Introduction to Genetics and Genomics

5b. Ancient Genomic Medicine

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Applying precision medicine to ancient DNA

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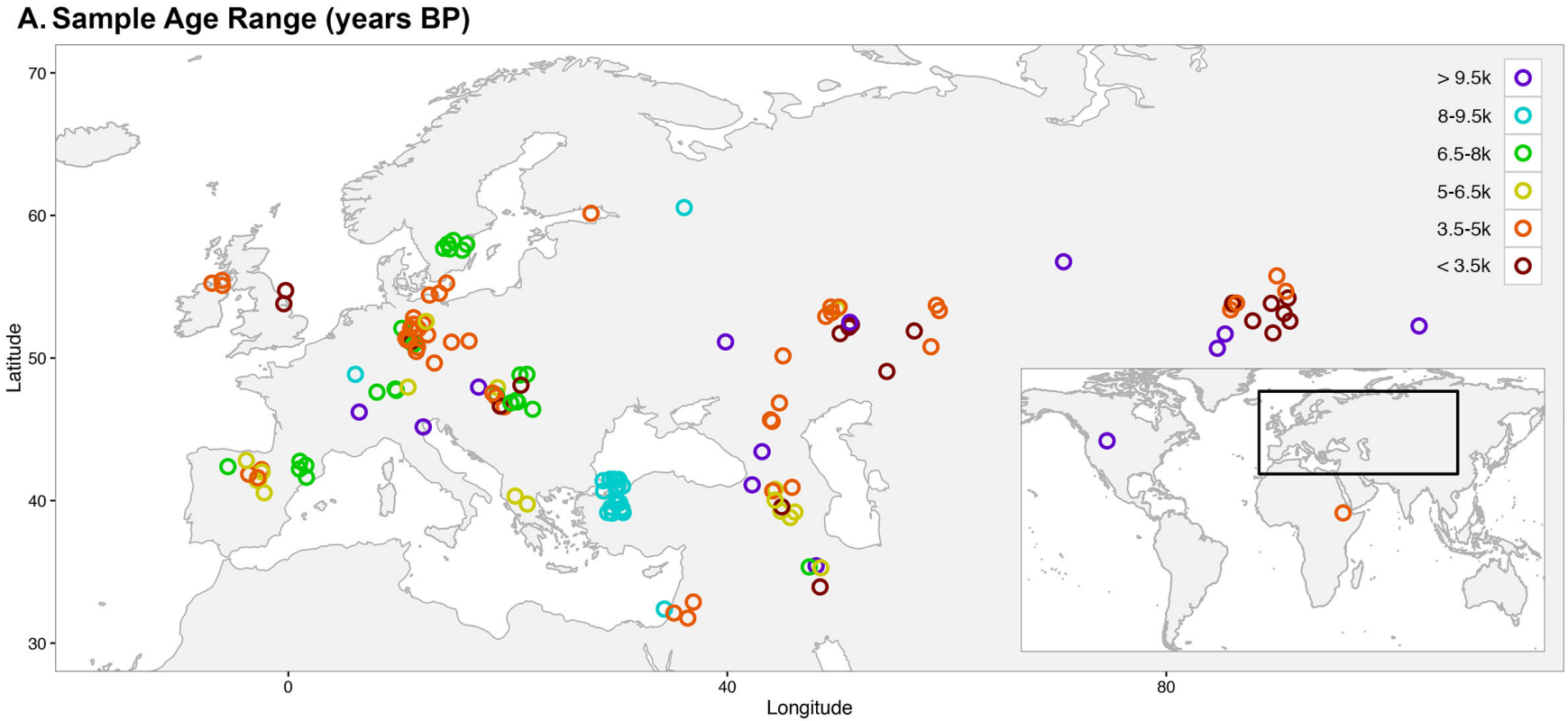
Ancient genomes



