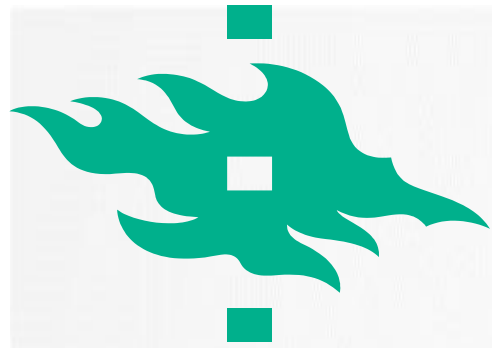


# Identification of ROH genotypes associated with reduced fertility and milk production traits in Finnish Ayrshire cattle

Katja Martikainen<sup>1</sup>, Pekka Uimari<sup>1</sup>, Minna Koivula<sup>2</sup>

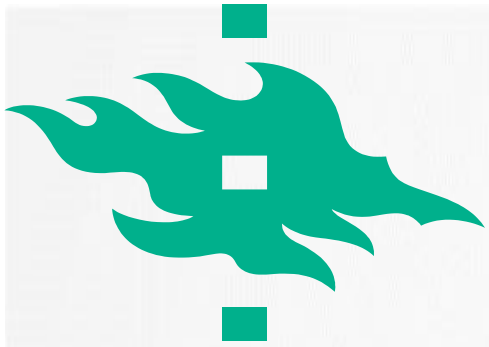
<sup>1</sup>University of Helsinki, Dept. of Agricultural Sciences, Finland

<sup>2</sup>Natural Resources Institute Finland (Luke)



# BACKGROUND

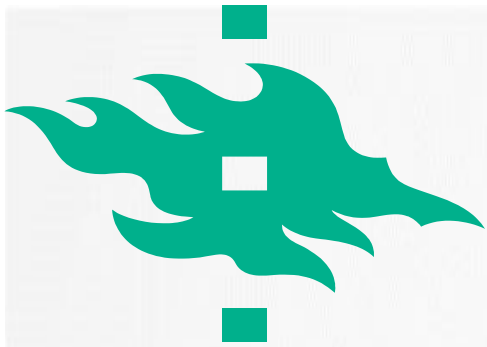
- Intensive selection in dairy cattle breeding
  - increased inbreeding
  - accumulation of recessive deleterious alleles
  - inbreeding depression
- Reduced profitability
  - decreased milk production
  - increased costs related to inseminations and veterinary treatments
  - involuntary culling
- Single nucleotide polymorphism (SNP) data: Estimation of the effects of inbreeding at the genome level



# OBJECTIVE

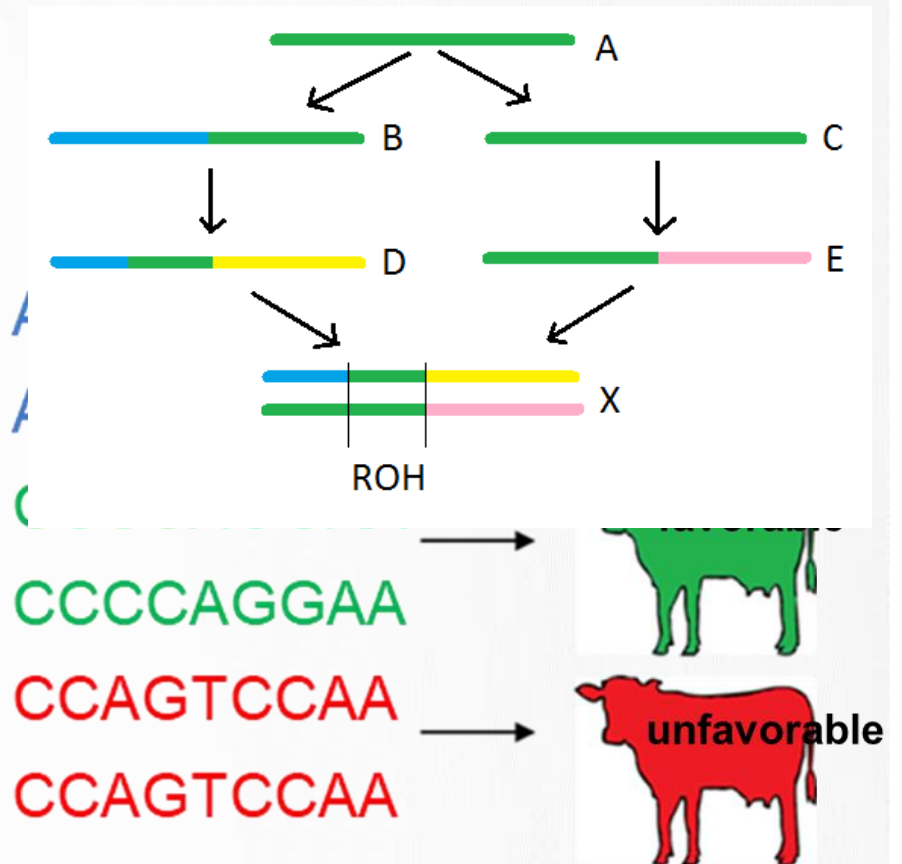
- Identification of specific ROH genotypes that result in reduced fertility and milk production traits in Finnish Ayrshire cows

