Evaluating inbreeding measures using a whole-genome sequenced cattle pedigree

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Introduction

- Inbreeding
  - Negative consequences such as increased occurrence of recessive genetic disorders and inbreeding depression
  - Considered in conservation programs
- Hypotheses for inbreeding depression (ID)
  - Increased homozygosity at rare recessive deleterious alleles
  - Decreased heterozygosity at variants presenting heterozygous advantage (overdominance)

Inbreeding coefficient *F*

- Estimation
  - Pedigree-based or genomic measures
- Numerous genomic estimates:
  - Maximum likelihood, method-of-moments, homozygosity or heterozygosity measures, diagonal elements of the GRM, ROH
- True inbreeding coefficients unknown:
  - Simple comparisons or simulations

Objectives

- Evaluation of inbreeding measures
  - In a livestock population
- Use whole-genome sequence data to mimic scenarios
  - Real genomic structure (LD, allele frequency spectrum, …)
  - Contains causative variants, rare alleles, different functional categories
- Estimation and prediction
- Genome-wide and locus specific

Data

- 266 sequenced Dutch-Holstein cattle
  - Cover > 15x
  - 145 parents
  - 100 offspring with both parents known
  - 13 x 10^6 SNPs
- Estimating of the inbreeding coefficient
  - 37,675 SNPs (50K array)
  - 5,977 SNPs (Low-density – LD array)

Inbreeding coefficients

- Pedigree-based F_{PED}
- Correlations between uniting gametes F_{UG} (GCTA)
- Based on diagonal elements GRM F_{GRM}
- Excess homozygosity F_{HOM} (PLINK)
- Maximum likelihood estimator F_{LIK} (TrioML - Coancestry)
- Homozygous-by-descent (HBD) segments (RZooRoH):
  - Four classes of HBD segments (length 20, 4, 0.8 and 0.2 cM)
  - Proportion of the genome in HBD classes with rate ≤ T F_{HBD-T}
  - Similar to F_{ROH} with 50K

Scores related to inbreeding

- Obtained from the sequence data
- Homozygous mutation load
  - Homozygosity at rare and young alleles
- Homozygosity score at intermediate frequency variants
  - Homozygosity at variants with MAF > 0.15
- Whole genome sequence homozygosity
  - Homozygosity at all variants

Variant classification

- Age of alleles
  - Allele frequency (rare)
  - Derived allele (less SNPs)
  - Not in another breed (not in Belgian Blue): enrichment in young alleles
- Functional annotation
  - All alleles (no assumption)
  - Synonymous versus non-synonymous
  - Excluding intergenic and intronic regions (functional space)

