Biology-driven genomic predictions for dry matter intake within and across-breeds using WGS data

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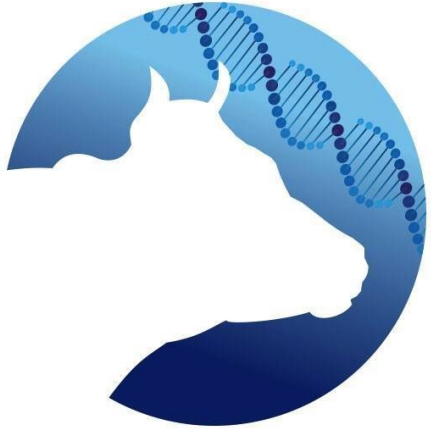

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BovReg Understanding cattle genomes

EuroFAANG

Biology-driven genomic predictions

- WGS: millions of variants → pinpoint **causal variants** affecting traits of interest
- Key traits: **biological efficiency**, e.g. **feed efficiency**
- BovReg: catalogue of functionally active **genomic features (GF)** in cattle
- **Functional GF** → SNP prioritization → **Biology-driven genomic predictions**

3. Aim of the study

Validation of within- and across-breed

biology-driven genomic predictions using **genomic features**

for **dry matter intake (feed efficiency)**

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Data available for genomic predictions

	NLD	CAN
Breed	Holstein	Beef crosses
Herds	6	14
Dependent variable	DRP on DMI	Pre-corrected DMI
n. animals DMI & geno (training - validation)	~3k (2.2k and 850)	~5.5k (4k and 1.5k)

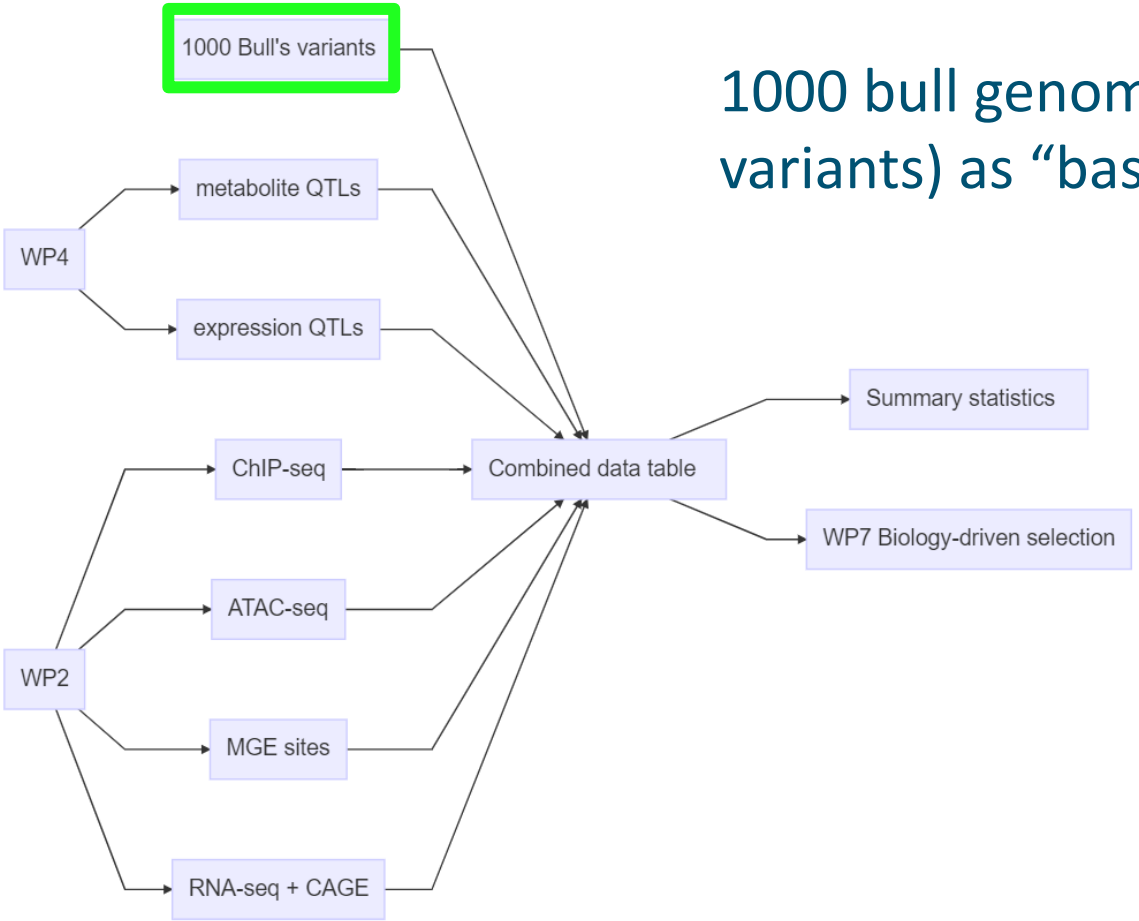
- **forward-in-time validation** (SE via bootstrapping): accuracy and bias
- 50k to imputed WGS (*Beagle*) → prioritize variants based on **GF**

