

# ACMG-ClinVar Penetrance RMarkdown

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**Working Directory:** /Users/jamesdiao/Documents/Kohane\_Lab/2017-ACMG-penetrance/ACMG\_Penetrance

# 1 Download, Transform, and Load Data

## 1.1 Collect ACMG Gene Panel

<http://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/>

## Table from ACMG SF v2.0 Paper 60 x 8 (selected rows):

	Phenotype	MIM_disorder	PMID_Gene_Reviews_entry
<b>N1</b>	Hereditary breast and ovarian cancer	604370 612555	20301425
<b>N2</b>	Hereditary breast and ovarian cancer	604370 612555	20301425
<b>N3</b>	Li-Fraumeni syndrome	151623	20301488
<b>N4</b>	Peutz-Jeghers syndrome	175200	20301443
<b>N5</b>	Lynch syndrome	120435	20301390

Table continues below

	Typical_age_of_onset	Gene	MIM_gene	Inheritance	Variants_to_report
<b>N1</b>	Adult	BRCA1	113705	AD	KP&EP
<b>N2</b>	Adult	BRCA2	600185	AD	KP&EP
<b>N3</b>	Child/Adult	TP53	191170	AD	KP&EP
<b>N4</b>	Child/Adult	STK11	602216	AD	KP&EP
<b>N5</b>	Adult	MLH1	120436	AD	KP&EP

## ACMG-59 Genes:

```
## [1] BRCA1 BRCA2 TP53 STK11 MLH1 MSH2 MSH6 PMS2
## [9] APC MUTYH BMPR1A SMAD4 VHL MEN1 RET PTEN
## [17] RB1 SDHD SDHAF2 SDHC SDHB TSC1 TSC2 WT1
## [25] NF2 COL3A1 FBN1 TGFBR1 TGFBR2 SMAD3 ACTA2 MYH11
## [33] MYBPC3 MYH7 TNNT2 TNNI3 TPM1 MYL3 ACTC1 PRKAG2
## [41] GLA MYL2 LMNA RYR2 PKP2 DSP DSC2 TMEM43
## [49] DSG2 KCNQ1 KCNH2 SCN5A LDLR APOB PCSK9 ATP7B
## [57] OTC RYR1 CACNA1S
```

## 1.2 Download ClinVar VCF

[ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/vcf\\_GRCh37/clinvar.vcf.gz](ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/vcf_GRCh37/clinvar.vcf.gz)

ClinVar is the central repository for variant interpretations. Relevant information from the VCF includes:

(a) CLNSIG = “Variant Clinical Significance, 0 - Uncertain, 1 - Not provided, 2 - Benign, 3 - Likely benign, 4 - Likely pathogenic, 5 - Pathogenic, 6 - Drug response, 7 - Histocompatibility, 255 - Other”

(b) CLNDBN = “Variant disease name”

(c) CLNDSDBID = “Variant disease database ID”

(d) CLNREVSTAT = “Review Status, no\_assertion, no\_criteria, single - criterion provided single submitter, mult - criteria provided multiple submitters no conflicts, conf - criteria provided conflicting interpretations, exp - Reviewed by expert panel, guideline - Practice guideline”

(e) INTERP = Pathogenicity (likely pathogenic or pathogenic; CLNSIG = 4 or 5)

##	VAR_ID	CHROM	POS	ID	REF	ALT
##	59912	4_68619662_A_G	4	68619662	.	A G
##	86327	7_977079_G_A	7	977079	.	G A
##	122198	10_103530370_C_T	10	103530370	.	C T
##	122206	10_103534589_G_C	10	103534589	.	G C
##	189946	17_7579368_A_G	17	7579368	.	A G
##	232565	X_585258_C_A	X	585258	.	C A
##	232567	X_585263_G_C	X	585263	.	G C
##	232569	X_591261_G_A	X	591261	.	G A
##	232571	X_591695_C_T	X	591695	.	C T
##	232573	X_591752_G_A	X	591752	.	G A
##	232575	X_591926_T_G	X	591926	.	T G
##	232577	X_595354_G_T	X	595354	.	G T
##	232579	X_595379_G_T	X	595379	.	G T
##	232581	X_595422_A_G	X	595422	.	A G
##	232585	X_601571_C_T	X	601571	.	C T
##	232587	X_601577_G_C	X	601577	.	G C
##	232589	X_601578_C_A	X	601578	.	C A
##	232592	X_601772_C_T	X	601772	.	C T
##	232595	X_605321_G_A	X	605321	.	G A
##	232598	X_605654_A_AAG	X	605654	.	A AAG
##	232600	X_1407492_T_C	X	1407492	.	T C
##	232602	X_1409305_G_C	X	1409305	.	G C
##	232604	X_1428421_G_T	X	1428421	.	G T
##	232700	X_8700077_T_C	X	8700077	.	T C
##	243456	Y_535123_N_NTGT	Y	535123	.	N NTGT
##					CLNSIG	INTERP
##	59912				Pathogenic	TRUE
##	86327				protective	FALSE
##	122198				Likely_pathogenic	TRUE
##	122206				Likely_pathogenic	TRUE
##	189946	Likely_benign, Uncertain_significance				FALSE
##	232565				Pathogenic	TRUE
##	232567				Pathogenic	TRUE
##	232569	Uncertain_significance				FALSE
##	232571	Benign, Likely_benign, not_provided				FALSE
##	232573				Likely_benign	FALSE
##	232575				Benign	FALSE
##	232577				Likely_benign	FALSE
##	232579				Pathogenic	TRUE
##	232581				Likely_pathogenic	TRUE

```
## 232585                Pathogenic  TRUE
## 232587                Pathogenic  TRUE
## 232589                Pathogenic  TRUE
## 232592                Pathogenic  TRUE
## 232595                Uncertain_significance  FALSE
## 232598                Uncertain_significance  FALSE
## 232600                Benign  FALSE
## 232602                Benign  FALSE
## 232604                Benign  FALSE
## 232700                Pathogenic  TRUE
## 243456                Pathogenic  TRUE
```

## Processed ClinVar data frame 224657 x 21 (selected rows/columns):

VAR_ID	CHROM	POS	ID	REF	ALT	CLNSIG	INTERP
1_955619_G_C	1	955619	.	G	C	Likely_benign	FALSE
1_957568_A_G	1	957568	.	A	G	Uncertain_significance	FALSE
1_957605_G_A	1	957605	.	G	A	Likely_benign	TRUE
1_957640_C_T	1	957640	.	C	T	Uncertain_significance	FALSE

Table continues below

GOLD_STARS	LMM	pathogenic	benign	conflicted	LMM_INTERP	CLNREVSTAT
1	0	FALSE	TRUE	FALSE	FALSE	1
1	0	FALSE	TRUE	FALSE	FALSE	1
0	0	TRUE	FALSE	FALSE	FALSE	1
1	0	FALSE	TRUE	FALSE	FALSE	1

Table continues below

CLNDSDBID
1
1
1
1

### 1.3 Download 1000 Genomes VCFs

ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/ALL.[chrom].phase3\_[version].20130502.genotypes.vcf.gz  
Downloaded 1000 Genomes VCFs are saved in: /Users/jamesdiao/Documents/Kohane\_Lab/2017-ACMG-penetrance/1000G/

## Download report: region and successes: 59 x 6 (selected rows):

gene	name	chrom	start	end	downloaded
BRCA1	NM_007294	17	41196311	41277500	TRUE
BRCA2	NM_000059	13	32889616	32973809	TRUE
TP53	NM_000546	17	7571719	7590868	TRUE
STK11	NM_000455	19	1205797	1228434	TRUE

gene	name	chrom	start	end	downloaded
MLH1	NM_000249	3	37034840	37092337	TRUE

## File saved as download\_output.txt in Supplementary\_Files

## 1.4 Import and Process 1000 Genomes VCFs

- Unnest the data frames to 1 row per variant\_ID key (CHROM\_POSITION\_REF\_ALT).
- Remove all insertions, deletions, CNV, etc, and keep only missense variants (1 REF, 1 ALT)
- For 1000 Genomes: convert genomes to allele counts. For example: (0|1) becomes 1, (1|1) becomes 2. Multiple alleles are unnested into multiple counts. For example: (0|2) becomes 0 for the first allele (no 1s) and 1 for the second allele (one 2).

## Processed 1000 Genomes VCFs: 141467 x 2516 (selected rows/columns):

GENE	AF_1000G	VAR_ID	CHROM	POS	ID	REF	ALT
BRCA1	0.004193290	17_41196363_C_T	17	41196363	rs8176320	C	T
BRCA1	0.008386580	17_41196368_C_T	17	41196368	rs184237074	C	T
BRCA1	0.000998403	17_41196372_T_C	17	41196372	rs189382442	T	C
BRCA1	0.342252000	17_41196408_G_A	17	41196408	rs12516	G	A
BRCA1	0.000399361	17_41196409_G_C	17	41196409	rs548275991	G	C

Table continues below

HG00096	HG00097	HG00099	HG00100	HG00101	HG00102
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
1	0	1	1	0	2
0	0	0	0	0	0

## 1.5 Import and Process gnomAD/ExAC VCFs

- Unnest the data frames to 1 row per variant\_ID key (CHROM\_POSITION\_REF\_ALT).
- Remove all insertions, deletions, CNV, etc, and keep only missense variants (1 REF, 1 ALT)
- Collect superpopulation-level allele frequencies: African = AFR, Latino = AMR, European (Finnish + Non-Finnish) = EUR, East.Asian = EAS, South.Asian = SAS.