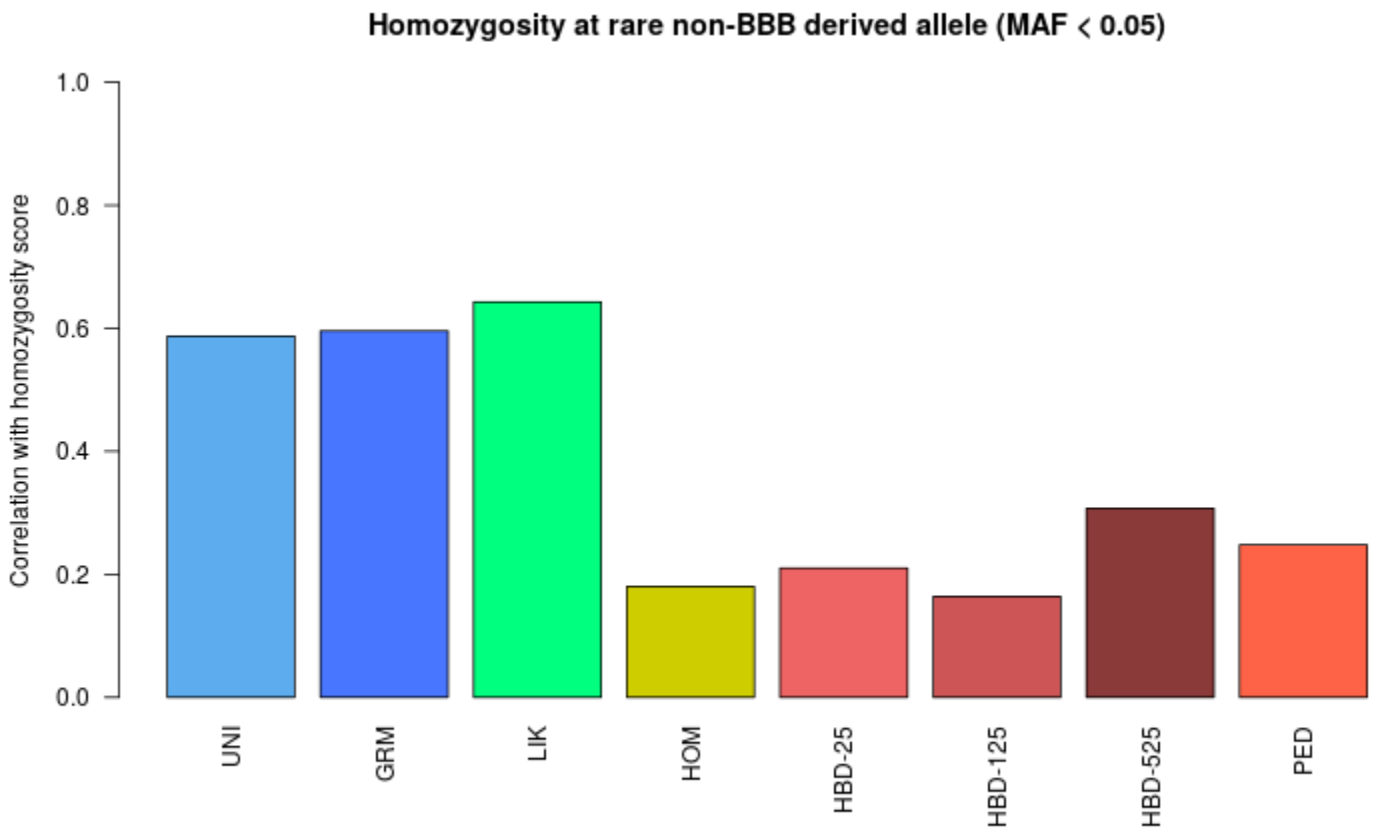
Age of alleles

- Using GEVA (Albers and McVean, 2019):
  - Genealogical Estimation of Variant Age
  - Recombination clock (in generations to TMRCA)

Allele frequency	All derived alleles		Alleles absent from the BBB sample	
	Number of alleles	Average TMRCA	Number of alleles	Average TMRCA
≤ 0.05	20480	641	4633	386
≤ 0.15	23667	1237	2165	575
≤ 0.30	20687	1637	635	773
> 0.30	28111	2606	36	1799

