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BovReg
Understanding cattle genomes

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Genetics Selection Evolution




RESEARCH ARTICLE

Open Access



Sequence-based GWAS meta-analyses for beef production traits

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INRAE

ETH zürich



ELIANCE
Des éleveurs. Une ambition.

Université de Limoges

Qualitas

UNIVERSITY OF ALBERTA



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WP4 – Integrative genotype-phenotype data analysis

WP leader: Hubert PAUSCH (ETH, Switzerland) - 11 partners / 20 involved in BovReg








T4.1 – Hubert PAUSCH (ETH, Switzerland)
GWAS and meta-analyses from whole-genome sequences (WGS) for biological efficiency, disease resistance and fertility traits

T4.2 – Carole CHARLIER (GIGA, Belgium)
Phenotypic impact of mobile element integration

T4.3 – Christa KUHN (FBN, Germany)
eQTLs and mQTLs analyses

T4.4 – Emily CLARK (UEDIN, UK)
Tools to prioritize candidate causative variants

GWAS & meta-analyses

<p>Within-breed GWAS</p>				
<p>4 groups of traits</p>	<p>Mastitis resistance</p>	<p>Milk yield & fertility</p>	<p>Feed efficiency</p>	<p>Beef traits</p>
<p>Meta-analyses</p>				
	<p>8-13 populations > 120 000 anim.</p>	<p>7-12 populations > 125 000 anim.</p>	<p>3-9 populations > 13 000 anim.</p>	<p>3-10 populations > 25 000 anim.</p>
<p>Bulls, cows, steers from purebred or crossbred populations Phenotypes (with weights): YD, DYD, DRP, AP</p>				

Within-breed GWAS & meta-analyses

All partners applied similar imputation and GWAS workflows before meta-analyses

Imputations

2 steps

50k → 777k (HD) Within-breed animals with HD genotypes

HD → WGS Animals of various breeds with WGS (1000 BG project)

Fimpute / Minimac / Beagle



tens of millions of variants
incl. causal variants



GWAS

GCTA

Linear mixed model to test individual variant effect together with a polygenic effect estimated from a GRM built using 50k genotypes (when required, phenotypes were weighted)

Meta-analyses

QC + METAL



« Beef » MA – populations

A large number of various populations

8 purebred populations from France (NOR, MON, CHA, LIM, BLA)



4 populations from Swiss breeds (BSW, OBR)



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2 crossbred populations
from Germany (HOL x CHA)



x



1 composite line from
Canada (ANG, CHA, beef)



« Beef » MA – traits analyzed

Grouping of traits in 16 MA

1	Growth	Birth Weight	BW
2	Growth	weight at month 15	W15
3	Growth	weight at 18 months	W18
4	Growth	weight at 24 months	W24
5	Growth	average daily gain	ADG
6	Growth	average daily gain during fattening	ADG
7	Morphology	muscularity score	MS30
8	Morphology	skeletal score	SS30
9	Morphology	thickness of bones	TB30
10	Morphology	Thighs	THIGHS
11	Morphology	Wither	WITHER
12	Morphology	Fat score	FS
13	Carcass	carcass weight	CW
14	Carcass	fat coverage	CF
15	Carcass	meatiness	MT
16	Carcass	Area of longissimus thoracis	ALT
17	Carcass	Carcass conformation	CC
18	Carcass	carcass fat score	FS
19	Carcass	carcass yield	CY
20	Carcass	Internal fat weight	IFW
21	Carcass	length of the leg	LL
22	Carcass	Rib Eye Area	REA
23	Carcass	Weight at slaughter	WS
24	Carcass	Maximum width of the thigh	WT
25	Carcass	age at slaughter	AS
26	Carcass	carcass grade	CG
27	Carcass	average backfat thickness	ABT
28	Carcass	hot carcass weight	CW
29	Carcass	lean meat yield	LMY
30	Carcass	fat content of 6th rib	FC6
31	Carcass	fat content measured by ultrasound	FCU
32	Carcass	muscular development	MD
33	Carcass	skeletal development	SD

Table 4 Traits and populations included in meta-analyses (MA)

