# Finding Rare Variants of Large Effects Related to Complex Disease

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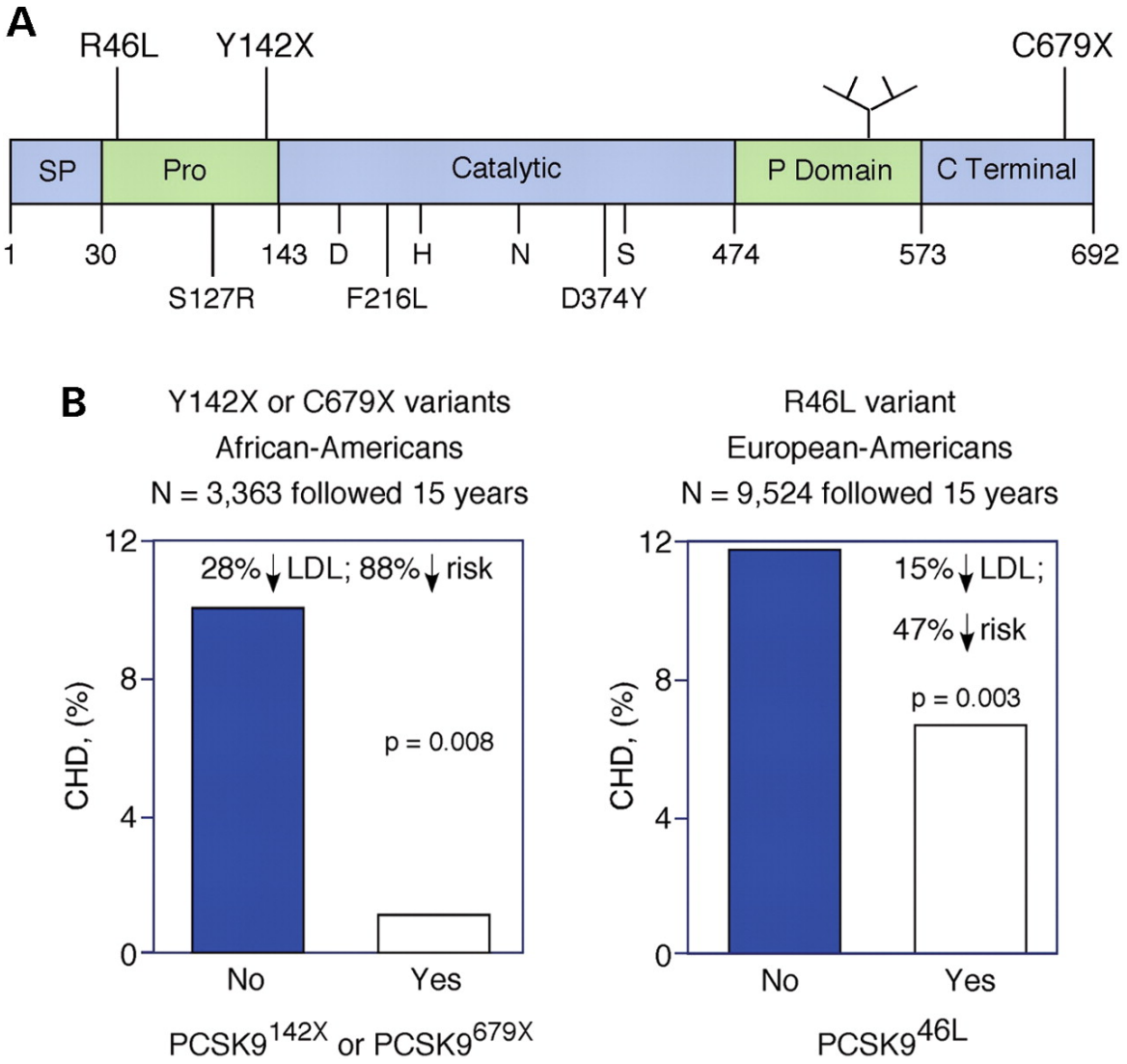
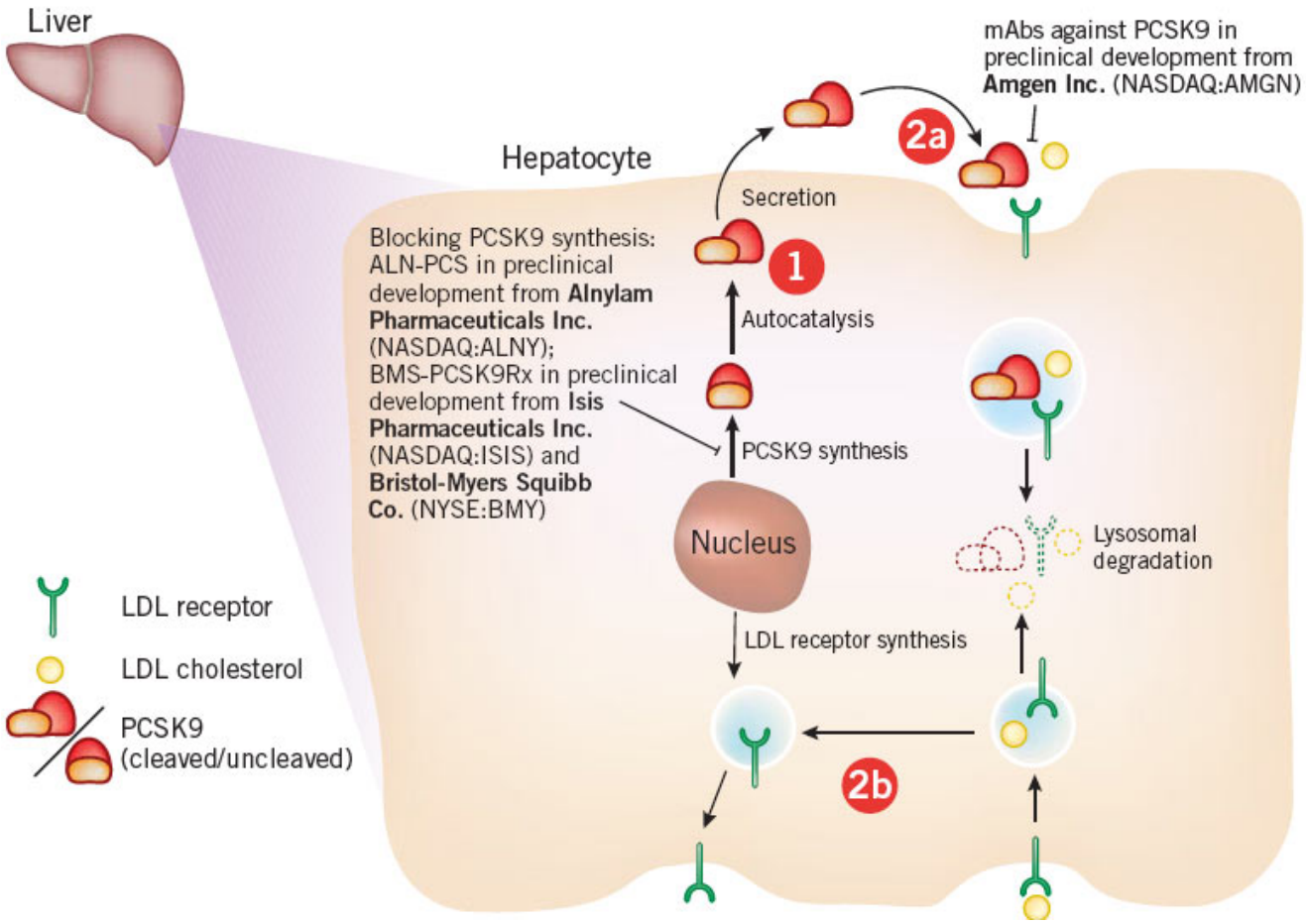
# Rare Variants