Genomic features available

GF	Work Package
Meta-GWAS QTL (QTL)	WP4
Expression QTL (eQTL)	WP4
Metabolic QTL (mQTL)	WP4
ATAC-seq	WP2
ChIP-seq	WP2
Mobile Genetic Elements (MGE)	WP2

- Different tissues/samples → Different formats for different GF
- Many files (~1,000) with large size → how to quickly access/query GF information?

Selection of genomic features



1000 bull genome project (~74.9 M variants) as “baseline” to map GF

Selection of genomic features

Variant ID	**CHR**	**POS**	**GF1** (DMI QTL)	**GF2** (liver eQTL)	**GF3** (ATAC tissue1)	**GF .**	**GF*n***
Variant 1	1	659	0	1	0	.	$1.1x10^{-13}$
Variant 2	1	1235	1	0	1	.	NA
Variant 3	1	1578	0	0	1	.	NA
Variant 4	1	1984	0	0	1	.	NA
Variant 5	1	2689	0	0	1	.	$3.9x10^{-5}$
Variant 6	1	3458	0	1	0	.	NA
Variant …	.	.	.	.	.	.	.
Variant 75M	29	49805987	0	0	1	.	NA

For each GF, store information on:

- Position/Intervals as (0/1 coding)
- *p*-value (if available) as (NA/value)

Selection of genomic features

GF mapped to 1000G for all traits/tissues
position/intervals & **p-value**

Select GF group
(across traits/tissues)

Awk/R

List of variants per GF "layer"
(overlapping with 1000G)

Exclude variants in 50K &
not in within-country WGS

Awk/R

Non-overlapping
variants list

Variant ID	CHR	POS	GF1 (DMI QTL)	GF2 (milk QTL)	GF3 (ATAC tissue1)	GF .	GF*n*
Variant 1	1	659	0	1	0	.	$1.1x10^{-13}$
Variant 2	1	1235	1	0	1	.	NA
Variant 3	1	1578	0	0	1	.	NA
Variant 4	1	1984	0	0	1	.	NA
Variant 5	1	2689	0	0	1	.	$3.9x10^{-5}$
Variant 6	1	3458	0	1	0	.	NA
Variant …	.	.	.	.	.	.	.
Variant 75M	29	49805987	0	0	1	.	NA

