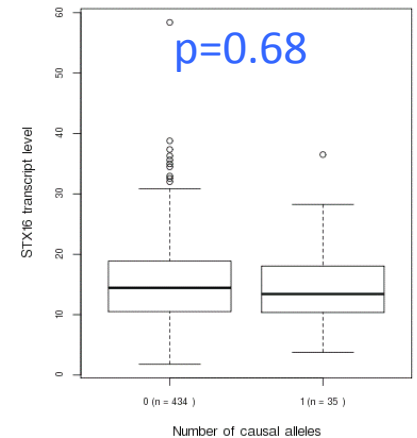


chr20:57253427 is located in the 3' UTR of STX16.

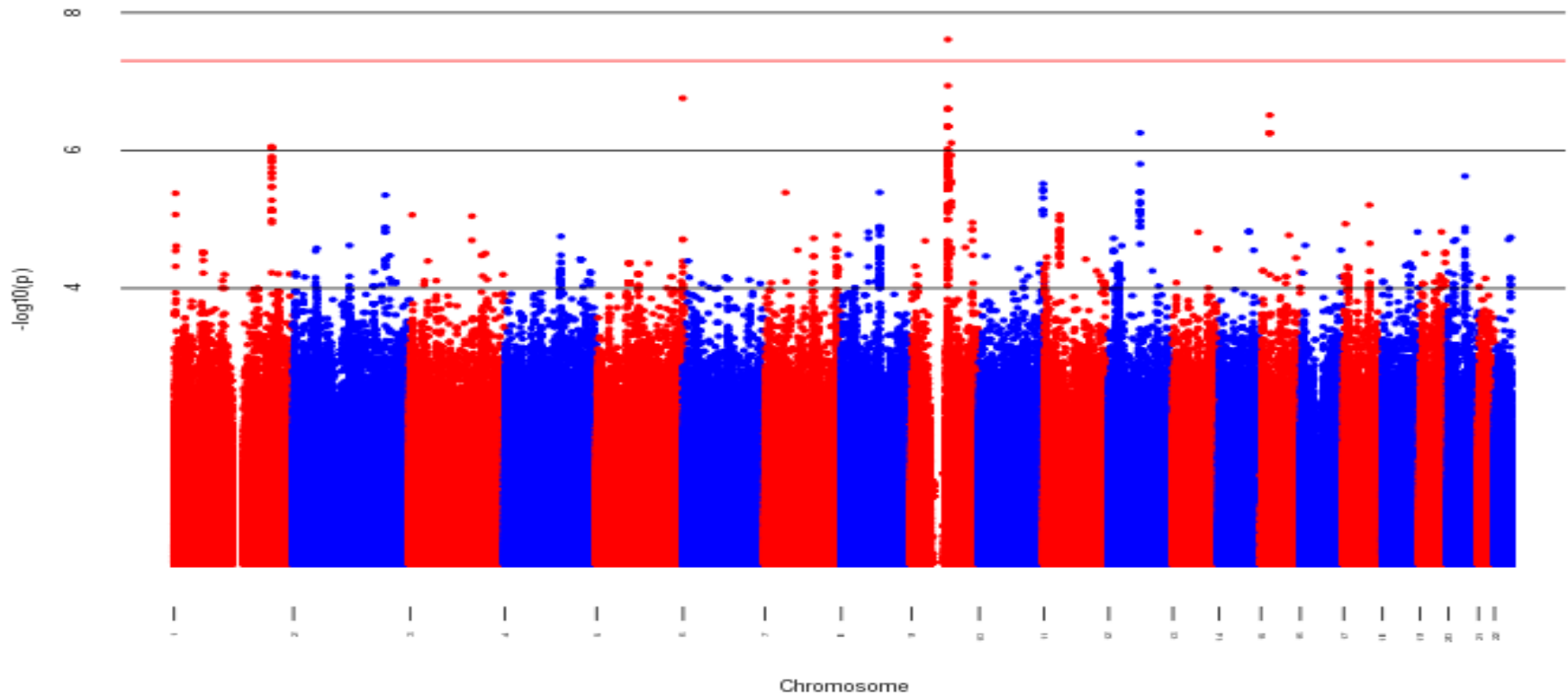
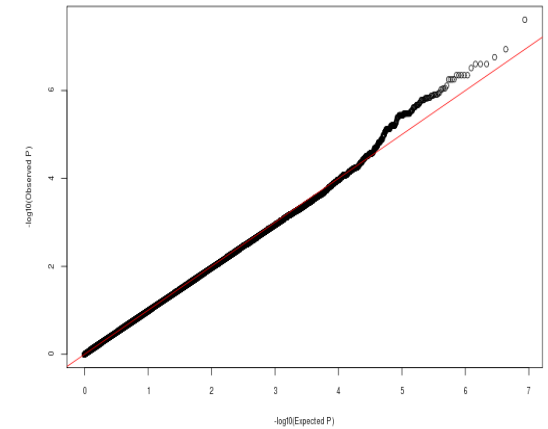
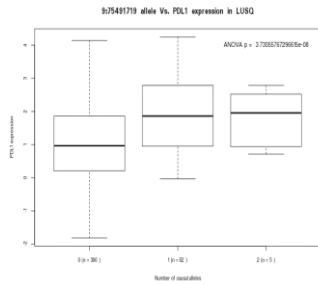
But no effect on STX16