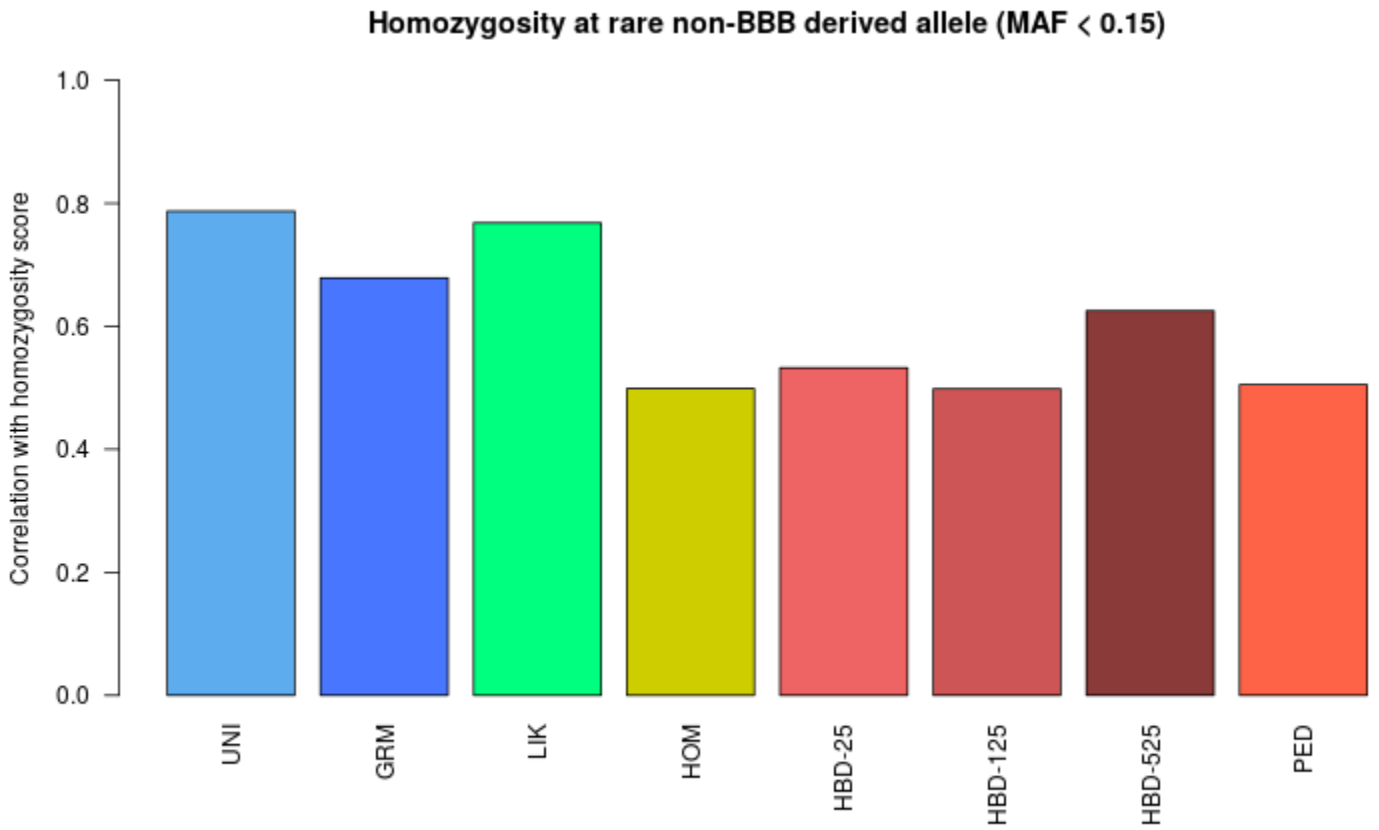
Homozygous mutation load

- Rare recessive deleterious alleles



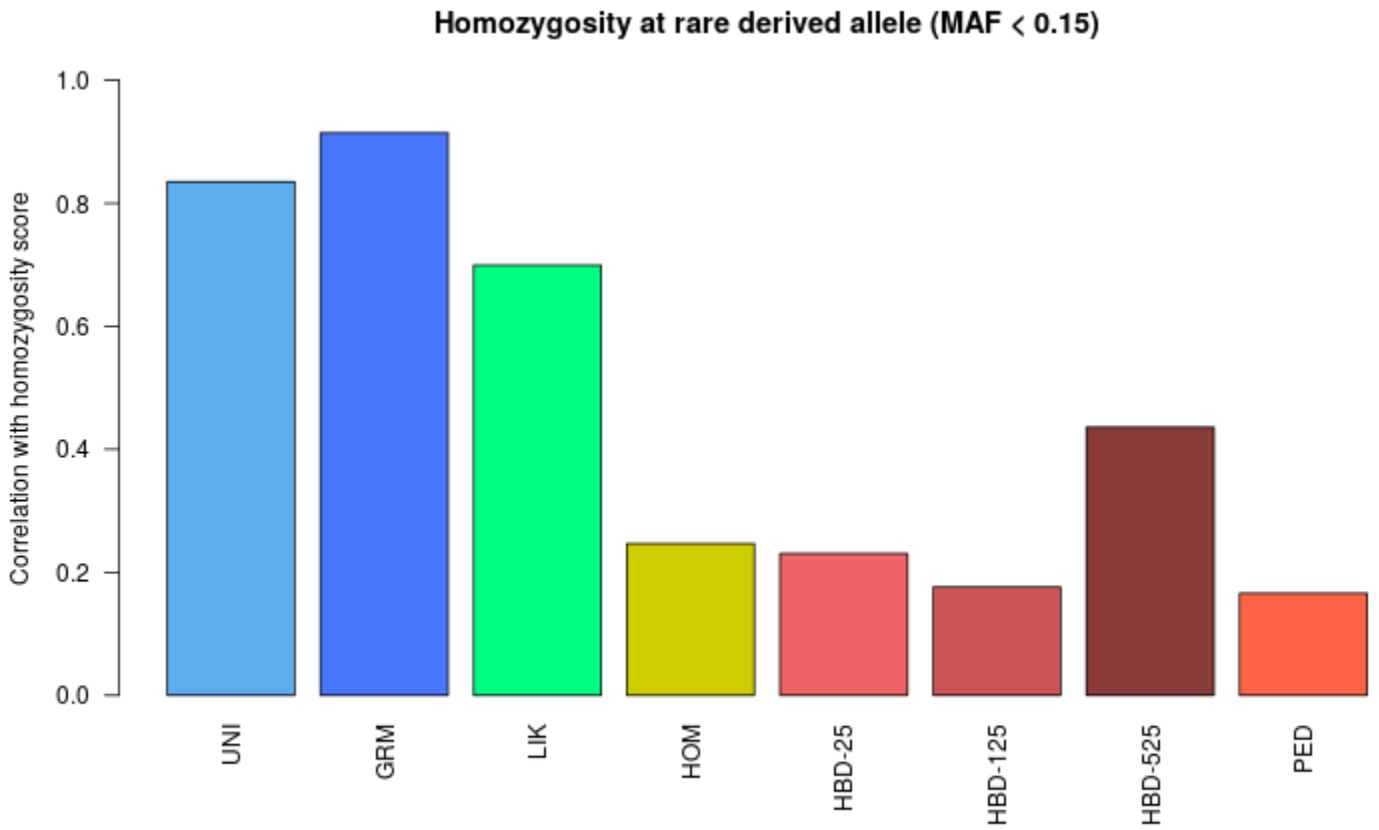
Homozygous mutation load

- Allele frequency < 15%



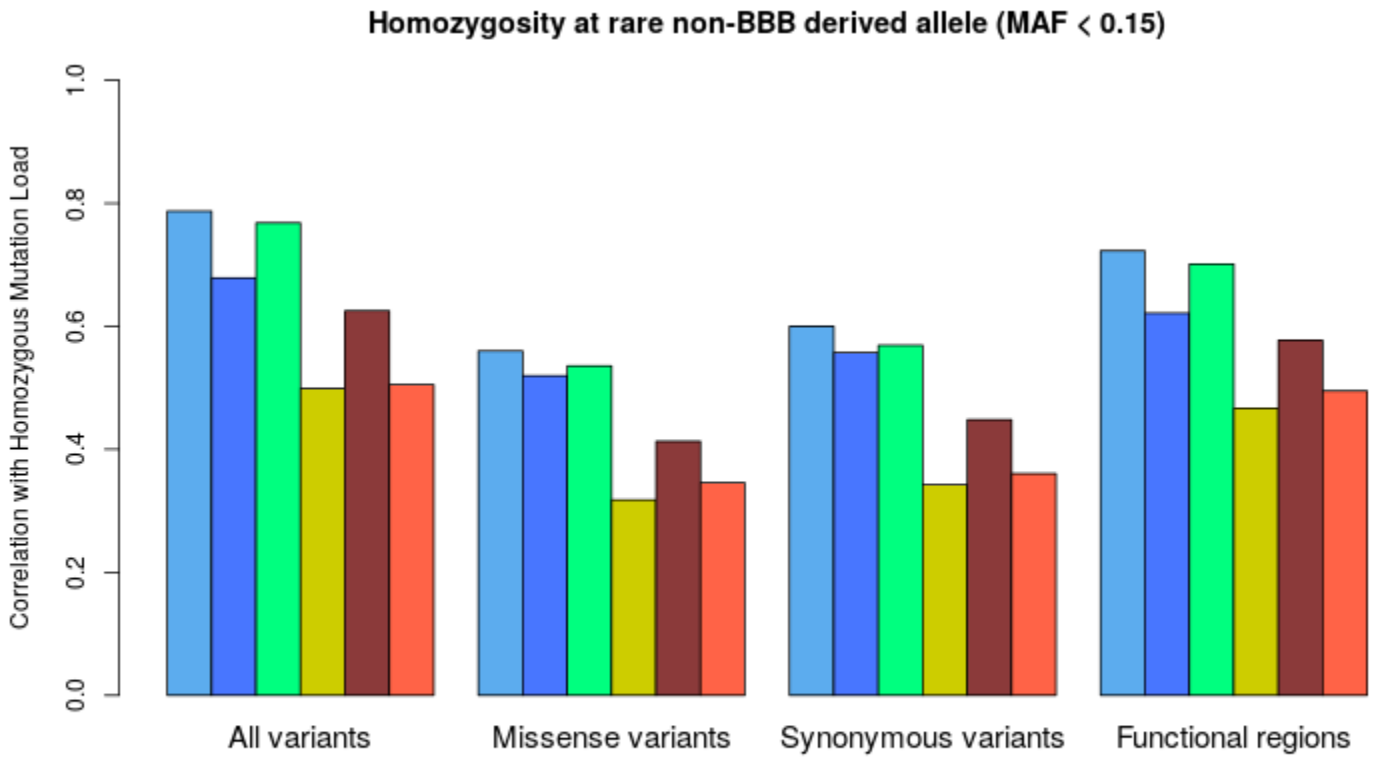
Homozygous mutation load

- Including derived alleles observed in BBB



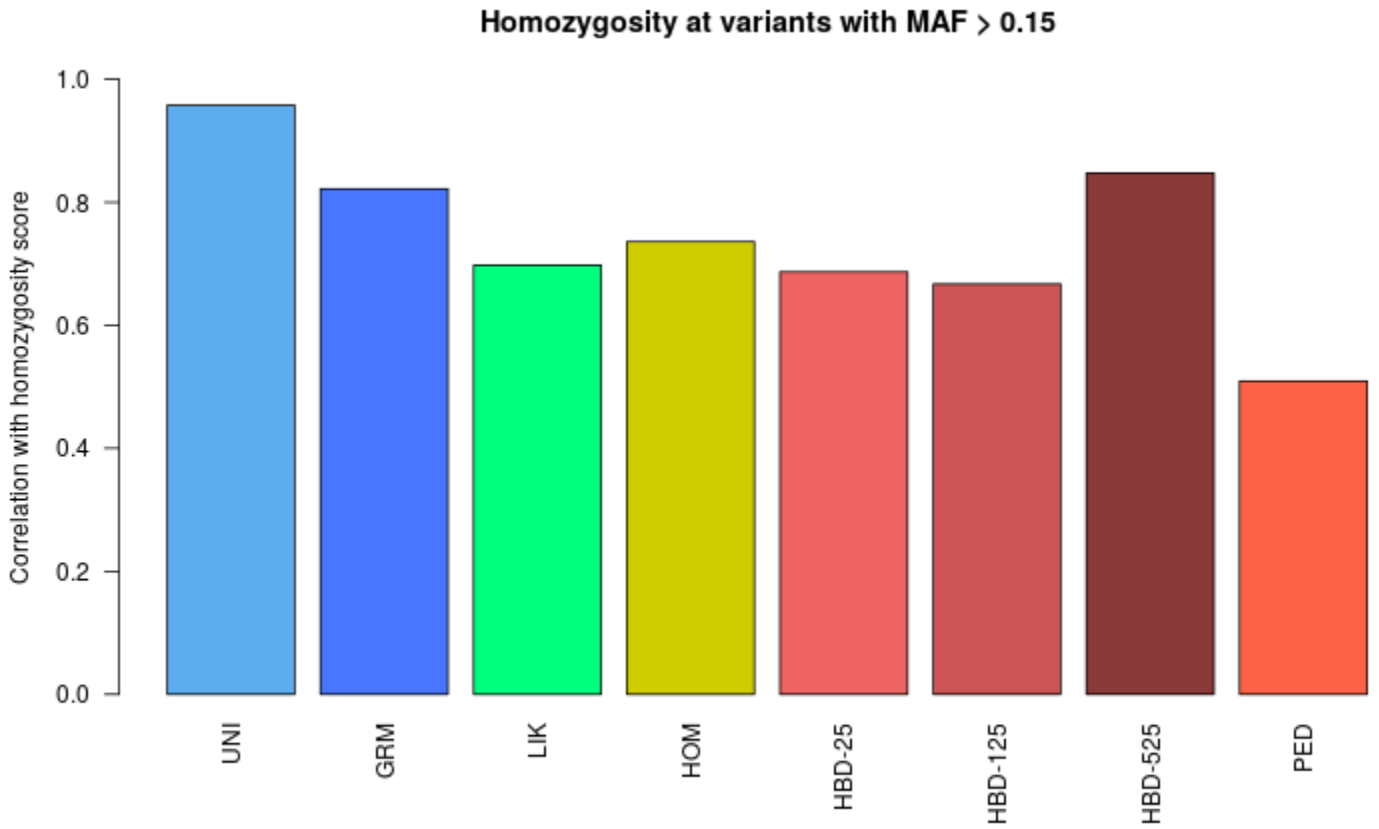
Homozygous mutation load