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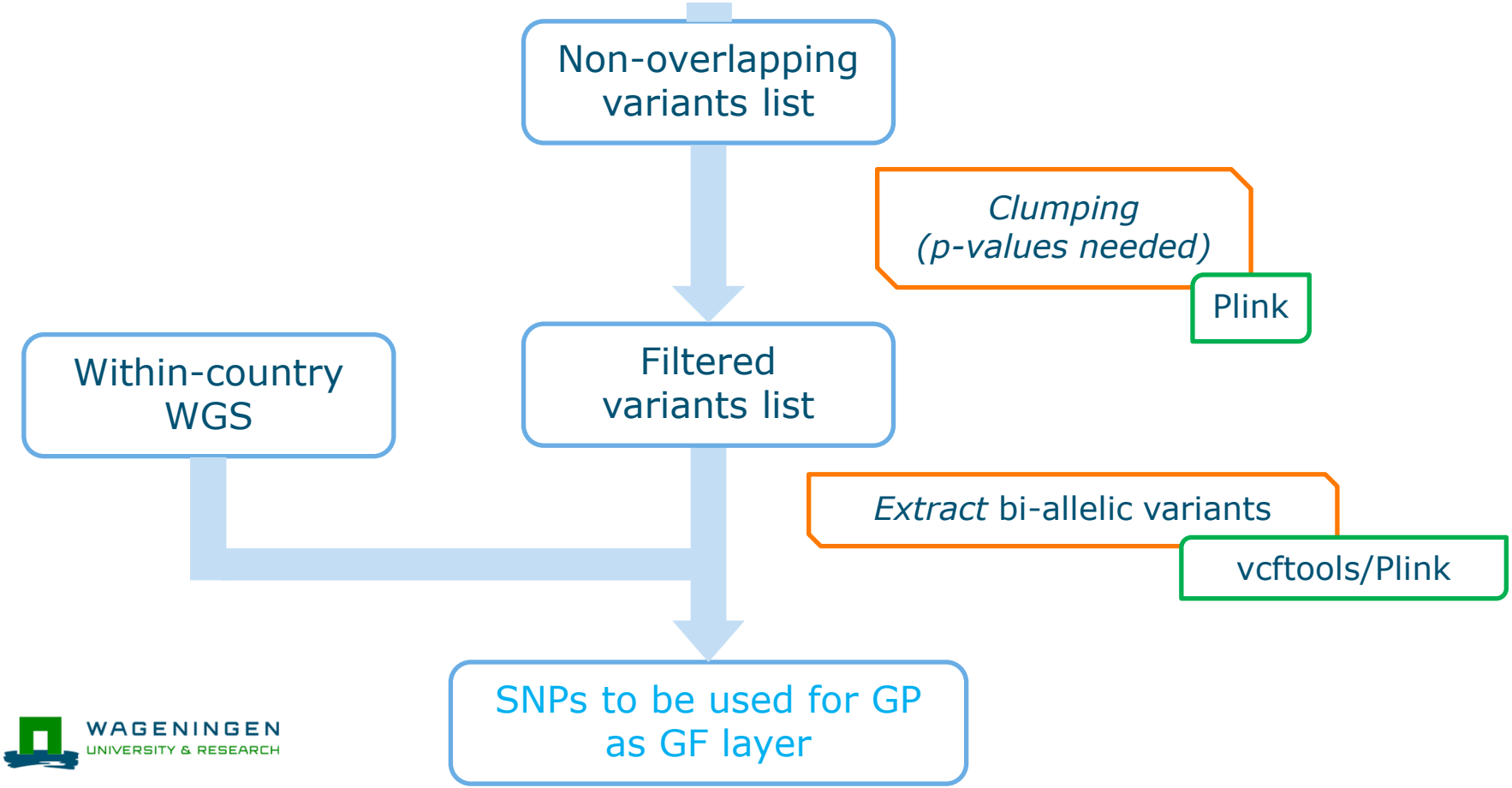
Selection of genomic features



