Analysis of a large cattle data set suggest that ZFAT has pleiotropic effects on cattle growth and lethality

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Content

- Data preparation
- Discovery and confirmation of haplotype lethality
- Pleiotropy
- Candidate genes
- Economic impact
- Conclusions

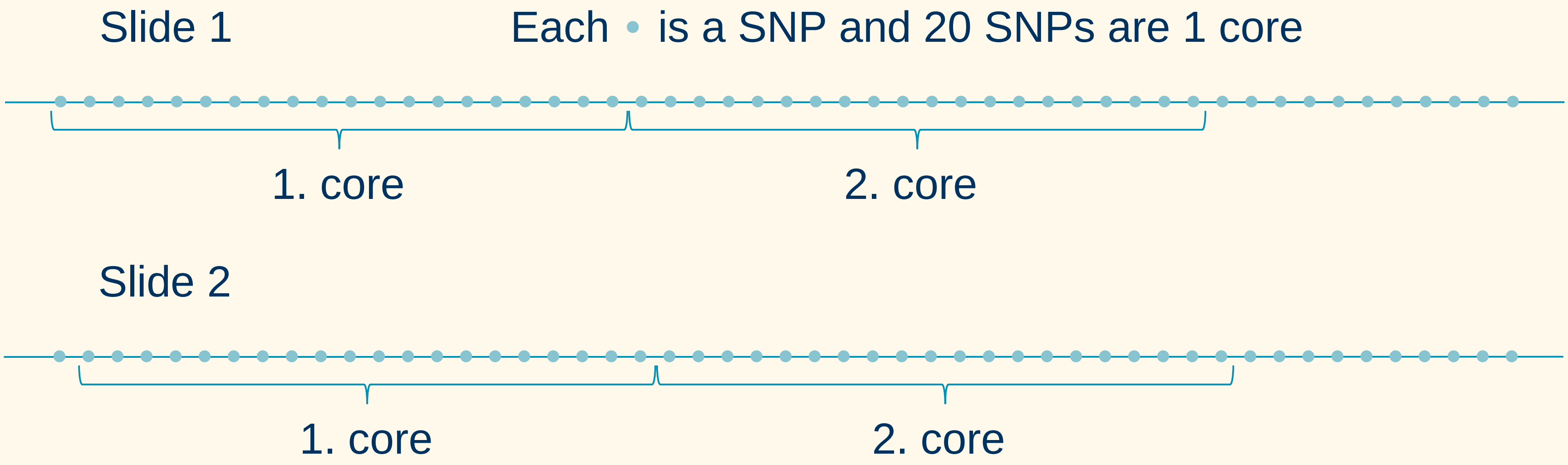
Genotypes

- Genotypes from >1 million Irish beef cattle

- Extraction of five purebreds
  - Aberdeen Angus (22,510)
  - Charolais (38,960)
  - Hereford (12,546)
  - Limousin (45,277)
  - Simmental (11,559)

Imputation and phasing

- Imputation to 53K array using AlphaImpute
- Phasing of imputed genotypes using sliding windows approach



Slide 1

Each • is a SNP and 20 SNPs are 1 core

1. core

2. core

Slide 2

1. core

2. core

Discovery of lethal haplotype alleles

- **No** or **lack of** homozygous individuals
- Analysis of haplotypes
  - Population approach
  - Mating approach