MA	Group of traits	Trait ^a (populations ^b)	Number of populations	Number of animals
G1	Growth	BW (INRAE-ULIM_CHA, INRAE-ULIM_LIM, FBN_calves)	3	2720
G2	Growth	W15 (FBN_bulls); W18 (INRAE_CHA_cows); ADG (UAL, INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA)	6	18,774
G3	Growth	WS (INRAE-ULIM_LIM, INRAE-ULIM_BLA, FBN_bulls, FBN_cows)	4	2636
M1	Morphology	MS30 (INRAE_CHA_cows); MD (UAL, INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA); THIGHS (INRAE_MON_bulls, INRAE_NOR_bulls)	7	17,418
M2	Morphology	MS30 (INRAE_CHA_cows); MD (UAL, INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA); WITHER (INRAE_MON_bulls, INRAE_NOR_bulls)	7	17,418
M3	Morphology	LL (UAL, INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA, FBN_bulls, FBN_cows)	6	3695
M4	Morphology	WT (INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA, FBN_bulls, FBN_cows)	5	3695
M5	Morphology	SD (INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA); SS30 (INRAE_CHA_cows)	4	12,140
C1	Carcass	CW (INRAE_CHA_steers, INRAE_MON_steers, INRAE_NOR_steers, FBN_bulls, FBN_cows, ETH_bulls, UAL)	7	19,989
C2	Carcass	AS (INRAE_CHA_steers, INRAE_MON_steers, INRAE_NOR_steers, INRAE-ULIM_CHA)	4	12,208
C3	Carcass	CY (INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA, FBN_bulls, FBN_cows)	5	3694
C4	Carcass	CG (INRAE_CHA_steers, INRAE_MON_steers, INRAE_NOR_steers); LMY (UAL); MT (ETH_bulls); CC (INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA, FBN_bulls, FBN_cows)	10	25,367
C5	Carcass	FS (INRAE_NOR_bulls); FCU (INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA); CFS (FBN_bulls, FBN_cows); ABT (UAL); FC (ETH_bulls)	8	14,622
C6	Carcass	ALT (INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA, FBN_bulls, FBN_cows)	5	3692
C7	Carcass	IFW (INRAE-ULIM_CHA, INRAE-ULIM_LIM, INRAE-ULIM_BLA, FBN_bulls, FBN_cows)	5	3686
C8	Carcass	REA (UAL, FBN_bulls, FBN_cows)	3	4453

A large number and a large diversity of traits

Growth (6)
Morphology (6)
Carcass (21)

- ✓ 1 to 5 traits / MA
- ✓ 3 to 10 populations / MA
- ✓ 2 to 5 partners / MA
- ✓ 2600 to 25,000 animals / MA

2 methods:
z-score & fixed effects
with METAL software (Willer et al., 2010)

Comparison of GWAS & meta-GWAS results

Table 5 Features of QTL identified in within-population GWAS and meta-analyses (MA)

MA ^a	Within-population GWAS				Fixed-effects MA		
	Number of QTL total	Number of QTL per GWAS ^b	Number of variants (CI)	Size in kb (CI)	Number of QTL	Number of variants (CI)	Size in kb (CI)
G1 (3)	8	8	135 (12–381)	1650 (415–2448)	6	124 (44–223)	1736 (569–3594)
G2 (6)	8	4,4	216 (22–707)	1823 (629–2903)	8	50 (14–100)	1310 (104–2828)
G3 (4)	6	4,1,1	215 (31–564)	2441 (1183–3922)	8	114 (5–419)	1696 (129–3426)
M1 (7)	15	1,6,2,6	153 (3–566)	1438 (52–2863)	8	81 (2–429)	1070 (109–2863)
M2 (7)	11	1,6,2,2	170 (3–566)	1526 (109–3101)	8	60 (2–411)	882 (49–2863)
M3 (6)	12	2,8,1,1	271 (17–793)	1937 (495–3823)	9	102 (4–421)	1519 (274–3038)
M4 (5)	8	1,3,3,1	333 (32–800)	2357 (1417–3578)	6	161 (5–409)	1701 (559–2386)
M5 (4)	12	1,10,1	182 (18–507)	1871 (416–3511)	11	125 (2–347)	1611 (146–2997)
C1 (7)	3	3	66 (34–126)	469 (174–823)	4	35 (7–87)	928 (78–1443)
C3 (5)	15	7,2,4,2	290 (4–902)	1840 (59–3821)	6	237 (71–850)	2392 (721–3614)
C4 (10)	11	3,1,3,3,1	207 (3–570)	1668 (680–2520)	8	33 (3–161)	1272 (24–2520)
C5 (8)	5	3,1,1	128 (1–403)	1547 (0–2664)	6	42 (1–90)	1025 (0–2623)
C6 (5)	8	3,2,3	176 (9–766)	1869 (1–3143)	5	266 (49–474)	1975 (935–2577)
C7 (5)	1	1	533	2205	1	95	2857
C8 (3)	6	4,1,1	195 (17–445)	2515 (989–3892)	7	66 (3–232)	1750 (98–3982)
Mean	8.6		218	1810	6.7	106	1582