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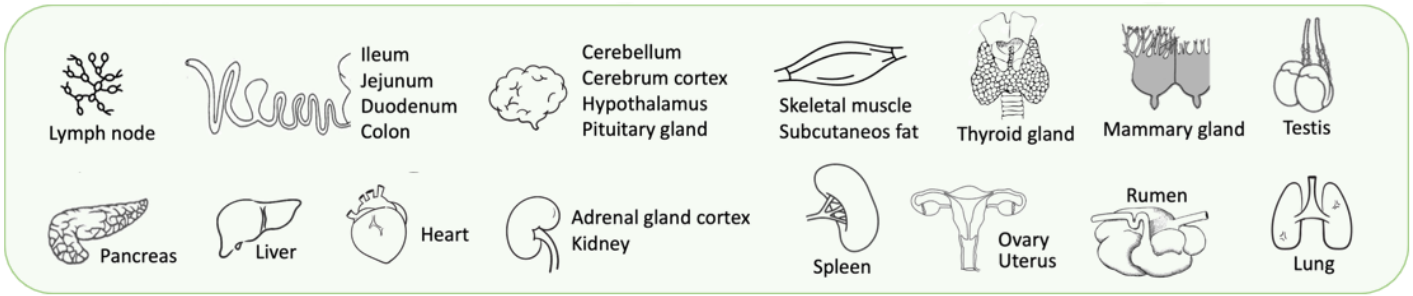
Genomic features used

GF	Traits / Tissues
QTL	Meat quality, Growth, Milk production, Morphology, Fertility, Health, Feed efficiency, Methane
eQTL	(Gene, Transcript, Splice) Jejunum, Blood, Liver, Mammary Gland, Adipose, Muscle, Milk, Rumen
ATAC-seq	

From GC Moreira et al., EAAP #939

Scenarios

Scenario	NLD	CAN
50K	48K	46K
50K + **QTL**	48K + 5,416	46K + 4,222
50K + **eQTL**	48K + 12,401	46K + 11,884
50K + **(QTL, eQTL, ATAC)**	48K + 17,796	46K + 16,089

- *NextGP.jl* [1]
- Base 50K: SNPBLUP (BayesC$_0$) common variance across SNPs
- GF as additional layer → SNPBLUP or Bayesian (2 mixture model – no advantage)
- ATAC-seq *consensus peaks* (across all samples and tissues)*
- QTL, eQTL, ATAC → Multi-GF → overlapping GF

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[1] https://github.com/datasciencetoolkit/NextGP.jl