Disease associations and modern genomes

NHGRI-EBI GWAS Catalog

1000 Genomes Project
(26 populations)

Genetic architecture matters

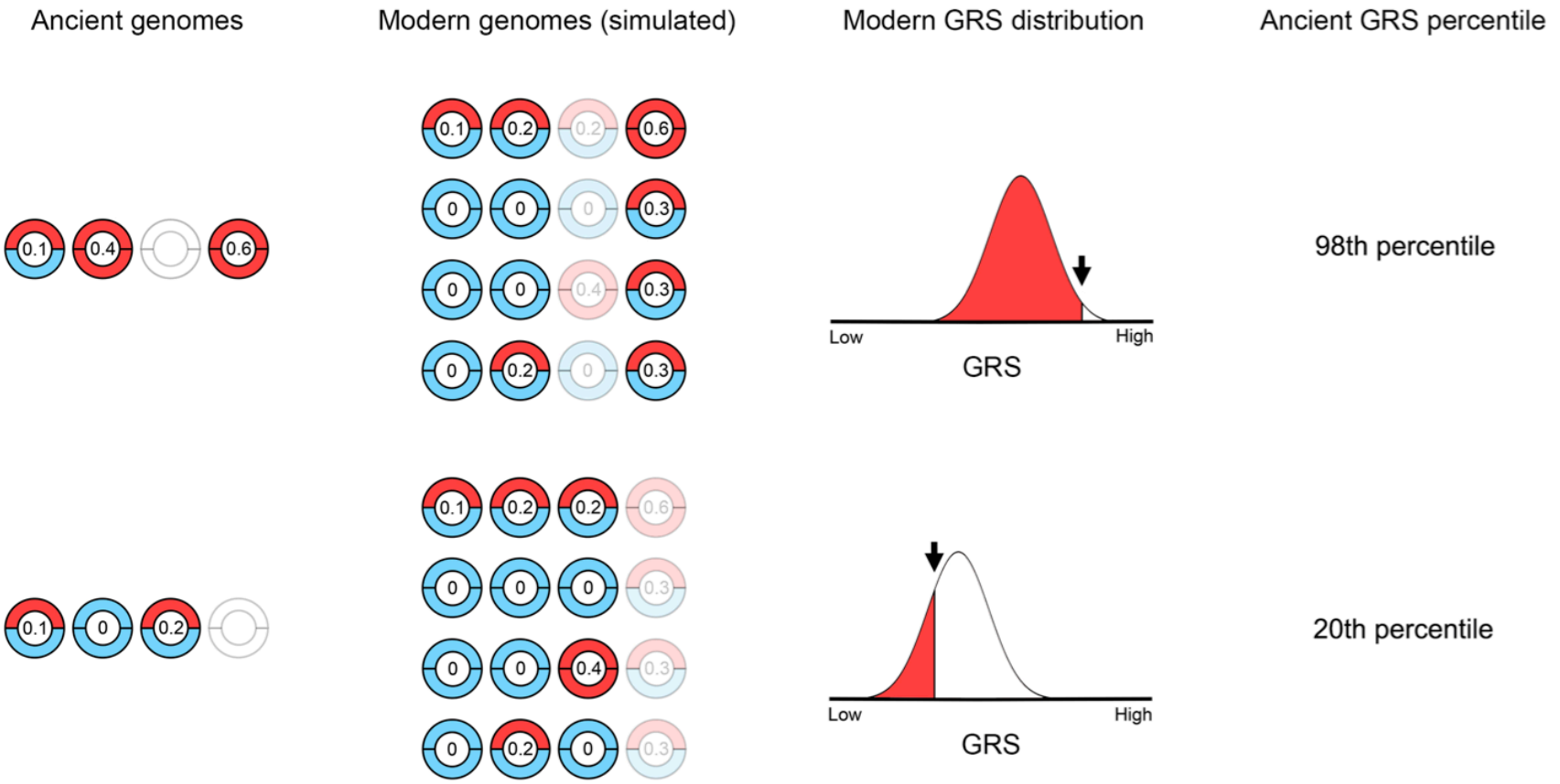
- Our model assumes additive genetic effects at each locus

$$GRS_i = \sum_{l=1}^{L_i} \beta_l \times (\#\ of\ copies\ of\ the\ risk\ allele\ at\ locus\ l\ in\ ancient\ individual\ i)$$

- How would our predictions be different if disease alleles are recessive?

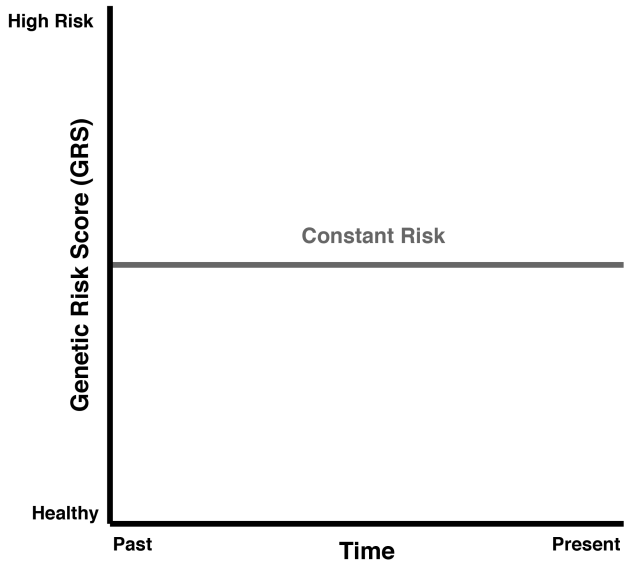
- What about dominant disease alleles?

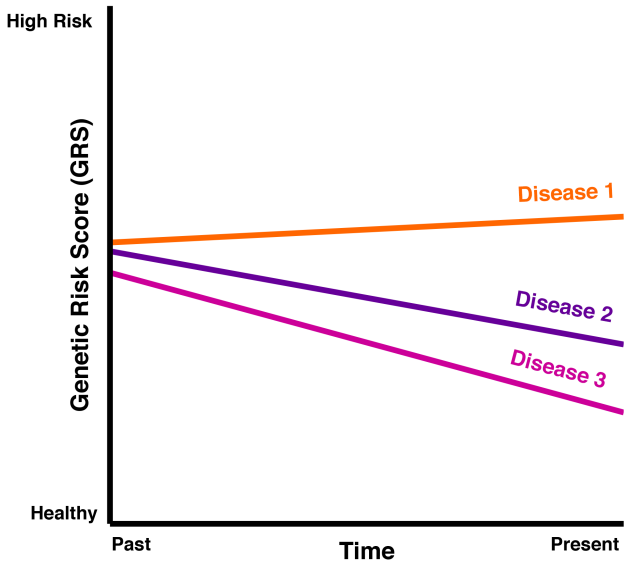
Calculating genetic risk



- Key assumption: each disease allele acts independently

What sorts of patterns do we expect to see?