CI confidence interval

QTL detected

- in 15 of the 16 MA
- in 1 to 5 GWAS

2 QTL detected in GWAS and not in MA

9 QTL detected in MA and not in GWAS

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2 QTL detected in GWAS and not in MA

9 QTL detected in MA and not in GWAS

Except in G1 and C3, the number of QTL detected in MA was higher than the number of QTL detected in each GWAS

Comparison of GWAS & meta-GWAS results

Table 5 Features of QTL identified in within-population GWAS and meta-analyses (MA)

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CI confidence interval

QTL detected

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- in 1 to 5 GWAS

2 QTL detected in GWAS and not in MA

9 QTL detected in MA and not in GWAS

Confidence Intervals

MA = 77 variants / 605 kb

GWAS = 218 variants / 1810 kb



Growth MA – results

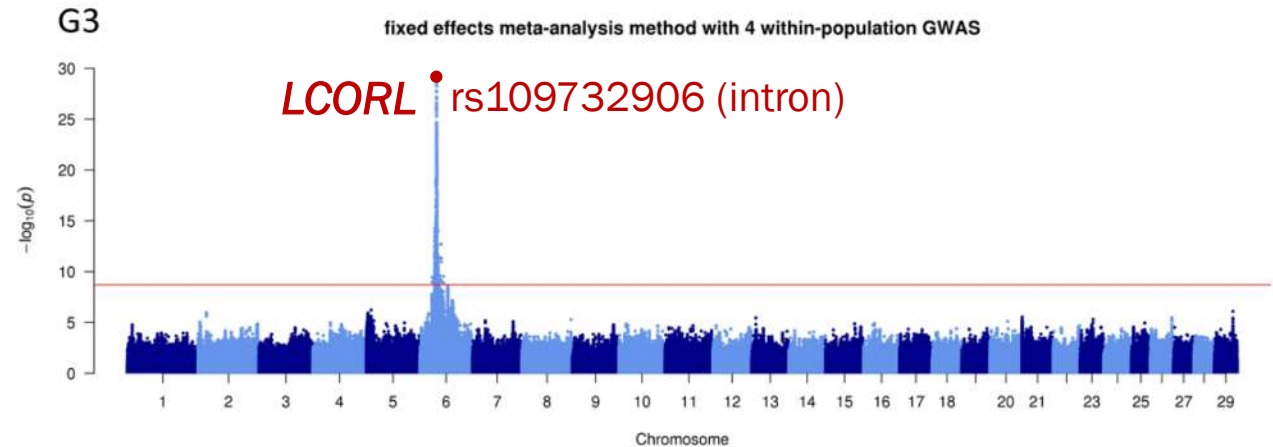
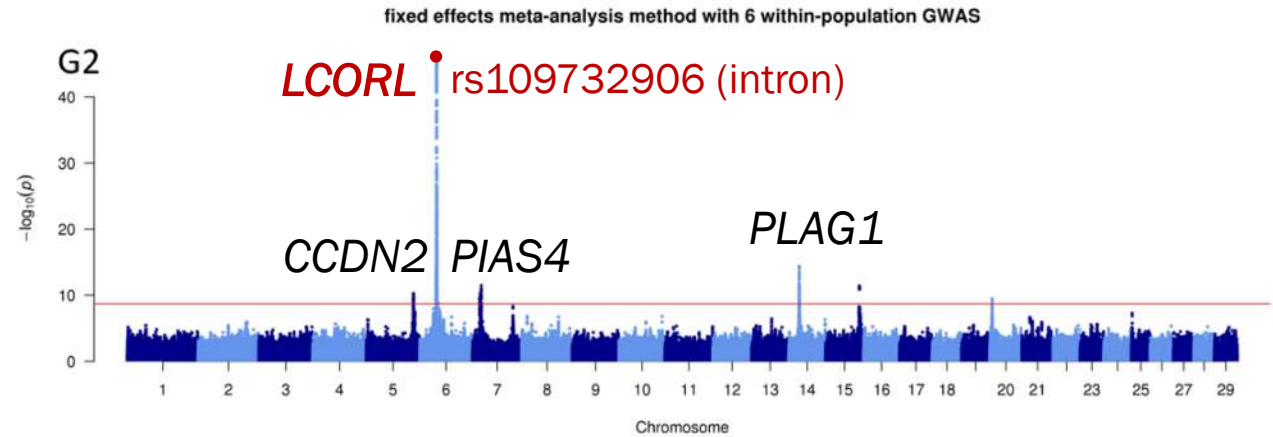
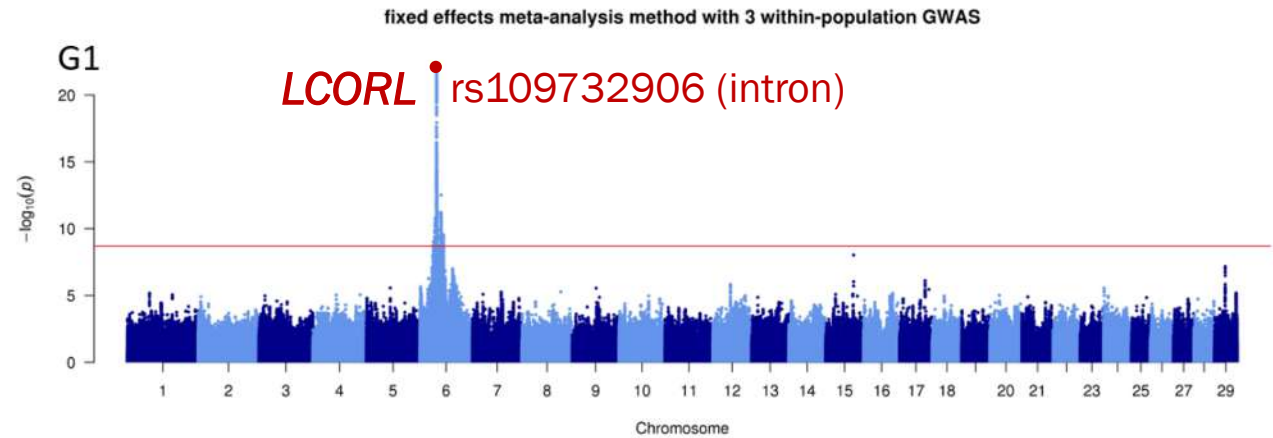
Growth traits

QTL with the most significant effects common to the 3 growth MA

⇒ **BTA6** ≈ 37 Mb

Variants in *LCORL* in all MA, not in GWAS
Transcription factor regulating expression of other genes

