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

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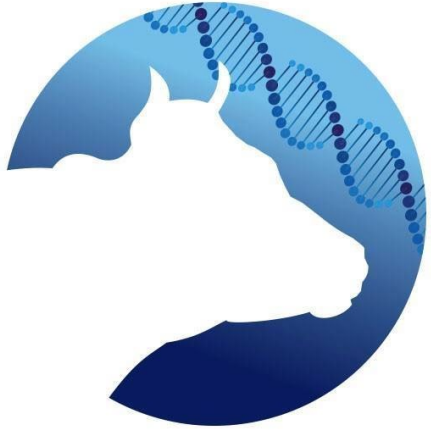

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BovReg Understanding cattle genomes

EuroFAANG

Outline

1. Background and project fit within BovReg
2. Biology-driven genomic predictions
3. Aim of the study
4. Data available, validation, BovReg genomic features
5. Selection and prioritization of genomic features
6. Scenarios and software
7. Within-breed results: NLD and CAN
8. Next steps and implications

1. Genomic predictions using WGS data

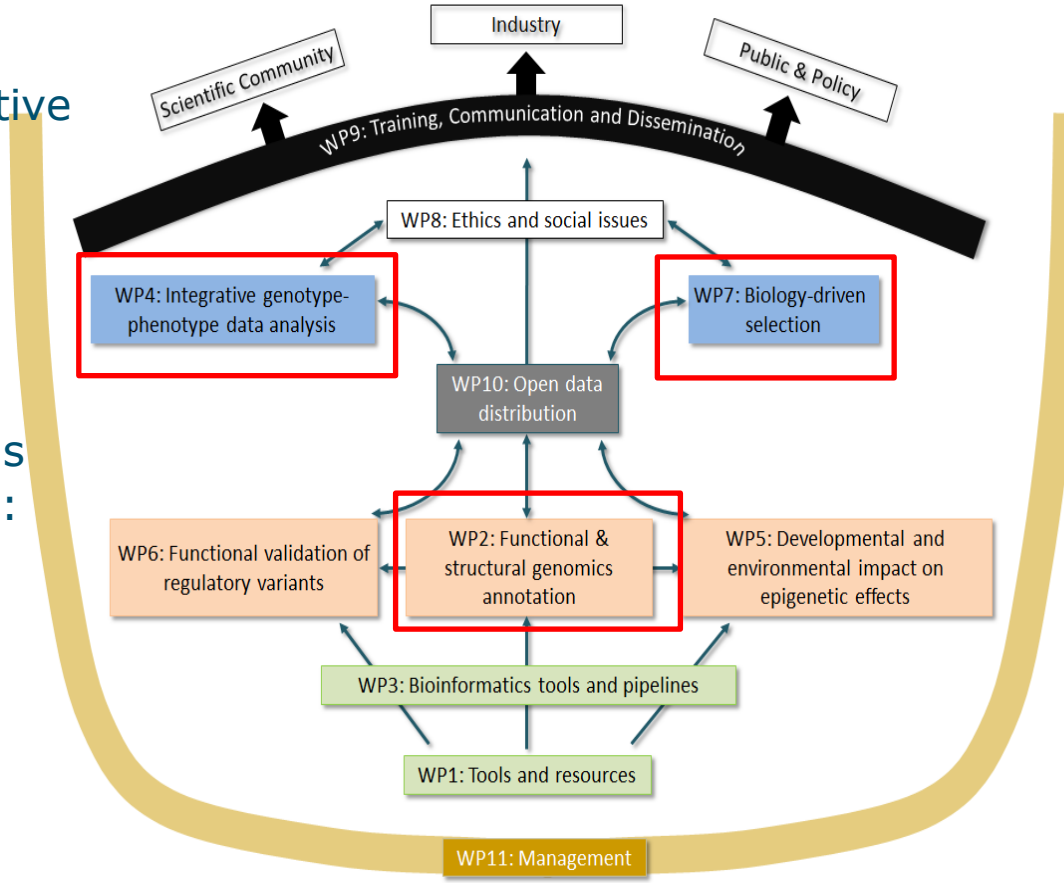
- Accuracy of genomic predictions (GP) → selection response (genomic selection efficiency)
- Large and representative reference populations (small breeds?)
- Whole-genome-sequence data (WGS) include causal variants with direct effects on the phenotypes
- GP using 50k → GP using WGS: no large benefits
- Pre-selecting SNPs from WGS → more accurate GP
- Using **genomic annotation** information could improve predictions across genetically lowly related individuals

1. The BovReg project

Catalogue of genomic annotation → BovReg: catalogue of functionally active **genomic features (GF)** in cattle

Work Package 7, biology-driven selection:

1. Development of novel GP methods integrating functional information: Genomic Features models
2. **Validate models in real data**, using results from WP2 and WP4