## Processed gnomAD VCFs: 96742 x 48 (selected rows/columns):

	GENE	AF_GNOMAD	VAR_ID
<b>496610</b>	RYR1	0.00004290	19_39008204_C_T
<b>5881</b>	STK11	0.00000830	19_1206958_G_A
<b>427111</b>	RYR1	0.00000396	19_38997066_C_G
<b>368710</b>	APOB	0.00000396	2_21252618_G_C
<b>134812</b>	APOB	0.00000397	2_21230572_C_A

## Processed ExAC VCFs: 59883 x 45 (selected rows/columns):

	GENE	AF_EXAC	VAR_ID
<b>1075</b>	BRCA1	0.000008246	17_41256134_T_C
<b>7528</b>	MSH6	0.000008397	2_48028276_G_A
<b>33266</b>	TNNI3	0.000280200	19_55671433_G_A
<b>42599</b>	TMEM43	0.000008245	3_14170920_T_G
<b>334710</b>	RYR1	0.000016520	19_39013830_G_A

## 1.6 Collect 1000 Genomes Phase 3 Populations Map

This will allow us to assign genotypes from the 1000 Genomes VCF to ancestral groups.

From: [ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/integrated\\_call\\_samples\\_v3.20130502.ALL.panel](ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/integrated_call_samples_v3.20130502.ALL.panel)

## Phase 3 Populations Map Table: 2504 x 4 (selected rows)

sample	pop	super_pop	gender
HG01912	ACB	AFR	male
HG00182	FIN	EUR	male
HG00239	GBR	EUR	female
NA21135	GIH	SAS	male
NA20849	GIH	SAS	female
HG04186	BEB	SAS	female

## 1.7 Merge ClinVar with gnomAD, ExAC, and 1000 Genomes

## Breakdown of ClinVar Variants

Subset_ClinVar	Number_of_Variants
Total ClinVar	224657
LP/P	42826
ACMG LP/P	9139
ACMG LP/P in gnomAD	141
ACMG LP/P in ExAC	100
ACMG LP/P in 1000 Genomes	12

## Breakdown of ACMG-gnomAD Variants

Subset_gnomAD	Number_of_Variants
ACMG in gnomAD	96742
ClinVar-ACMG in gnomAD	14517
LP/P-ACMG in gnomAD	141

## Breakdown of ACMG-ExAC Variants

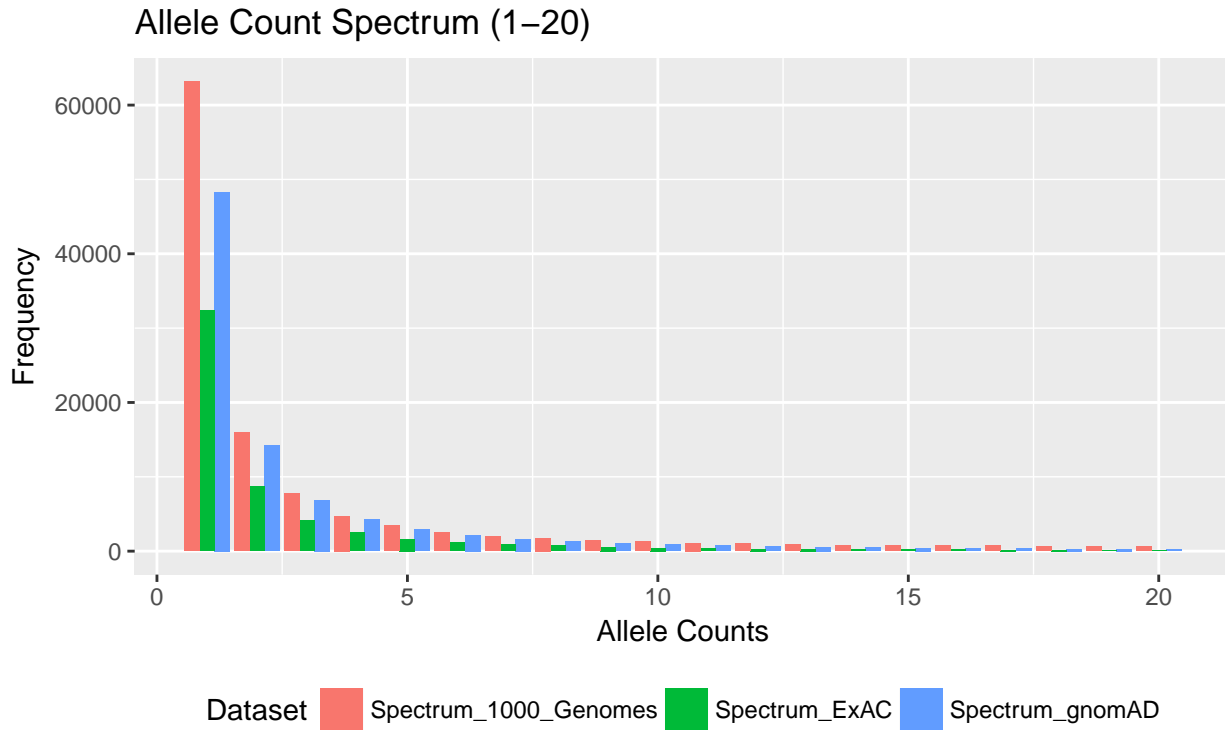
Subset_gnomAD	Number_of_Variants
ACMG in ExAC	59883
ClinVar-ACMG in ExAC	11155
LP/P-ACMG in ExAC	100

## Breakdown of ACMG-1000G Variants

Subset_gnomAD	Number_of_Variants
ACMG in 1000G	141466
ClinVar-ACMG in 1000G	6080
LP/P-ACMG in 1000G	12

## 2 Plot Summary Statistics Across Populations

### 2.1 Distribution of Allele Counts

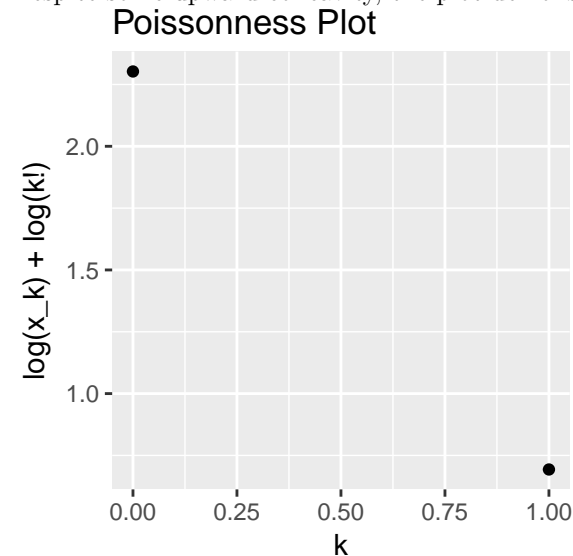


We can model this as a Poisson binomial- the summed occurrence of variants with different allele frequencies. If we assume that the allele frequencies are approximately the same and that variants are independent, (may not be good assumptions), then the distribution follows  $\text{Binom}(n, p)$ ,  $n = \#$  samples and  $p =$  allele frequency. Because  $n$  is large and  $p$  is small, we can then use a Poisson approximation to the binomial.

The fit of this approximation may be tested by the Poissonness plot (Hoaglin 1980), or  $\log(x_k) + \log(k!)$  vs.  $k$ .

If  $x_k = n \Pr(X = k) = n \left( \frac{\lambda^k e^{-\lambda}}{k!} \right)$ , then  $\ln x_k + \ln k! = \ln n + k \ln \lambda - \lambda =$  linear function of  $k$ .

Despite some upward concavity, the plot demonstrates reasonable Poissonness, with correlation = -1.





## 2.2 Overall Non-Reference Sites

### 2.2.0.1 For 1000 Genomes

Each individual has  $n$  non-reference sites, which can be found by counting. The mean number is computed for each population.

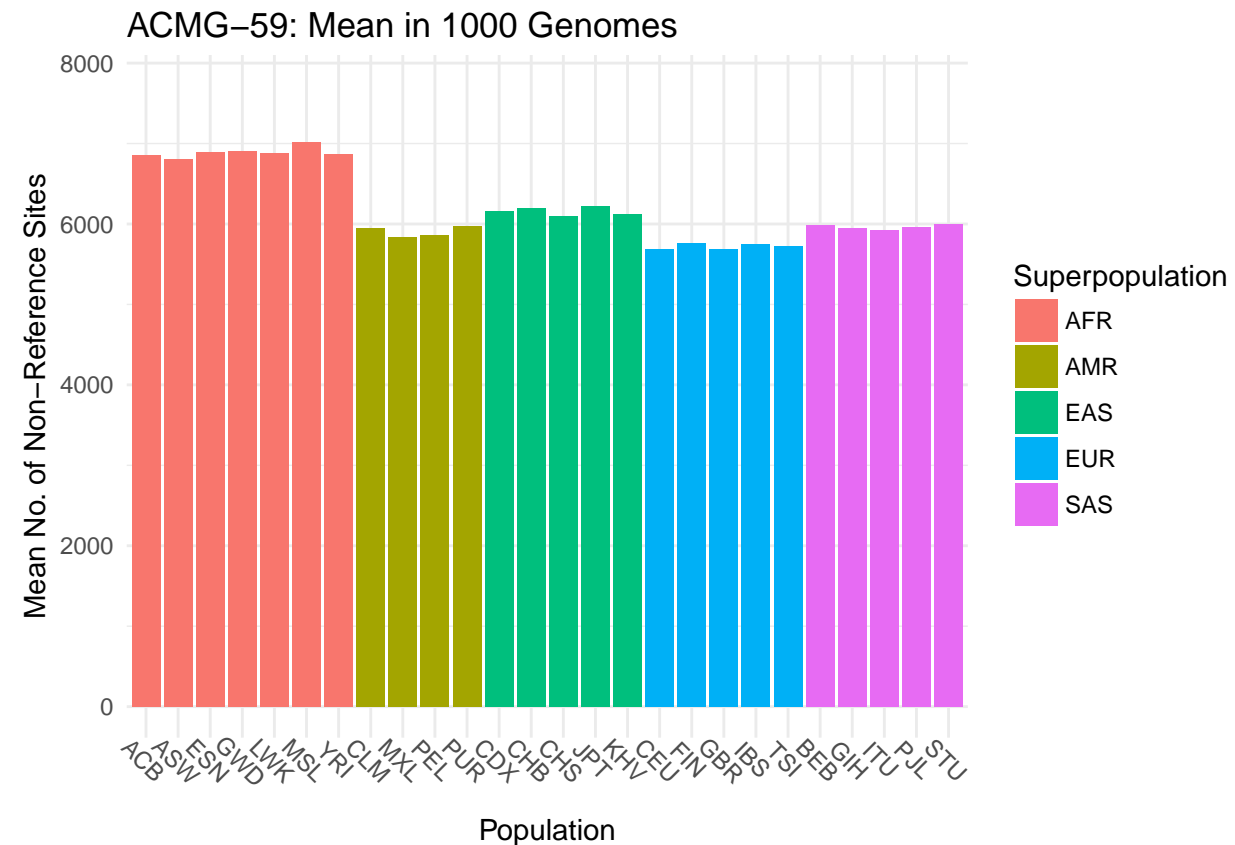
Ex: the genotype of 3 variants in 3 people looks like this:

