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# Age at Menarche

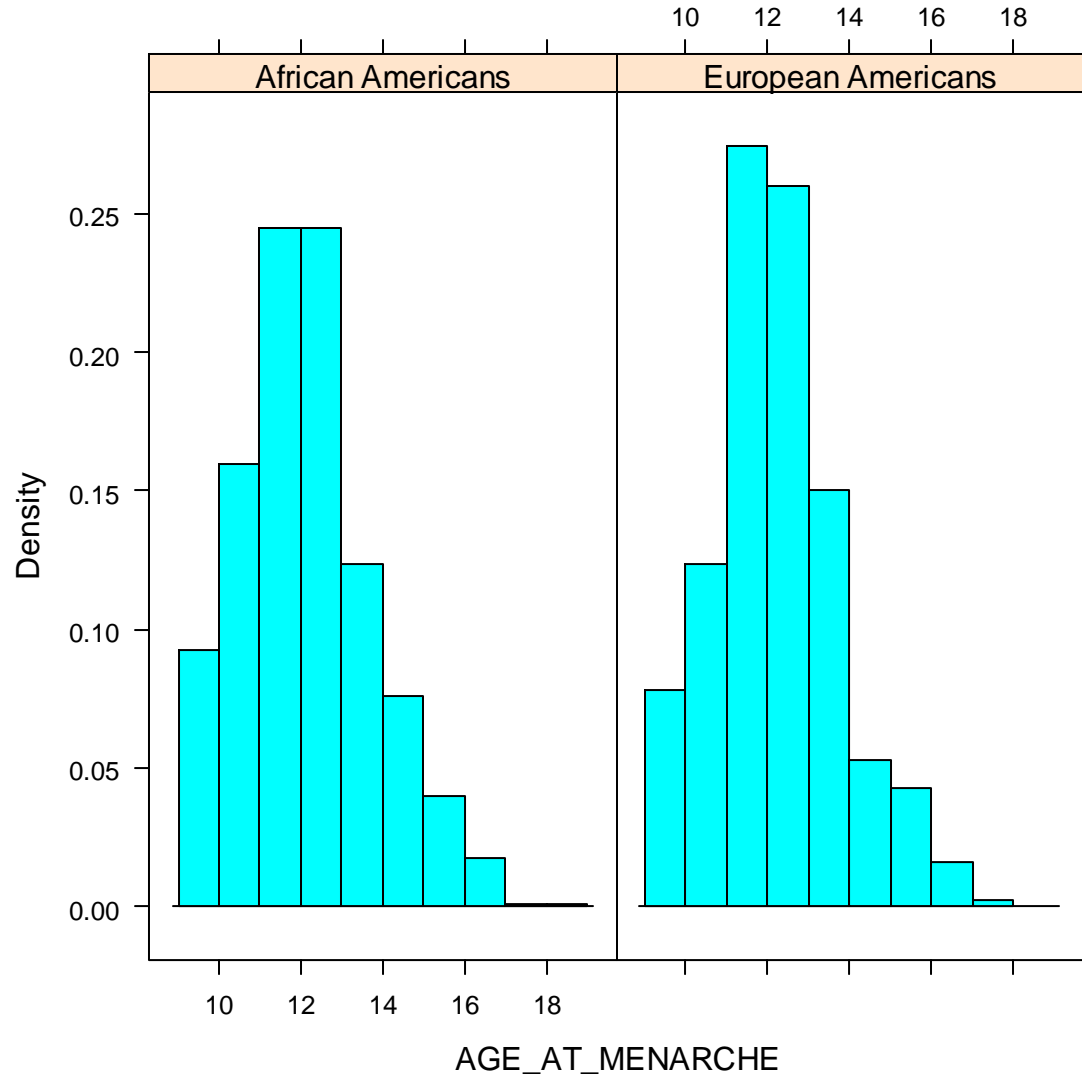
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Kristine Bucasas and Suzanne Leal

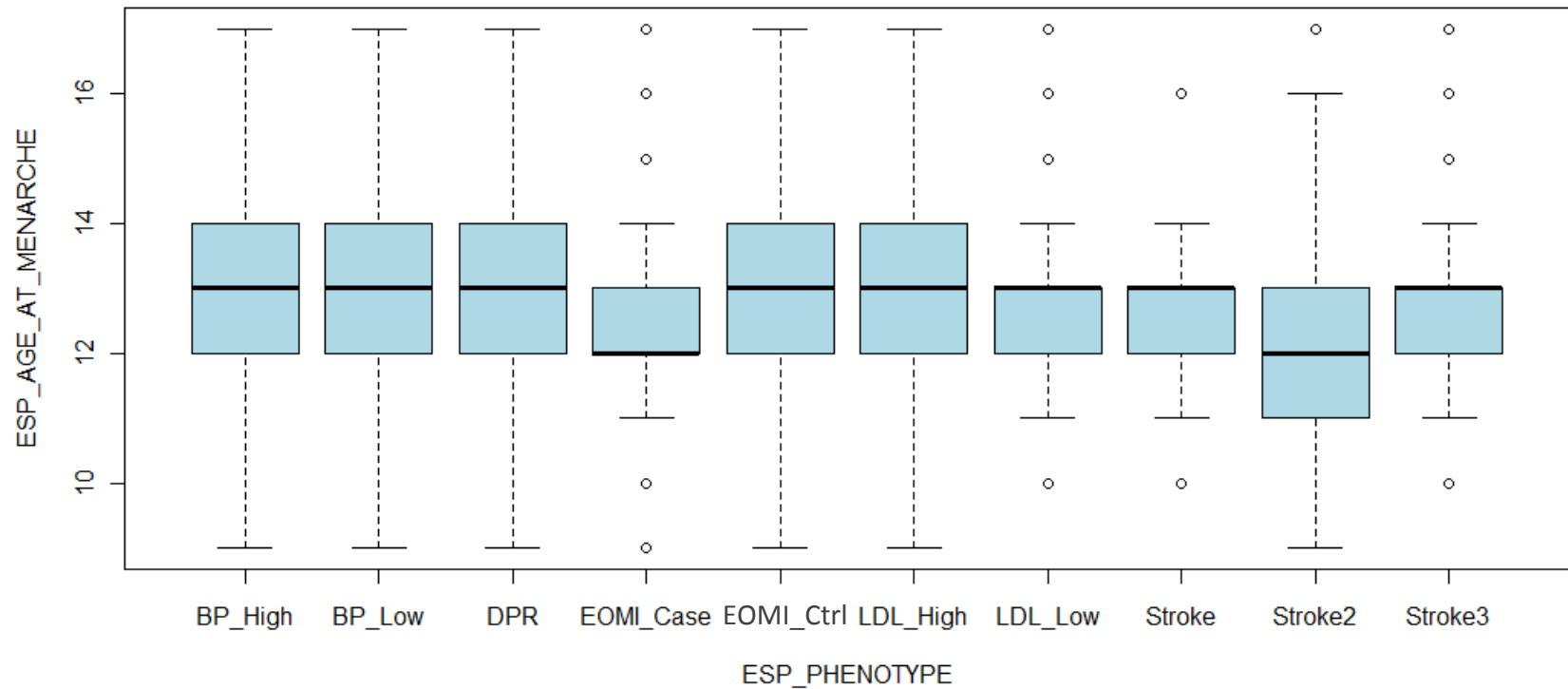
# Age at Menarche Summary

Age at Menarche	ALL	EA	AA
Mean	12.64	12.68	12.60
Median	13	13	13
Stdev	1.66	1.61	1.71
Range	[9,18]	[9,18]	[9,18]
N	2325	1246	1079

# Age at Menarche by Race



# Age at Menarche Distribution by Cohort



# MODELS

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## 1. Age at Menarche African Americans

$$Y = G + \mathbf{PC1}^* + \mathbf{PC2}^* + \text{BMI} + \text{Target} + \text{Cohort} + \text{AGE}^{**}$$

## 2. Age at Menarche European American

$$Y = G + \mathbf{PC1}^* + \text{BMI} + \text{Target} + \text{Cohort}$$

\* PC1 & PC2 were computed separately for AA and EA

\*\* Age at recruitment to control for generational effect

# Association Pipeline

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## 1. Single Nucleotide Variant (SNV) Analyses\*