*GC Moreira et al. 2023, EAAP

nf-core/atacseq

Overlapping genomic features

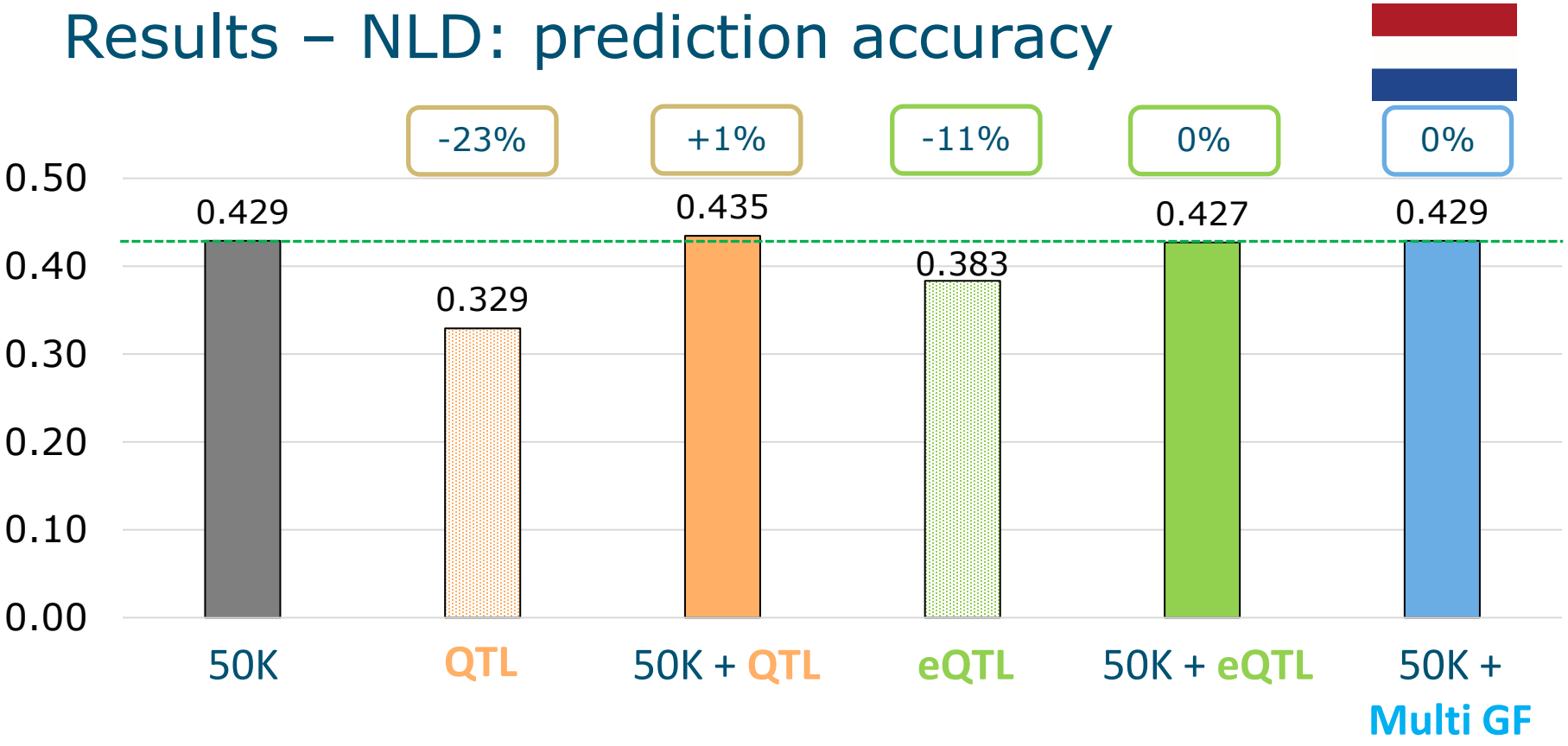
Multi-GF

QTL	eQTL	ATAC	Variants	%
1	1	0	5	0
1	1	1	16	0
1	0	0	2,576	14
1	0	1	2,819	16
0	1	0	5,051	28
0	1	1	7,329	41
			17,796	100

BayesRCπ (2 classes)

Mollandin *et al.* 2022, BMC bioinformatics

Results – NLD: prediction accuracy



- SE: ±0.03
- No impact on dispersion (slope = 0.68 for 50k)