- Who cares?

# PCSK9 schematic of nonsense mutations associated with low LDL cholesterol



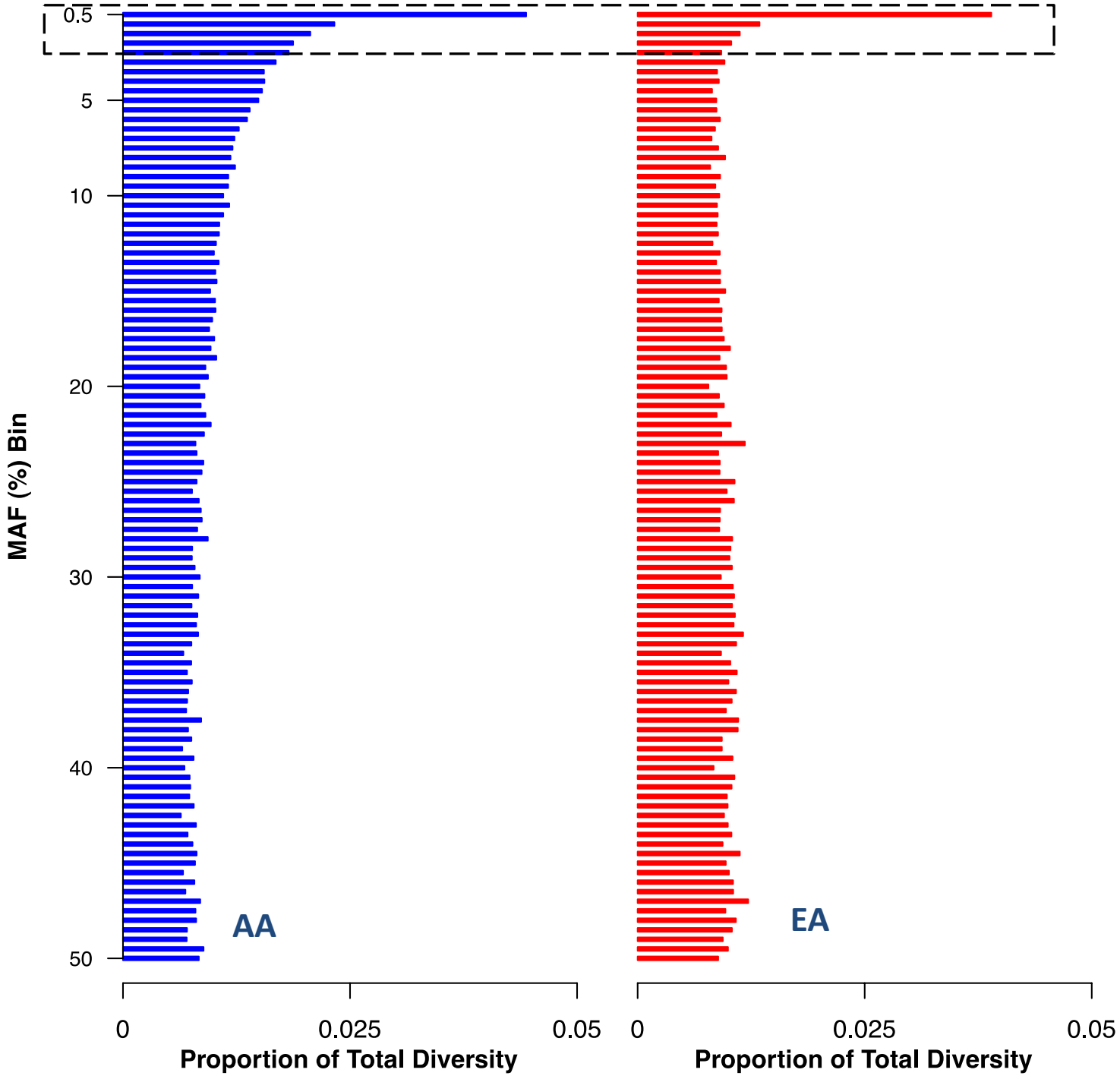
# PCSK9 as a Therapeutic



# Rare Variants

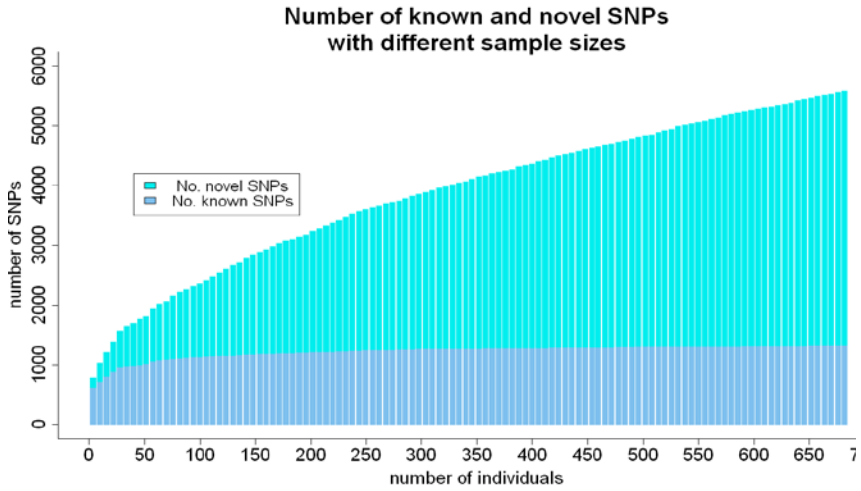
- Who cares?
- How many are there?