## 2. Rare Variant Association Analyses\*

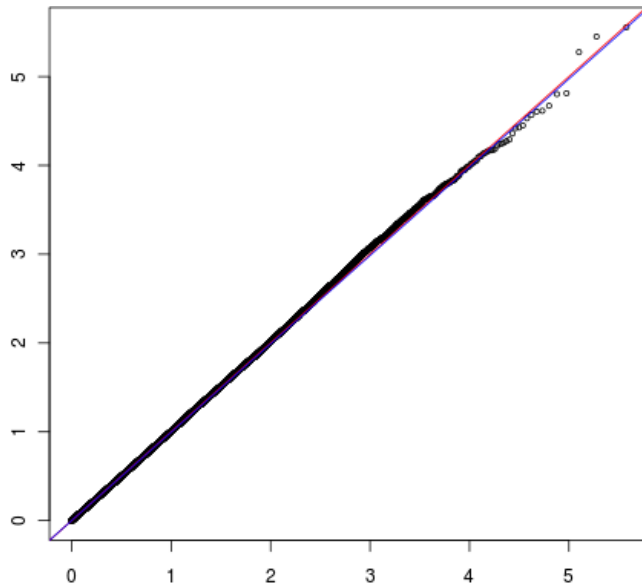
- Types of variants used in analyses:
  - Nonsynonymous
  - Splice sites
- Methods
  - Combined Multivariate & Collapsing Method (CMC)
  - Morris and Zeggini (MZ)
  - Weighted Sum Statistics (WSS)
  - Variable Threshold (VT)

\*Linear regression framework, 2-sided test

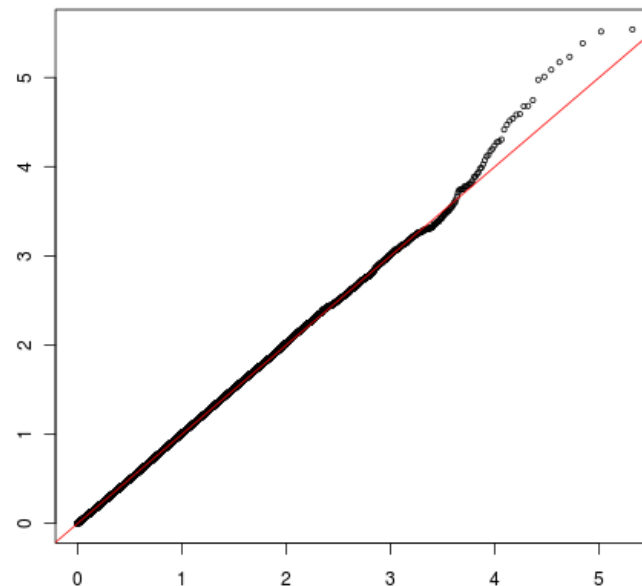
# Single Nucleotide Association Tests

maf  $\geq$  0.01

(A) African American



(B) European American



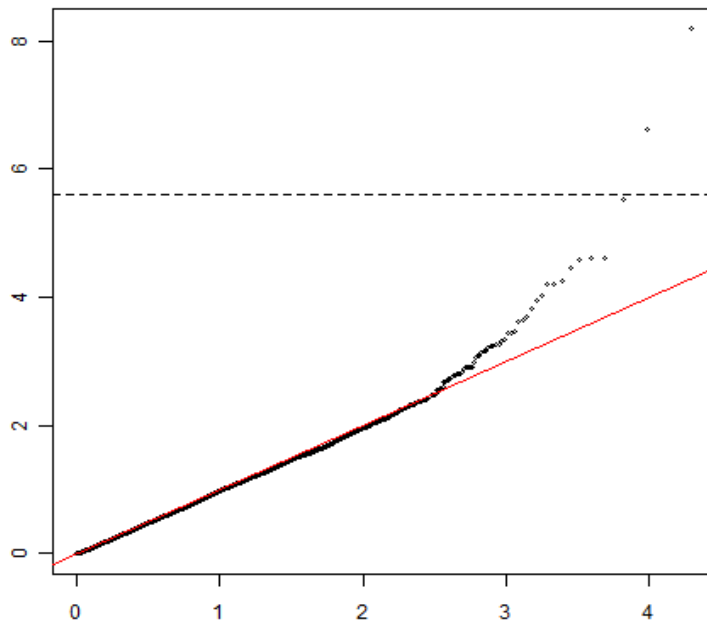
Position	p value	Variant Type
10p11.1	2.78E-06	synonymous
2p13.1	3.54E-06	nonsynonymous
6q21	5.3E-06	nonsynonymous
3p22.2	1.54E-05	nonsynonymous
19p13.3	1.57E-05	synonymous

Position	p value	Variant Type
8q24.11	2.89E-06	intronic
8p22	3.05E-06	nonsynonymous
9q21.33	4.13E-06	synonymous
13q13.3	5.86E-06	intronic
11p15.4	8.19E-06	nonsynonymous

# Aggregate Rare Variant Association Analysis

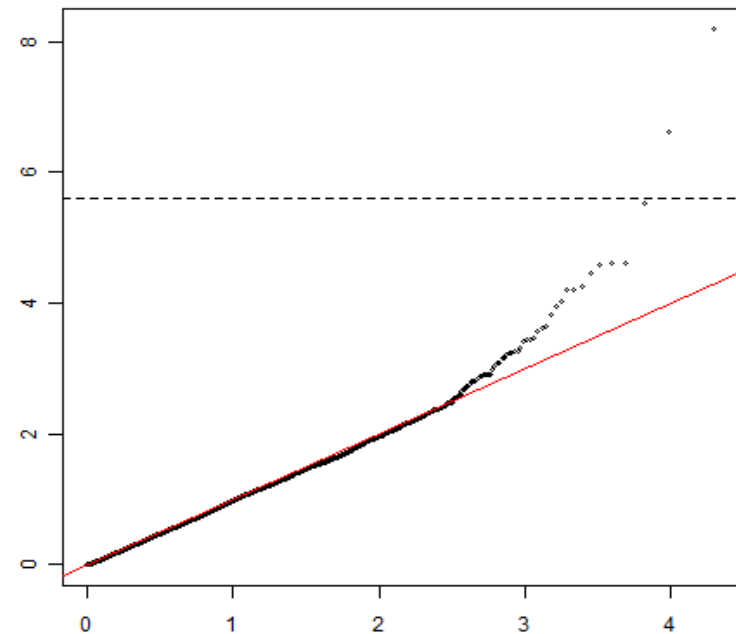
European Americans, maf  $\leq$  1%

(A) MZ



Gene	p value
C1orf27	8.68e-6
PADI2	4.60e-5
TRMT112	4.96e-5
MCM4	5.34e-5

(B) CMC



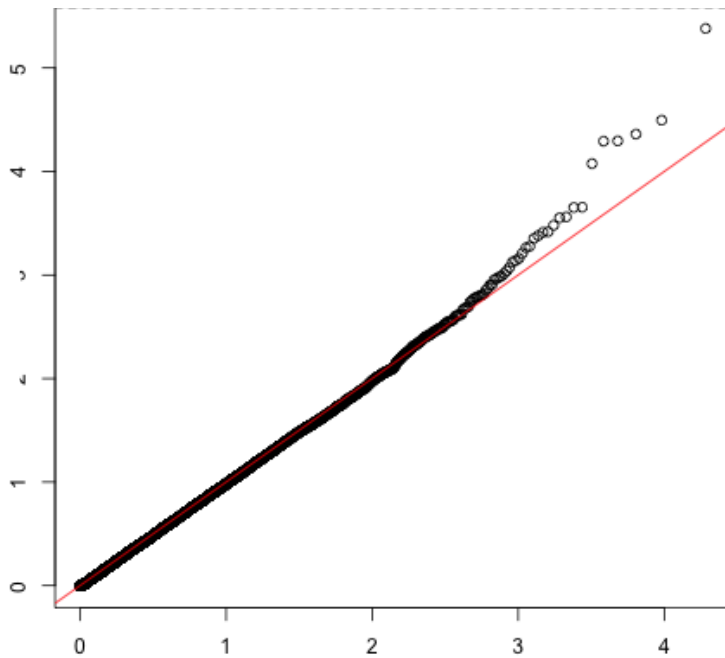
Gene	p value
C1orf27	8.68e-6
TRMT112	4.96e-5
MCM4	5.34e-5
PADI2	5.90e-5



# Aggregate Rare Variant Association Analyses

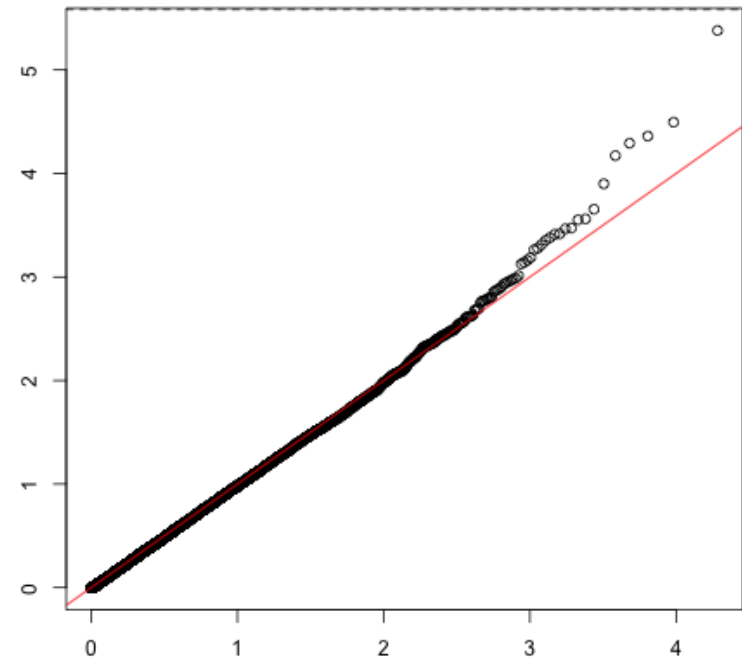
African Americans, maf  $\leq$  1%

(A) MZ



Gene	p value
<b>CNTD2</b>	4.159E-06
NPEPL1	3.198E-05
ANP32E	4.358E-05
ATG4B	5.105E-05