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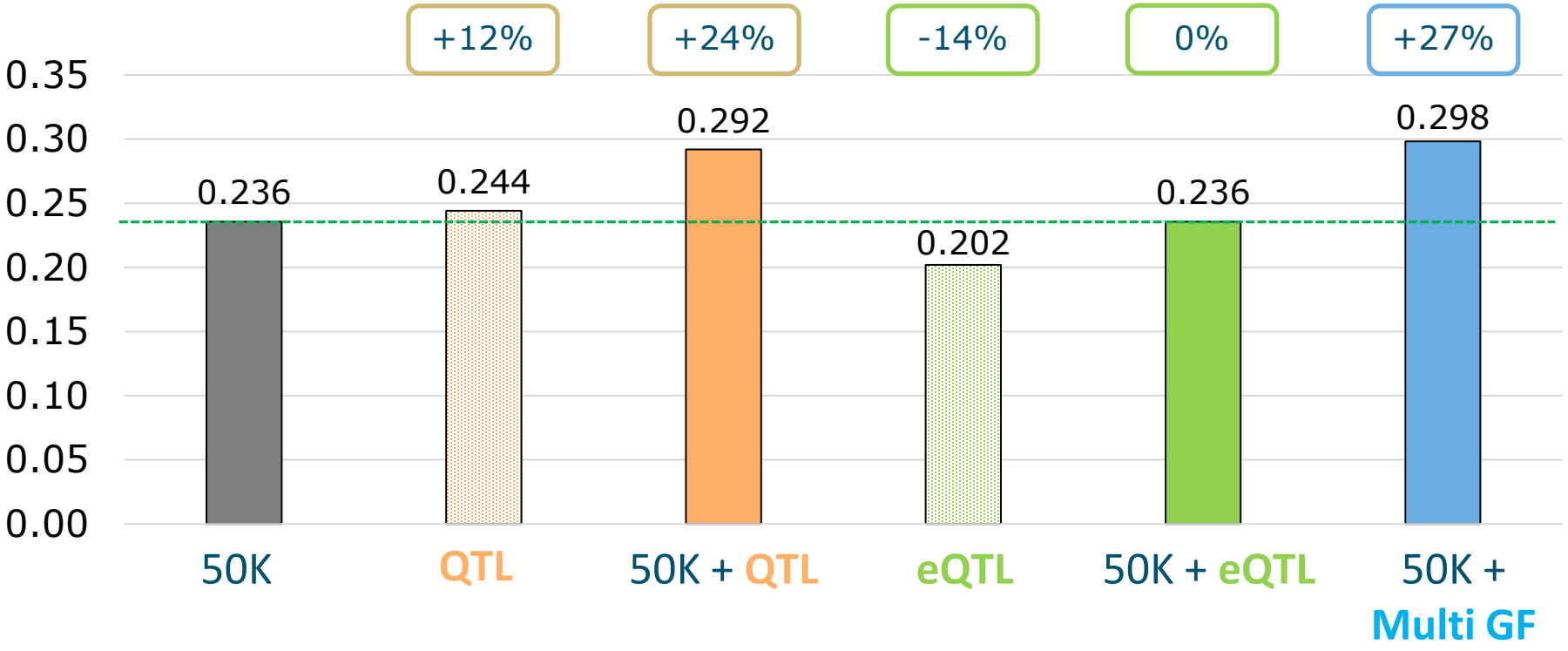
Results – CAN: prediction accuracy



- SE between ±0.02 and ±0.03
- Similar pattern for dispersion (slope = 0.56 for 50k)

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Manhattan plots meta-GWAS QTL for DMI