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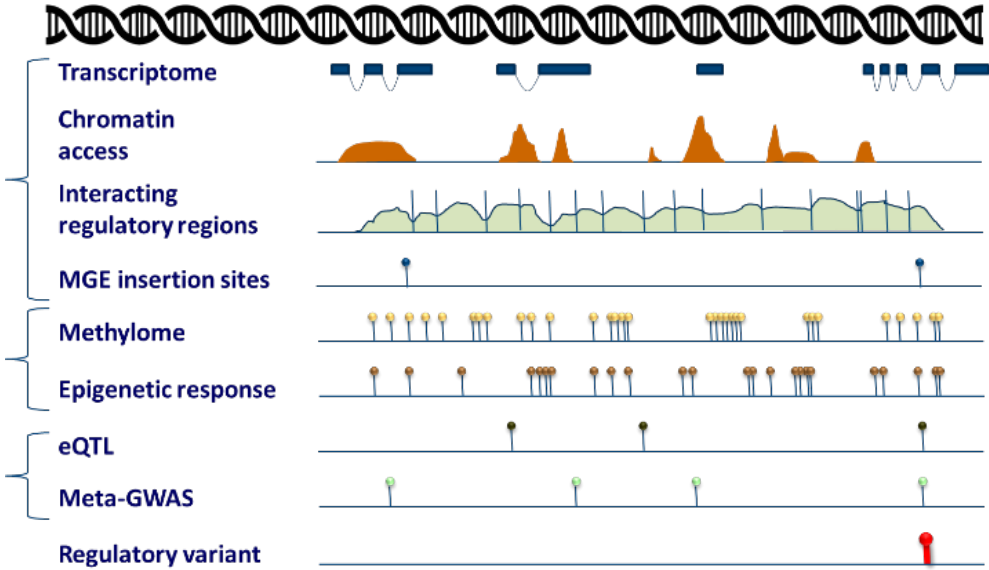
2. Biology-driven genomic predictions

- WGS: millions of variants → pinpoint **causal variants** affecting traits of interest
- Key traits: **biological efficiency**, e.g. **feed efficiency**, small ref. populations
- **GF catalogue** of **"multi-omics"** data: genomics (QTL), transcriptomics (eQTL), epigenomics (mQTL), chromatin accessibility (ATAC-seq/ChIP-seq), …
- **Functional GF** → SNP prioritization → **Biology-driven genomic predictions**



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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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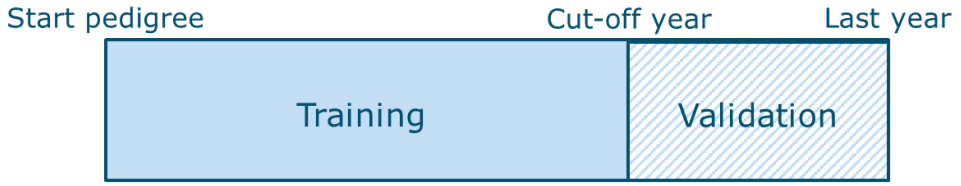
4. Data available for genomic predictions

- **Netherlands (NL)**
- Dairy cattle: Holstein-Friesian
- 6 research farms
- EBVs from routine DMI evaluations for lactation 1, 2, 3+
- Average de-regressed proofs (DRP) as pseudo-phenotypes
- 3,628 cows with genotypes (50K) and DRPs
- Genotypes at 50K SNPs → imputed to HD → imputed to WGS (*Beagle*)

4. Data available for genomic predictions

- **Canada (CAN)**
- Composite crossbred beef cattle
- 14 research farms
- Individual DMI (one observation) → pre-corrected phenotypes (Y^*) for fixed effects & breed composition
- 5,584 individuals (males and females) with genotypes and Y^*
- Genotypes at 50K SNPs → imputed to HD → imputed to WGS (*Beagle*)

4. Validation approach



- Different possible approaches
- Mimic breeding program application → **forward-in-time** cross-validation
- Exclude pedigree relationships >0.5 in validation set (e.g. parent-offspring)
- **Accuracy**: correlation between dependent variable and GEBVs
- **Dispersion**: regression coefficient of dependent variable on GEBVs (expectation in absence of dispersion = 1)
- Standard errors via bootstrapping with replacement (R)