(B) CMC

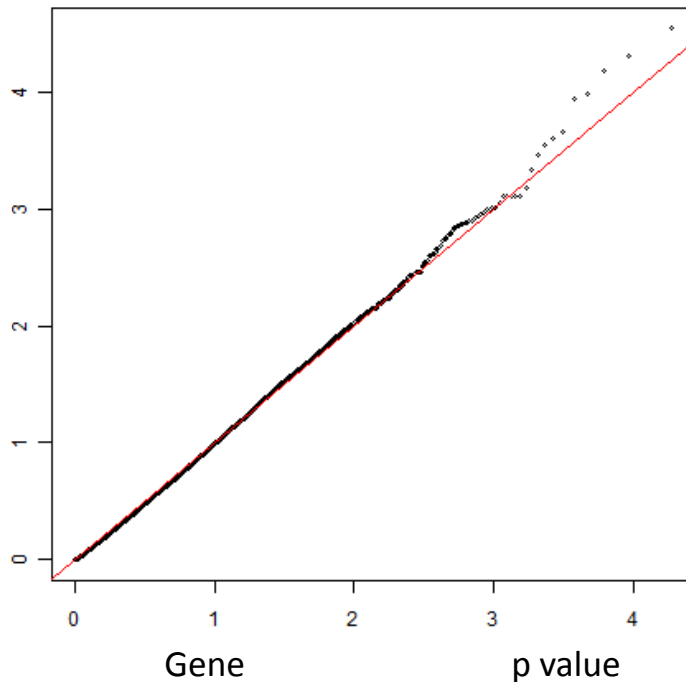


Gene	p value
<b>CNTD2</b>	4.159E-06
NPEPL1	3.198E-05
ANP32E	4.358E-05
ATG4B	5.105E-05

# Aggregate Rare Variant Association Analyses

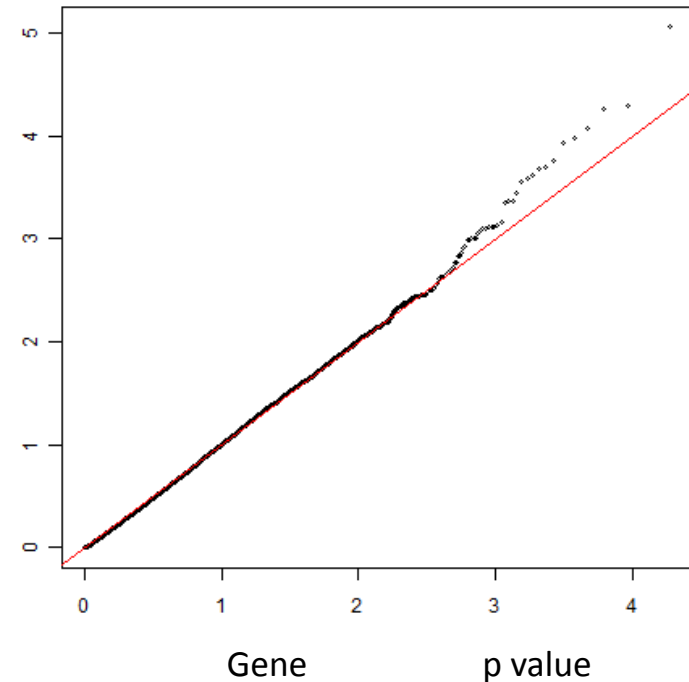
European Americans

(A) MZ at MAF  $\leq 1\%$



<b>C1orf27</b>	8.68e-6
PADI2	4.60e-5
TRMT112	4.96e-5
MCM4	5.34e-5

(B) MZ at MAF  $\leq 5\%$

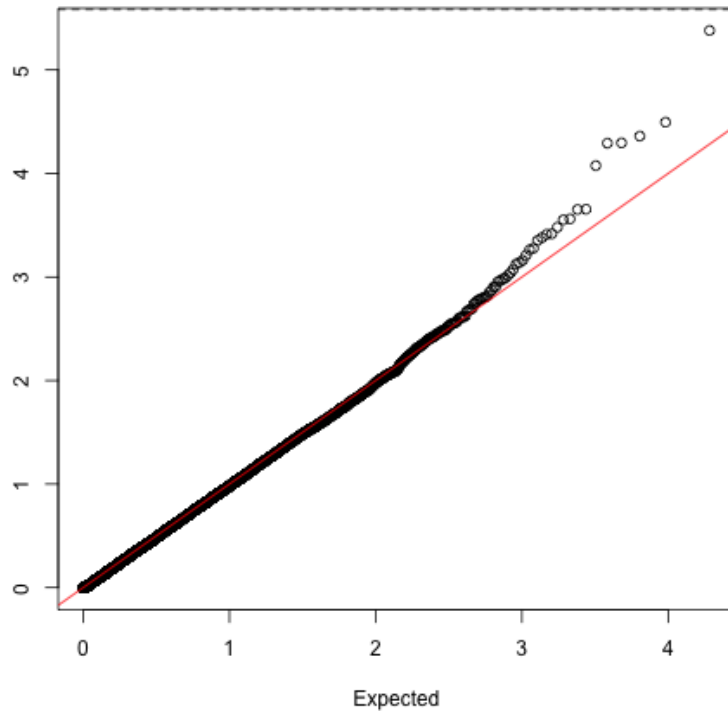


<b>C1orf27</b>	8.68e-6
TRMT112	4.96e-5
MCM4	5.34e-5
STUB1	8.38e-5

# Aggregate Rare Variant Association Analyses

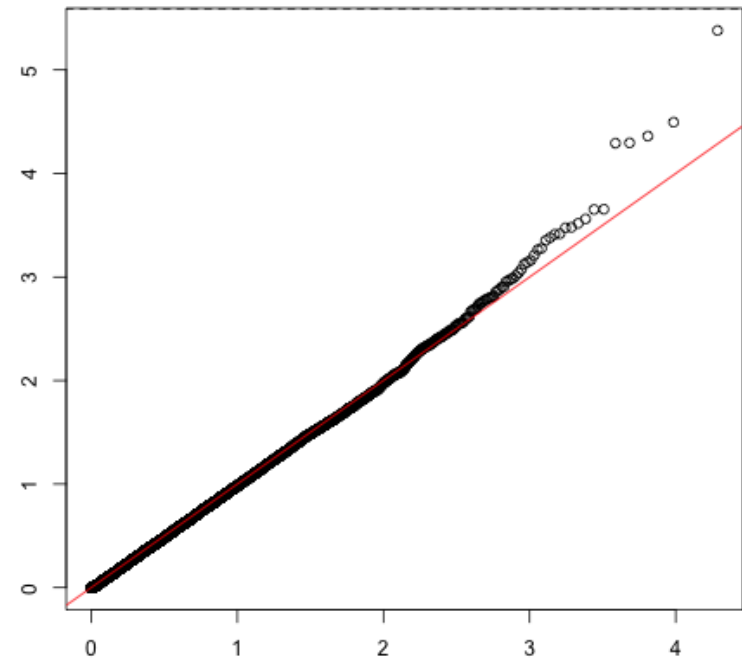
African Americans

(A) MZ at MAF  $\leq 1\%$



Gene	p value
<b>CNTD2</b>	4.159E-06
NPEPL1	3.198E-05
ANP32E	4.358E-05
ATG4B	5.105E-05