	HG00366	HG00367	HG00368
<b>Variant 1</b>	2	1	1
<b>Variant 2</b>	2	1	1
<b>Variant 3</b>	1	0	0

Count the number of non-reference sites per individual:

HG00366	HG00367	HG00368
3	2	2

## Mean = 2.33



Note: the error bars denote standard deviation, not standard error.

### 2.2.0.2 For gnomAD/ExAC

The mean number of non-reference sites is  $E(V)$ , where  $V = \sum_{i=1}^n v_i$  is the number of non-reference sites at all variant positions  $v_1$  through  $v_n$ .

At each variant site, the probability of having at least 1 non-reference allele is  $P(v_i) = P(v_{i,a} \cup v_{i,b})$ , where  $a$  and  $b$  indicate the 1st and 2nd allele at each site.

If the two alleles are independent,  $P(v_{i,a} \cup v_{i,b}) = 1 - (1 - P(v_{i,a}))(1 - P(v_{i,b})) = 1 - (1 - AF(v_i))^2$

If all variants are independent,  $E(V) = \sum_{i=1}^n 1 - (1 - AF(v_i))^2$  for any set of allele frequencies.

Ex: the allele frequencies of 3 variants across the 5 superpopulations looks like this:

	AFR	AMR	EAS	EUR	SAS
<b>Variant 1</b>	0.1	0.2	0	0	0.3
<b>Variant 2</b>	0.2	0	0.3	0	0.1

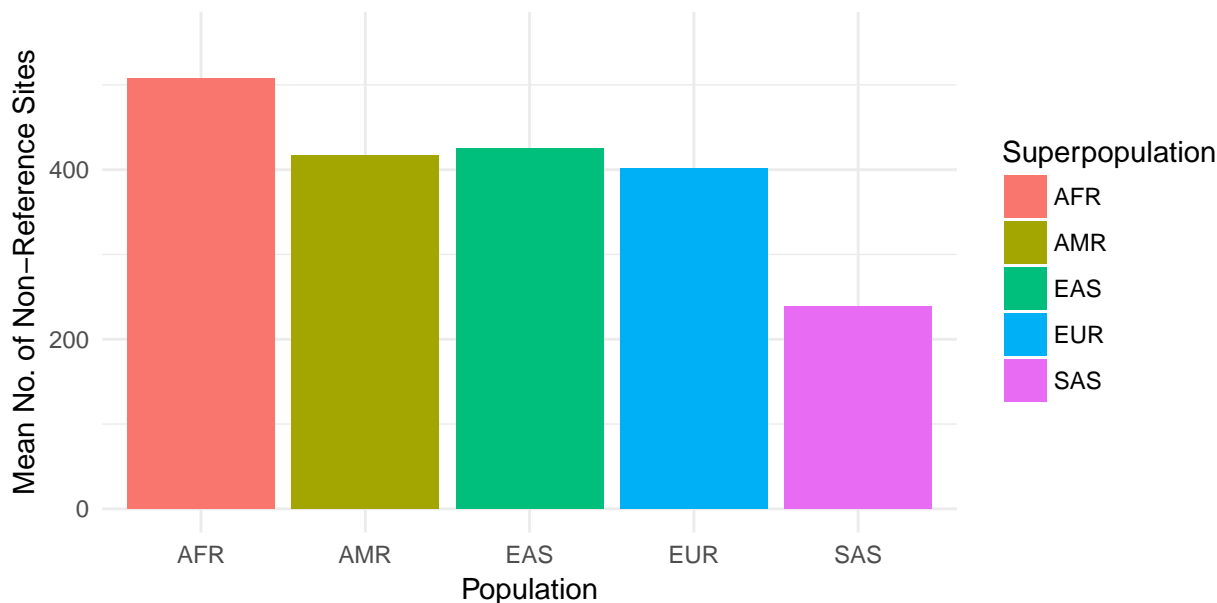
The probability of having at least 1 non-reference site at each variant - (0|1) (1|0) or (1|1) is given by  $1 - (1 - AF)^2$ . Note that this is approximately  $2 * AF$  when  $AF$  is small:

	AFR	AMR	EAS	EUR	SAS
<b>Variant 1</b>	0.19	0.36	0	0	0.51
<b>Variant 2</b>	0.36	0	0.51	0	0.19

By linearity of expectation, the expected (mean) number of non-reference sites is  $\sum E(V_i) = \sum (columns)$ .

AFR	AMR	EAS	EUR	SAS
0.55	0.36	0.51	0	0.7

ACMG-59: Mean in gnomAD



## 2.3 Fraction of Individuals with Pathogenic Sites

### 2.3.0.1 For 1000 Genomes

We can count up the fraction of individuals with 1+ non-reference site(s) in each population. This is the fraction of individuals who would receive a positive genetic test result in at least 1 of the ACMG-59 genes.

Ex: the genotype of 3 variants in 3 people looks like this:

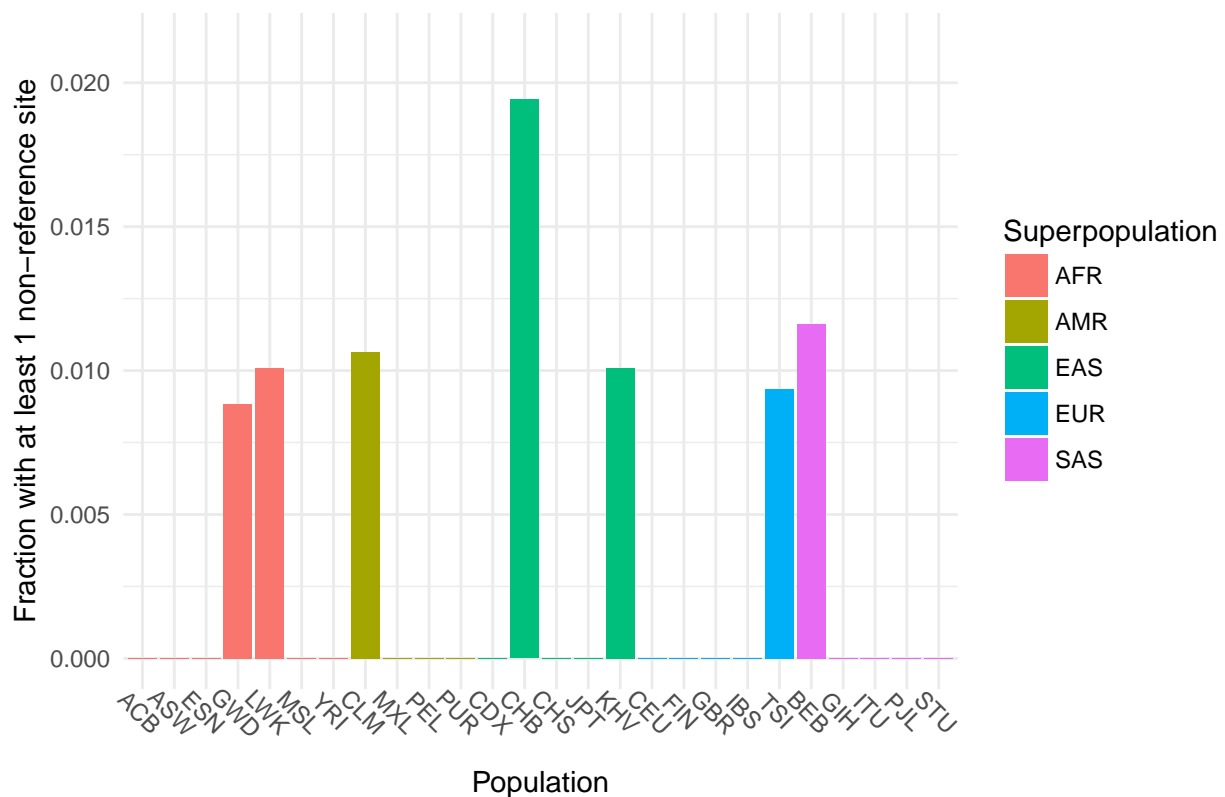
	HG00366	HG00367	HG00368
<b>Variant 1</b>	2	1	1
<b>Variant 2</b>	2	1	1
<b>Variant 3</b>	1	0	0

Count each individual as having a non-reference site (1) or having only reference sites (0):

HG00366	HG00367	HG00368
1	1	1

## Mean = 1

### ACMG-59 Pathogenic: Fraction in 1000 Genomes



### 2.3.0.2 For gnomAD/ExAC

The probability of having at least 1 non-reference site is  $P(X)$ , where  $X$  indicates a non-reference site at any variant position  $v_1$  through  $v_n$ .