Effect NPEPL1 expression and STX16-NPEPL1

20:57253427 allele Vs. STX16 transcript level



GWAS for *PDL1* expression in LUSC



Summary

Genetic ancestry is associated with multiple immune signatures

Preliminary studies of genome wide heritability suggests some immune signatures are heritable

Preliminary GWAS of immune signatures identifies some candidate loci. Some cross-cancer loci and some cancer specific loci

Future Directions

Complete heritability across all cancer types

Complete GWAS

Perform rare variant association analysis (exome seq)

TCGA Germline Variation and Immune Response Working Group

**SIDRA MEDICAL AND
RESEARCH CENTER**

Davide Bedognetti

Younes Mokrab

Wouseter Henrickx

Najeeb Syed

**UNIVERSITY OF CALIFORNIA,
SAN FRANCISCO**

Elad Ziv

Rosalyn Sayaman

Scott Huntsman

Donglei Hu

Denise Wolf

Karen Wong

Farshad Farshifar

Vestein Thorsson

Kuan-Lin Huang

Eduard Porta

Jian Carrot-Zhang

Michele Ceccarelli

Andrew Cherniak

Nora Disis

Franco Marincola

Akinyemi Ojesena

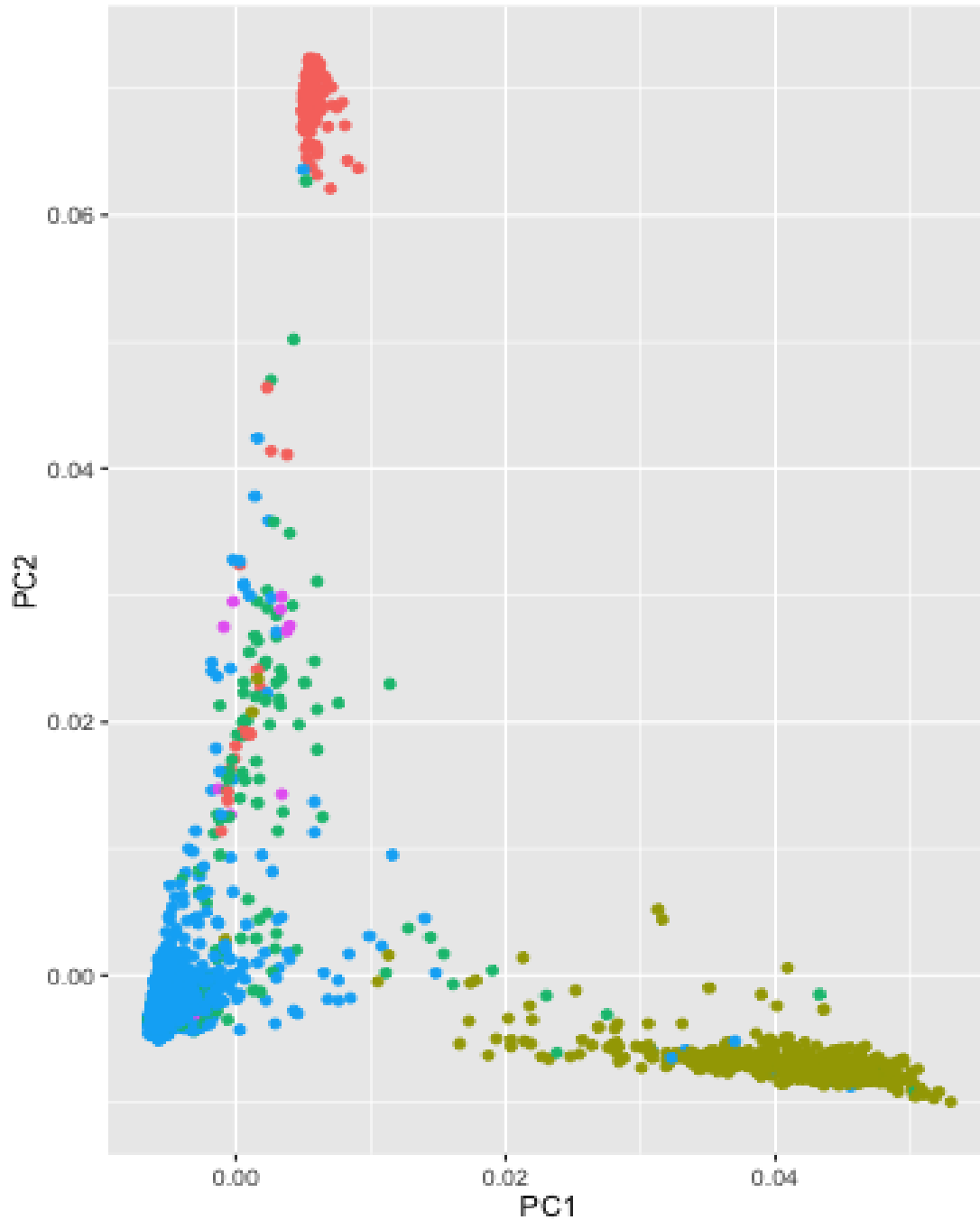
Janet Rader

Mohammad Saad

Simon Shelley

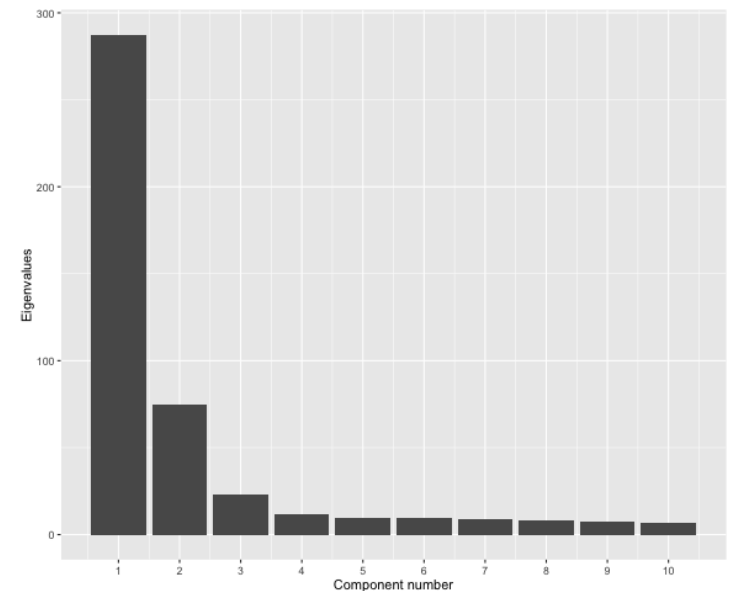
Linghua Wang

PCA Results

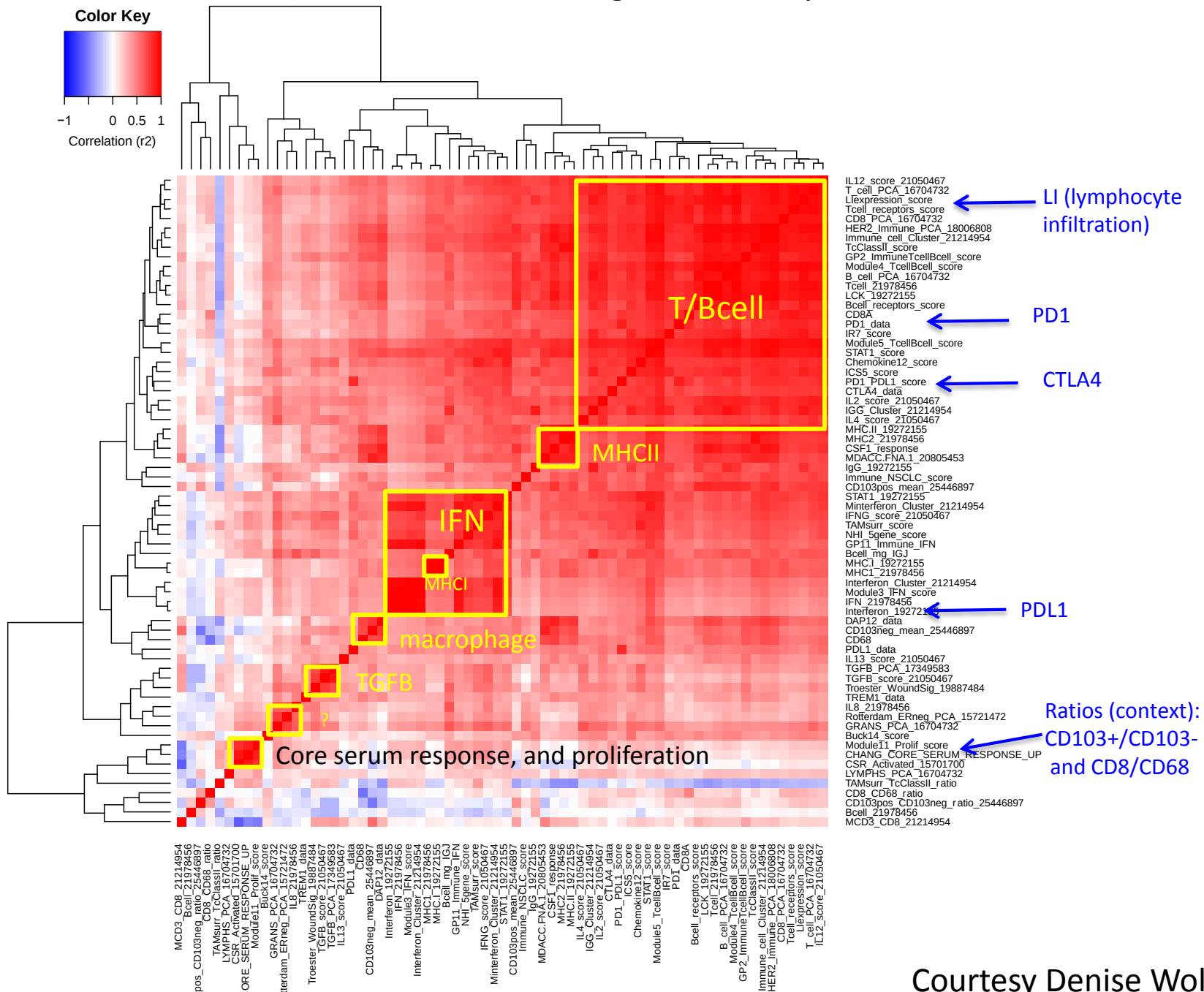


ethnicities

- ASIAN
- BLACK OR AFRICAN AMERICAN
- HISPANIC OR LATINO
- WHITE
- AMERICAN INDIAN OR ALASKA NATIVE



Immune signatures analyzed



Courtesy Denise Wolf