- For different annotations categories



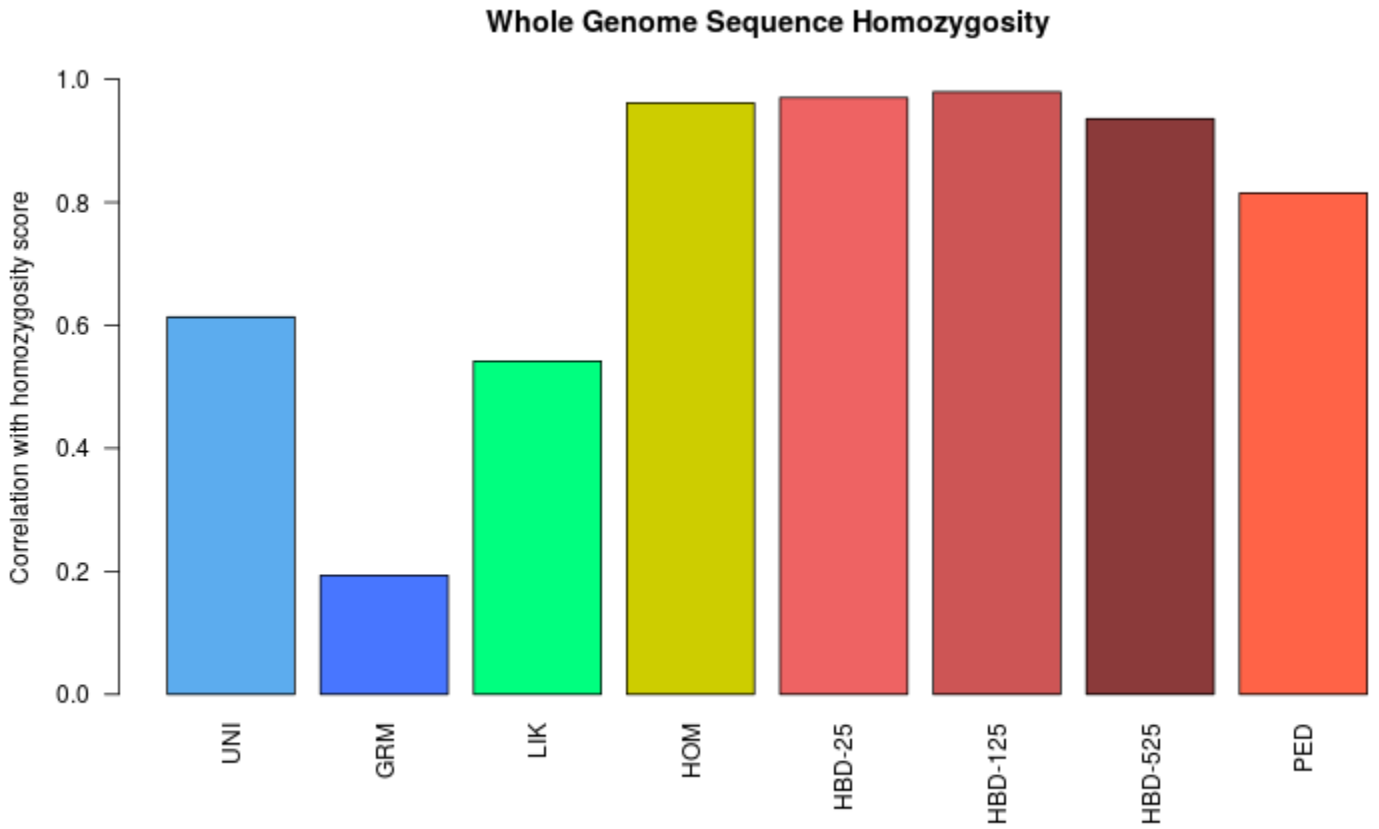
Heterozygous advantage

- Scenario 2: decreased heterozygosity



Whole genome sequence homozygosity

- Homozygosity at all alleles



Using low-density array

- Modest decrease of correlations
- Same ranking with LD array
  - Across scenarios
- Methods still efficient with 6K

Predicting *F*