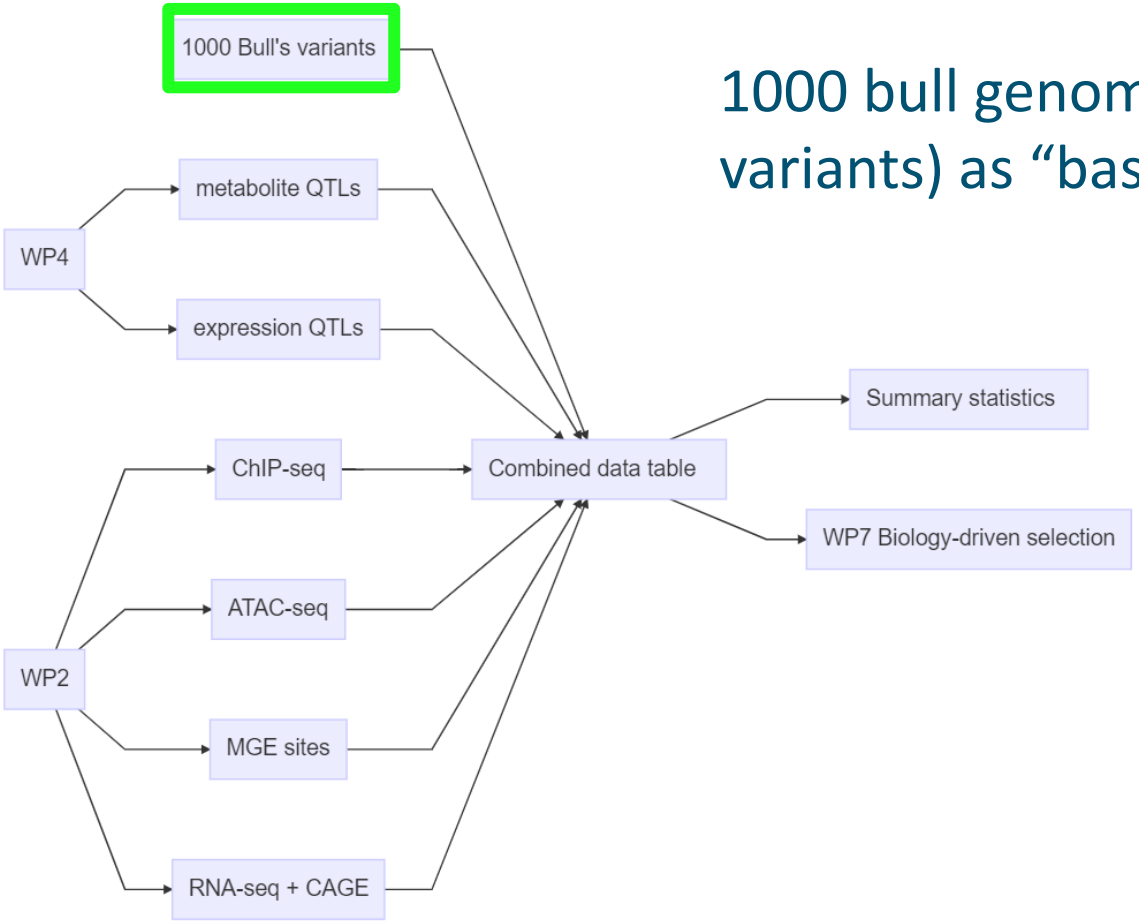
	NLD	CAN
Dependent variable	DRP	Pre-corrected DMI
Cut-off year	2018	2013
# animals training	2,769	4,091
# animals validation	859	1,493

5. 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

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

5. Selection of genomic features



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

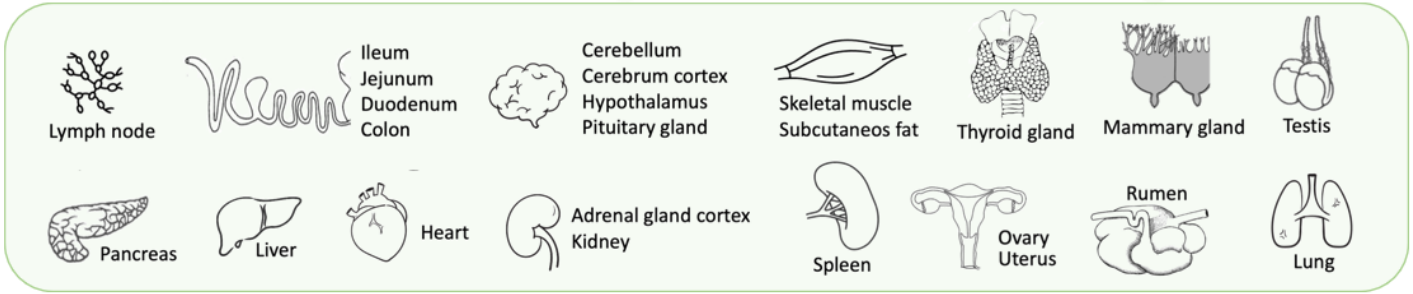
5. Selection of genomic features

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, information store:

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

5. 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	

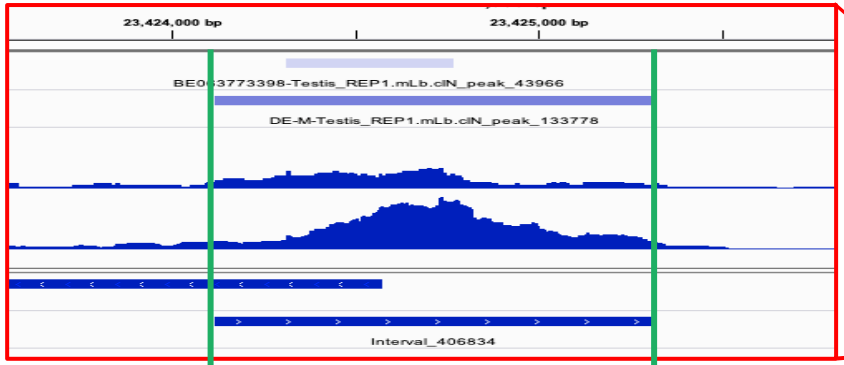
From GC Moreira et al., 2023 EAAP

(intermezzo) ATAC-seq

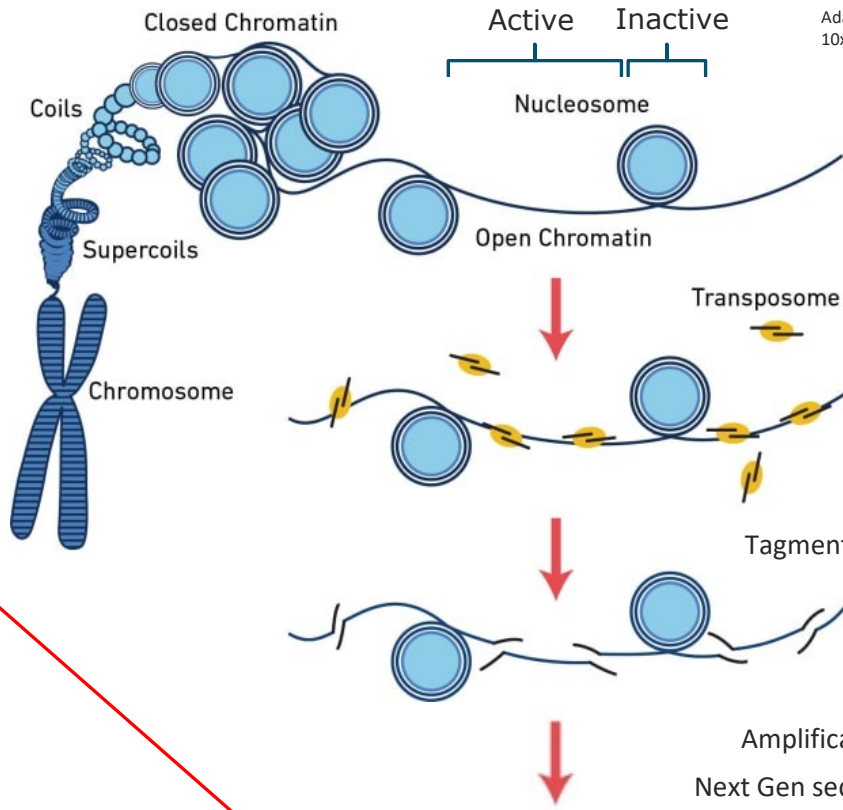
Genome-wide mapping of **chromatin accessibility → accessible DNA**

⇩

Promotor regions
Enhancers
Regulatory elements



Consensus peaks across samples



Adapted from 10xgenomics.com

GC Moreira et al. 2023, EAAP

nf-core/atacseq

5. 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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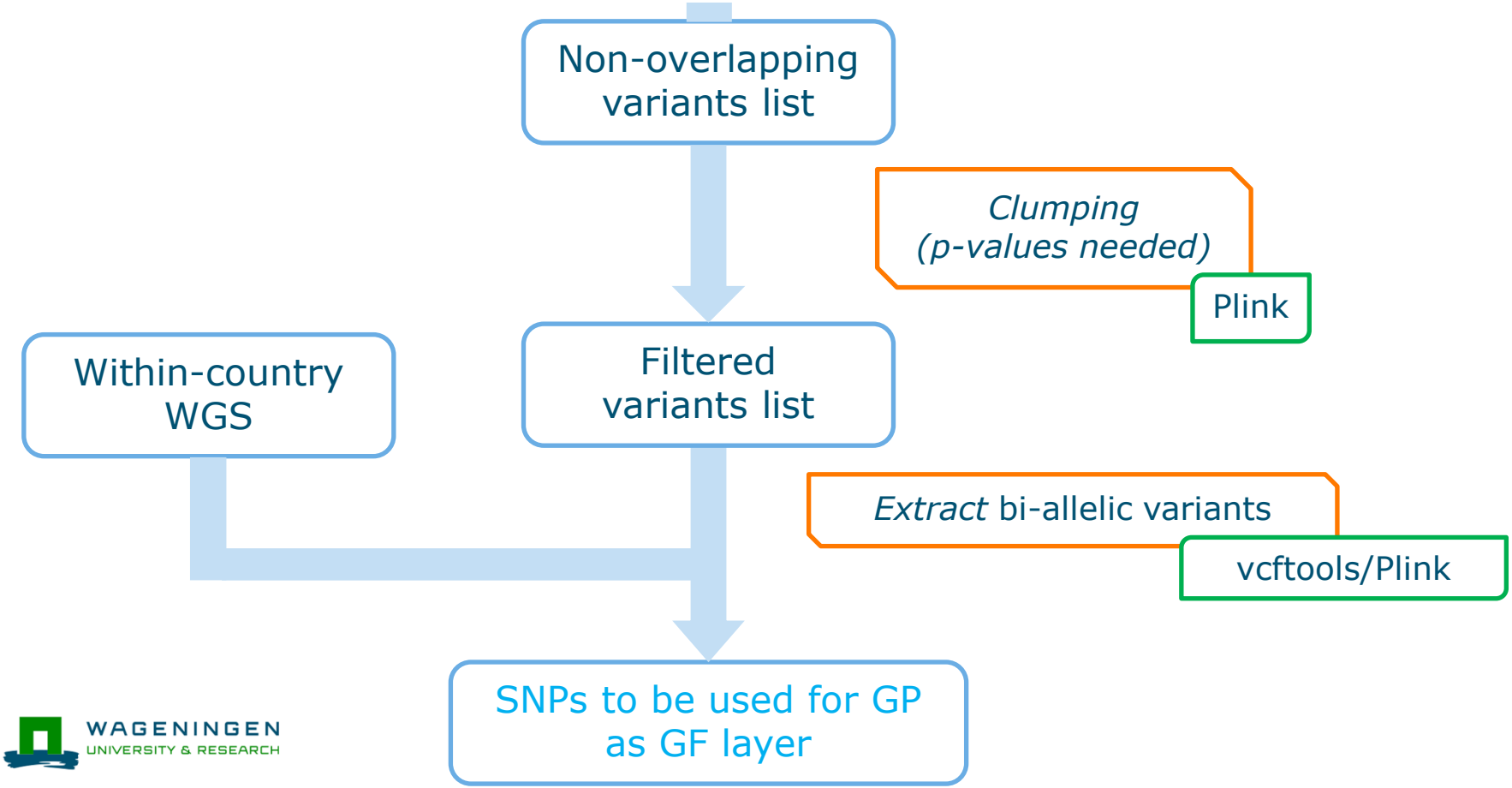
5. Selection of genomic features