+ QTL on BTA 5, 7, 14, 15, and 20



Morphology MA – results

Morphology traits

QTL with the most significant effects

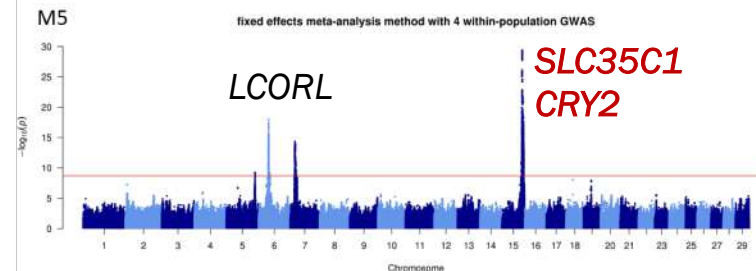
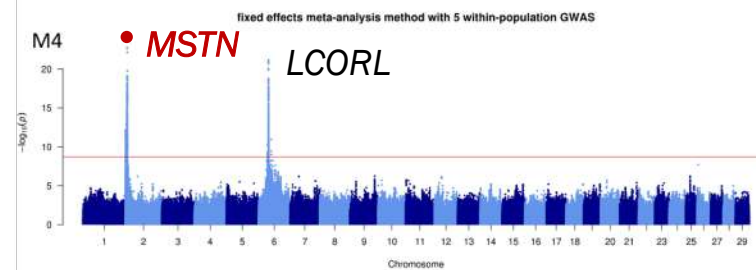
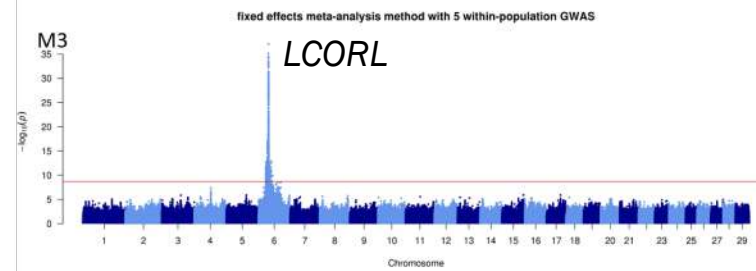
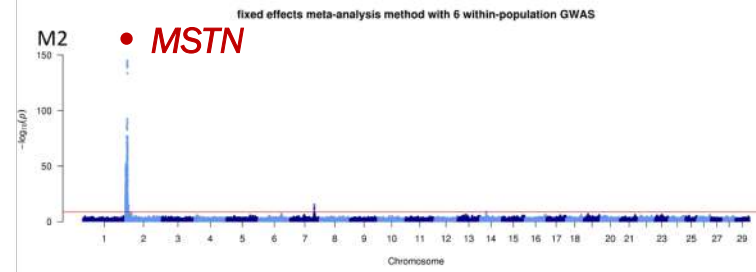
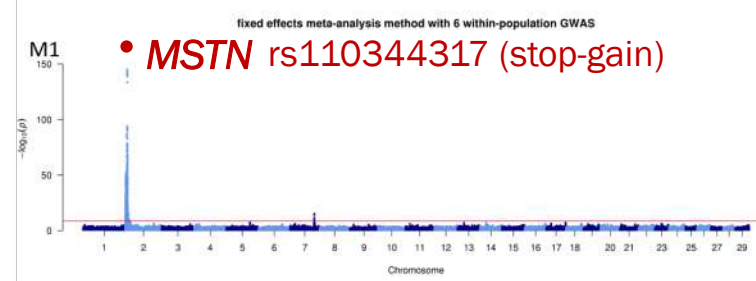
⇒ **BTA2** (*MSTN*)

⇒ **BTA6** (*LCORL*)

⇒ **BTA15** (*SLC35C1*, *CRY2*)

MSTN encodes myostatin, with known mutations responsible for muscular hypertrophy