- Prediction of inbreeding coefficients
  - 100 sequenced trios
  - Use genotypes of parents to predict *F*
  - Compute scores with sequence of progeny
- Same trends across scenarios

Local trends

- Estimate scores in 1 Mb windows
  - Some filtering on number of markers, homozygotes
  - Huge variation
  - Average correlation

	Hom (< 0.15)	Hom (MAF > 0.15)	Hom WGS
F_{PED}	0.02	0.05	0.07
F_{UG}	0.45	0.72	0.67
F_{GRM}	0.43	0.57	0.44
F_{HBD}	0.38	0.73	0.75

Local trends – LD array

- Estimate scores in 1 Mb windows
  - Some filtering on number of markers, homozygotes
  - Huge variation
  - Average correlation

	Hom (< 0.15)	Hom (MAF > 0.15)	Hom WGS
F_{PED}	0.02	0.05	0.07
F_{UG}	0.24	0.48	0.43
F_{GRM}	0.25	0.40	0.32
F_{HBD}	0.35	0.60	0.62

Conclusions

- F_{UG} and F_{GRM} better for inbreeding depression
  - Focus on rare allele (and not young)
- F_{HBD}, F_{HOM} and F_{PED}: proportion genome IBD
  - Improve with young alleles (“breed specific”)
- Lower correlations with NS variants
  - And with homozygosity at rare variants
- For locus-specific estimation and low-density, F_{HBD} performed well

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