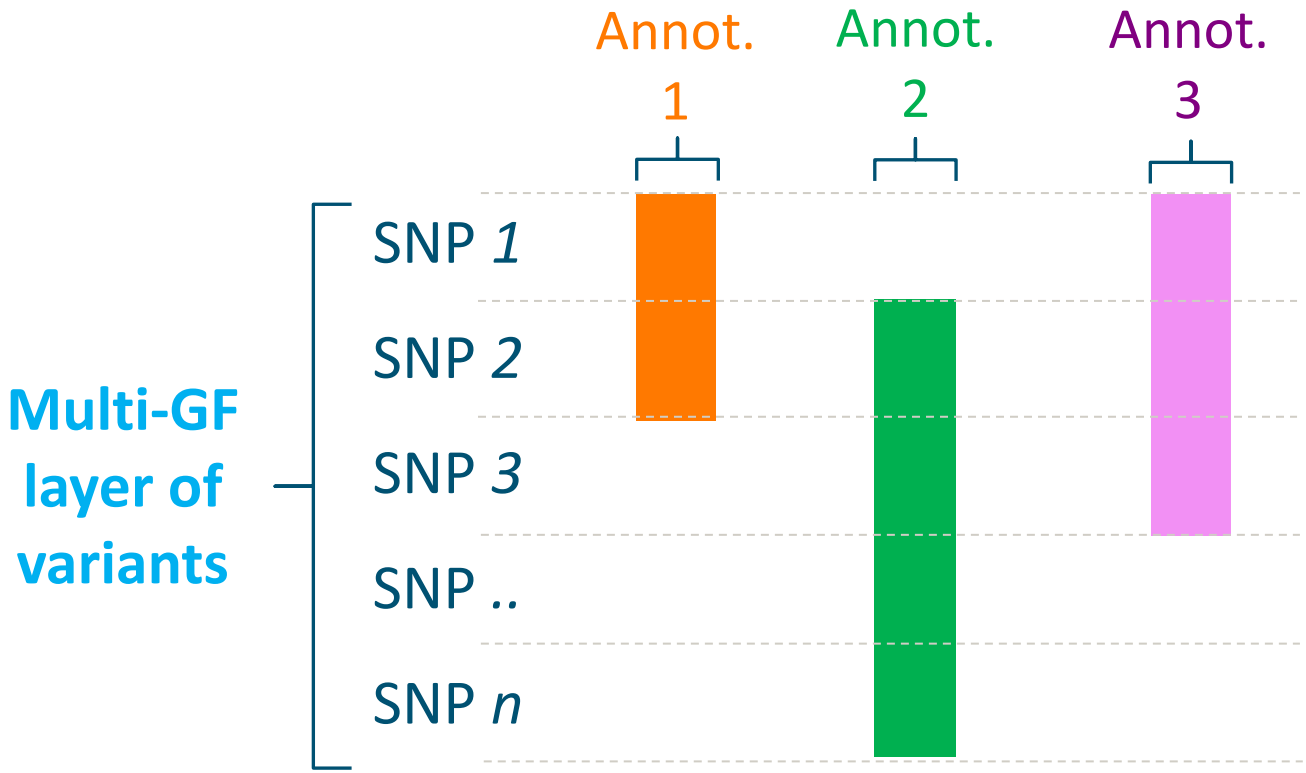


6. Scenarios

Scenario	NLD 	CAN 
50K	48K	46K

- GF as additional layer
- QTL, eQTL, ATAC → Multi-GF → overlapping GF

6. Overlapping genomic features



6. 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)