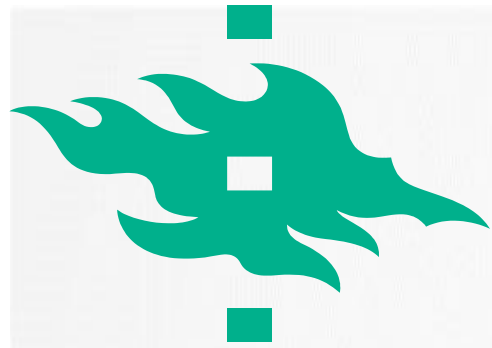




# UNFAVORABLE ROH

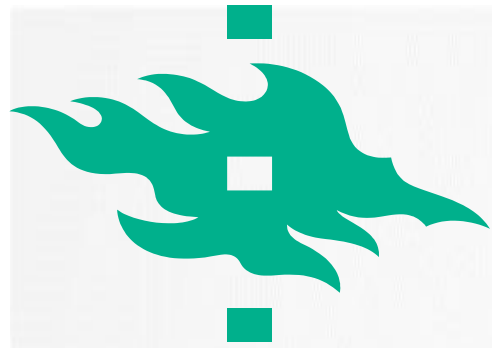
- ROH = continuous stretches of homozygous genotypes inherited from a common ancestor
- The unfavorable effect likely due to a single unique ROH within a region of interest
  - Other ROH on that region may have a neutral or even favorable effect
- If all ROH are assumed to have an unfavorable effect, regions containing an unfavorable ROH together with a large number of neutral ROH could be missed





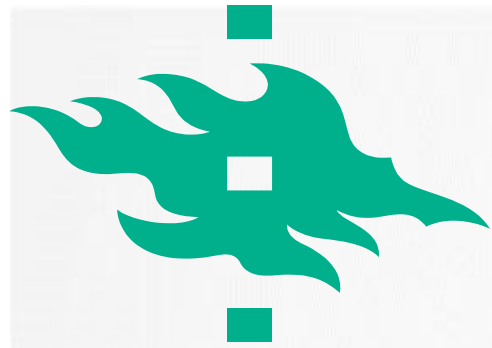
# GENOMIC DATA

- SNP genotypes generated with low density panel (8K), imputed to 50K
- SNP with MAF < 0.01 removed
- LD pruning for SNP with the variance inflation factor (VIF) greater than 10 (correspond to  $r^2 > 0.9$ ) within a 50 SNP window with PLINK v1.9 (Purcell et al., 2007)
- After quality control and LD-pruning, **29 227 SNP** remained for the analysis



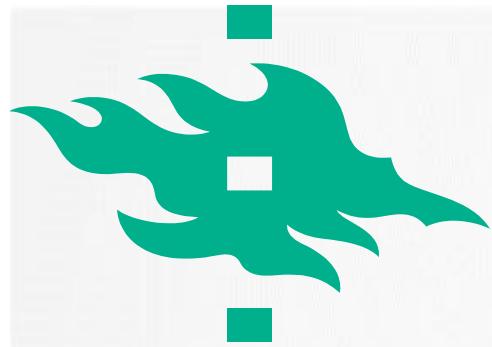
# PHENOTYPIC DATA

- Phenotypes of **female fertility** traits available for 13 712 genotyped animals
  - Interval (number of days) from calving to first insemination (ICF), interval (number of days) from first to last insemination (IFL), number of inseminations (AIS)
- Traits considered separately for heifers (lactation 0) and for cows with first three lactations (1-3)
- The raw phenotypic values adjusted for fixed effects: herd-birth year (for heifers) or herd-year of first calving (for cows), insemination year-month, calving year-month, age at insemination
- Phenotypes of **milk production** traits available for 12 233 genotypes animals
  - De-regressed proofs (DRP) of the first lactation of milk yield (MILK), protein yield (PROT), and fat yield (FAT) expressed in kilograms