**Rare variation makes a significant contribution to genetic diversity**

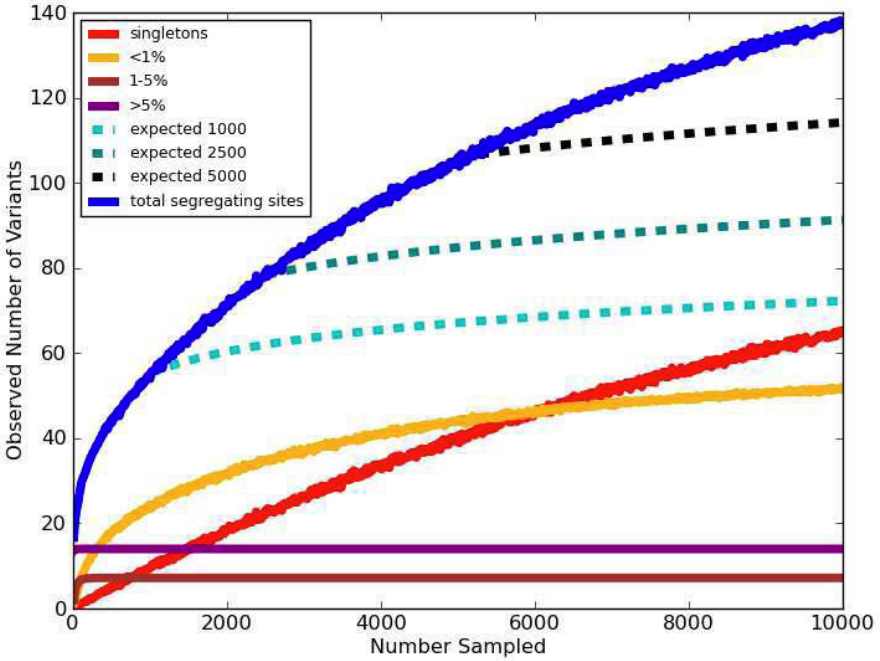


# How many rare variants?

## (Predicting $n^{th}$ Genome)




**ENCODE 3 Sequence Data**
**~ 700 samples. 1 Mb each**

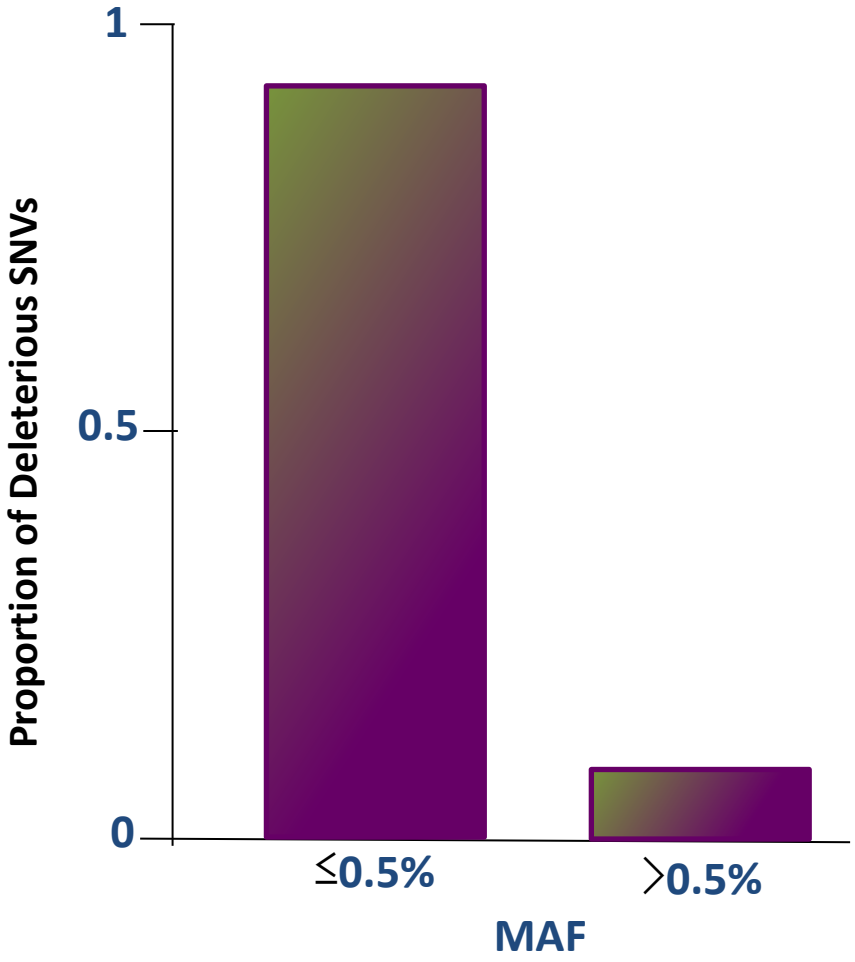