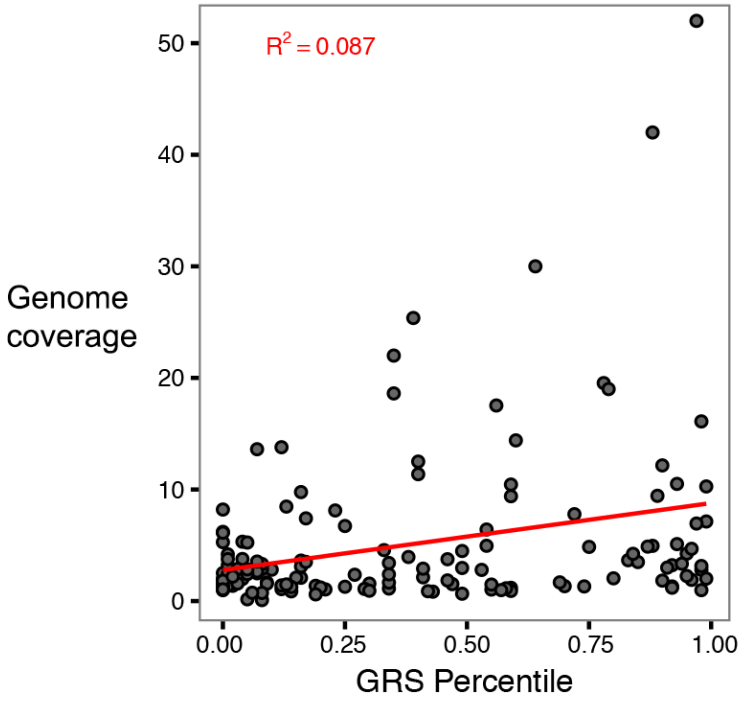


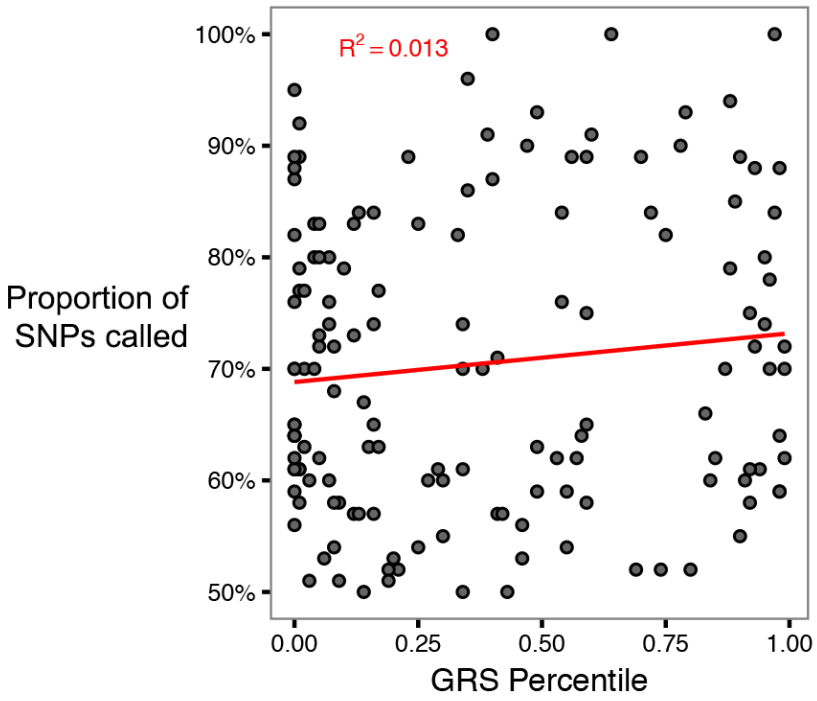


- Has the genomic health of humans changed over time?

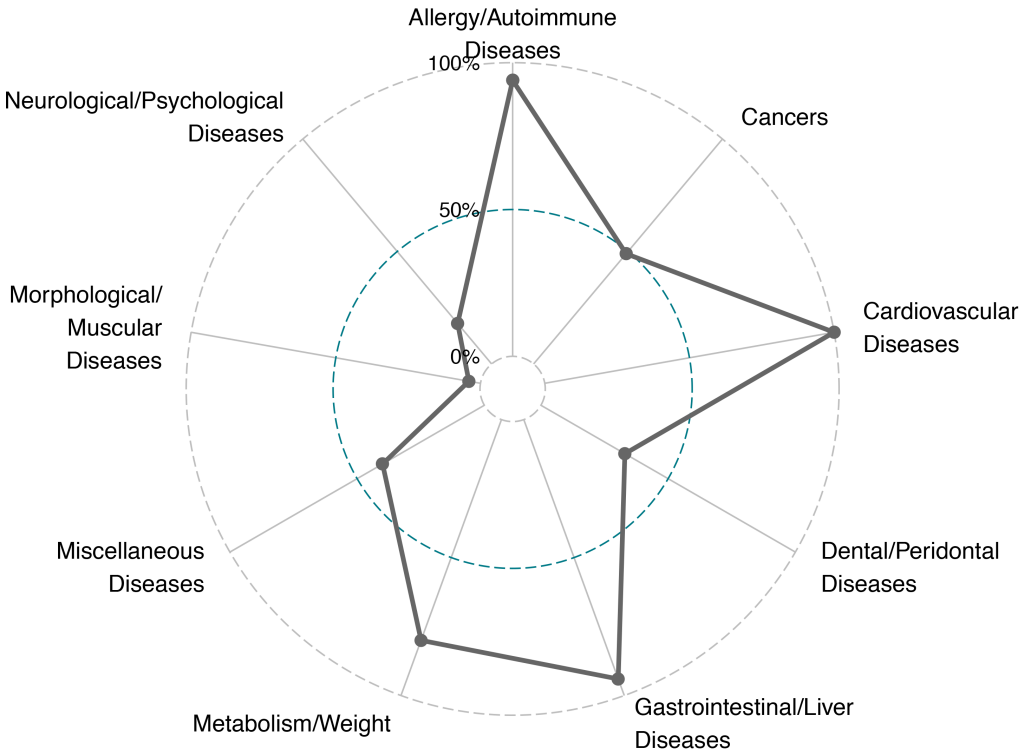
- Which diseases show the largest effect?