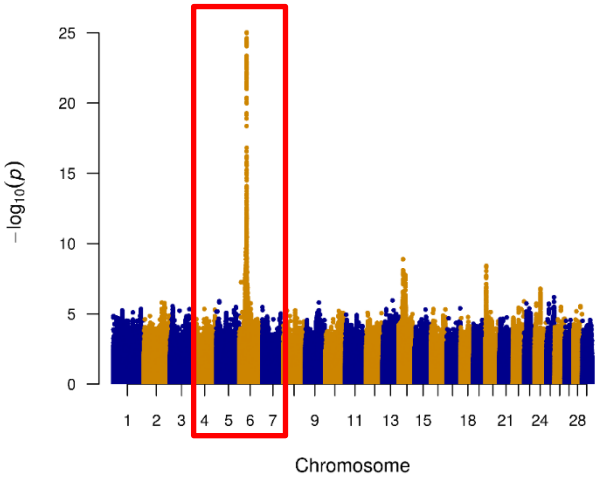
Gredler-Grandl *et al.* 2022, WCGALP

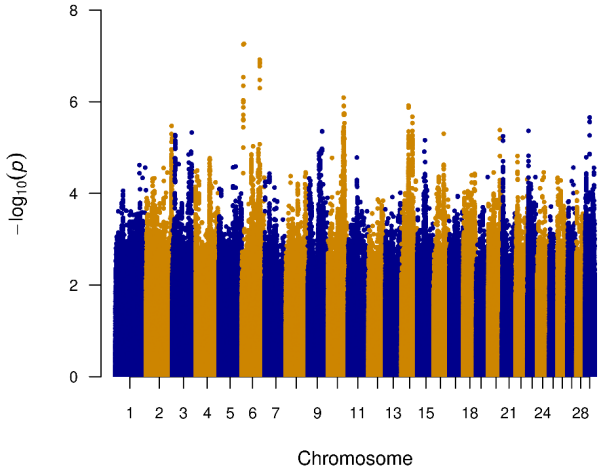
ALL
10,539 animals
Beef, Holstein, Finnish Red
~30M variants

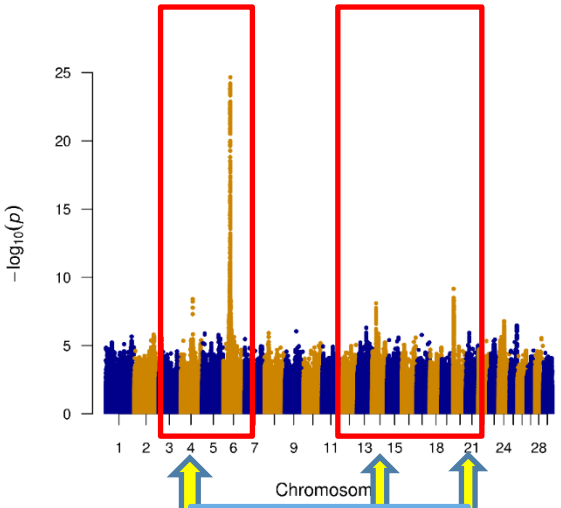
HOL
2,368 animals
Only Holstein
~20M variants

BEEF
7,805 animals
Only Beef
~28M variants

Zhang *et al*. 2020, BMC genomics





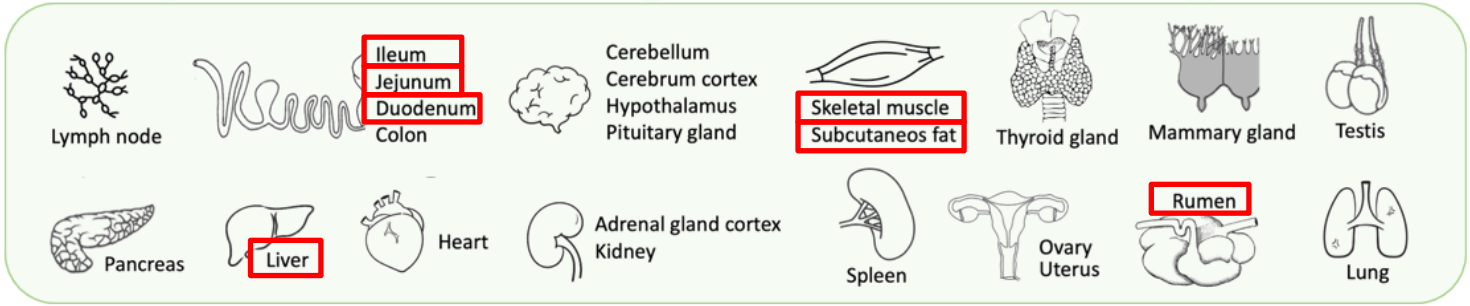


chr 6, 14, 20

data → filter SNPs with $2pq\alpha^2 \geq 0.0001$

chr	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
count	1	16	6	0	19	21	0	0	1	1	2	0	0	30	6	3	2	1	2	13	0	0	0	2	1	0	1	0	1