Recall that  $P(v_i) = P(v_{i,a} \cup v_{i,b}) = 1 - (1 - AF(v))^2$  when alleles are independent.

If all alleles are independent,  $P(X) = P(\bigcup_{i=1}^n v_i) = 1 - \prod_{i=1}^n (1 - AF(v_i))^2$

Ex: the allele frequencies of 3 variants across the 5 superpopulations looks like this:

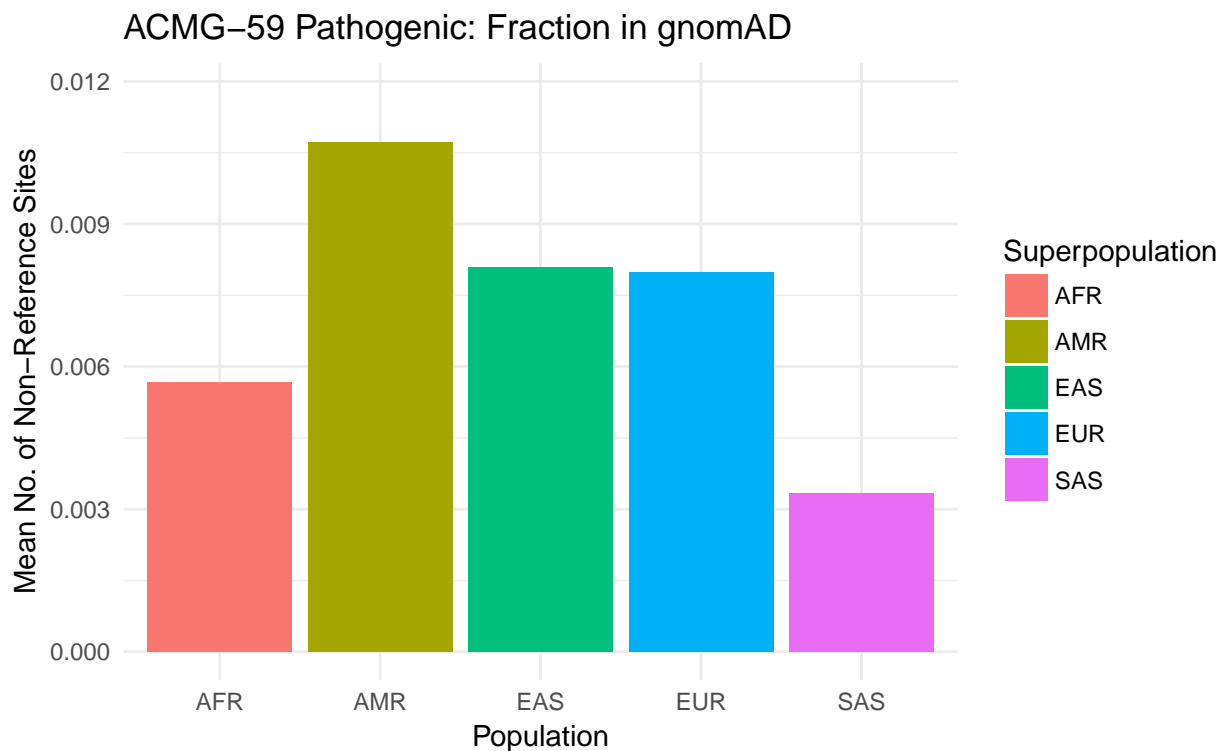
	AFR	AMR	EAS	EUR	SAS
<b>Variant 1</b>	0.1	0.2	0	0	0.3
<b>Variant 2</b>	0.2	0	0.3	0	0.1

The probability of having at least 1 non-reference site at each variant - (0|1) (1|0) or (1|1) is given by  $1 - (1 - AF)^2$ . Note that this is approximately  $2 * AF$  when  $AF$  is small:

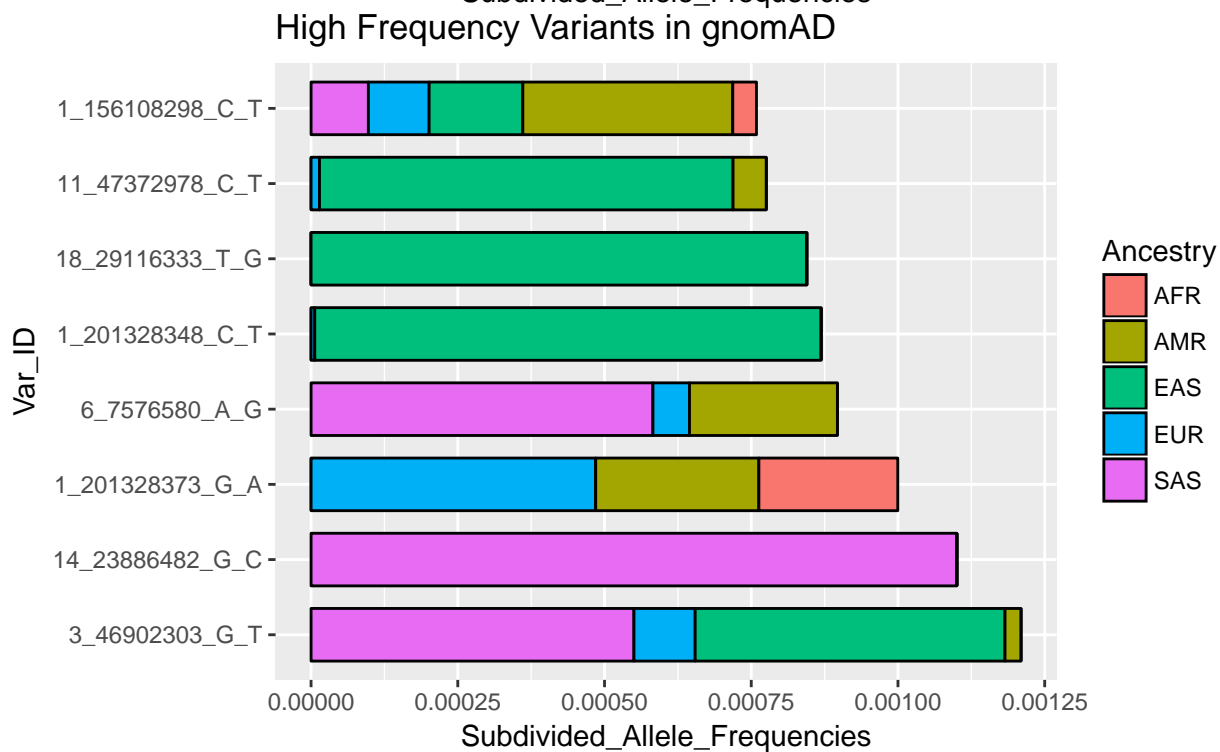
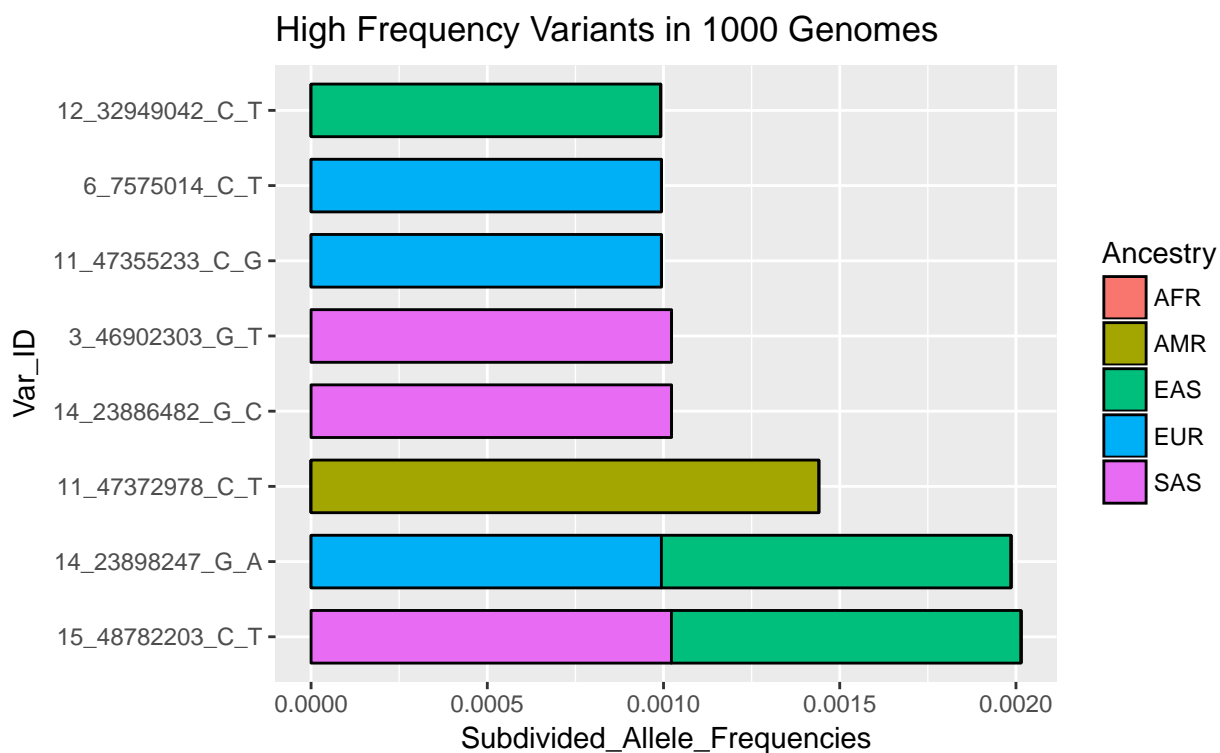
	AFR	AMR	EAS	EUR	SAS
<b>Variant 1</b>	0.19	0.36	0	0	0.51
<b>Variant 2</b>	0.36	0	0.51	0	0.19

The expected (mean) number of non-reference sites is given by  $1 - \prod (1 - AF)^2$ .