**ARIC:**
**~ 11,000 samples, ~ 25 kb**

# ~ 10-300 novel ns / genome!

# ~90% of Predicted Deleterious Alleles are Rare

- 15% of SNVs (77,746) are predicted to be functionally important



# Rare Variants

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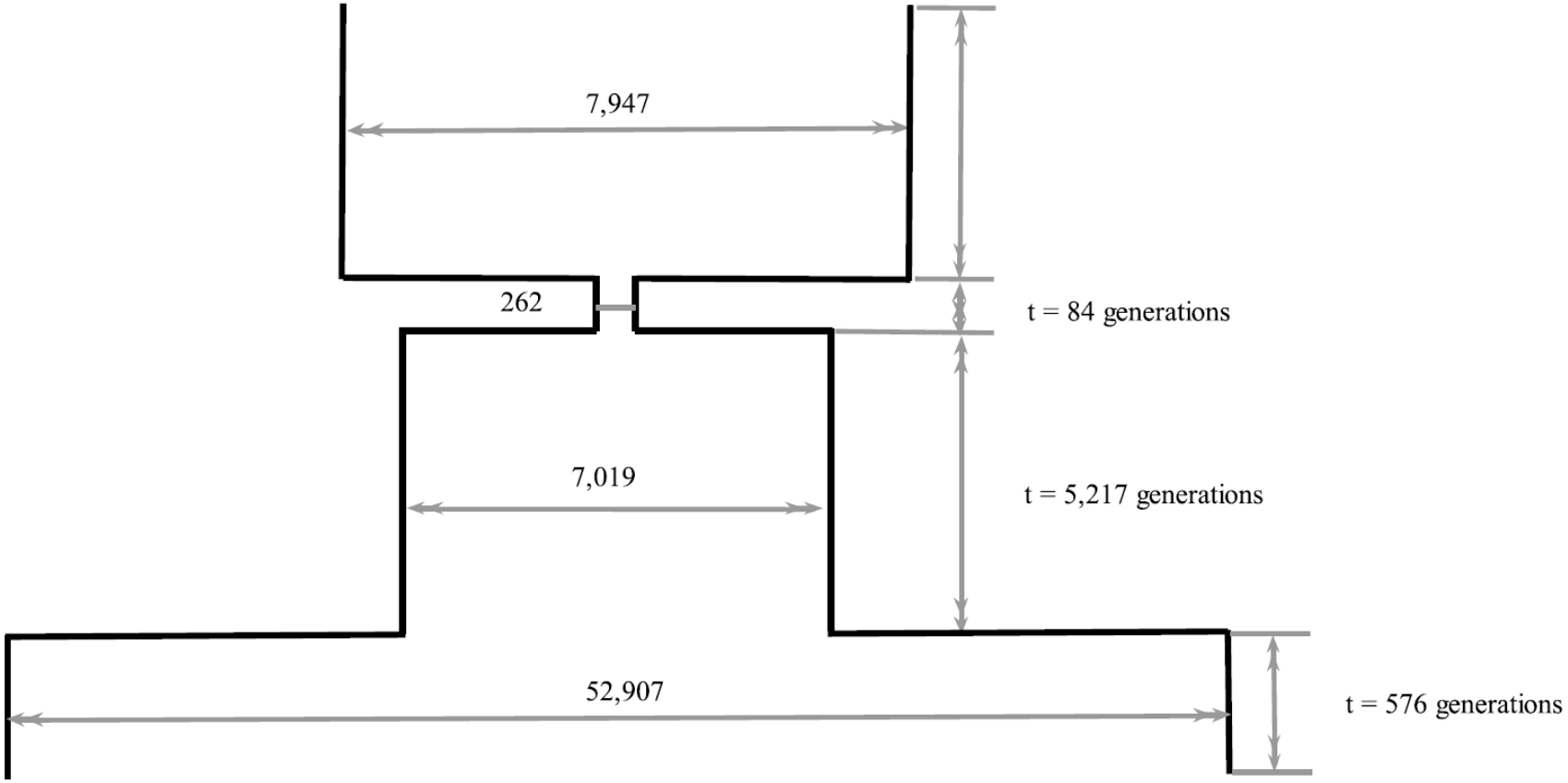
- Where did they come from?