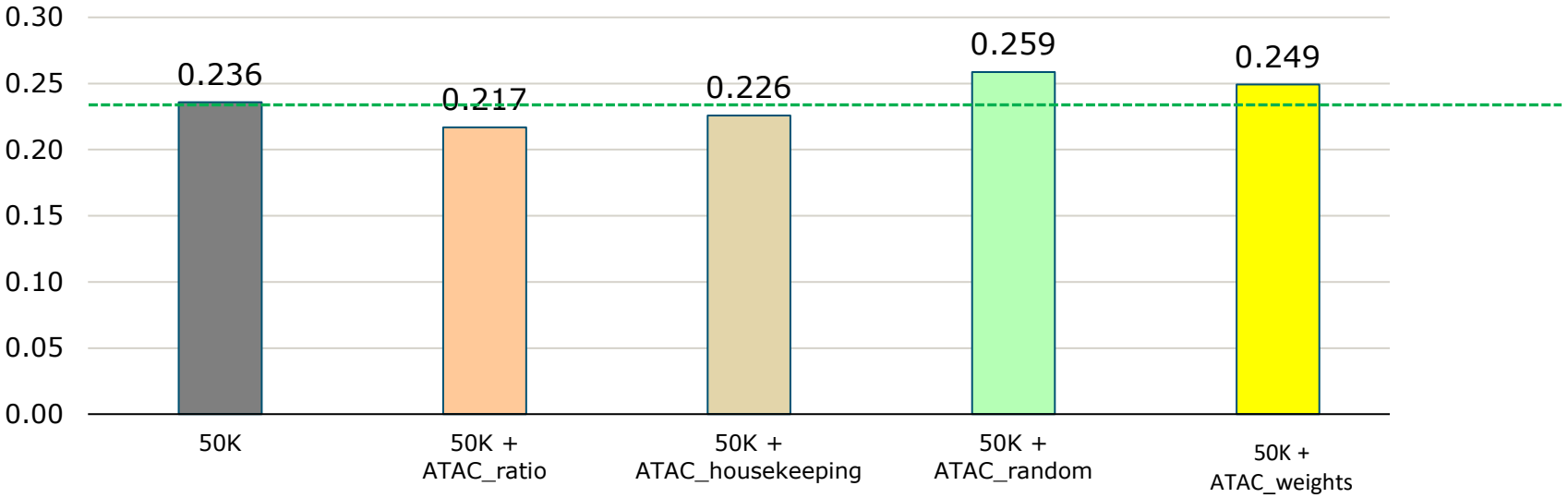
Use of narrow-peaks ATAC-seq



Different scenarios implemented using *ATAC-seq* narrow peaks for selected tissues

Scenario	Description	SNPs
ATAC_ratio	Top 10K variants from narrow peaks ratio (overlaps selected/ total tissues) **+ adjacent SNPs (200Kb)**	210,919 → 19,523 (LD pruning)
ATAC_housekeep	Top 10K variants that overlaps across all narrow peaks ("**housekeeping" set**)	10,000
ATAC_random	**Random** selection Segment size: 150K / 200K / **250K** Percentile cutoff threshold: **top 10%** / top 20% / top 30%	3,318
ATAC_weights	**Higher weights on less frequent variants** (e.g., QTLs) Segment size: 150K / 200K / **250K** Percentile cutoff threshold: **top 10%** / top 20% / top 30%	390

Results (SNPBLUP models)



- Randomly selected variants gave same or higher accuracy (# SNPs)
- ATAC-seq modelled as additional SNP layer → Next: model narrow-peaks as different layers into NextGP
- Narrow-peaks not as useful as consensus-peaks information?
- How did you model/consider ATAC-seq?

Next steps

- Model as detailed annotation layers trait/tissues-specific into NextGP
- BayesLV using *p*-values (test on implemented scenarios)
- Across-breed (using SNP effects) and multi-breed (combined reference population) GP for NLD-CAN

Conclusions

- Inclusion of **Genomic Features** could increase **genomic prediction accuracies** for **Dry Matter Intake**
- Results may vary across breeds/datasets
- Complex traits: find causal variants
- No advantage using Bayesian (2 mixture model) over SNPBLUP for GF
- ATAC-seq narrow-peaks showed low added value

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Thanks for your attention

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