AFR	AMR	EAS	EUR	SAS
0.4816	0.36	0.51	0	0.6031



## 2.4 Common Pathogenic Variants by Ancestry



### 3 Penetrance Estimates

#### 3.1 Bayes' Rule as a Model for Estimating Penetrance

Let  $V_x$  be the event that an individual has 1 or more variant related to disease  $x$ , and  $D_x$  be the event that the individual is later diagnosed with disease  $x$ .

In this case, we can define the following probabilities:

1. Prevalence =  $P(D_x)$
2. Population Allele Frequency (PAF) =  $P(V_x)$
3. Case Allele Frequency (CAF) =  $P(V_x|D_x)$
4. Penetrance =  $P(D_x|V_x)$

By Bayes' Rule, the penetrance of a variant related to disease  $x$  may be defined as:

$$P(D_x|V_x) = \frac{P(D_x) * P(V_x|D_x)}{P(V_x)} = \frac{(Prevalence)(Population\ Allele\ Frequency)}{(Case\ Allele\ Frequency)}$$

To compute penetrance estimates for each of the diseases related to the ACMG-59 genes, we will use the prevalence data we collected into `Literature_Prevalence_Estimates.csv`, allele frequency data from 1000 Genomes/ExAC/gnomAD, and a broad range of values for case allele frequency.

#### 3.2 Import Literature-Based Disease Prevalence Data

Data Collection:

1. Similar disease subtypes were grouped together (e.g., the 8 different types of familial hypertrophic cardiomyopathy), resulting in 30 disease categories across 59 genes.
2. The search query "[disease name] prevalence" was used to find articles using Google Scholar.
3. Prevalence estimates were recorded along with URL, journal, region, publication year, sample size, first author, population subset (if applicable), date accessed, and potential issues. Preference was given to studies with PubMed IDs, more citations, and larger sample sizes.

Prevalence was recorded as reported: either a point estimate or a range. Values of varying quality were collected across all diseases.

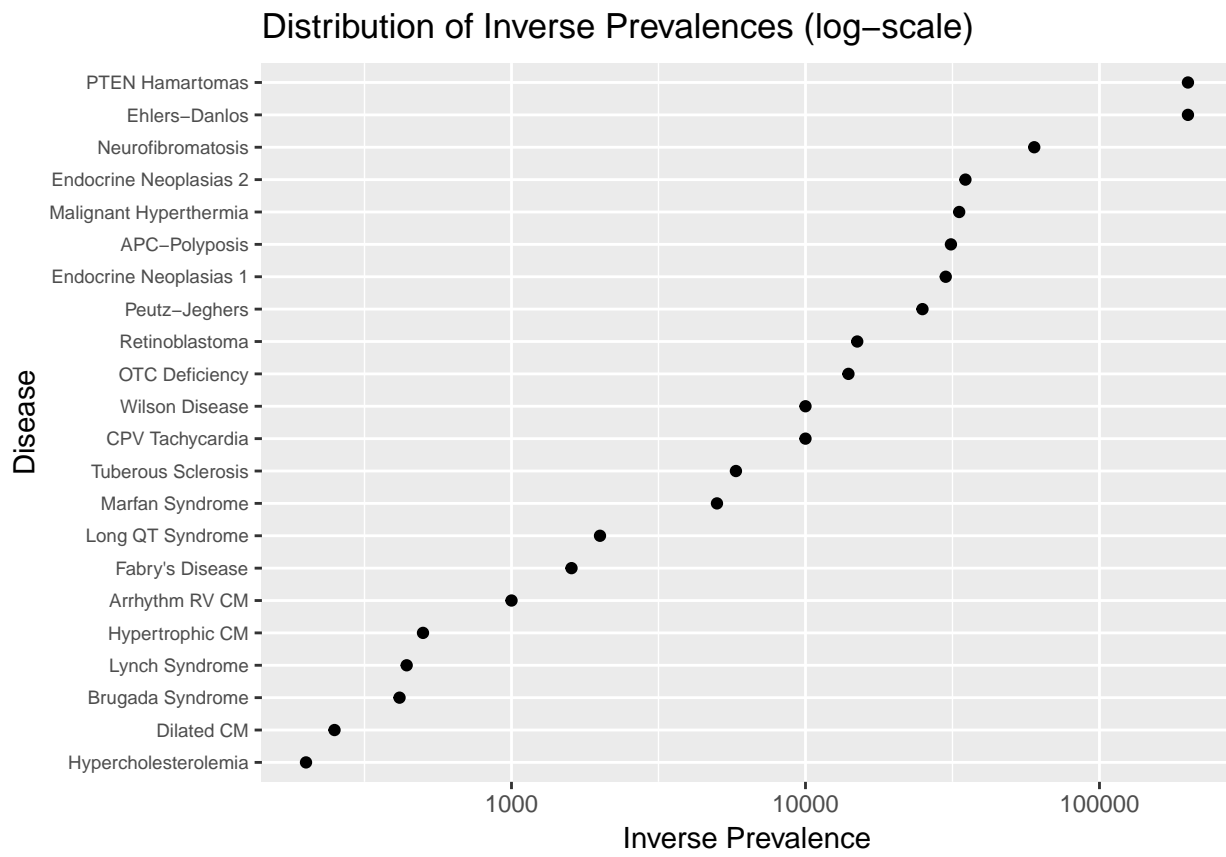
## Table of Literature-Based Estimates 22 x 20 (selected rows/columns):

Gene	Phenotype
APC	Familial adenomatous polyposis
MEN1	Multiple endocrine neoplasia type 1
MYH7 TPM1 MYBPC3 PRKAG2 TNNT3 MYL3 MYL2 ACTC1	Hypertrophic cardiomyopathy
STK11	Peutz-Jeghers syndrome

Table continues below

Inverse_Prevalence	Case_Allele_Frequency
31250	0.9
30000	0.9
500	0.6
25000	0.96

### 3.3 Distribution of Prevalences



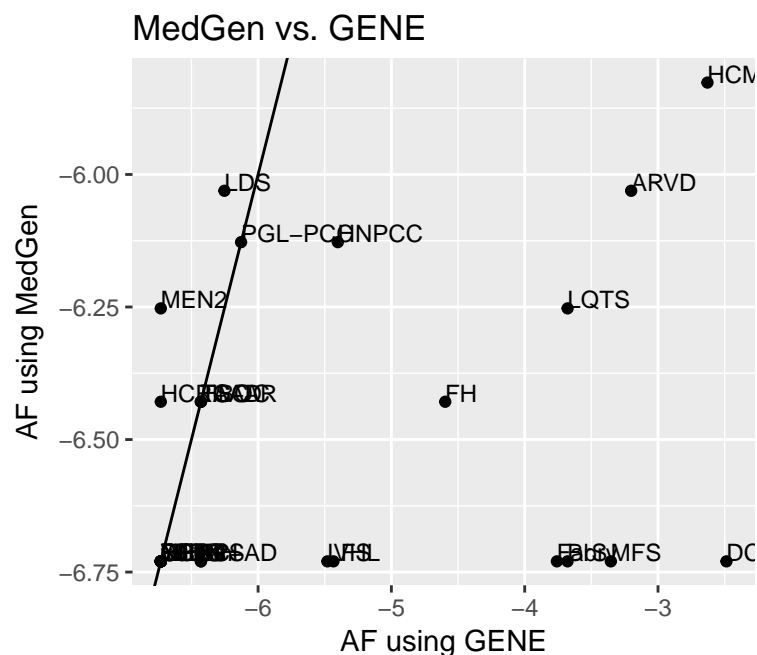
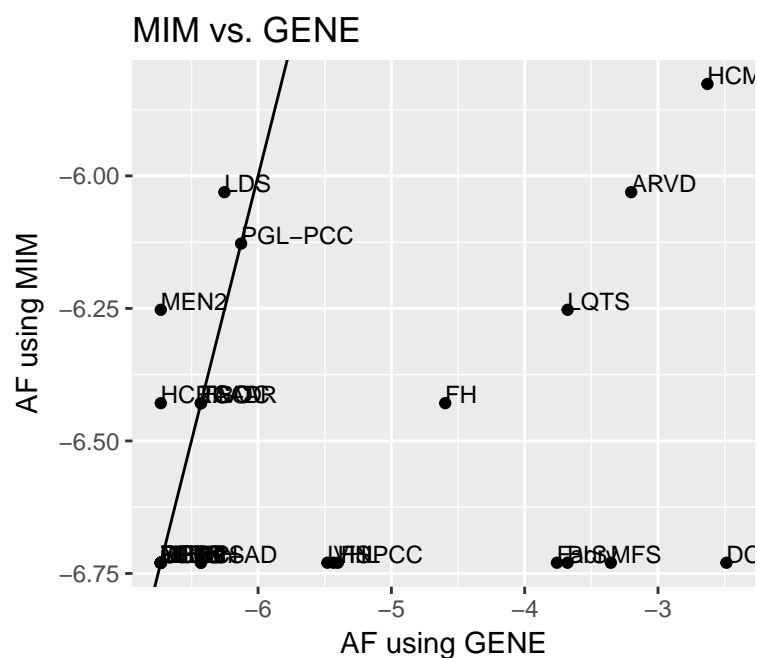
### 3.4 Collect and Aggregate Allele Frequencies at the Disease-Level

We define  $\text{AF}(\text{disease})$  as the probability of having at least 1 variant associated with the disease. The variants can be assigned to diseases in two ways:

- (1) By associating it by MIM. An MIM code is assigned for around 31% of assertions in each dataset.
- (1) By associating it by MedGen. An MIM code is assigned for around 22% of assertions in each dataset.
- (2) By associating it by gene. All variants are associated with genes, but some variants may be designated as pathogenic for non-ACMG conditions.