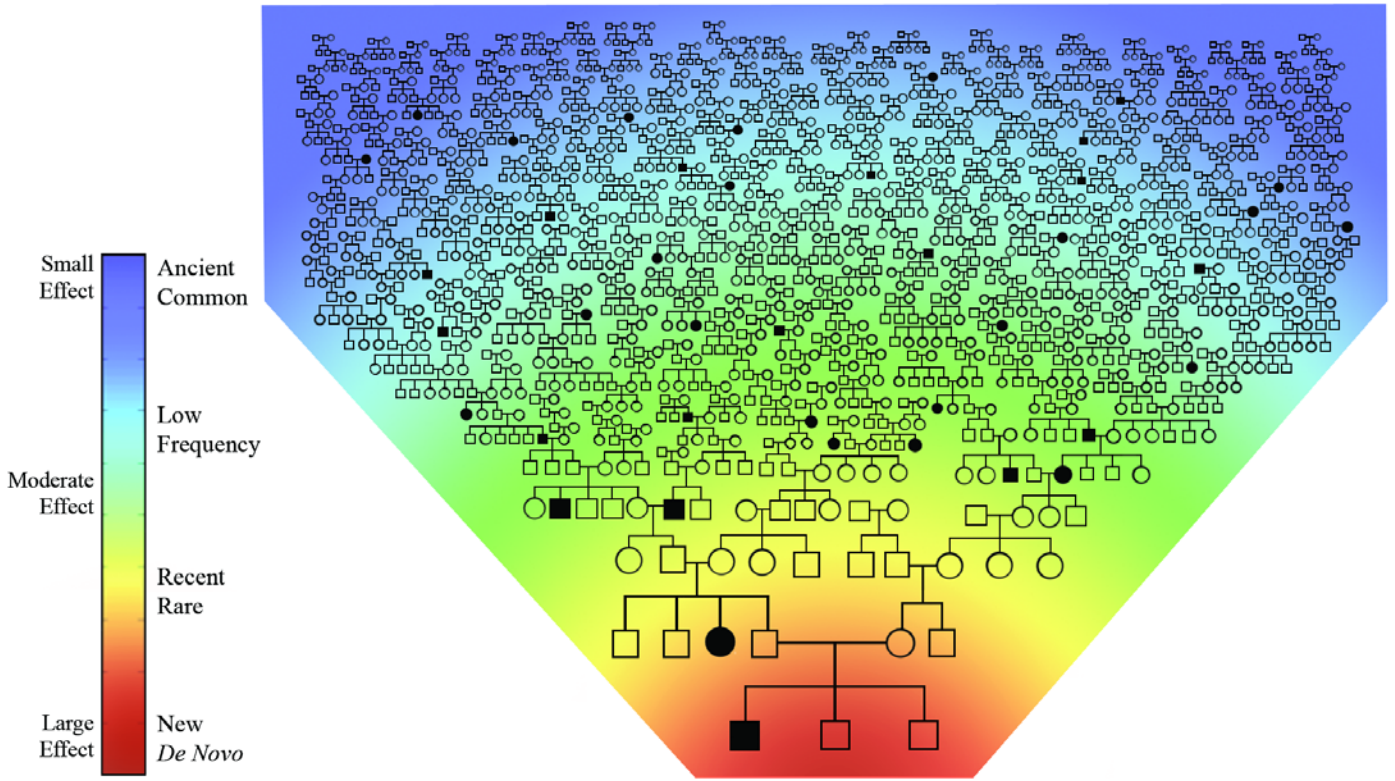
# Simulation of Variant Data

- Demographic history of European population




- Population genetic model incorporating demographic change (Boyko et al PloS Genet 2008)

# Genomics in a Historic Context




Lupski et al (2011) Cell

# Rare Variants

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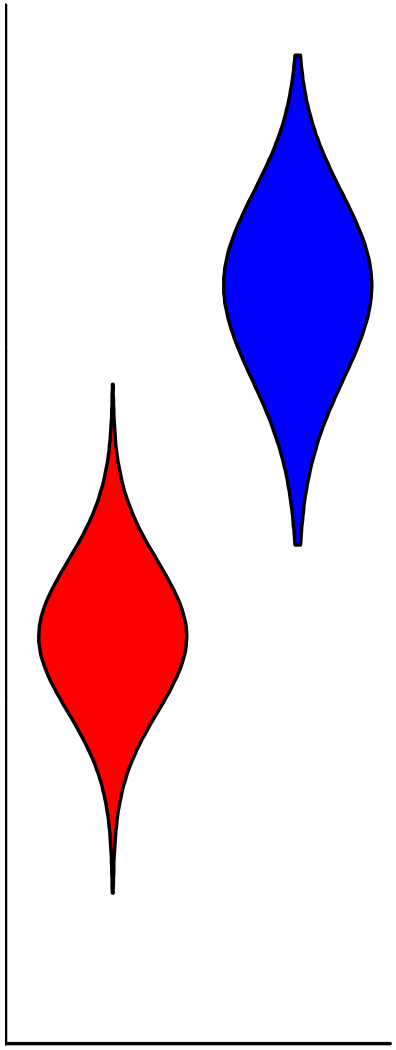
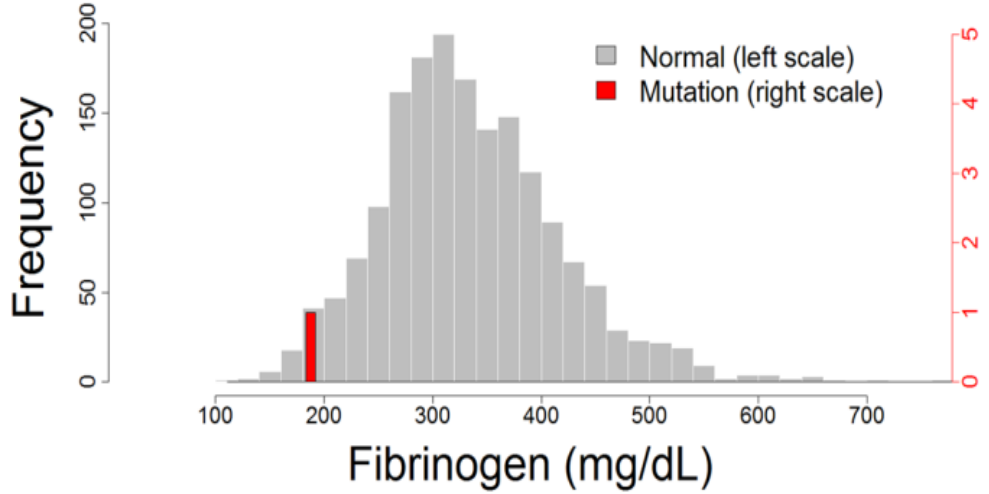
# How Many Deleterious SNVs Do We Carry?