Minimal effects of DNA quality



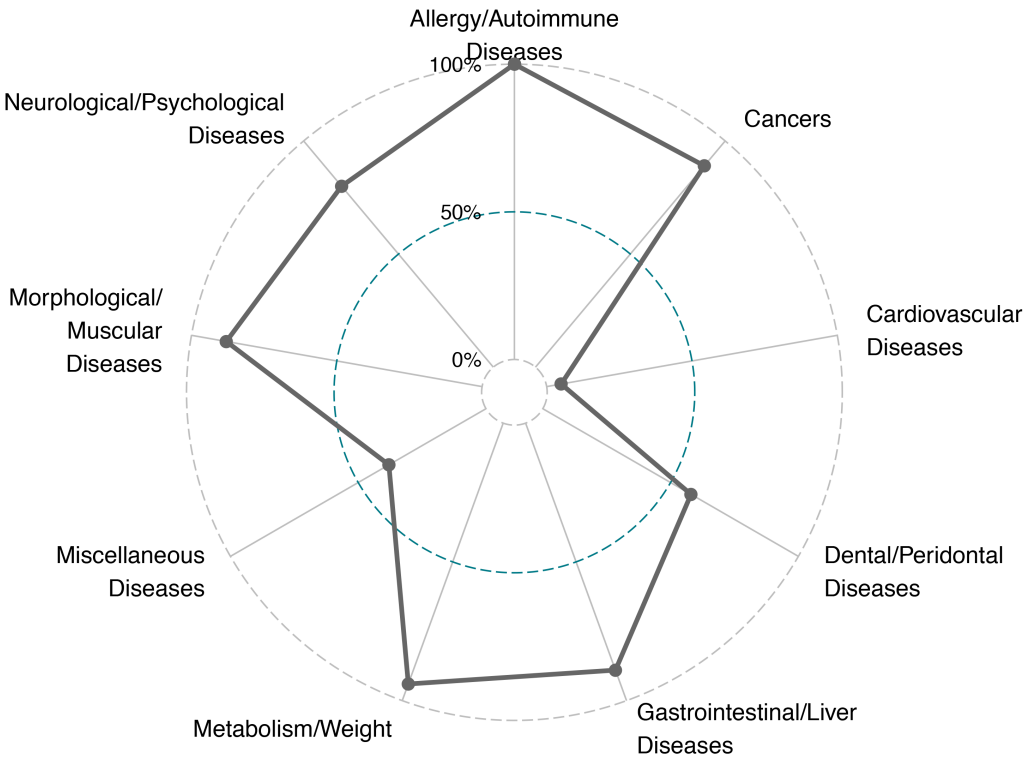


Ötzi the Tyrolean Iceman

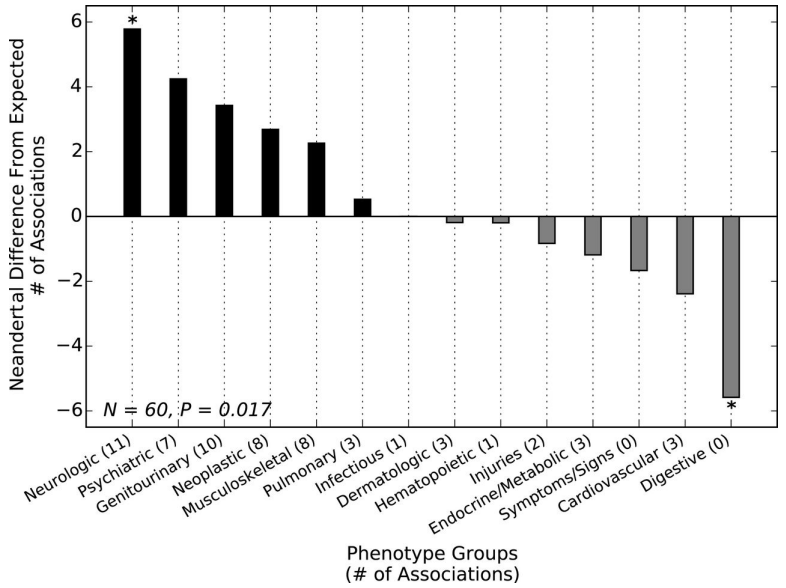


Murphy, et al. (*Radiology*, 2003)
Keller, et al. (*Nature Communications*, 2012)