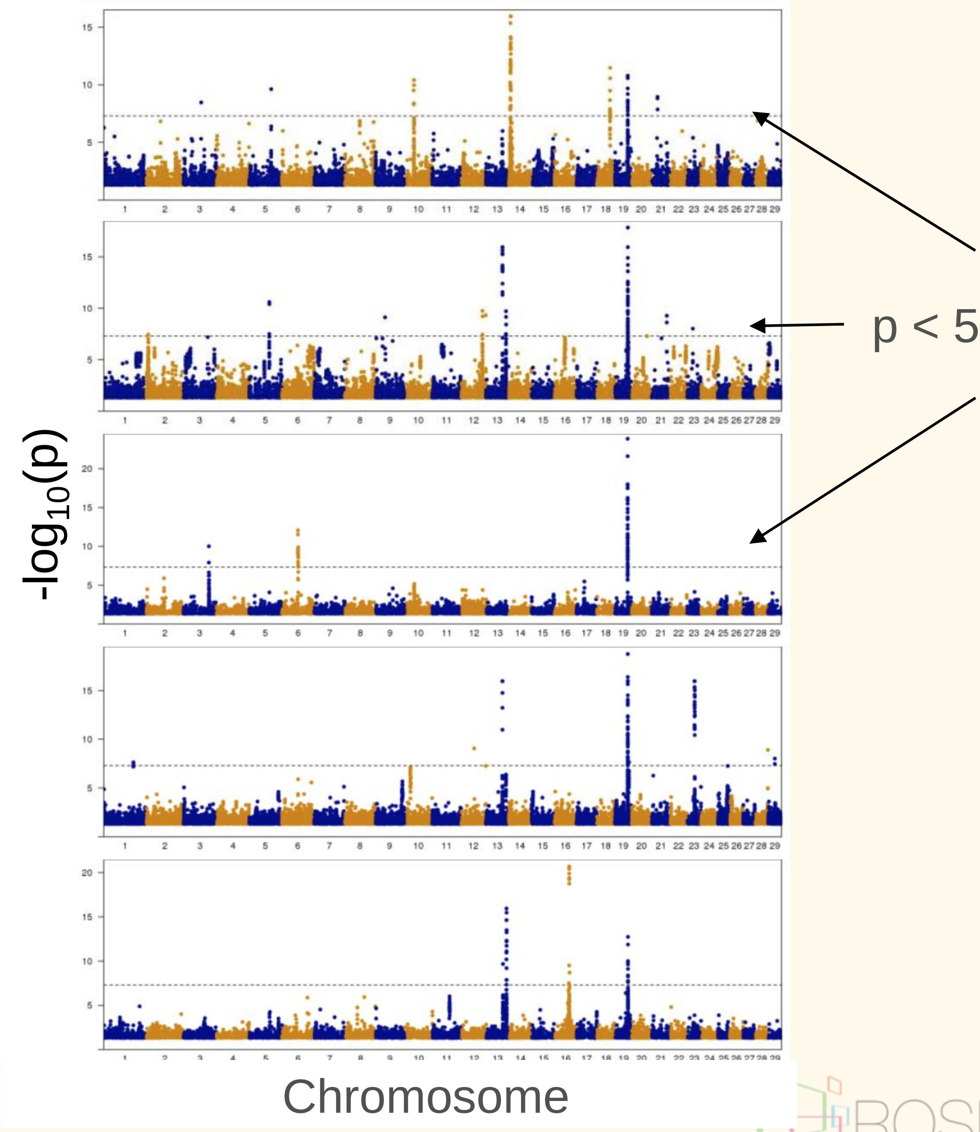
Confirmation of haplotype lethality

- Phenotypic data
  - Artificial insemination success rate and insemination to calving interval
  - Survival analysis