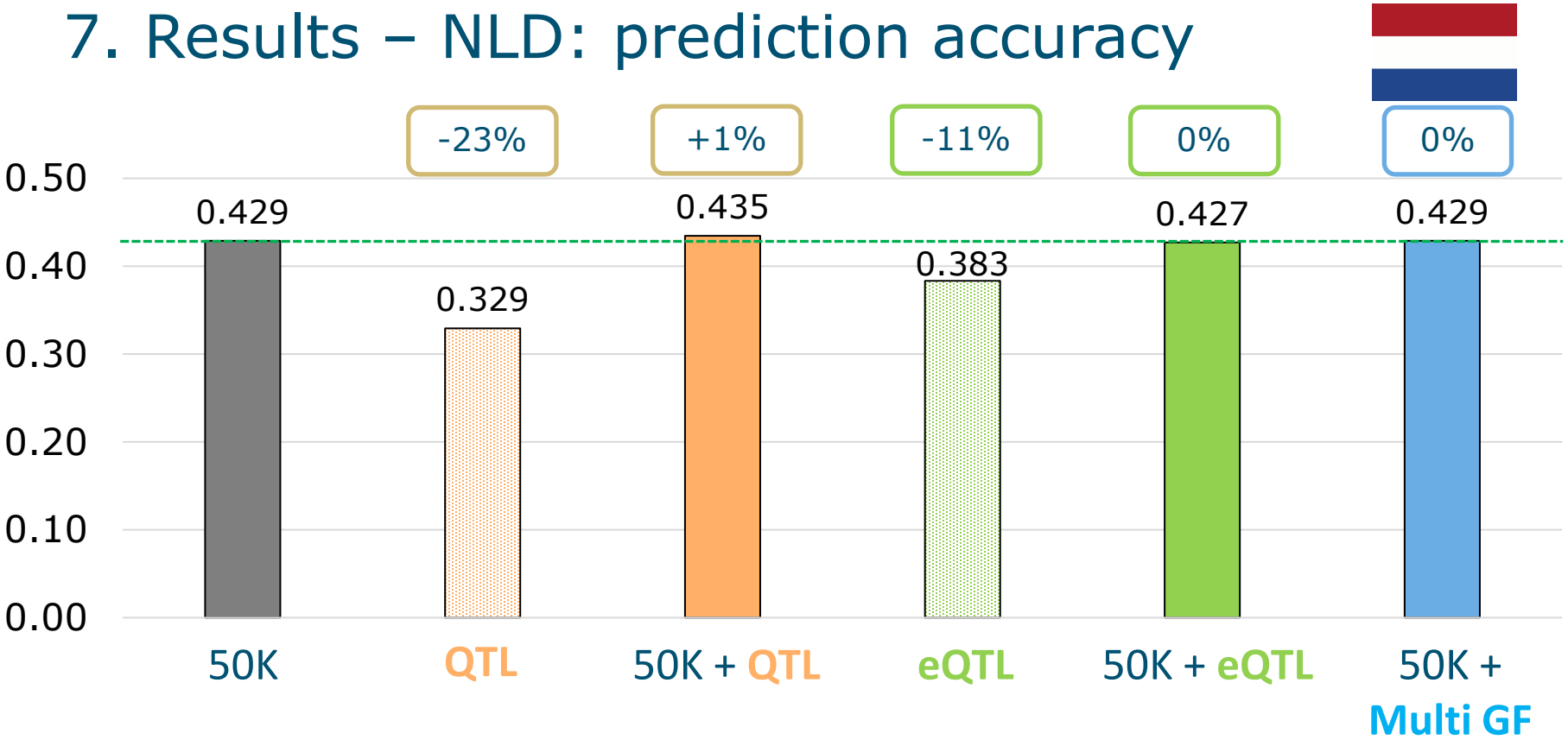
Mollandin *et al.* 2022, BMC bioinformatics

6. Software and settings

- *NextGP.jl* (https://github.com/datasciencetoolkit/NextGP.jl)
- Base 50K: SNPBLUP (BayesC_0), common variance across SNPs
- Additional GF layer (QTL, eQTL, ATAC): SNPBLUP or Bayesian (2 mixture model)
- SNP variance prior: sum(2*pq*) from training genotypes
- No advantage of Bayesian 2 mixture model

Scenario (NLD)	**SNPs**	**Running time**
50k panel, as SNPBLUP	48K	3.98 hours
50k panel, as 2 mix model (pi estim.)	48K	4.96 hours
50k panel, as 2 mix model (pi fixed)	48K	6.41 hours
50k panel + eQTL, both as SNPBLUP	48K + 12K	6.38 hours