(B) MZ at MAF  $\leq 5\%$

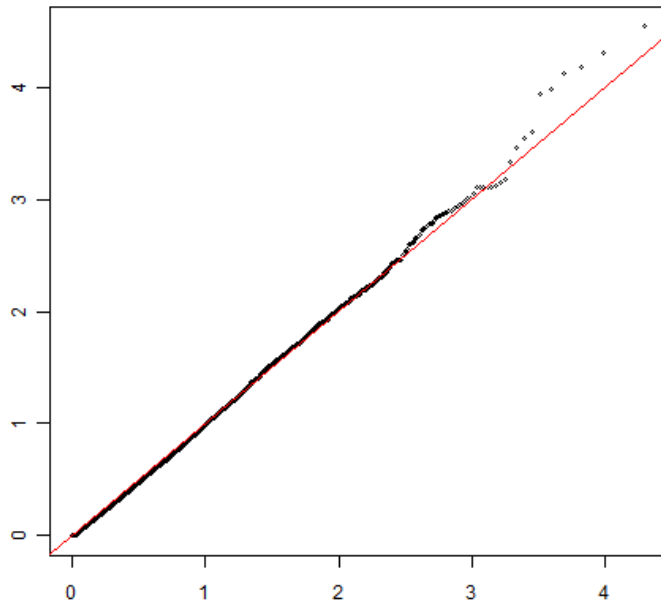


Gene	p value
<b>CNTD2</b>	4.159E-06
NPEPL1	3.198E-05
ANP32E	4.358E-05
PODN	5.069E-05

# Rare Variant Association Analysis

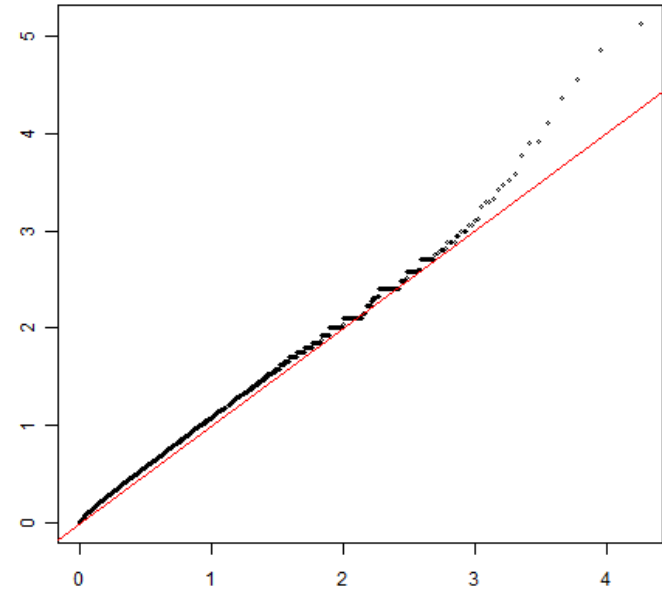
European Americans, maf  $\leq$  5%

(A) WSS



Gene	p value
<b>C1orf27</b>	8.25e-5
TRMT112	4.96e-5
STUB1	6.47e-5
THEM5	1.04e-4

(B) VT

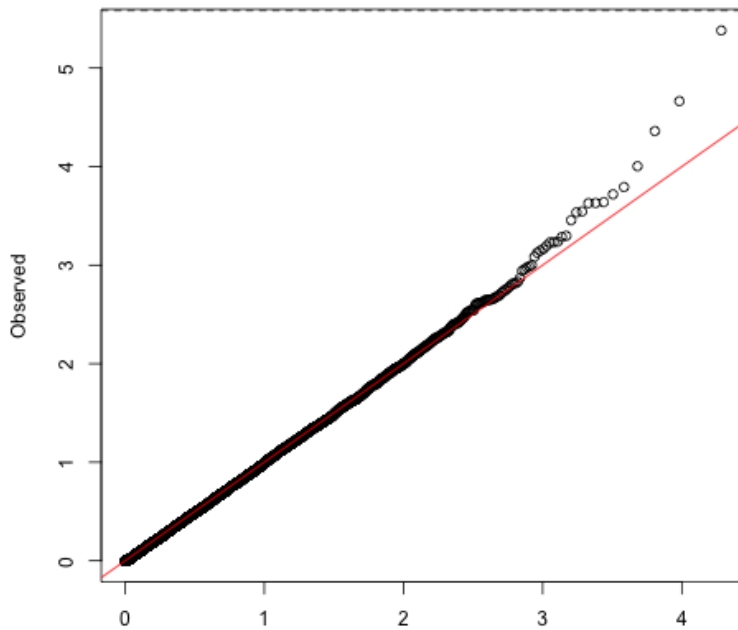


Gene	p value
<b>C1orf27</b>	7.64e-6
RHBDF2	1.42e-5
ETS2	2.84e-5
PRM1	4.29e-5

# Rare Variant Association Analyses

African Americans, maf  $\leq$  5%

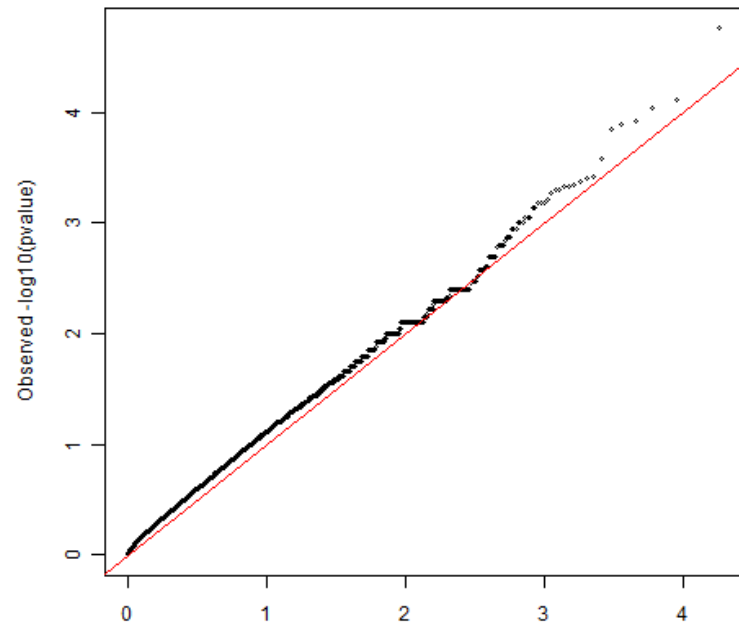
(A) WSS



Gene p value

CNTD2	4.159E-06
PODN	2.165E-05
ANP32E	4.358E-05
CHTOP	9.917E-05

(B) VT



Gene p value

CNTD2	1.74e-5
ANP32E	7.63e-5
CHTOP	9.17e-5
PODN	1.19e-4

# Summary

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- Novel top hits found using SNV and aggregate rare variant analyses
- Different associations detected for European and African Americans
  - Due to different allelic spectrum between African and European Americans
- Different methods replicate the top hit

# Future Directions

---

- Re-evaluate QC
  - correct for inflation
  - Apply more stringent QC filters
  - 5% missingness per target
  - Scan for hits with potential CNV
- Redo analyses with all available phenotype data from ESP6900
- Replication with exome chip data
  - Collaboration with Becky Johnson on 4000 European American women
- Association analyses for age of menopause

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# Central Adiposity

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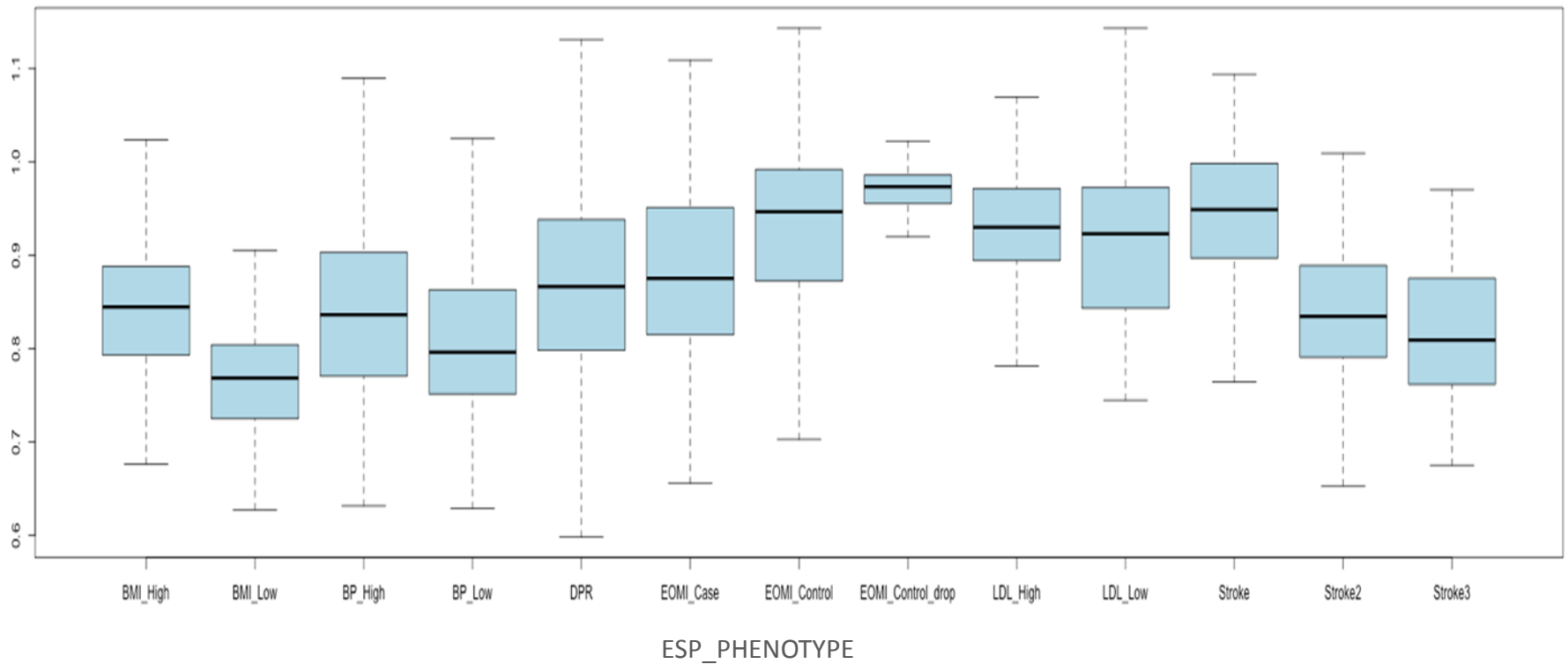
Kristine Bucasas and Suzanne Leal