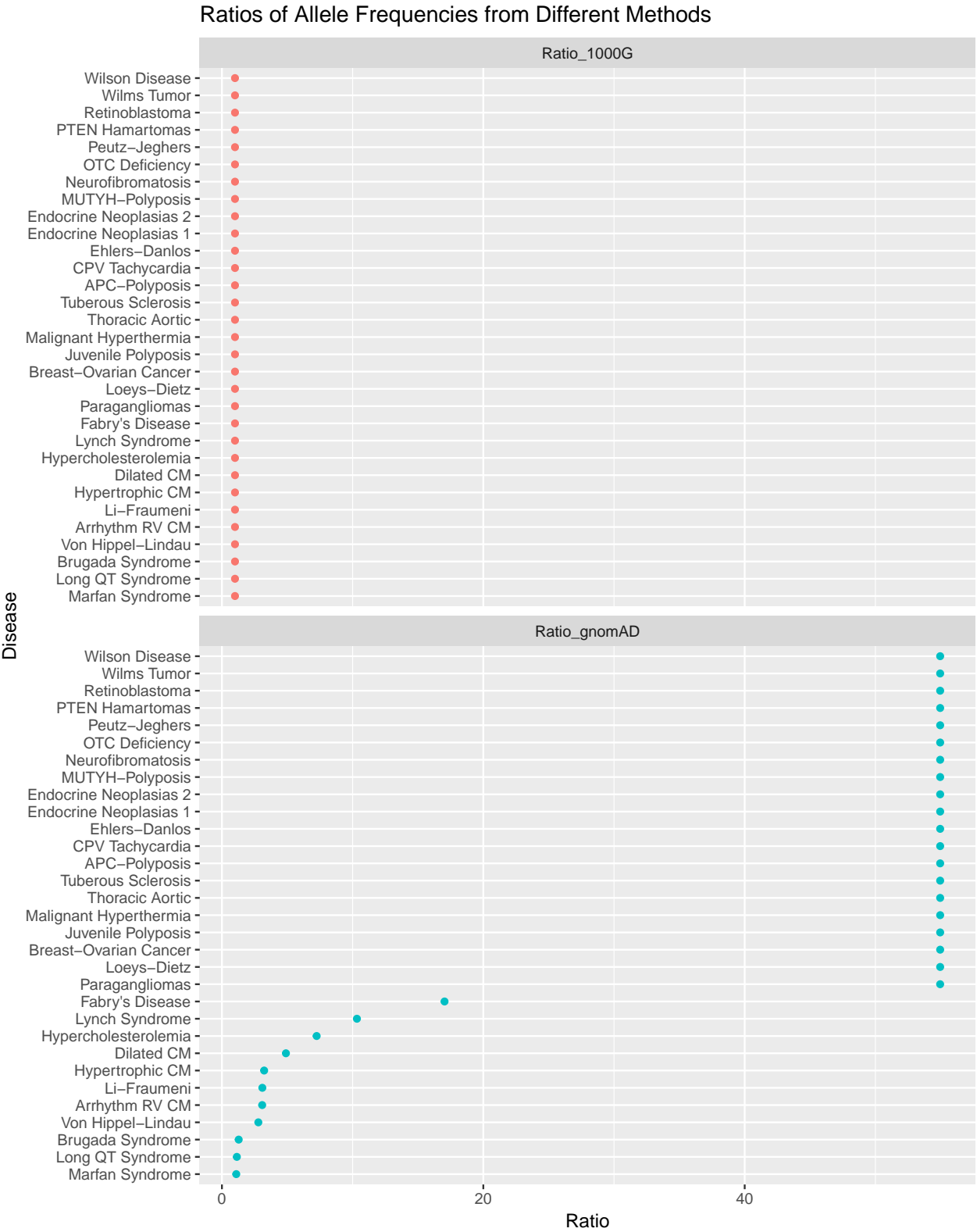
The frequencies across the relevant variants can be aggregated in two ways:

- (1) By direct counting, from genotype data in 1000 Genomes.  
(2)  $AF(\text{disease}) = 1 - \prod_{\text{variant}} (1 - AF_{\text{variant}})$ , from population data in 1000 Genomes, ExAC, or gnomAD (assumes independence).



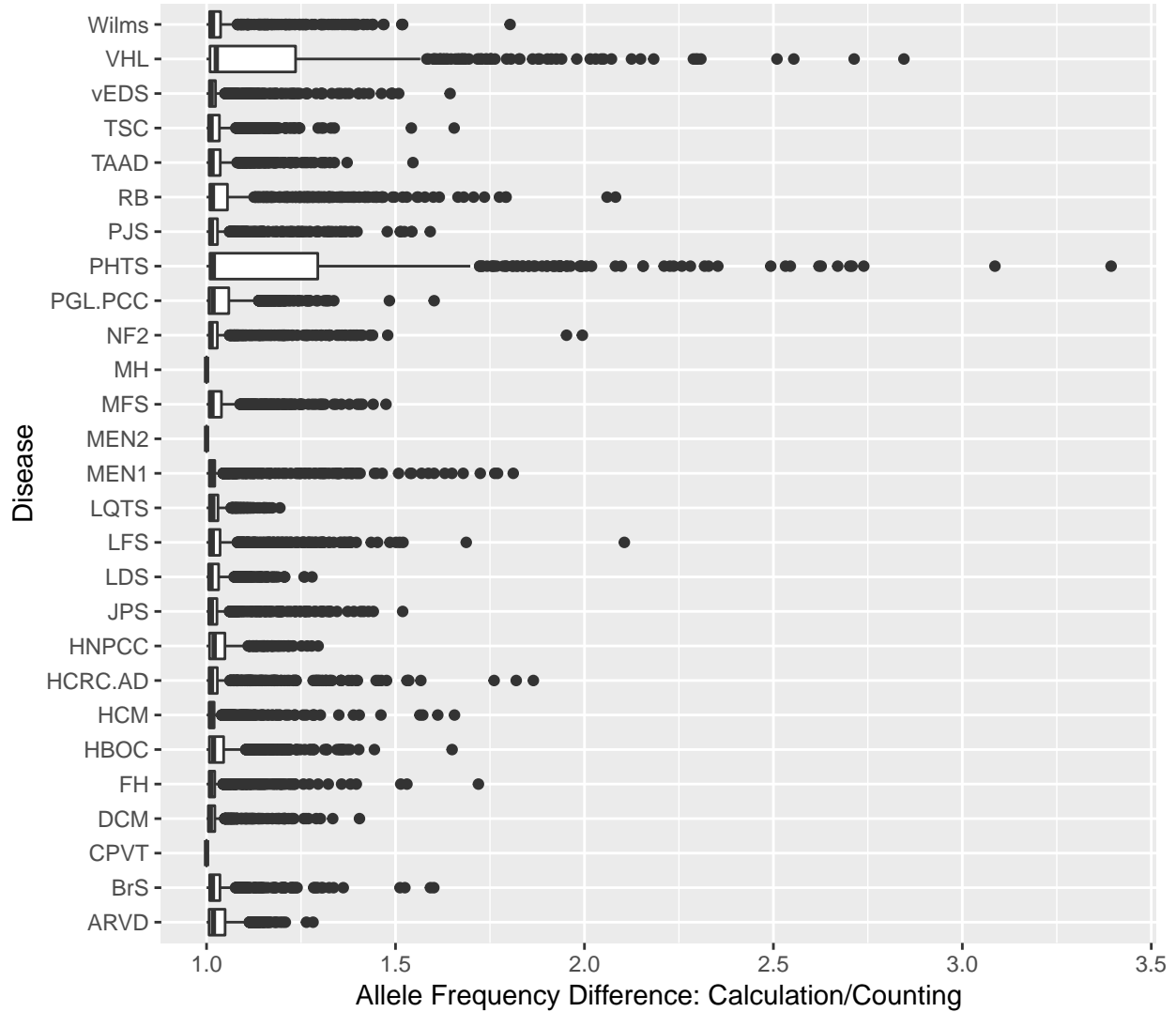


Ratio\_1000G (red, top) computes  $AF(\text{calculation in 1000 Genomes}) / AF(\text{counting in 1000 Genomes})$ .  
Ratio\_gnomAD (blue, bottom) computes  $AF(\text{calculation in gnomAD}) / AF(\text{calculation in 1000 Genomes})$ .