Altai Neanderthal

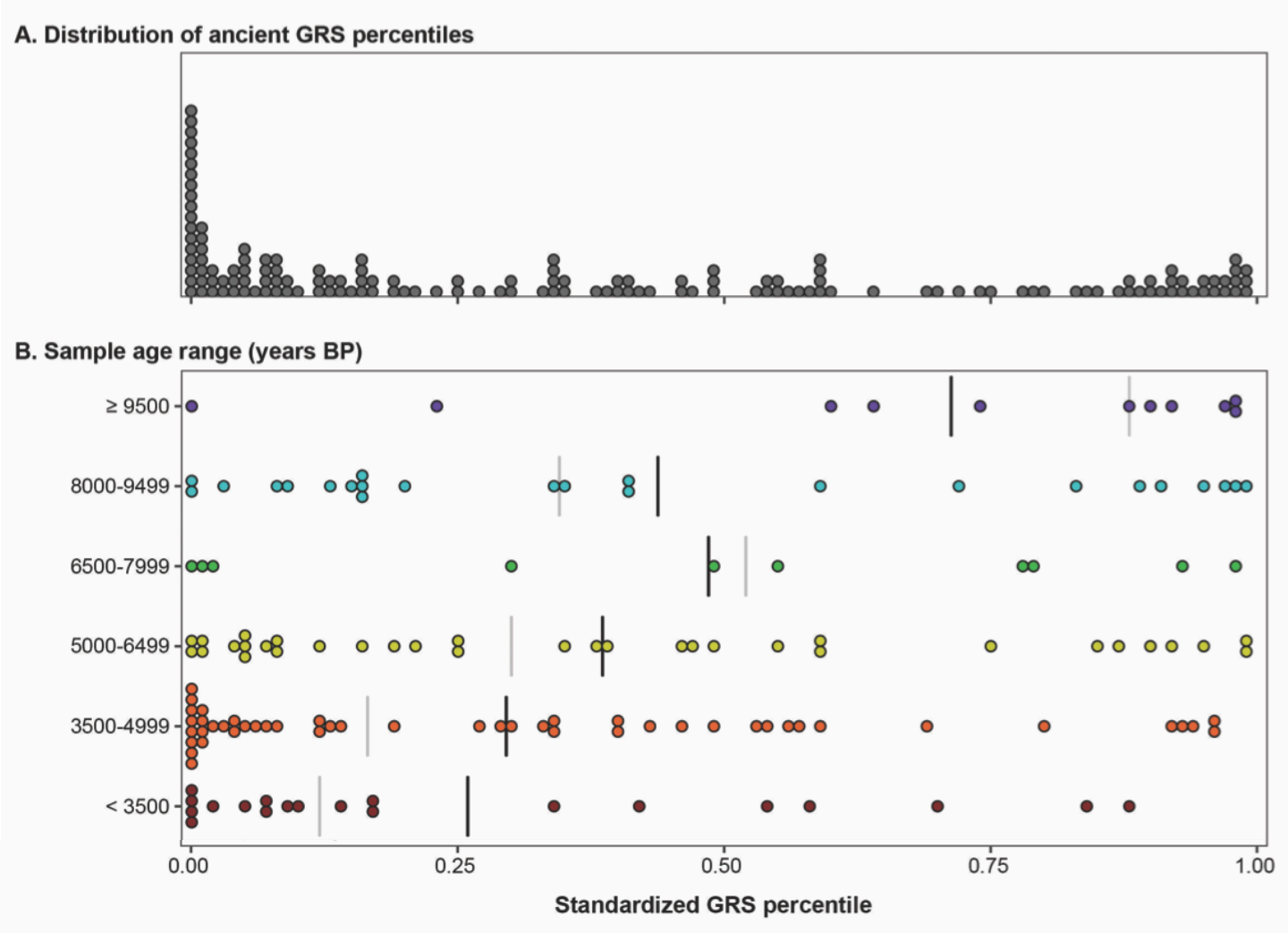


Phenotype	Discovery (E1)		Replication (E2)		Replication (E2; two-GRM)	
	Risk explained	*P*	Risk explained	*P*	Risk explained	*P*
Actinic keratosis	0.64%	0.066	3.37%	0.0059	2.49%	0.036
Mood disorders	1.11%	0.0091	0.75%	0.018	0.68%	0.029
Depression	2.03%	0.0023	1.15%	0.020	1.06%	0.031
Obesity	0.59%	0.048	1.23%	0.030	0.39%	0.27
Seborrheic keratosis	0.77%	0.038	0.61%	0.045	0.41%	0.13
Overweight	0.60%	0.037	0.53%	0.052	0.23%	0.24
Acute upper respiratory infections	0.70%	0.043	0.56%	0.062	0.34%	0.18
Coronary atherosclerosis	0.68%	0.04	0.42%	0.098	0.34%	0.15



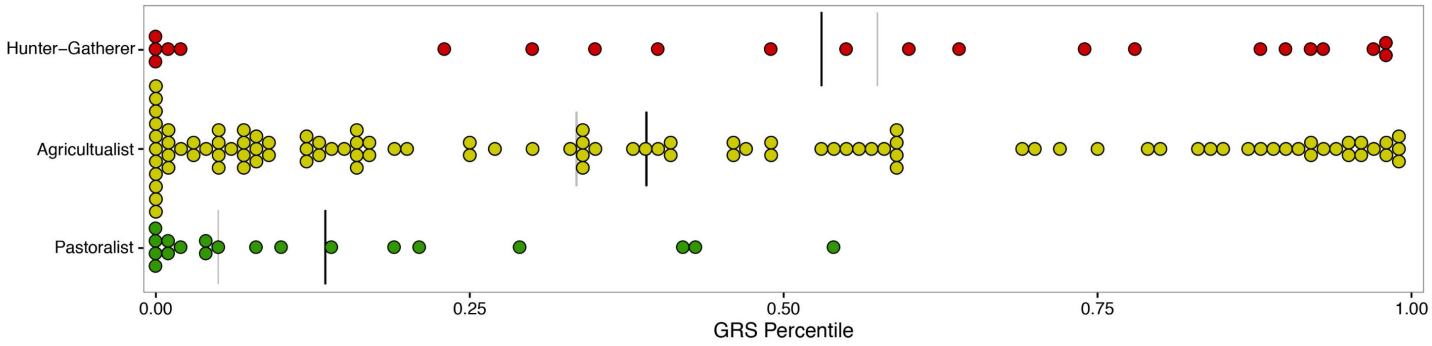
(Simonti et al. 2016, *Science*)