+ QTL on BTA 7, and 14



Carcass MA – results

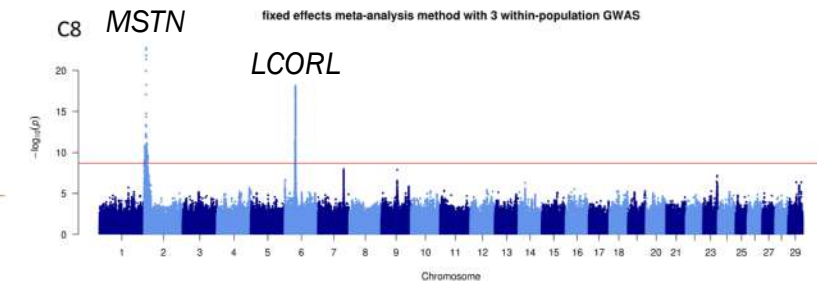
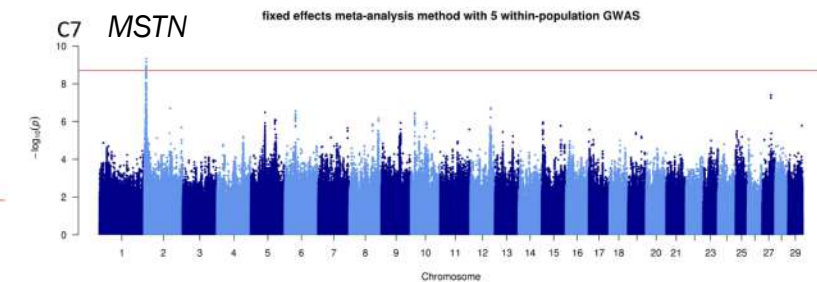
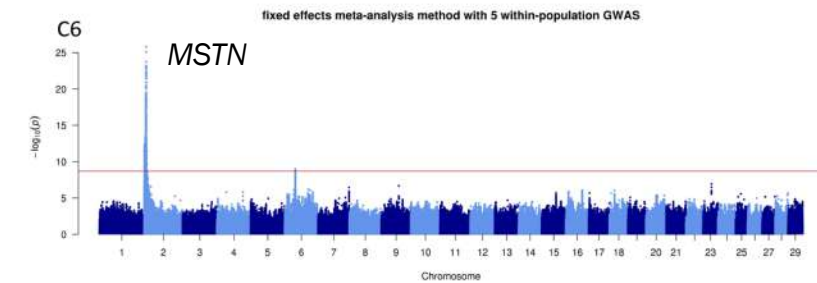
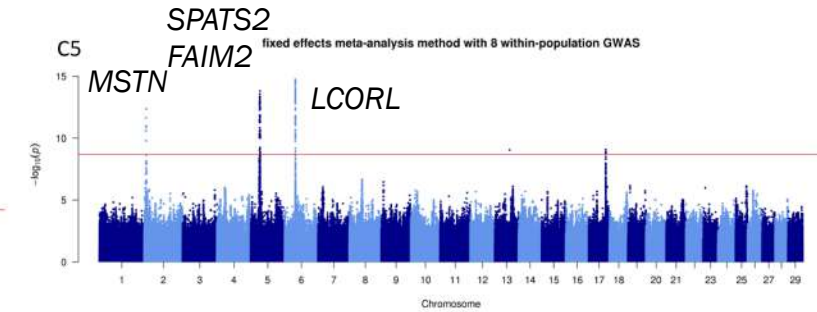