# DETECTION OF UNFAVORABLE ROH

- Unfavorable ROH genotype detection with software Unfavorable Haplotype Finder (Howard et al. 2017)
- **Step 1:** Identification of ROH genotypes associated with an unfavorable effect on phenotype
  - a) A sliding window method to detect ROH genotypes (no heterozygous SNP, frequency  $\geq 0.01$ ), other genotypes placed in the non-ROH category
  - b) If ROH genotype associated with an unfavorable phenotype  $\rightarrow$  window is stored
  - c) Window size decreased from 50 to 15 SNP to reduce the ROH genotypes to smallest possible length  $\rightarrow$  these core ROH genotypes serve as a tag for full ROH



# DETECTION OF UNFAVORABLE ROH

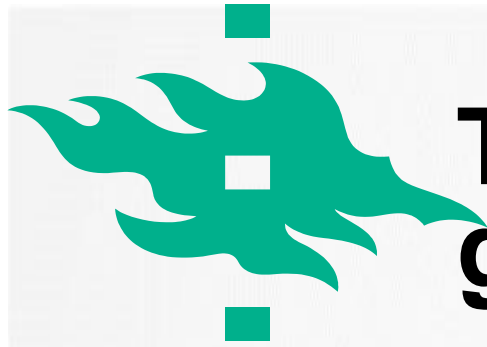
- **Step 2:** the significance of each ROH genotype detected in step 1 tested using a linear mixed model:  $y_i = \mathbf{Xb} + \mathbf{Za} + \mathbf{e}$ , where
  - $y_i$  is a pre-adjusted phenotype (fertility traits) or DRP (production traits) of the trait of interest
  - $\mathbf{b}$  is a vector including the effect of ROH genotype (specific ROH genotype or non-ROH)
- **Step 3:** nested windows removed





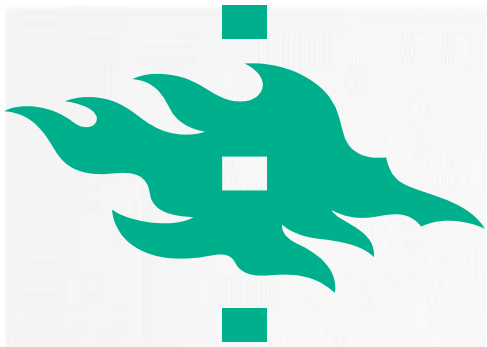
# The most significant unfavorable ROH genotypes for fertility traits

Trait		CHR	Position (Mb)	Frequency	Effect (SE)	p-value
Interval from calving to first insemination	ICF1	12	65.13 – 66.37	0.01	9.2 days (2.5)	2.22e-04
	ICF2	10	62.34 – 64.20	0.02	9.5 days (2.5)	1.92e-04
	ICF3	12	61.67 – 62.73	0.02	17.1 days (4.6)	2.20e-04
Number of inseminations	AIS0	17	9.47 – 10.59	0.02	0.3 (0.05)	8.59e-07
	AIS1	14	81.76 – 83.07	0.01	0.5 (0.10)	2.26e-06
	AIS2	15	7.31 – 9.15	0.01	0.6 (0.14)	1.83e-05
	AIS3	18	4.90 – 6.93	0.02	1.0 (0.22)	2.34e-05
Interval from first to last insemination	<b>IFL0</b>	17	9.21 – 10.31	0.02	12.8 days (2.4)	4.84e-08
	IFL1	5	27.54 – 31.16	0.03	13.2 days (3.2)	2.85e-05
	IFL2	8	65.01 – 69.12	0.02	29.6 days (6.5)	4.96e-06
	IFL3	18	8.01 – 8.85	0.02	37.7 days (9.8)	1.16e-04