Results

Putative lethal haplotypes - 5 breeds

- Aberdeen Angus
- Charolais
- Hereford
- Limousine
- Simmental

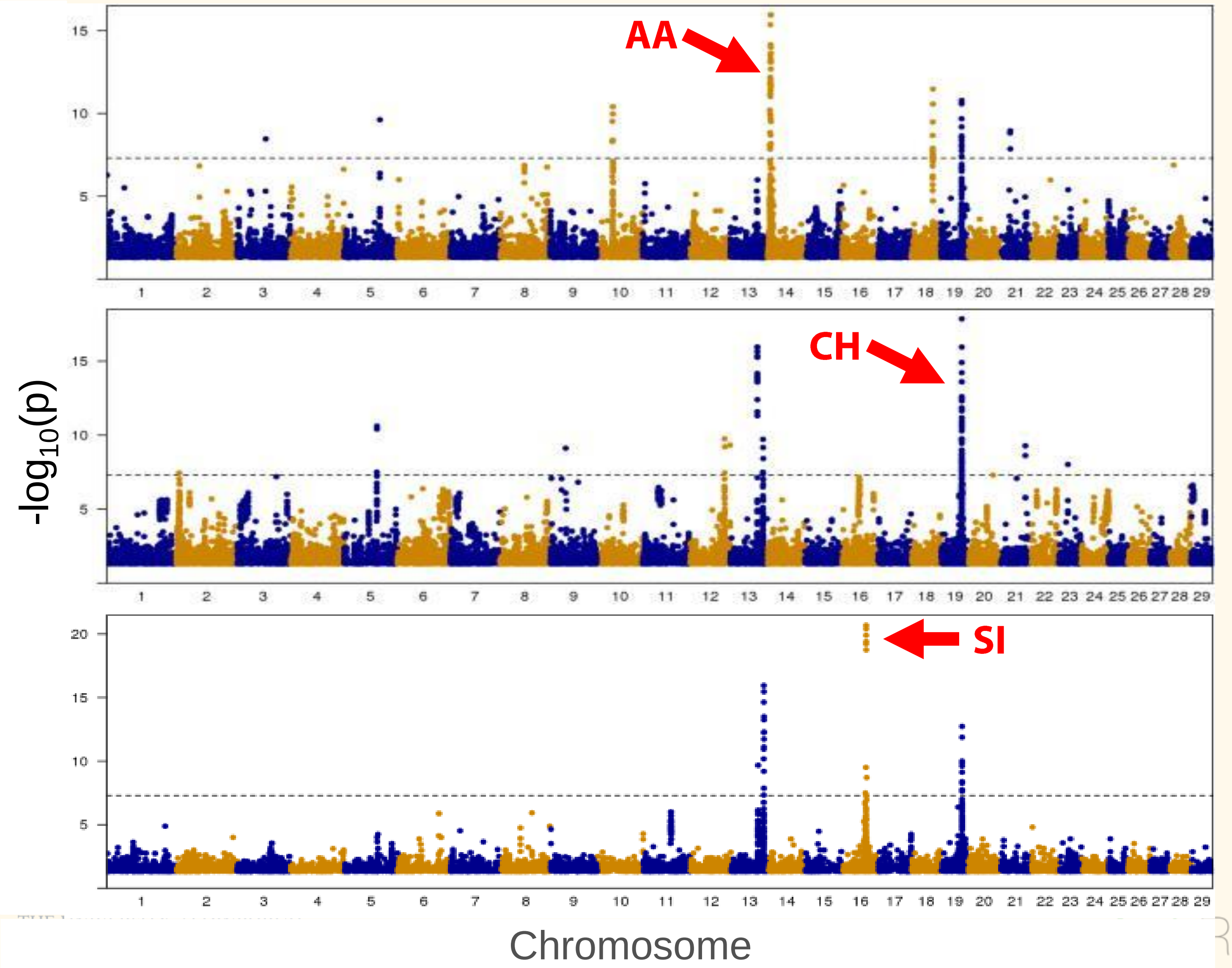


$p < 5*10^{-8}$

Candidate haplotype alleles

- Select regions of 1 MB long with ≥9 significant haplotypes
  - There were 19 regions
- From these regions select the most significant haplotype from different test
  - 22 haplotypes
- Confirm lethality with phenotypic data
  - 3 haplotypes with confirmed lethality

Putative lethal haplotypes



Haplotype test statistics

	AA	CH	SI
Genotyped animals	22,510	38,960	11,559
Haplotype frequency (%)	15.2	14.4	8.8
Expected homozygous individuals	194	256	48
Homozygous individuals	95	83	0
Sire × Dam carrier matings	220	256	17
Expected homozygous progeny from Sire × Dam carrier matings	55	64	4
Homozygous progeny from Sire × Dam carrier matings	2	6	0

Lethality validation

- Compared with non-carrier × non-carrier matings carrier × carrier matings had:
  - **20%** lower insemination success rate and **30 days** longer first insemination to calving interval for AA haplotype
  - **53%** lower insemination success rate and **30** days longer first insemination to calving interval for SI haplotype
  - **36%** higher probability of dying or being slaughtered during their life for CH haplotype

Pleiotropy

- The effect of one haplotype copy on terminal and replacement index

Haplotype	Terminal Index	Replacement index
AA	**0.18 [0.14, 0.21]**	**-0.11 [-0.14, -0.08]**
CH	**0.07 [0.04, 0.09]**	0.02 [-0.01, 0.05]
SI	**0.10 [0.05, 0.16]**	-0.03 [-0.08, 0.02]