# Central Adiposity Summary

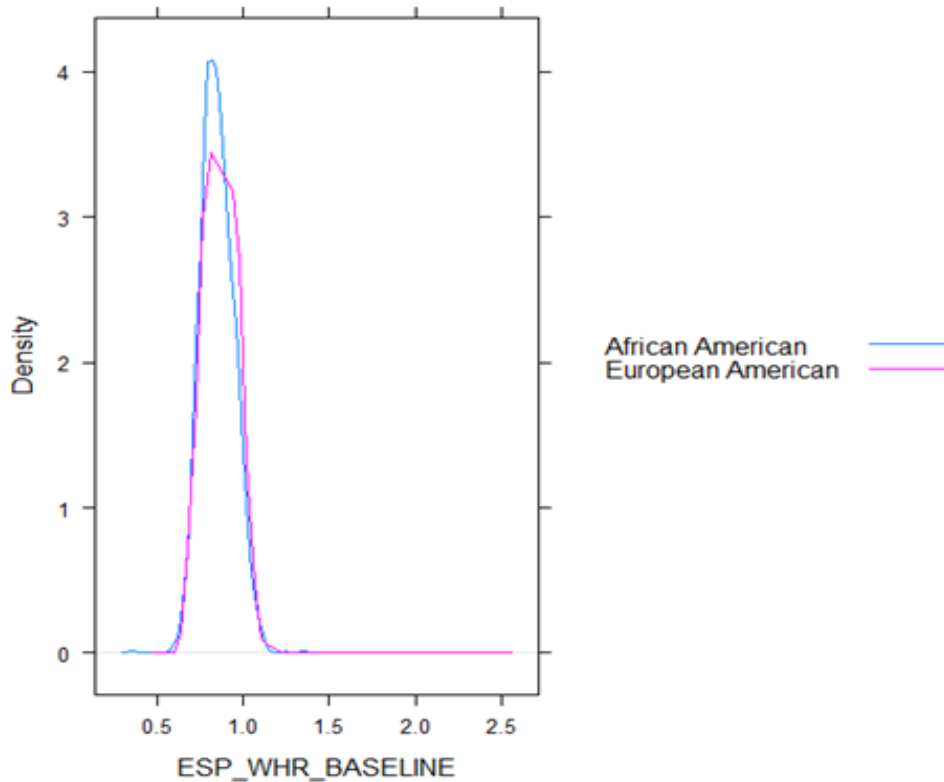
Summary	Waist-to-Hip (WHR) Ratio
Mean	0.863
Median	0.859
Standard Deviation	0.102
Range	(0.463,2.490)
European Americans	2056
African Americans	1452
Male	755
Female	2753
N	<b>3508</b>