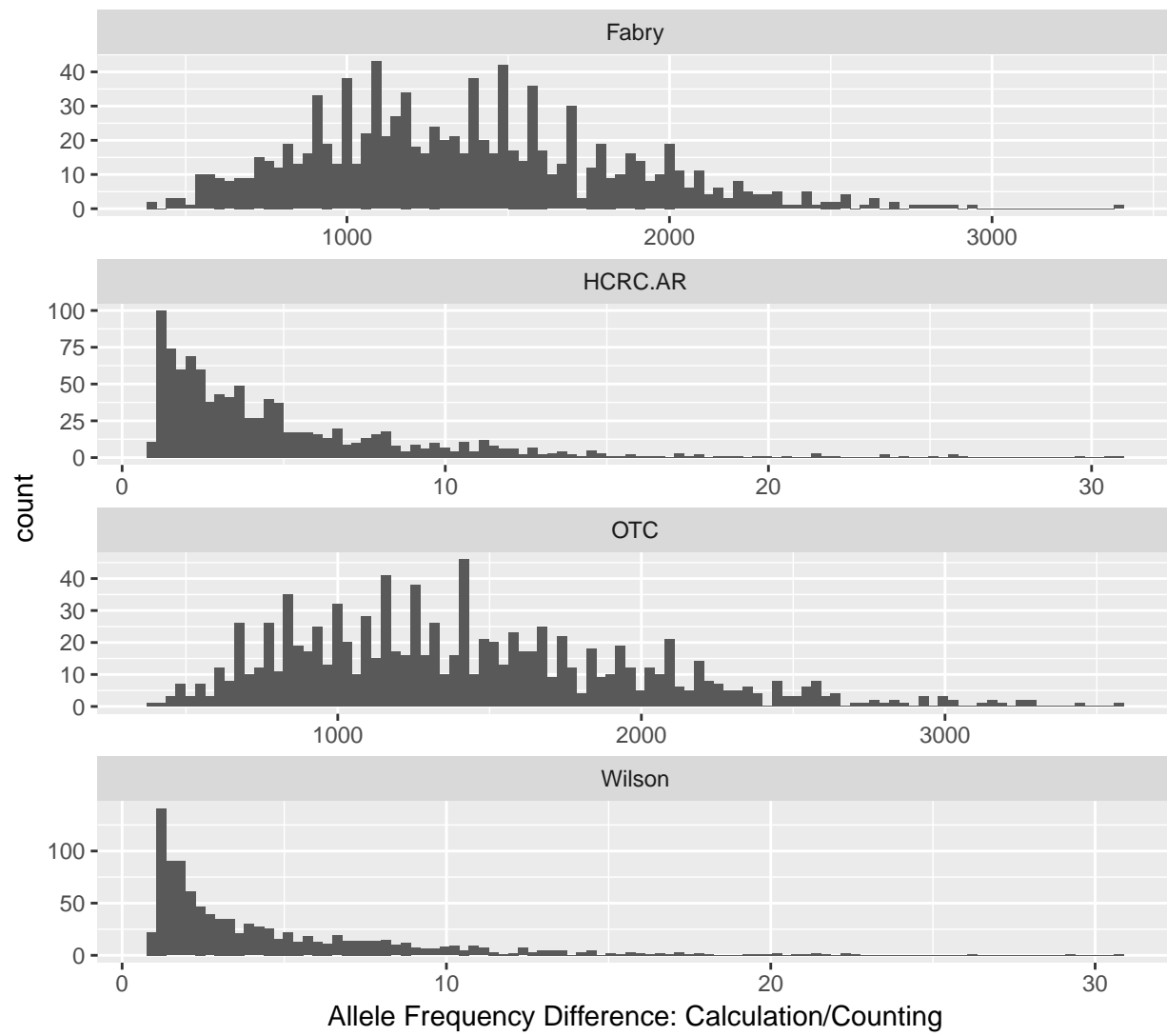


Sampling 1000 variants from all variants in 1000 Genomes to test deviations from independence assumptions. Repeat for 1000 trials and plot the distribution of disease-level allele frequencies (1000 points per disease). Only variants with allele frequency  $< 1\%$  are evaluated. Since we look at 17 variants per disease, the maximum is approximately  $1 - (1 - 0.01)^{34} \approx 0.29$

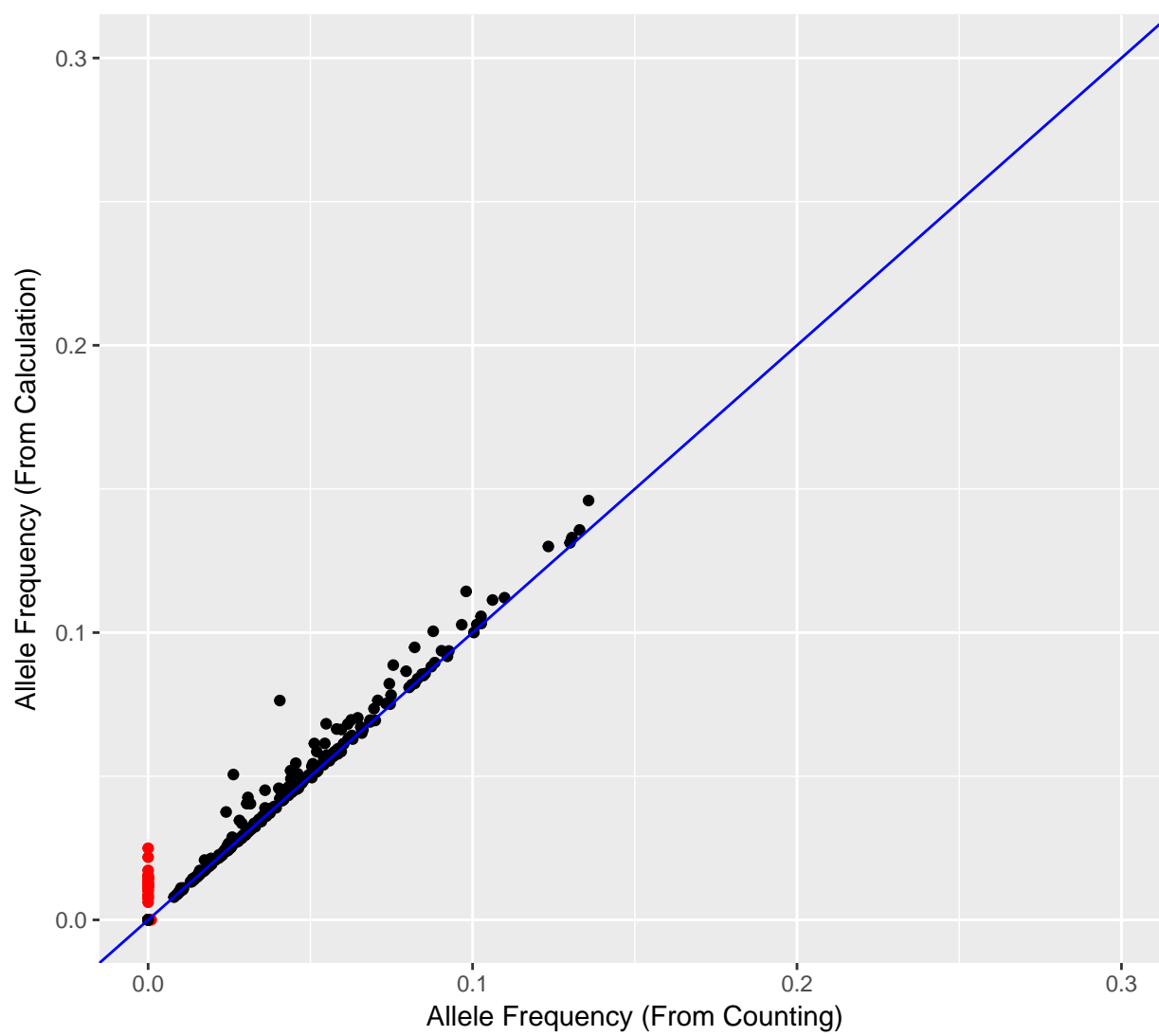
### Differences in AF Methods: by Disease



## Differences in AF Methods: by Disease (Outliers)



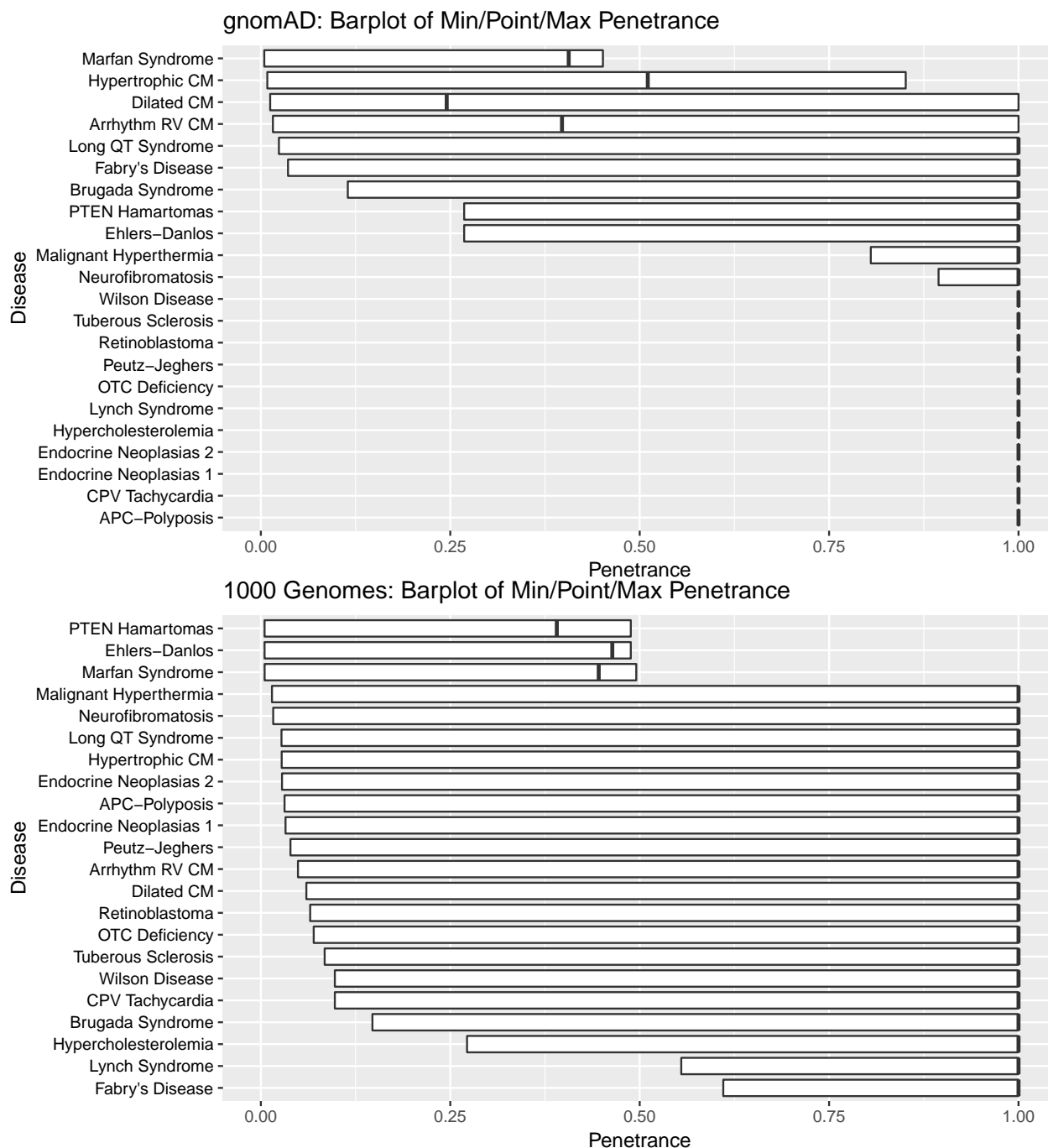
## Testing Independence with Random Sampling



```
## 31 diseases x 1000 points = 31,000 points.  
## This plot has been downsampled 100x and contains 310 points.  
## AR (autosomal recessive) and XL (X-linked) diseases are colored in red.  
## Pearson correlation: 0.989
```