Candidate protein coding genes

- 1 gene overlapping with AA haplotype
  - – ZFAT
    - Prenatal or perinatal lethality in the mouse
    - Affects human height
    - Affects body size in horses
- 64 overlapping genes with SI haplotype
- No overlapping genes with CH haplotype

Economic effect

- Estimation of haplotype economic effect based on current Irish population structure

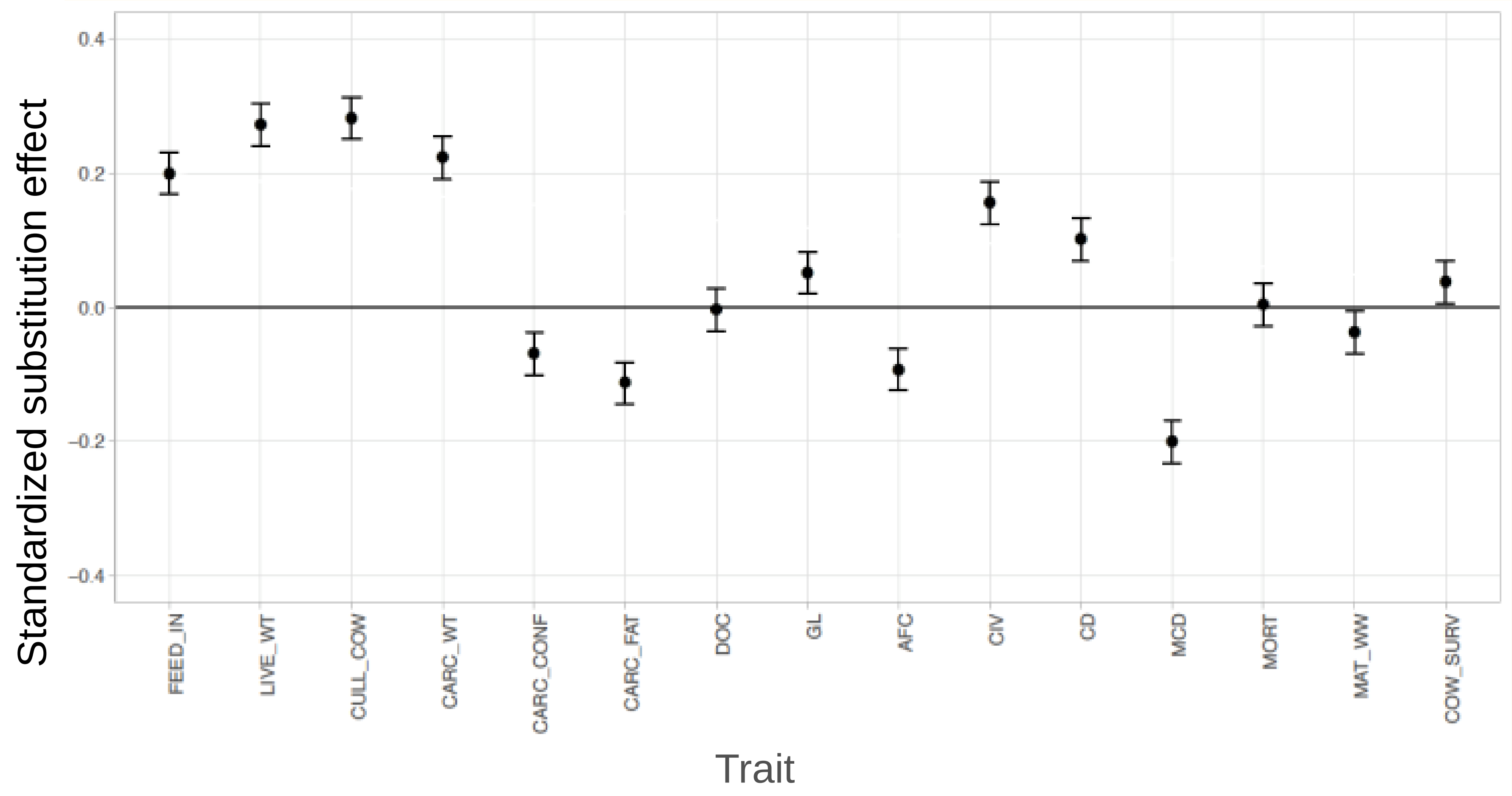
Haplotype	Economic loss (€)	Economic gain (€)	Net effect (€)
AA	290,000	260,000	-30,000
CH	890,000	160,000	-730,000
SI	50,000	42,000	-10,000