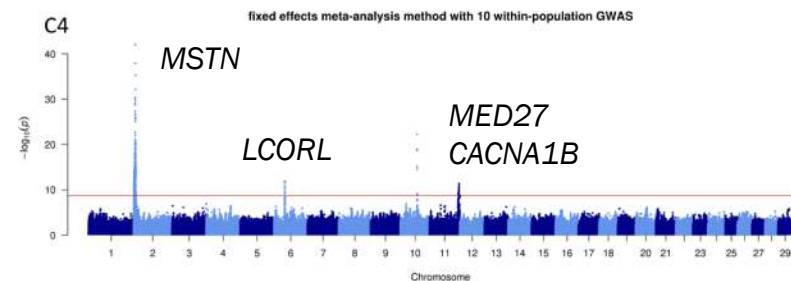
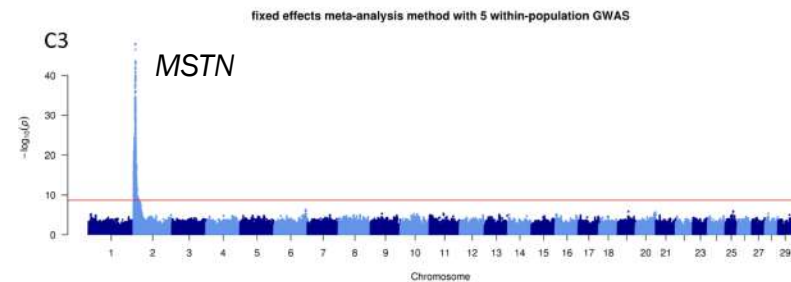
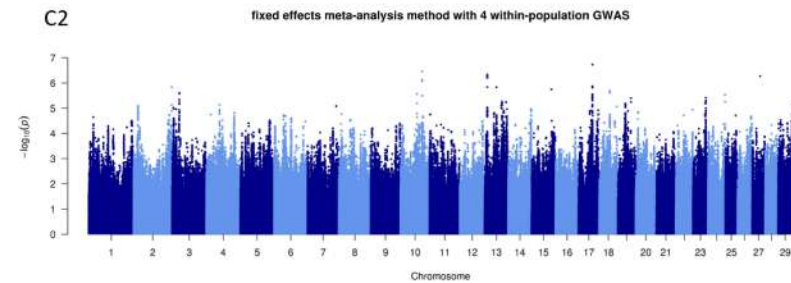
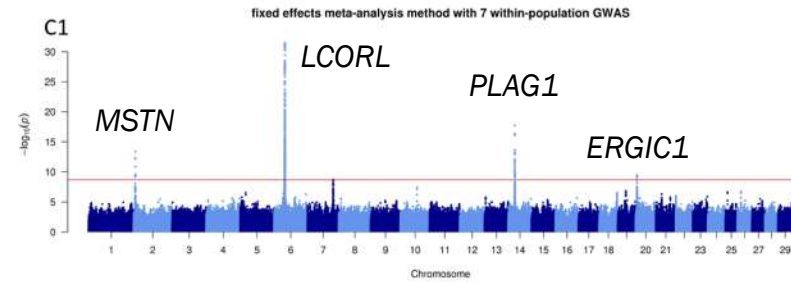
Carcass traits