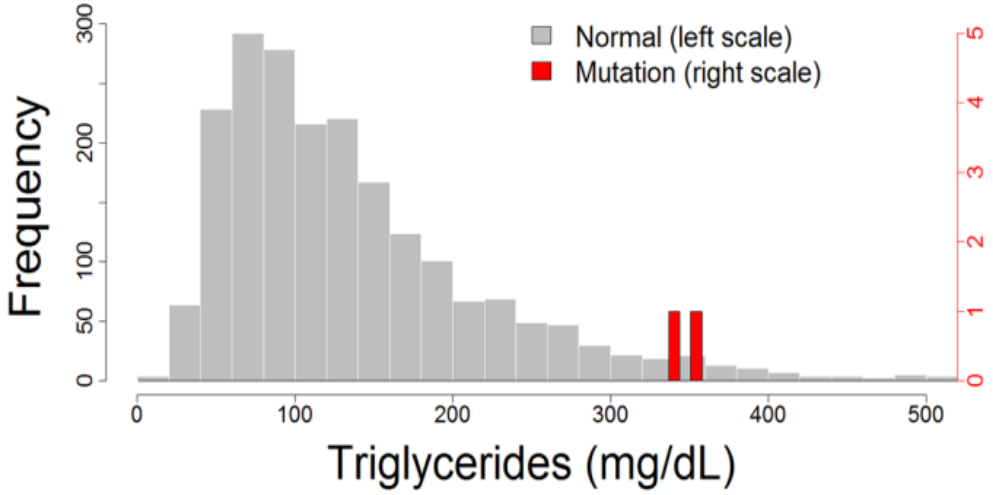
AA

EA



# Two Preliminary Examples



# Rare Variants

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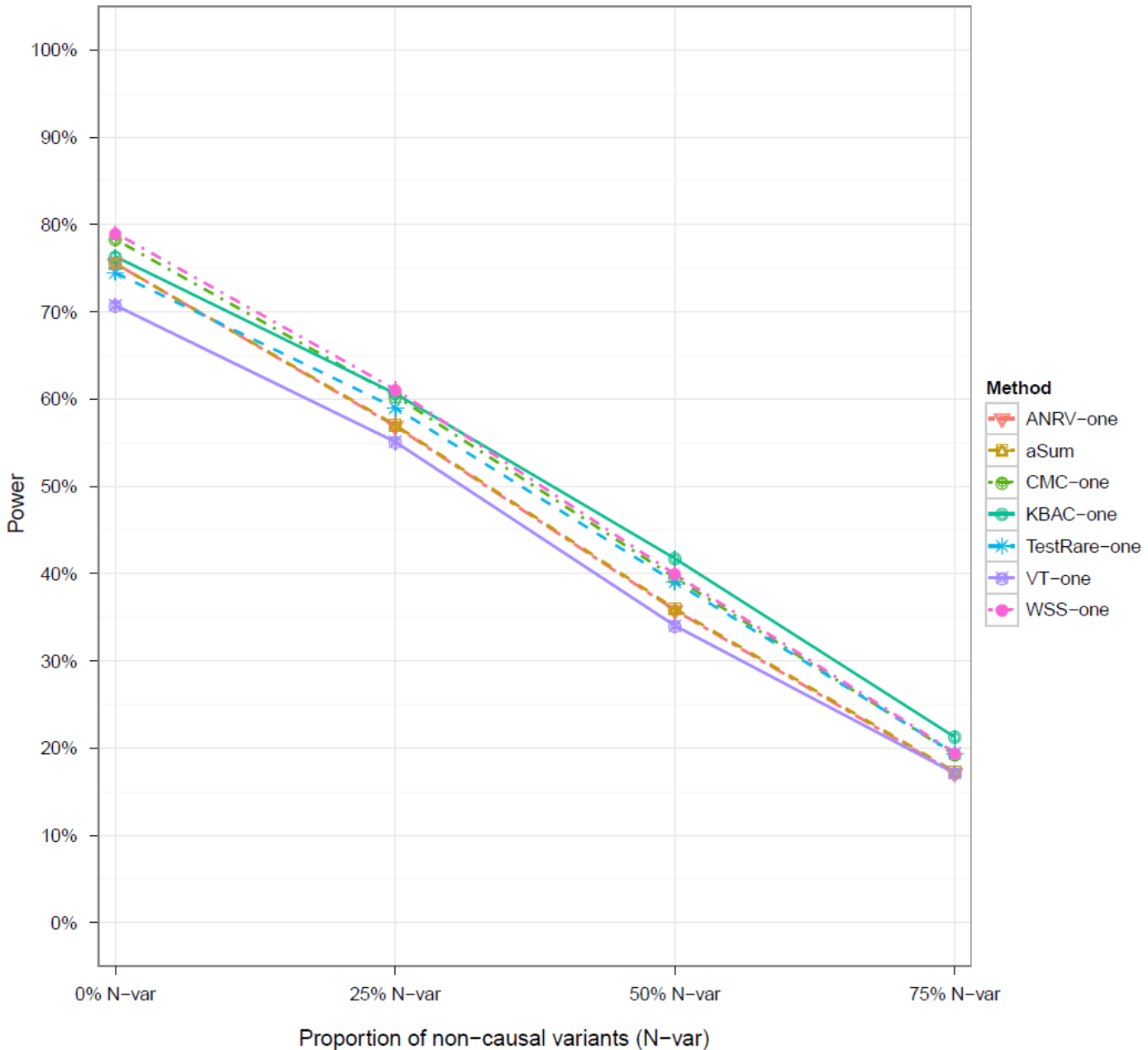
- How do we analyze rare variants?