# Central Adiposity Distribution in Cohorts



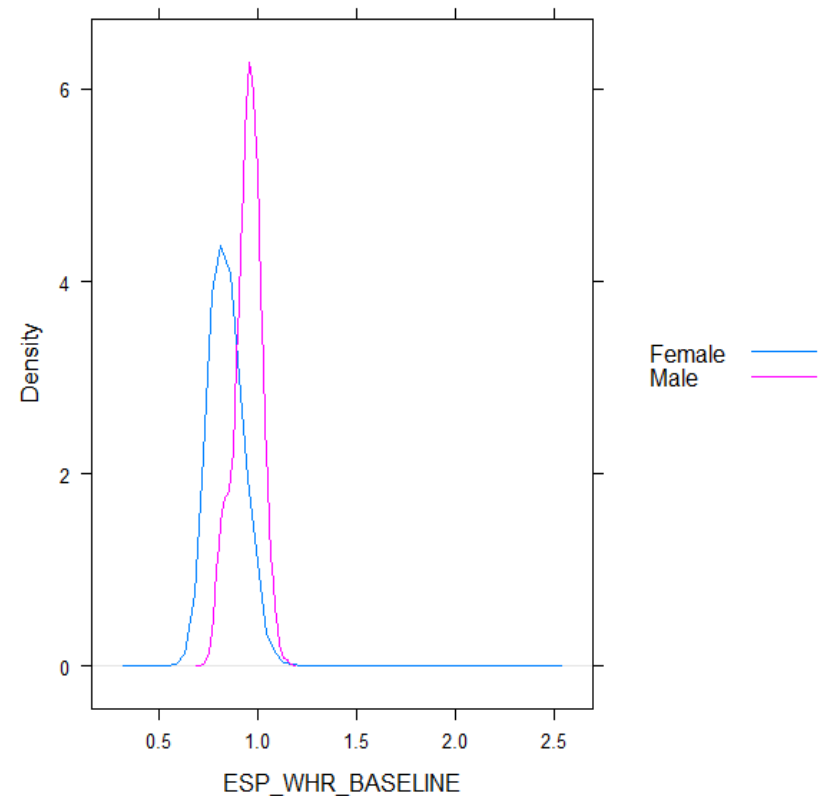
# Central Adiposity Distribution

## A. By Race



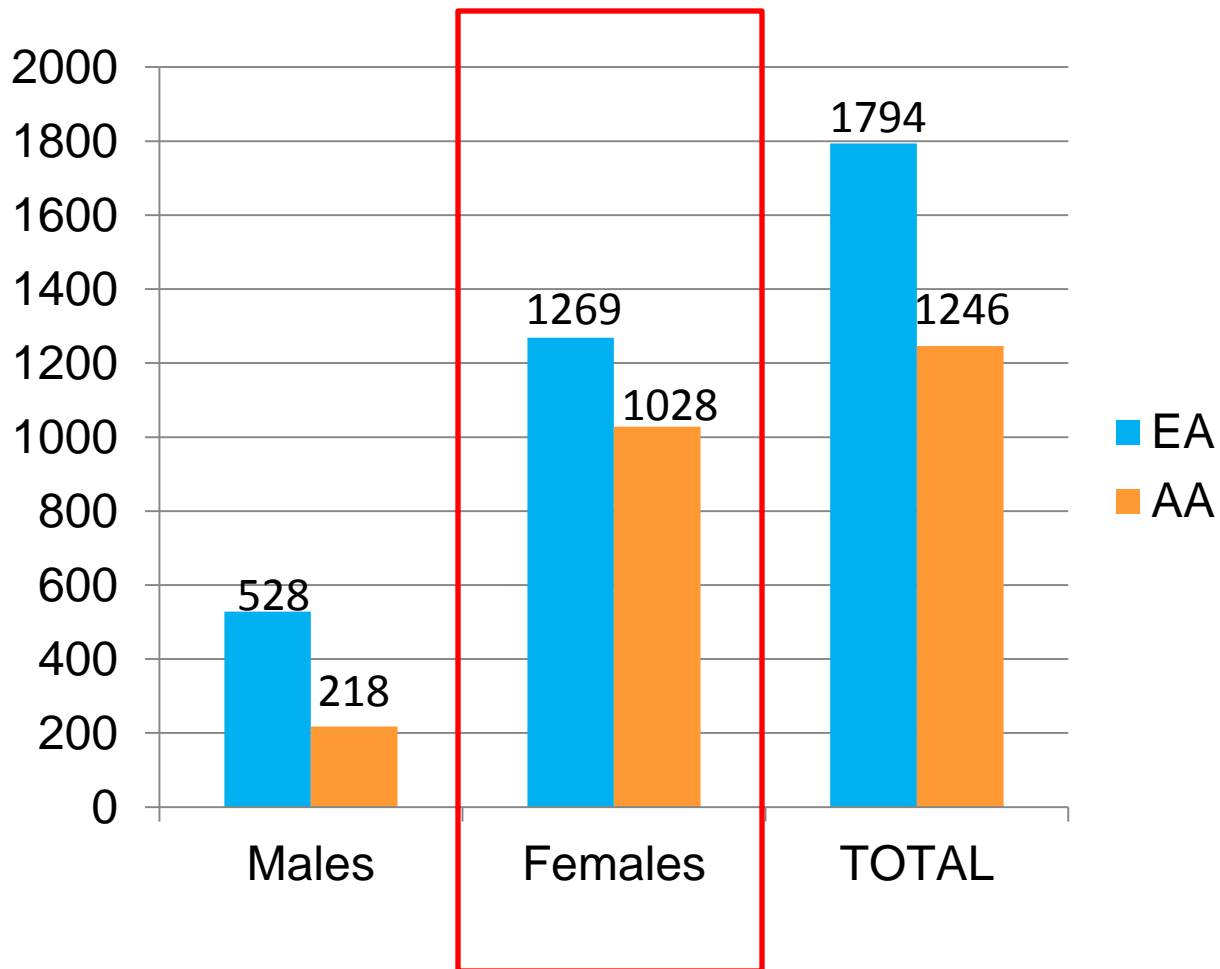
$p=3.03E-3$

## B. By Sex



$p=5.03E-6$

# Sex and Race Distribution of Selected Individuals



# MODELS

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Data Stratified by Race and Sex

$$\text{WHR}_{\text{EA-females}} = G + \mathbf{PC1^*} + \text{BMI} + \text{Smoking} + \text{Age} + \text{Cohort}$$

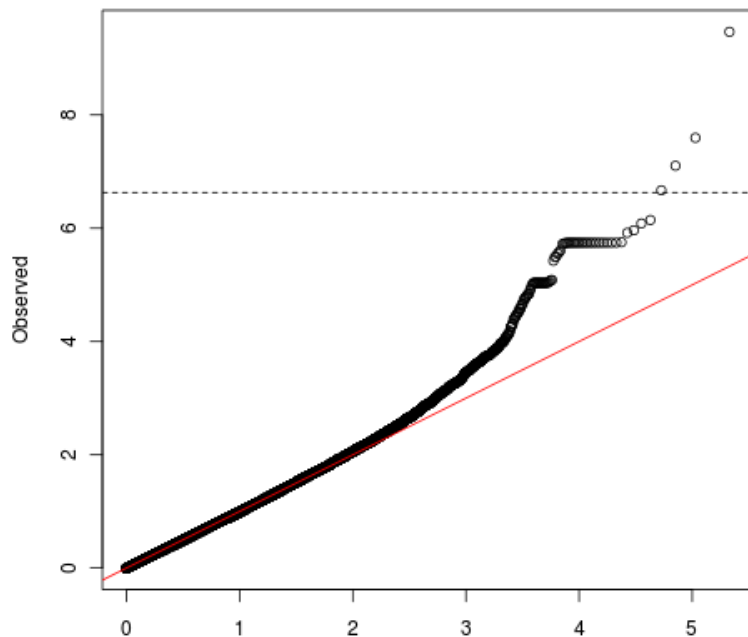
$$\begin{aligned} \text{WHR}_{\text{AA-females}} = G + \mathbf{PC1^*} + \mathbf{PC2^*} + \text{BMI} + \text{Smoking} \\ + \text{Age} + \text{Cohort} \end{aligned}$$

\*PCA components estimated separately in AA and EA

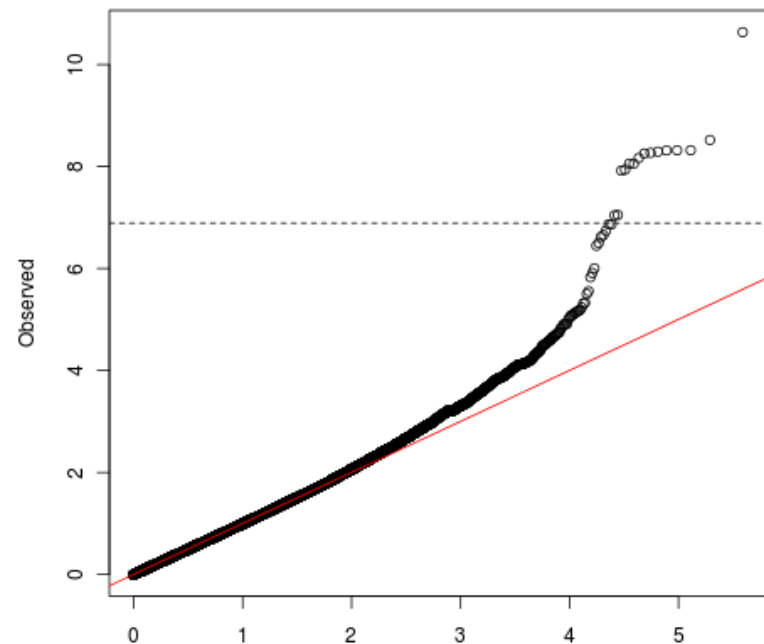
# Single Nucleotide Association Tests

maf  $\geq$  0.01

(A) European American



(B) African American



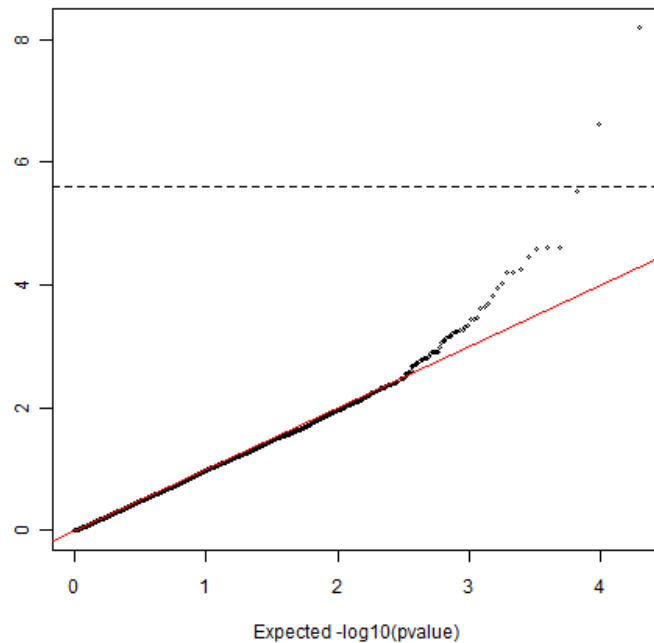
Chr	Position	p value	Variant Type
15	77471361	2.52E-08	nonsynonymous
4	48512169	8.20E-07	nonsynonymous
19	17954011	1.08E-06	intronic
2	110053372	1.20E-06	nonsynonymous
1	248756474	1.76E-06	nonsynonymous

Chr	Position	p value	Variant Type
16	72094802	2.32E-11	UTR3
22	28195332	3.01E-09	synonymous
10	29932891	4.79E-09	intronic SVIL
10	61552480	4.80E-09	UTR3
11	65271233	4.84E-09	ncRNA
9	33220931	5.11E-09	intergenic