Conclusions

- Three putative lethal haplotypes identified
- Haplotypes have pleiotropic effect
- ZFAT is a good candidate gene for lethality and pleiotropy in Aberdeen Angus
- Fine-mapping to identify causal variants

Thank you
for your attention

Standardized substitution eff. for AA



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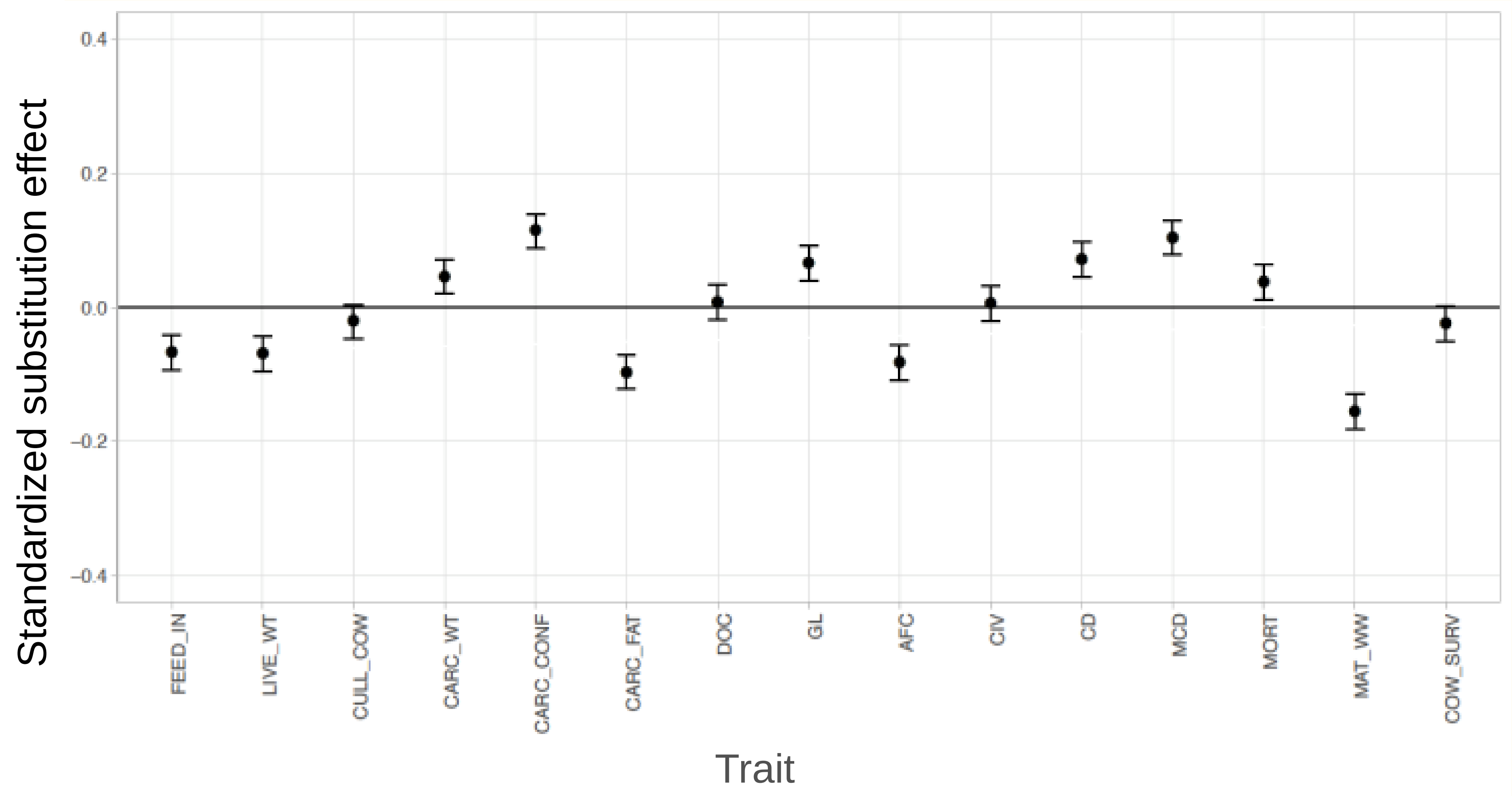
Standardized substitution eff. for CH