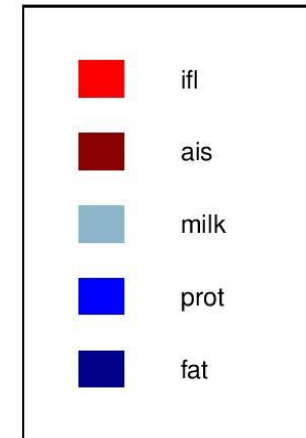
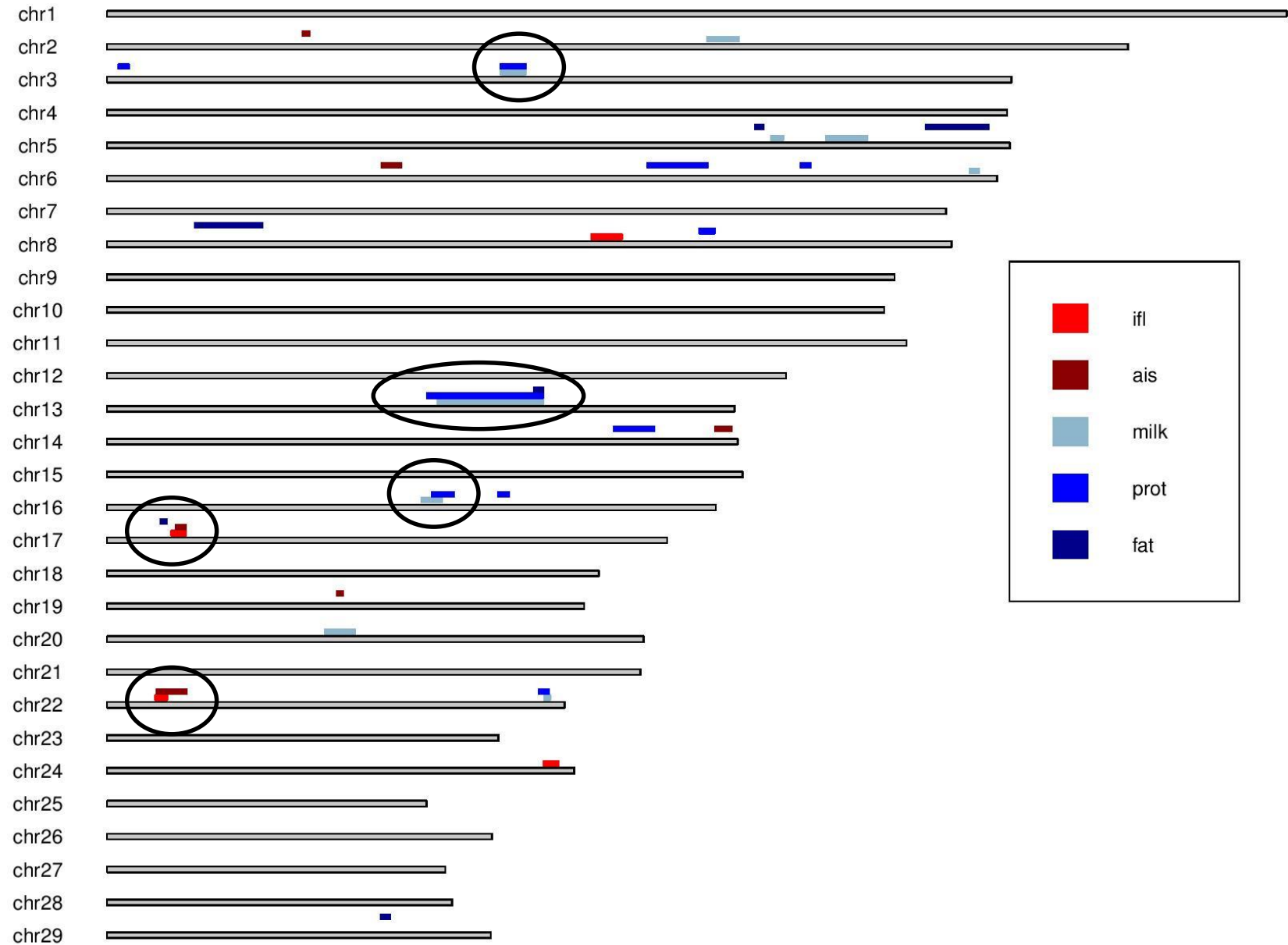


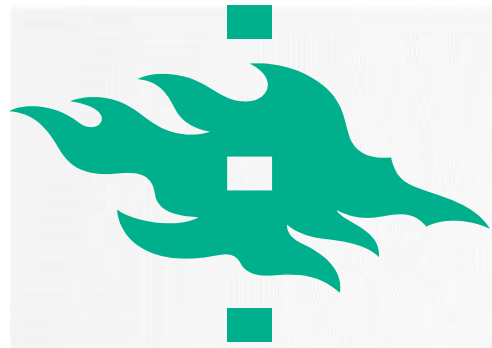
# The most significant unfavorable ROH genotypes for milk production traits

Trait	CHR	Position	Frequency	Effect in kg (SE)	p-value
<b>MILK</b>	20	31.55 – 33.15	0.05	-207.8 (38.9)	9.30e-08
<b>PROT</b>	13	53.66 – 55.64	0.06	-7.0 (1.12)	3.60e-10
<b>FAT</b>	5	87.02 – 88.11	0.01	-15.7 (1.69)	8.60e-09



Regions with unfavorable ROH genotypes with P-value < 1.0e05





# SUMMARY

- Several unique ROH genotypes identified with detrimental effect on female fertility and milk production traits
- Regions containing ROH genotypes with unfavorable effect across multiple traits sensitive to inbreeding → particularly interesting
- Further investigation of these ROH genotypes needed for more insight into the effects of inbreeding in dairy cattle

Thank you!