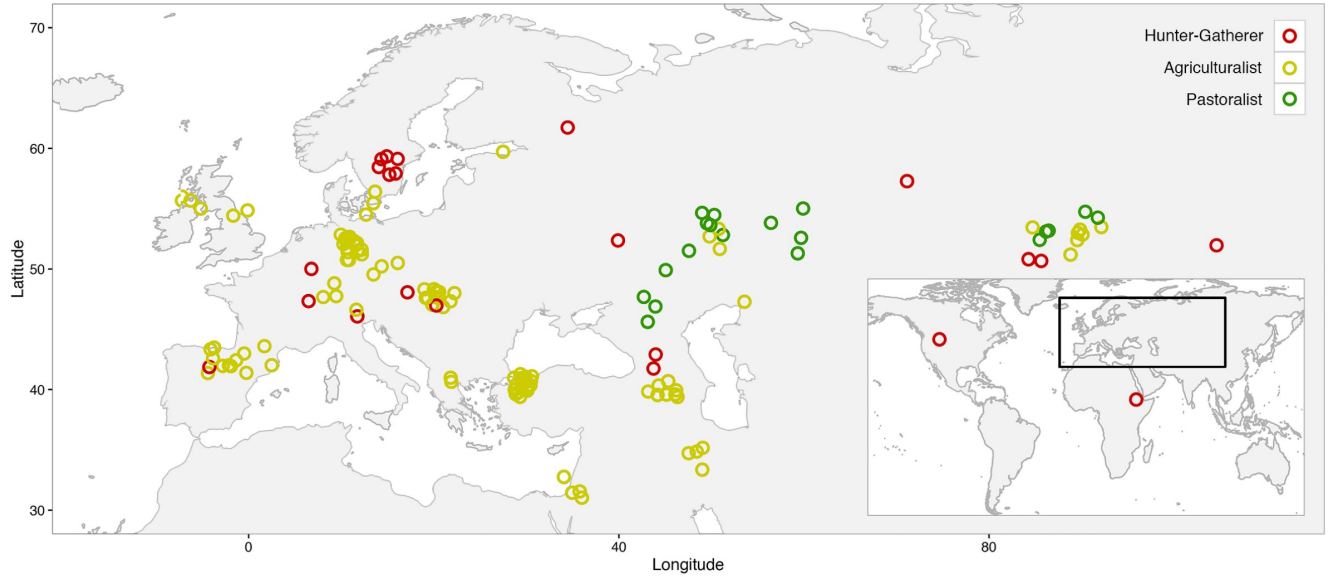
Temporal trends



Jonckheere-Terpstra test, p-value = 0.001

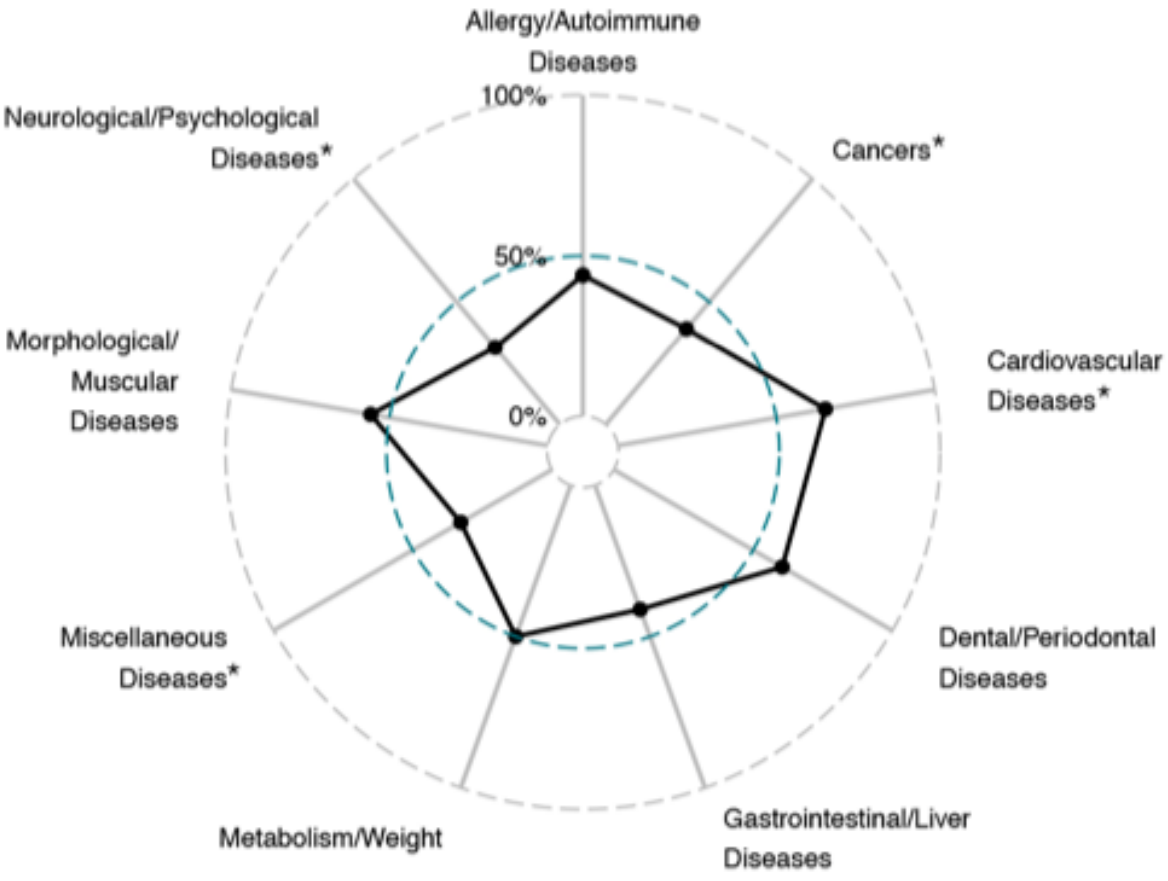
Subsistence patterns





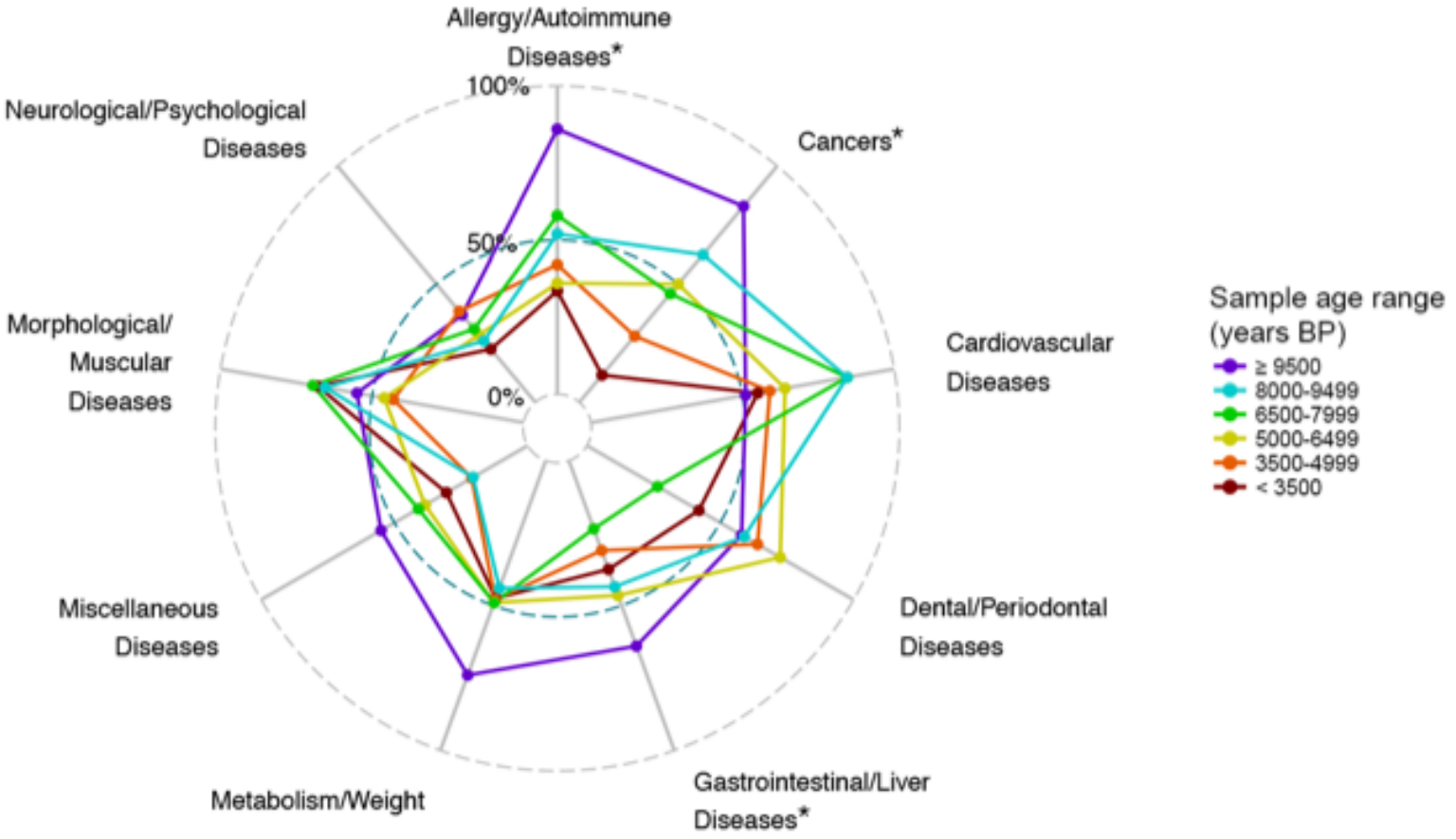