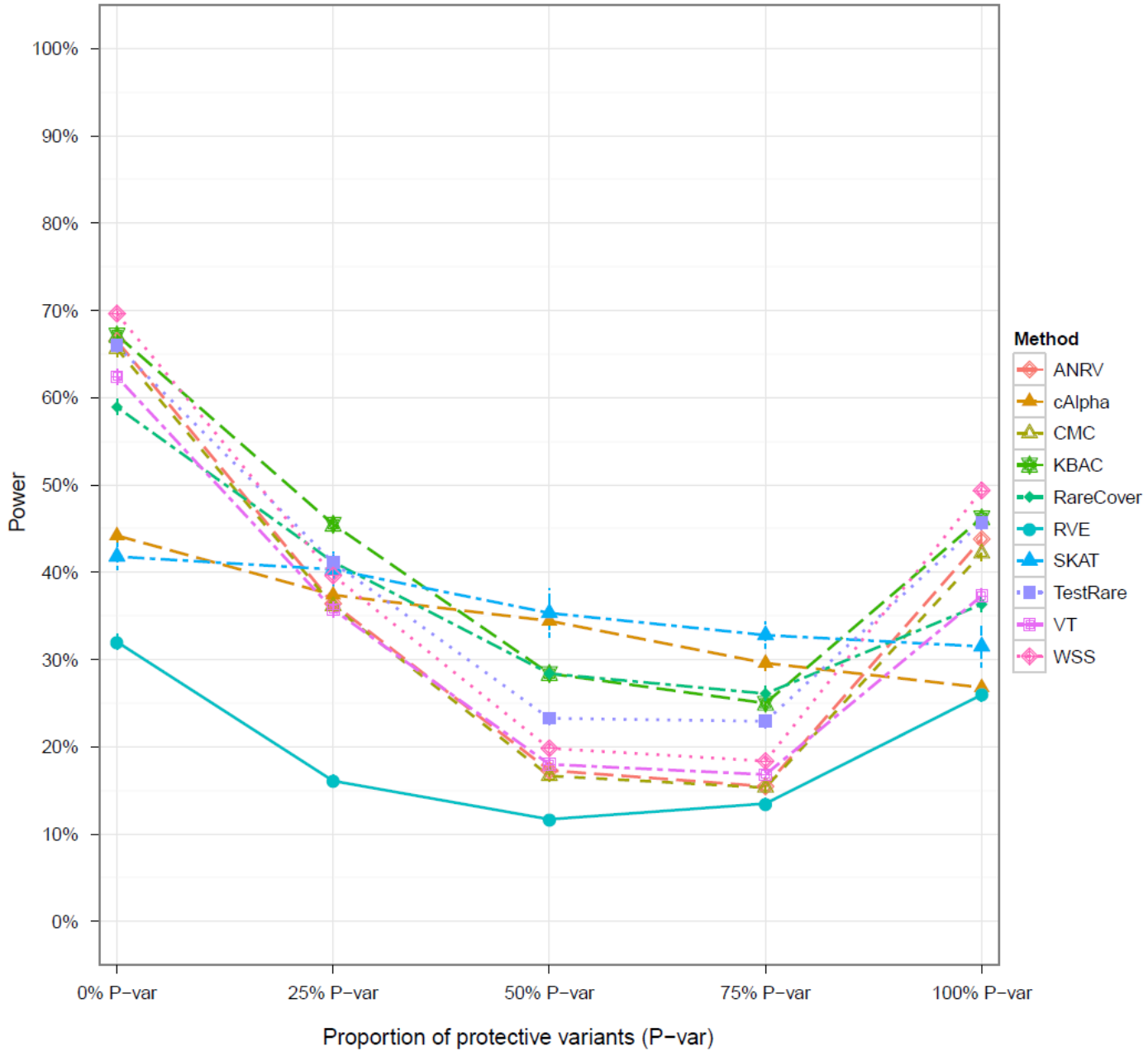
# NS Allele count for top protective gene: *NBEAL1*

| | Cases | Controls |
|---|---|---|
| European ancestry | 9 | 22 |
| African Americans | 1 | 8 |
| Uncorrected P | $2 \times 10^{-4}$ | |