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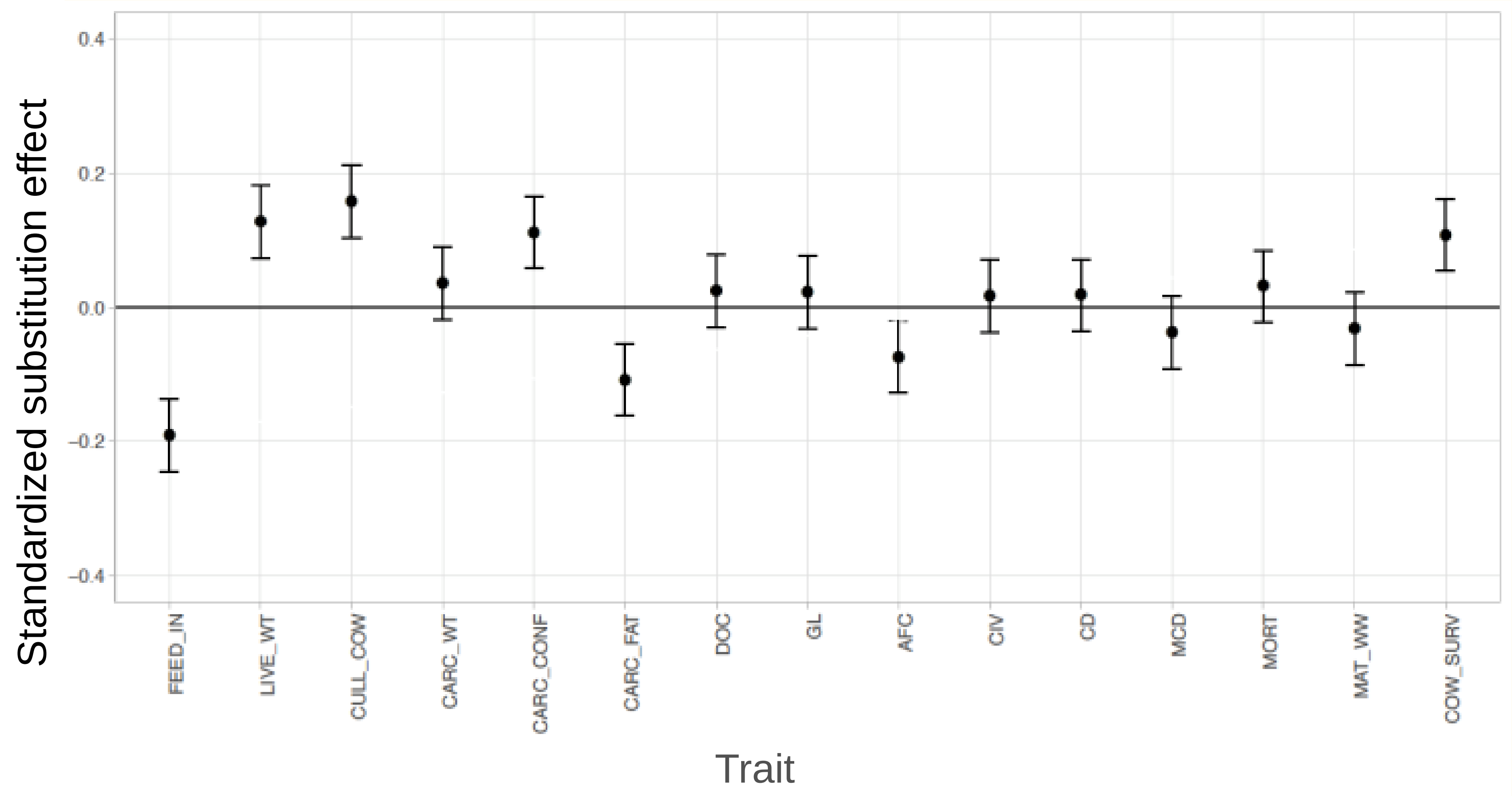
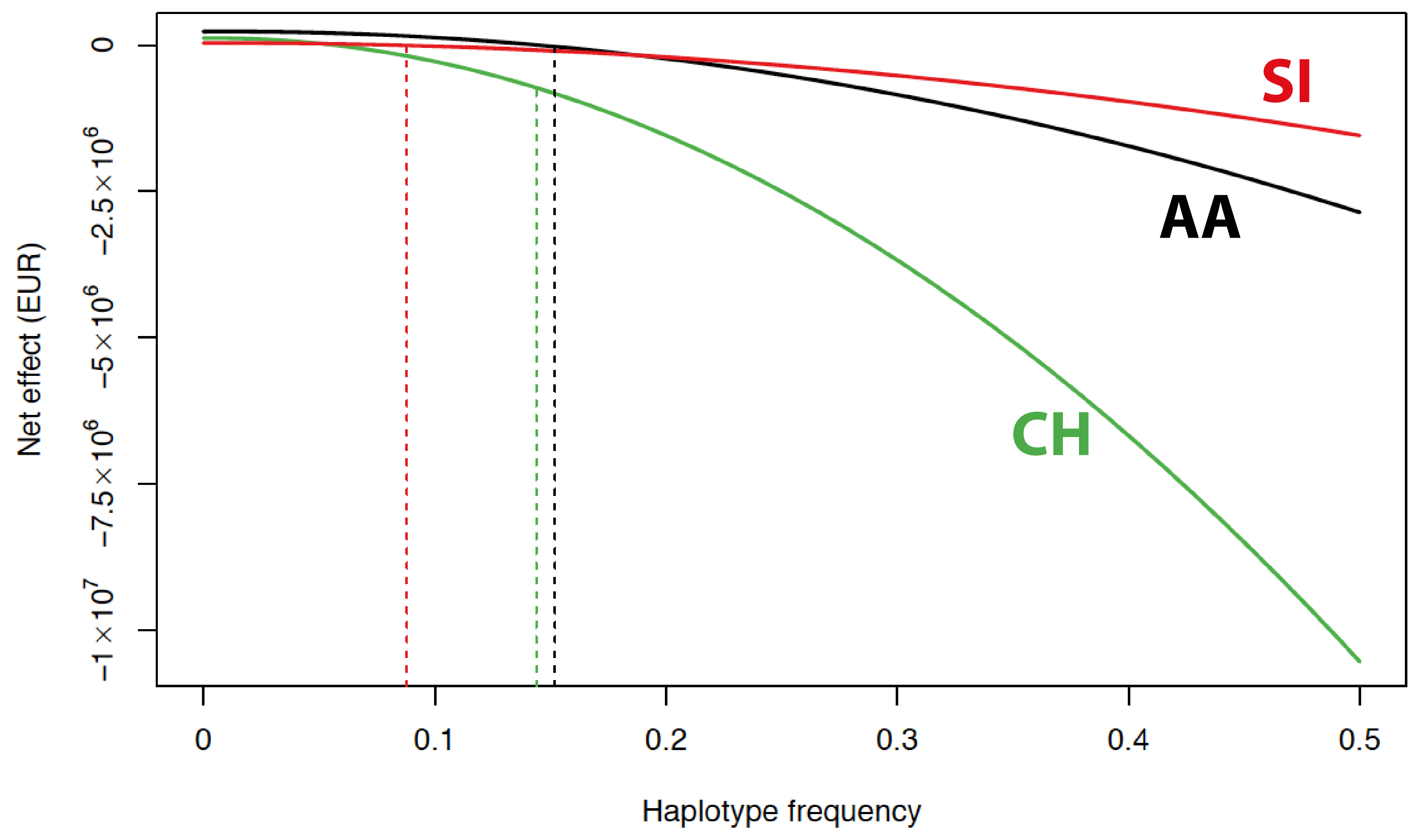
Standardized substitution eff. for SI



Net effect vs haplotype frequencies



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- Tsunoda et al. 2010: “Immune-related zinc finger gene ZFAT is an essential transcriptional regulator for hematopoietic differentiation in blood islands”