Kruskal-Wallis test, p-value = 0.002

Disease categories



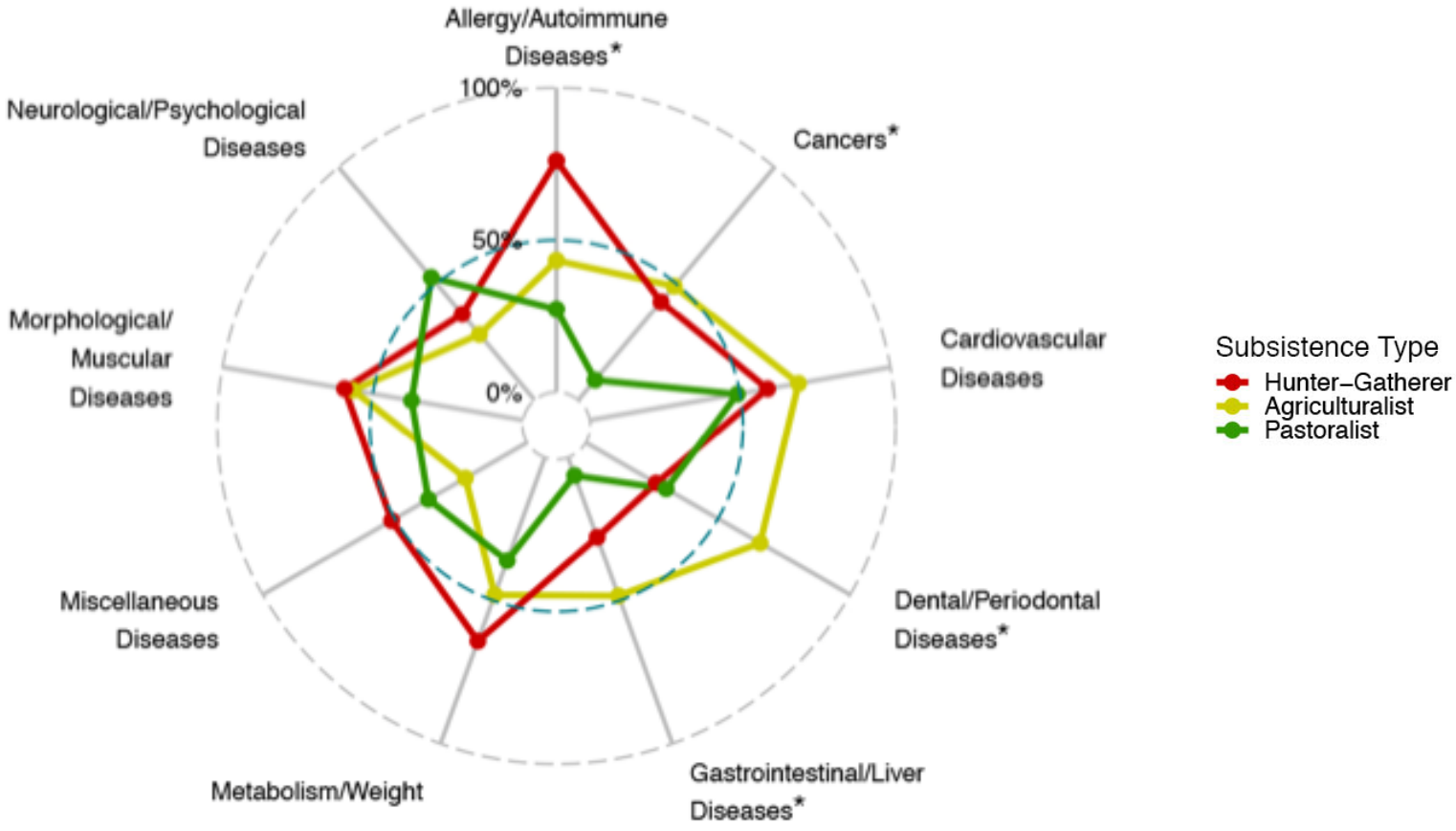
*Wilcoxon sign-ranked test, p-value < 0.05

Disease categories (temporal trends)