# Aggregate Rare Variant Association Analysis

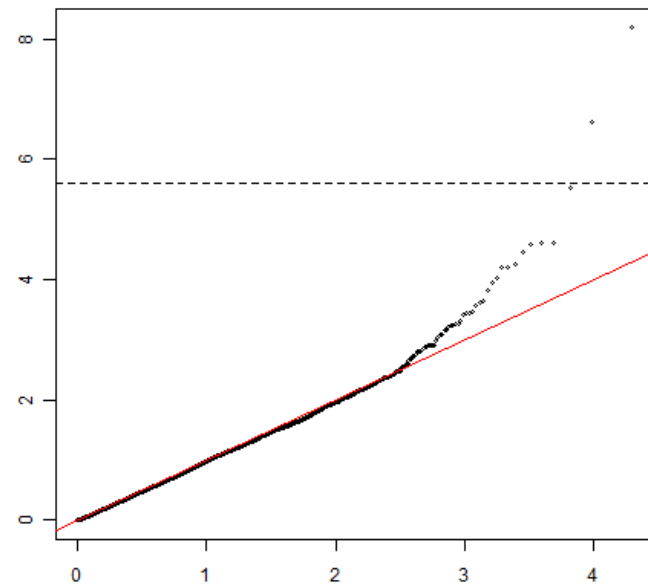
European Americans, maf  $\leq$  1%

(A) MZ



Gene	p value
ITM2A	6.54e-9
TMLHE	2.46e-7
OR2T10	4.05e-6

(B) CMC

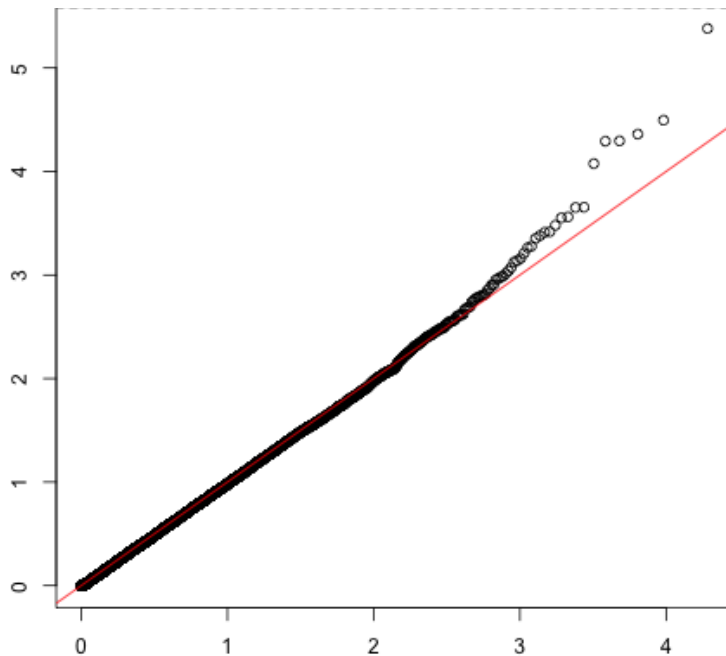


Gene	p value
ITM2A	6.54e-9
TMLHE	2.46e-7
OR2T10	4.05e-6

# Aggregate Rare Variant Association Analyses

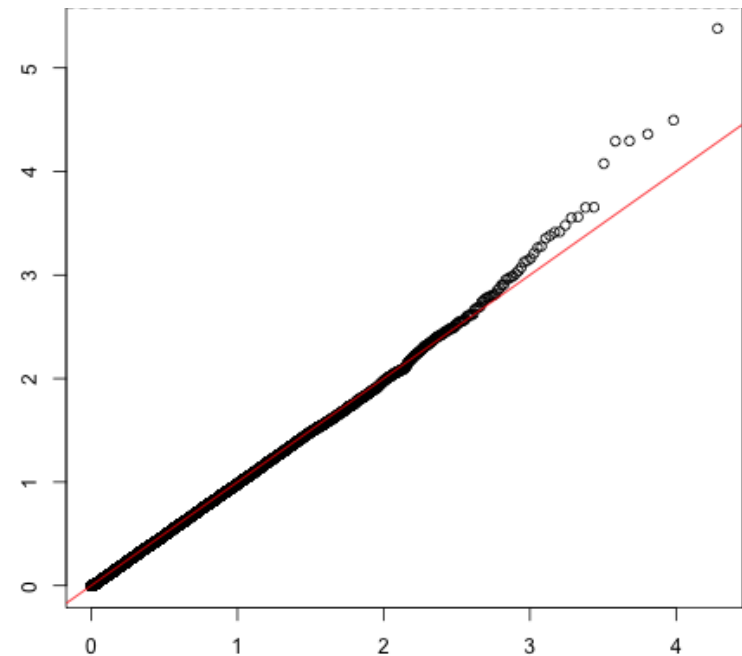
African Americans, maf  $\leq$  1%

(A) MZ



Gene	p value
<b>RANBP1</b>	8.601E-06
ME1	1.472E-05
ESD	1.670E-05
BMP2K	2.049E-05

(B) CMC



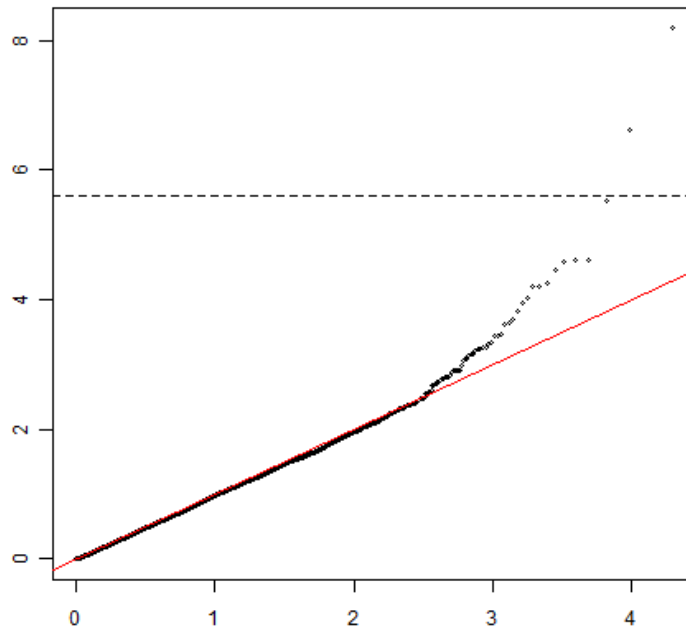
Gene	p value
<b>RANBP1</b>	8.601E-06
ME1	1.472E-05
ESD	1.670E-05
BMP2K	2.049E-05