7. Results – NLD: prediction accuracy



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

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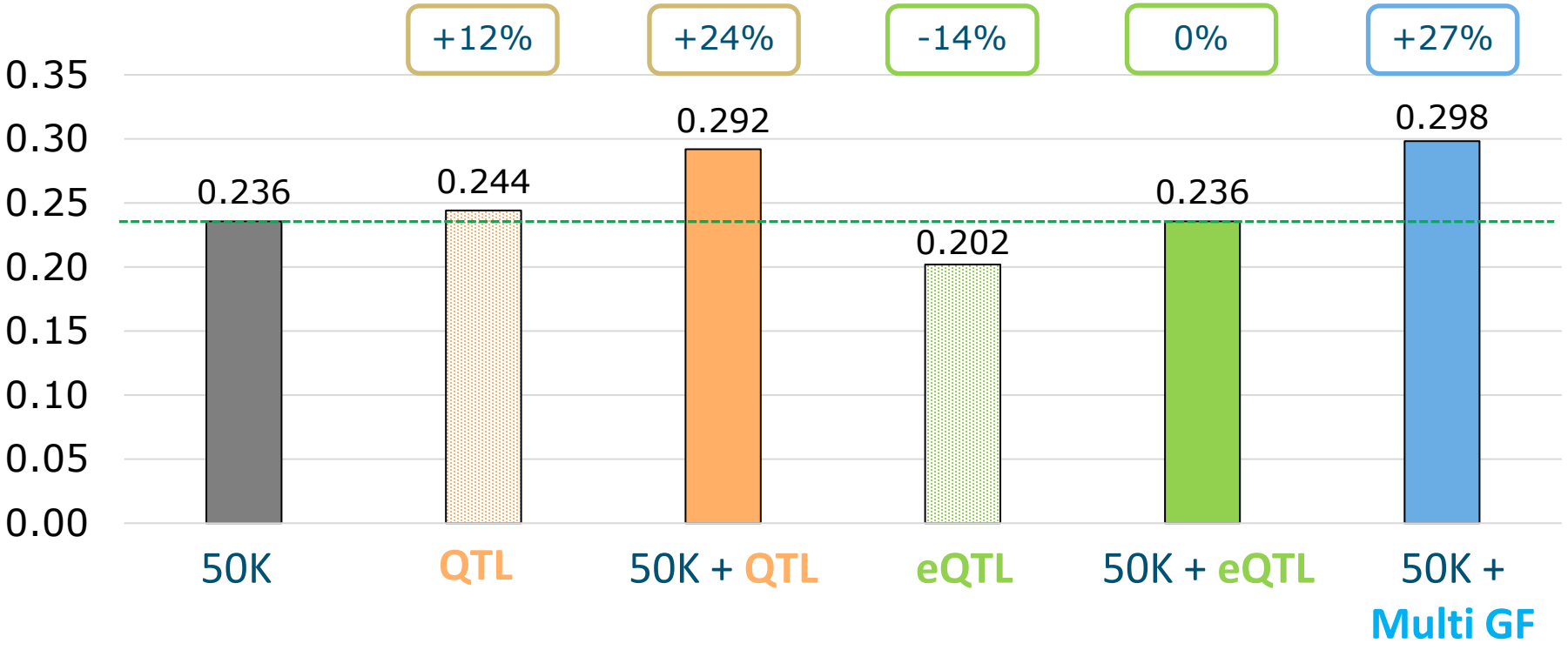
7. Results – CAN: prediction accuracy



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

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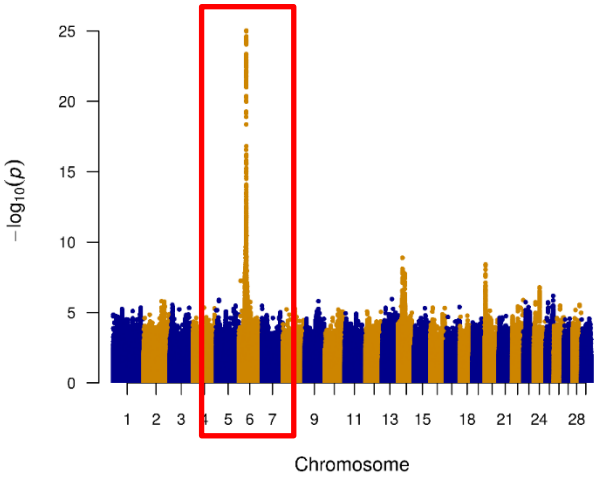
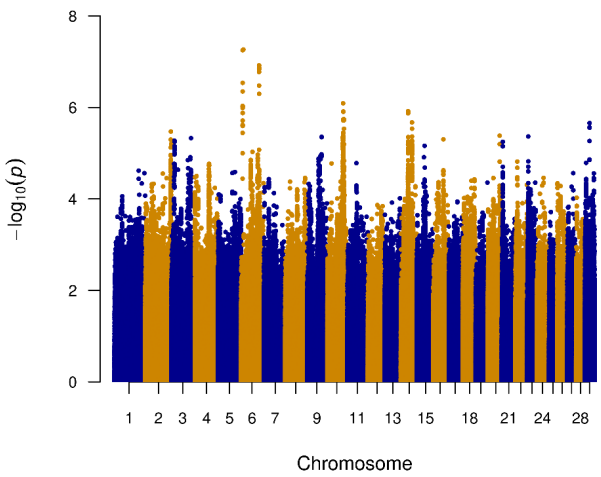
7. Manhattan plots meta-GWAS QTL for DMI