37 QTL
with the most significant
effects

⇒ BTA2

⇒ BTA6

+ QTL on BTA 5, 10, 11, 13,
14, 17, and 20



QTL enrichment analyses

Comparison with QTL referenced in CattleQTLdb

% of production, meat and carcass QTL detected

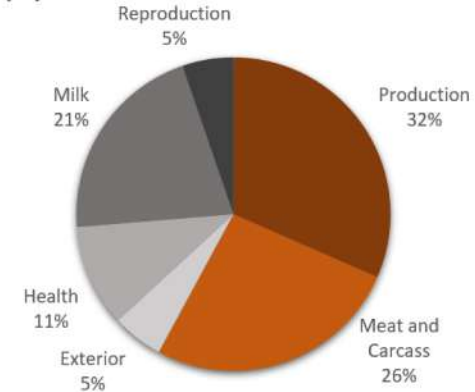
⇒ **58%** in within-population GWAS

⇒ **65%** in fixed effects MA

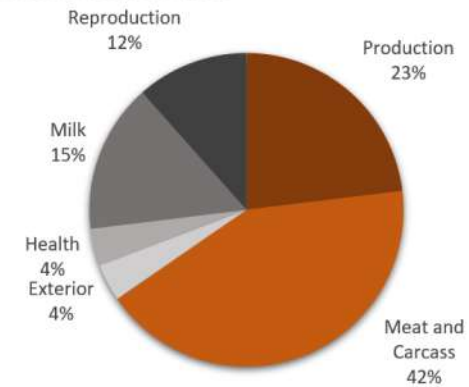
⇒ **72%** in z-score MA

Enrichment of QTL related to the traits analyzed more pronounced in MA than in GWAS

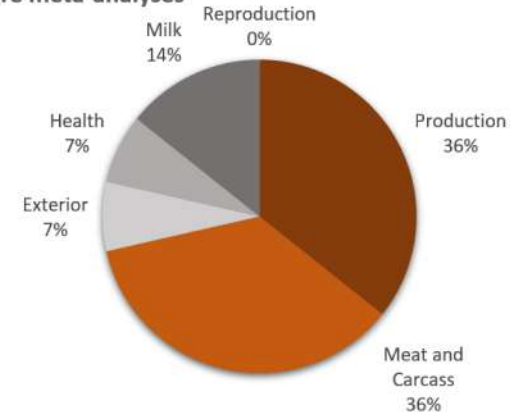
Within-population GWAS



Fixed effects meta-analyses



Z-score meta-analyses



Overlapping between QTL and cis-e/sQTL

A limited number of variants detected in MA that are cis-e/sQTL in CattleGTEx

Cis-eQTL

54 eQTL x tissue x
MA x method
combinations

Fixed Effects / z-score

Tissue	Total
Adipose	2/2
Blood	1/0
Embryo	1/0
Intramuscular_fat	1/1
Leukocyte	4/4
Liver	2/2
Lung	0/1
Lymph_node	4/1
Mammary	1/1
Mammary_L	1/1
Milk_cell	1/0
Monocytes	2/3
Muscle	5/3
Pituitary	0/1
Rumen	2/0
Spleen	5/2
Total	32/22