# Aggregate Rare Variant Association Analyses

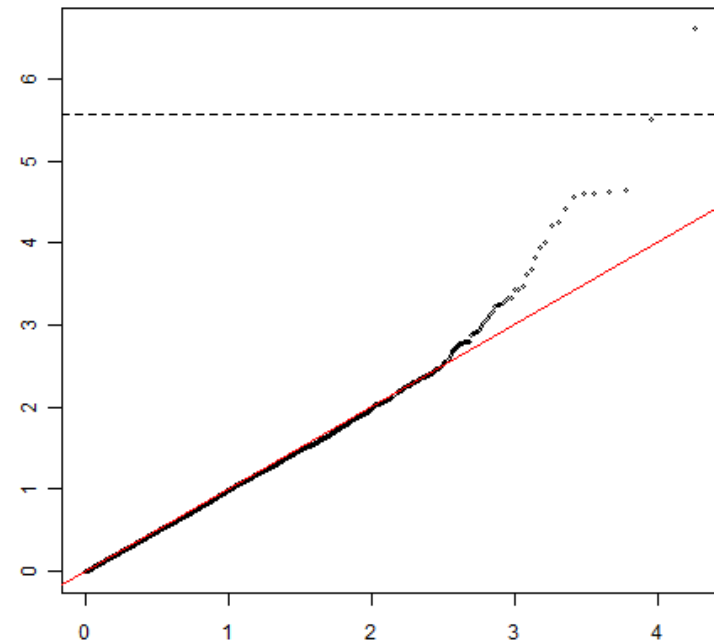
European Americans

(A) MZ at MAF  $\leq 1\%$



Gene	p value
ITM2A	6.54e-9
TMLHE	2.46e-7
OR2T10	4.05e-6

(B) MZ at MAF  $\leq 5\%$

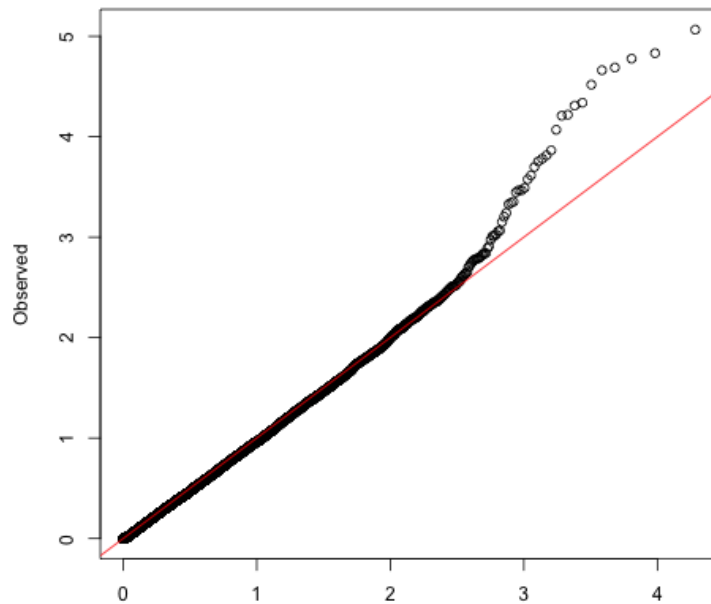


Gene	p value
ITM2A	1.54e-7
TMLHE	4.46e-6
OR2T10	3.05e-6

# Aggregate Rare Variant Association Analyses

African Americans

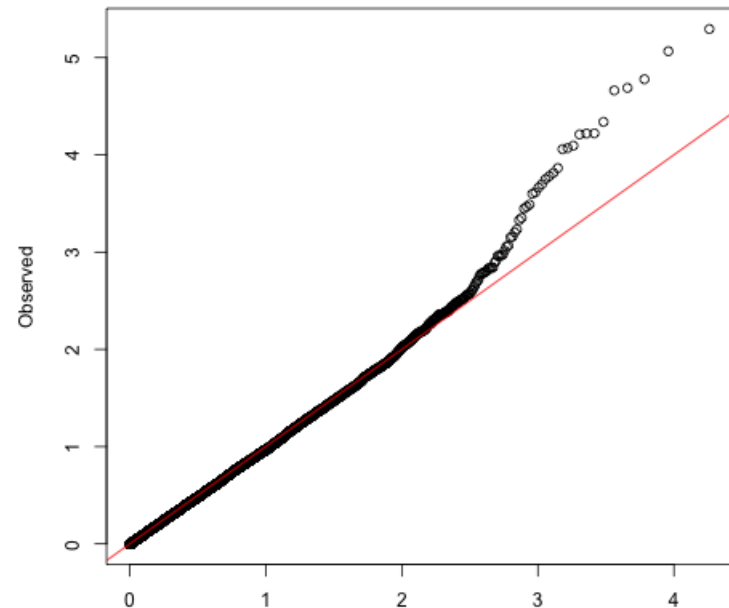
(A) MZ at MAF  $\leq 1\%$



Gene p value

<b>RANBP1</b>	8.601E-06
ME1	1.472E-05
ESD	1.670E-05
BMP2K	2.049E-05

(B) MZ at MAF  $\leq 5\%$



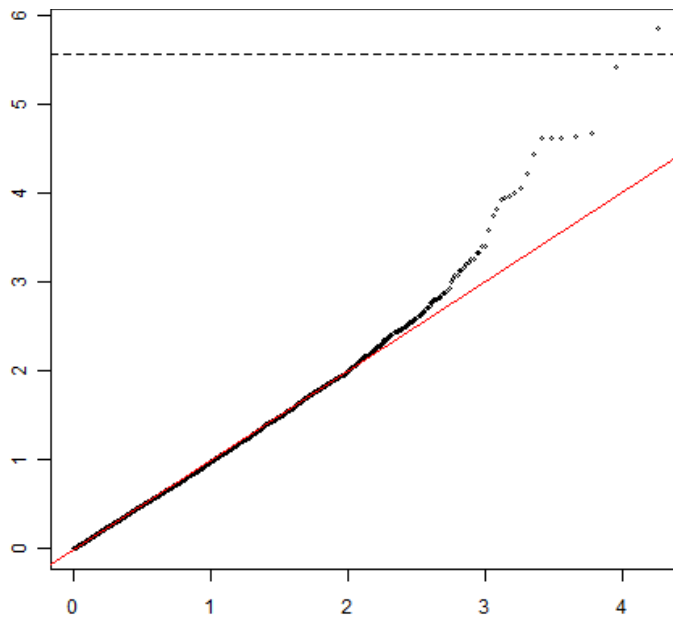
Gene p value

ME1	5.09E-06
<b>RANBP1</b>	8.60E-06
ESD	1.67E-05
BMP2K	2.05E-05

# Rare Variant Association Analysis

European Americans, maf  $\leq$  5%

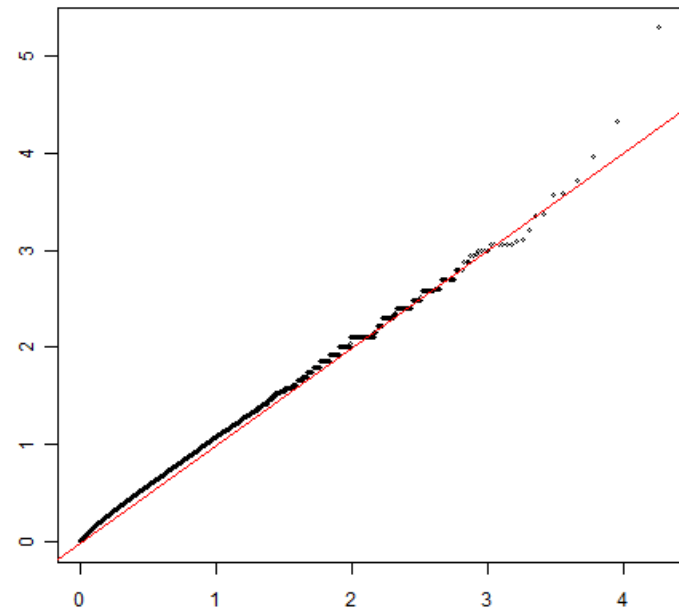
(A) WSS



Gene p value

Gene	p value
ITM2A	1.44e-6
TMLHE	3.89e-6
EVX2	2.11e-5
AMELX	2.31e-5

(B) VT



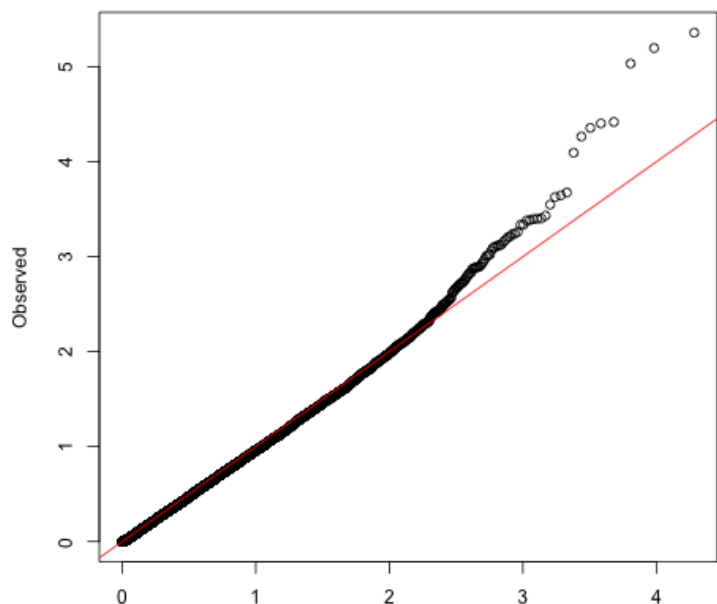
Gene p value

Gene	p value
IKBKB	5.20e-6
EVX2	4.85e-5
CATSPER4	1.11e-4
ZNF257	1.96e-4

# Rare Variant Association Analyses

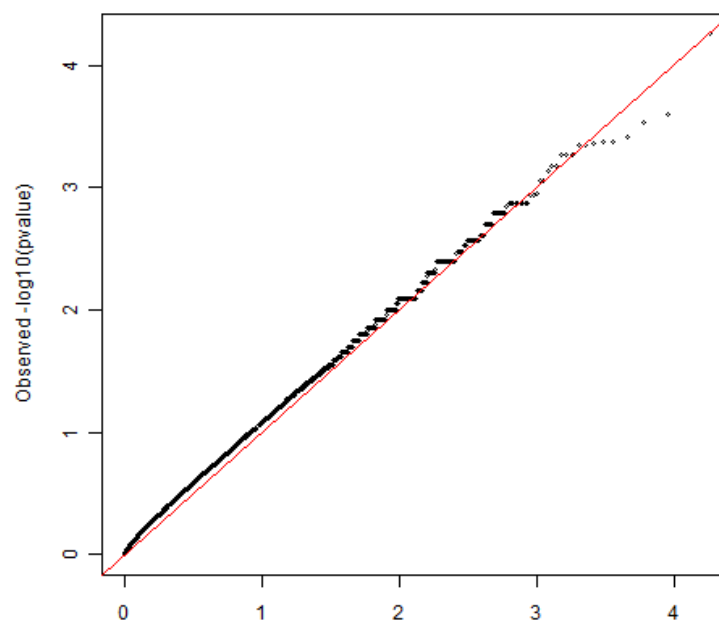
African Americans, maf  $\leq$  5%

(A) WSS



Gene	p value
ESD	4.370E-06
NMT1	6.334E-06
<b>RANBP1</b>	9.251E-06
ME1	3.810E-05

(B) VT



Gene	p value
RGPD1	5.56e-5
POLR2B	2.50e-4
C17orf109	2.96e-4
LRRC39	3.81e-4

# Summary

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- Most top hits are novel found using SNV and aggregate rare variant analyses
- Different association hits between European and African Americans
  - Due to different allelic spectrum between African and European Americans

# Future Directions

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- Improve model and use lambda correction to control inflation
- Reevaluate QC
  - correct for inflation
  - Apply more stringent QC filters
  - 5% missingness per target
  - Scan for hits with potential CNV
- Redo analyses with all available phenotype data from ESP6900
- Attempt replication using the exome chip

# Acknowledgements

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## NHLBI-ESP

With special thanks to:

- Paul Auer
- Debbie Nickerson
- Leslie Lange
- Gao Wang
- Mengyuan Kan
- Alejandra Rodriguez
- Kari North
- Alex Reiner
- Goncalo Abecasis
- Goo Jun
- Hyun Min Kang
- Stanley Hooker

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