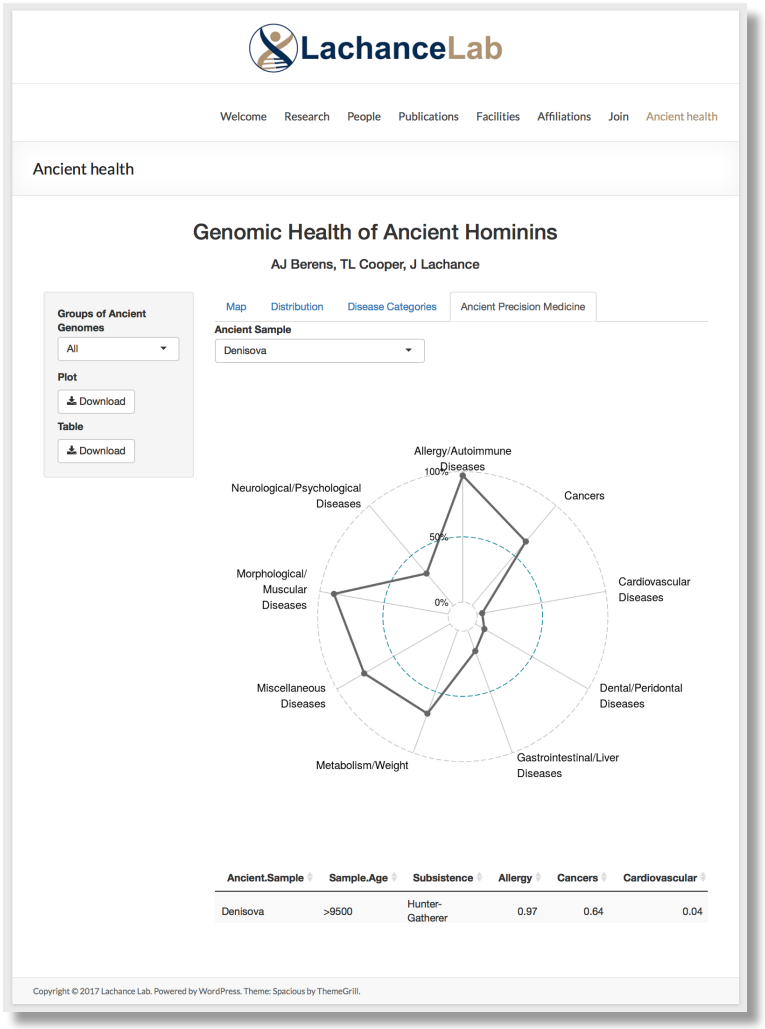
*Jonckheere-Terpstra test, p-value < 0.05

Disease categories (subsistence type)



*Kruskal-Wallis test, p-value < 0.05

http://popgen.gatech.edu/ancient-health/



Explore the data!