# Impact of Non-Causal Variants (tests for detrimental variants)



# Detrimental and Protective Variants ("two-sided" tests)



# Rare variants

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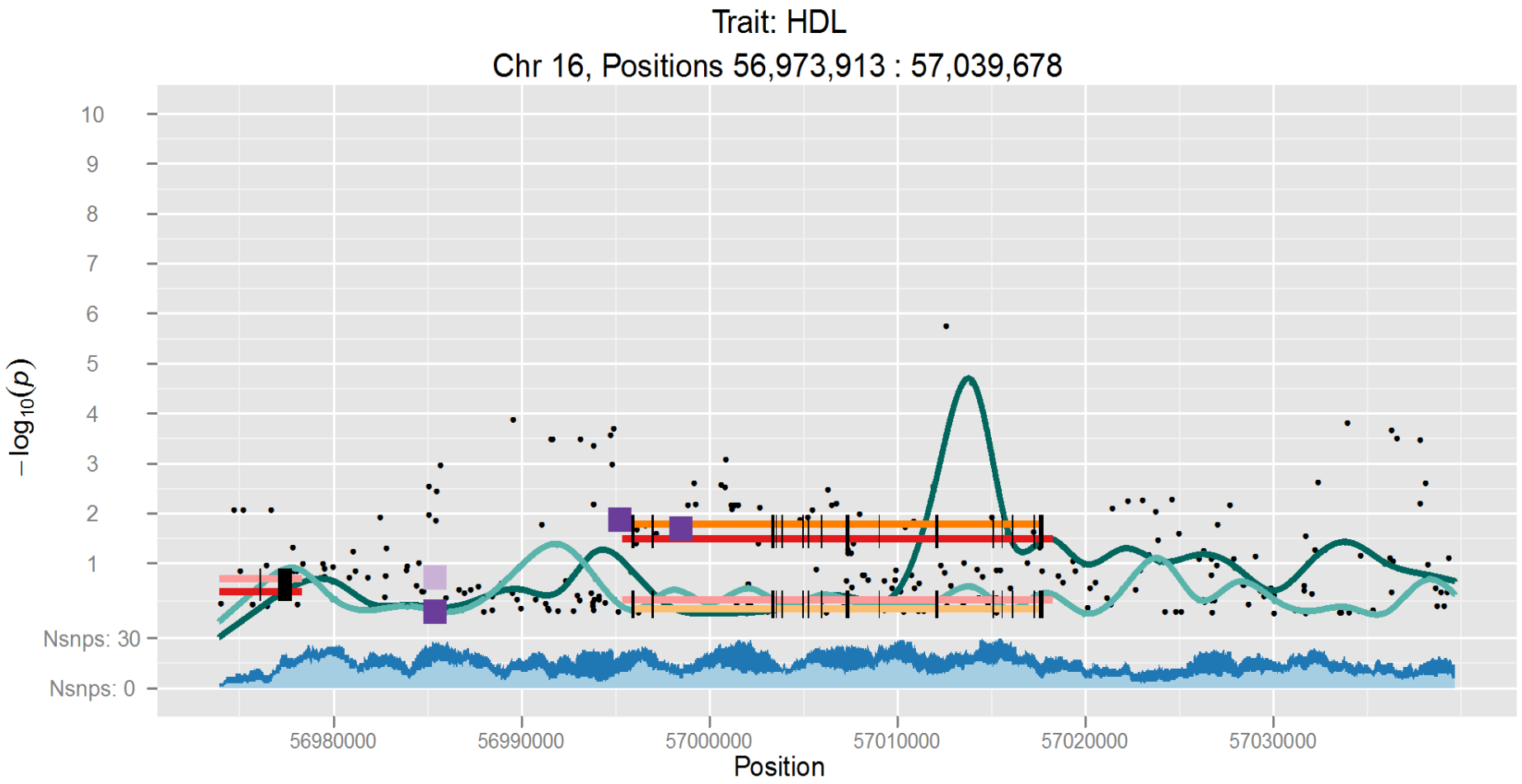
- How do we analyze rare variants?
- What are we going to do with WGS?

# Whole Genome Sequence Variation (N=990)

| Chr | #var | #mono | #single | #double | %MAF>.01 | %MAF>.05 | %Novel | TiTv | TiTv-singletons |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2093374 | 141080 | 775364 | 175532 | 0.378 | 0.378 | 0.544 | 2.07 | 2.019 |
| 2 | 2388603 | 172173 | 902211 | 200964 | 0.368 | 0.368 | 0.538 | 1.986 | 1.968 |
| 3 | 2000450 | 146724 | 754784 | 168949 | 0.368 | 0.368 | 0.533 | 1.973 | 1.982 |
| 4 | 2084913 | 165137 | 785378 | 174737 | 0.368 | 0.368 | 0.539 | 1.945 | 1.977 |
| 5 | 1827054 | 137193 | 691946 | 152439 | 0.37 | 0.37 | 0.539 | 1.973 | 1.978 |
| 6 | 1772868 | 124536 | 639915 | 143292 | 0.395 | 0.395 | 0.516 | 2.039 | 2.004 |
| 7 | 1614398 | 111886 | 594679 | 133168 | 0.386 | 0.386 | 0.531 | 2.019 | 1.97 |
| 8 | 1551600 | 105194 | 580819 | 131643 | 0.375 | 0.375 | 0.527 | 1.856 | 1.885 |
| 9 | 1233030 | 87525 | 456776 | 100802 | 0.38 | 0.38 | 0.539 | 1.914 | 1.91 |
| 10 | 1334721 | 84208 | 476347 | 107987 | 0.4 | 0.4 | 0.51 | 2.058 | 2.011 |
| 11 | 1347518 | 90082 | 498092 | 110821 | 0.386 | 0.386 | 0.524 | 1.988 | 1.973 |
| 12 | 1300915 | 86964 | 476183 | 109475 | 0.387 | 0.387 | 0.518 | 2.066 | 1.999 |
| 13 | 1025342 | 79869 | 386227 | 84437 | 0.375 | 0.375 | 0.539 | 2.02 | 2.011 |
| 14 | 899366 | 61431 | 329197 | 74412 | 0.386 | 0.386 | 0.525 | 2.038 | 1.978 |
| 15 | 784724 | 49117 | 282976 | 63790 | 0.395 | 0.395 | 0.52 | 2.003 | 1.961 |
| 16 | 830172 | 40649 | 294231 | 69934 | 0.403 | 0.403 | 0.501 | 1.846 | 1.796 |
| 17 | 710857 | 33871 | 249763 | 60821 | 0.406 | 0.406 | 0.5 | 2.254 | 2.044 |
| 18 | 780205 | 55099 | 286866 | 64334 | 0.384 | 0.384 | 0.522 | 2.043 | 2.02 |
| 19 | 550002 | 19172 | 178085 | 44026 | 0.454 | 0.454 | 0.472 | 2.186 | 1.957 |
| 20 | 570402 | 28374 | 201379 | 47880 | 0.412 | 0.412 | 0.485 | 2.186 | 2.041 |
| 21 | 373298 | 24933 | 133630 | 30665 | 0.396 | 0.396 | 0.521 | 2.089 | 2.003 |
| 22 | 342159 | 13967 | 113253 | 27538 | 0.442 | 0.442 | 0.479 | 2.285 | 2.017 |
| Total | 27415971 | 1859184 | 10088101 | 2277646 | 0.384 | 0.384 | 0.526 | 2.008 | 1.975 |

# Annotation and Analysis of Whole Genomes



# Thank You

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