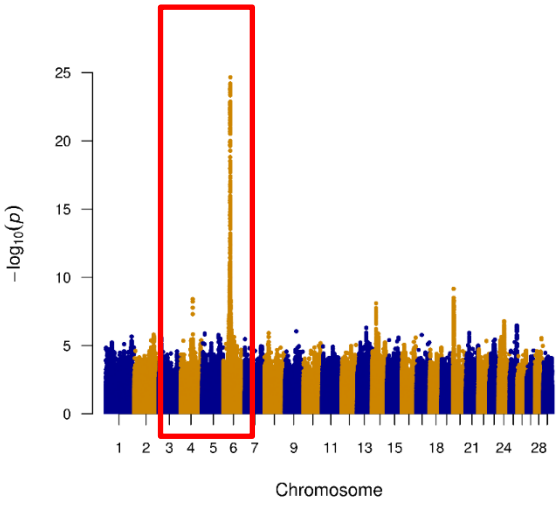
ALL
10,539 animals
Beef, Holstein, Finnish Red
MAF >0.005
30,216,688 variants

HOL
2,368 animals
Only Holstein
MAF >0.005
19,647,876 variants

BEEF
7,805 animals
Only Beef
MAF >0.005
27,839,929 variants







Zhang *et a*l. 2020, BMC genomics

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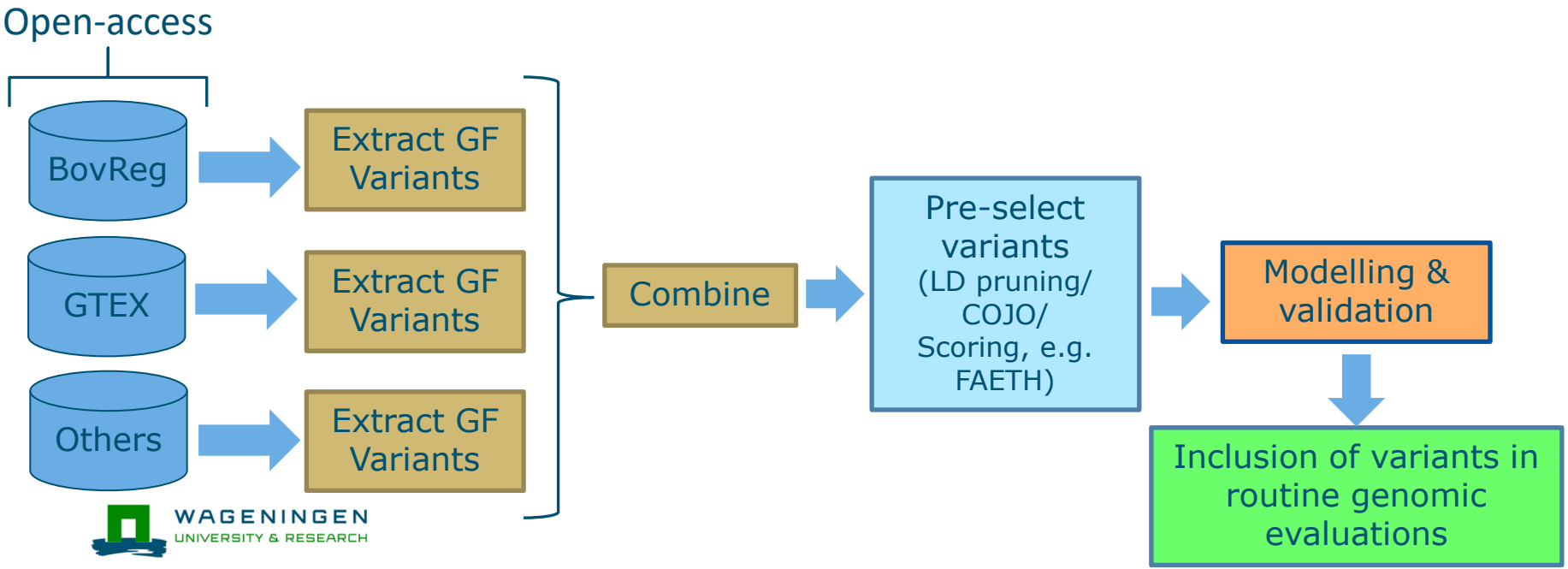
From Gredler-Grandl *et al.* 2022, WCGALP

8. Next steps

- Checking on variants with larger effects on CAN DMI predictions → match with meta-GWAS QTLs?
- GP focussing on trait/tissues-specific variants (now across tissues/traits)
- More detailed annotation modelling using BayesLV (considering *p*-values across annotation layers)
- Across-/multi-breed NLD-CAN

8. Implications

- How can this be used in (routine) genomic predictions?
- CAN case → include QTL variants as markers in 50k chips



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

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Thanks for your attention

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Take-home messages

- Inclusion of Genomic Features could increase genomic prediction accuracies for Dry Matter Intake
- Results vary across breeds/datasets
- No advantage using Bayesian (2 mix model) over SNPBLUP for GF

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