### 3.5 Penetrance as a Function of $P(V|D)$

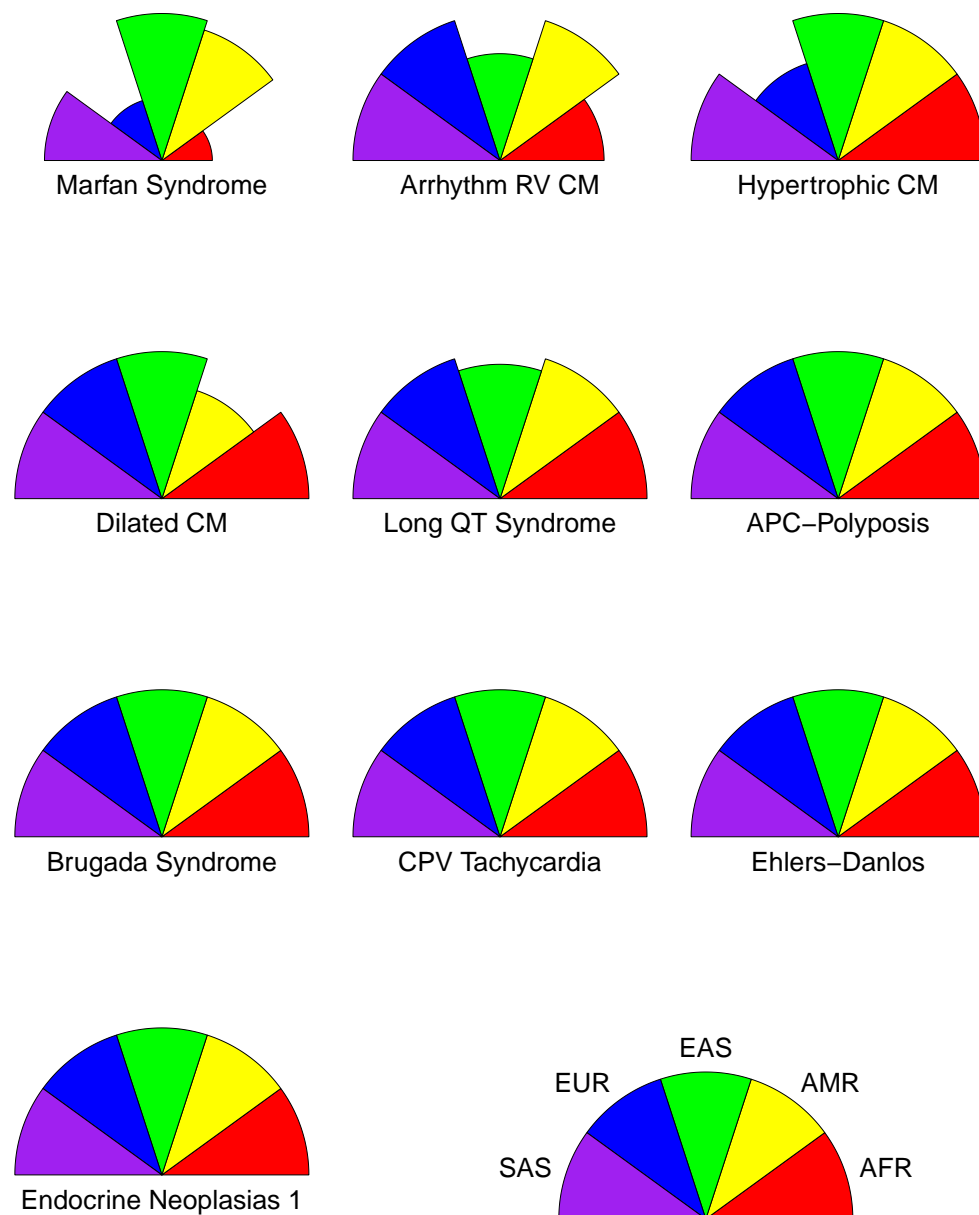
The left end of the boxplot indicates  $P(V|D) = 0.01$ ,  
the bold line in the middle indicates  $P(V|D) = \text{point value}$ ,  
the right end of the boxplot indicates  $P(V|D) = 1$ .



Note: Some diseases have mean theoretical penetrance = 1 because the assumed allelic heterogeneity is greater than is possible, given the observed prevalence and allele frequencies.

### 3.6 Penetrance Estimates by Ancestry

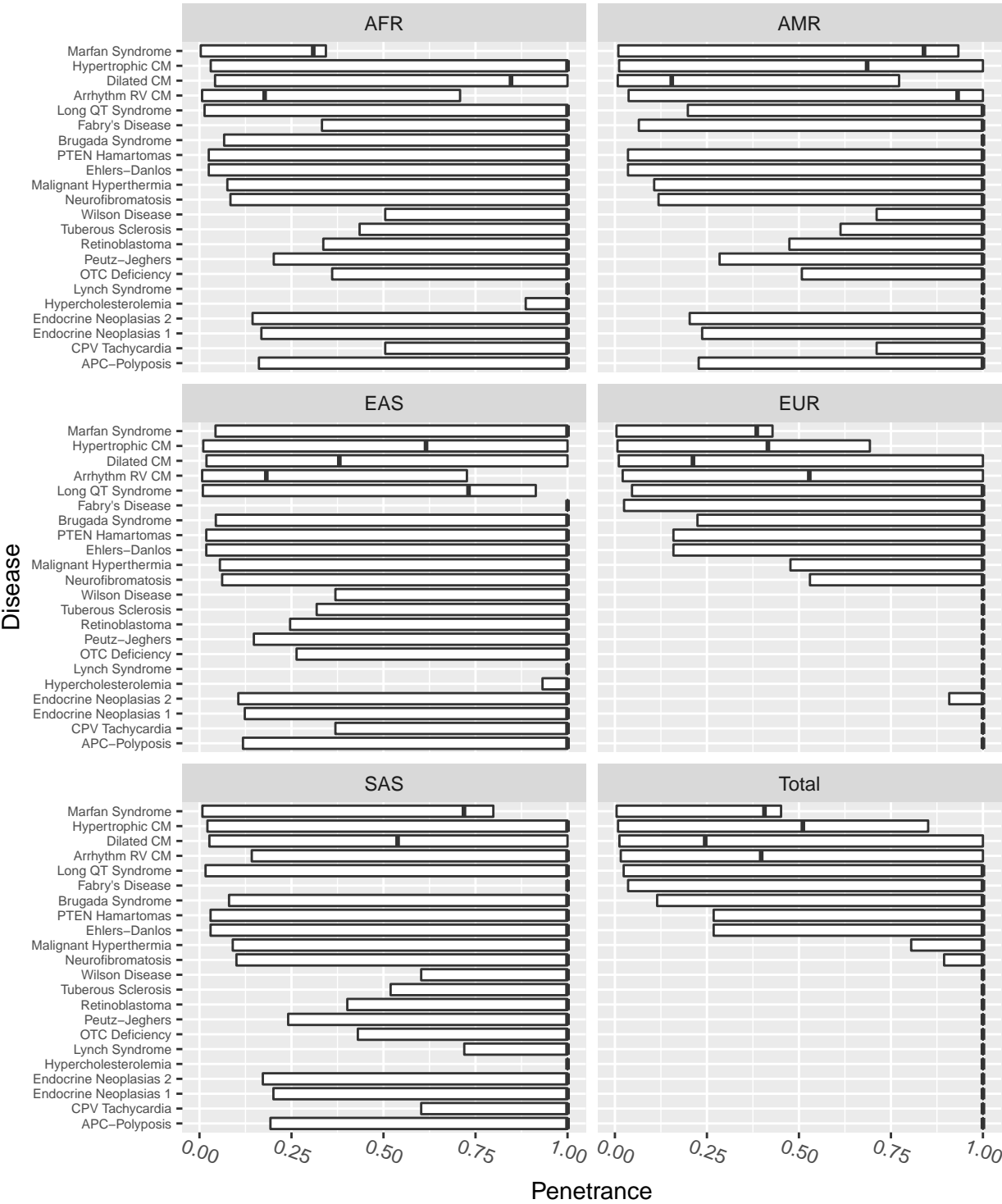
#### Radar Plot: Max Penetrance by Ancestry (gnomAD)



## [1] These are the top 10 diseases by summed allele frequencies. NULL values are not plotted.

## [1] Each radius is proportional to the penetrance of the disease in the given population.

Barplot: Penetrance by Ancestry (gnomAD)



Heatmap: Max Penetrance by Ancestry (gnomAD)