Cis-sQTL

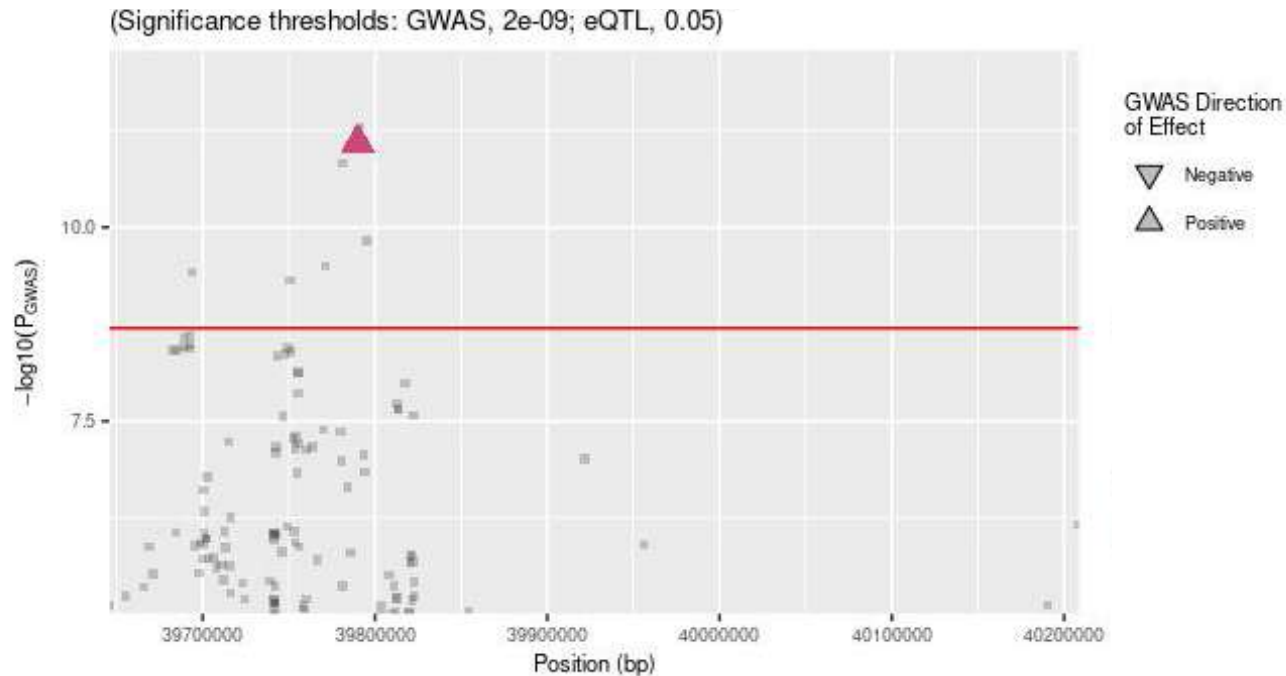
170 sQTL x tissue x
MA x method
combinations

Tissue/MA	Total
Adipose	11/6
Blood	3/5
Embryo	2/0
Hypothalamus	4/2
Jejunum	4/0
Kidney	5/4
Liver	6/0
Lung	9/2
Lymph_node	3/7
Macrophage	6/4
Mammary	7/6
Mammary_L	2/7
Milk_cell	1/3
Monocytes	0/2
Muscle	4/8
Ovary	1/0
Oviduct	5/7
Pituitary	3/3
Rumen	4/4
Spleen	5/5
Testis	4/4
Uterus	2/0
Total	91/79

Tissues in which
e/sQTL colocalizing
with MA results
related to the traits
analyzed

Overlapping between QTL and cis e/sQTL

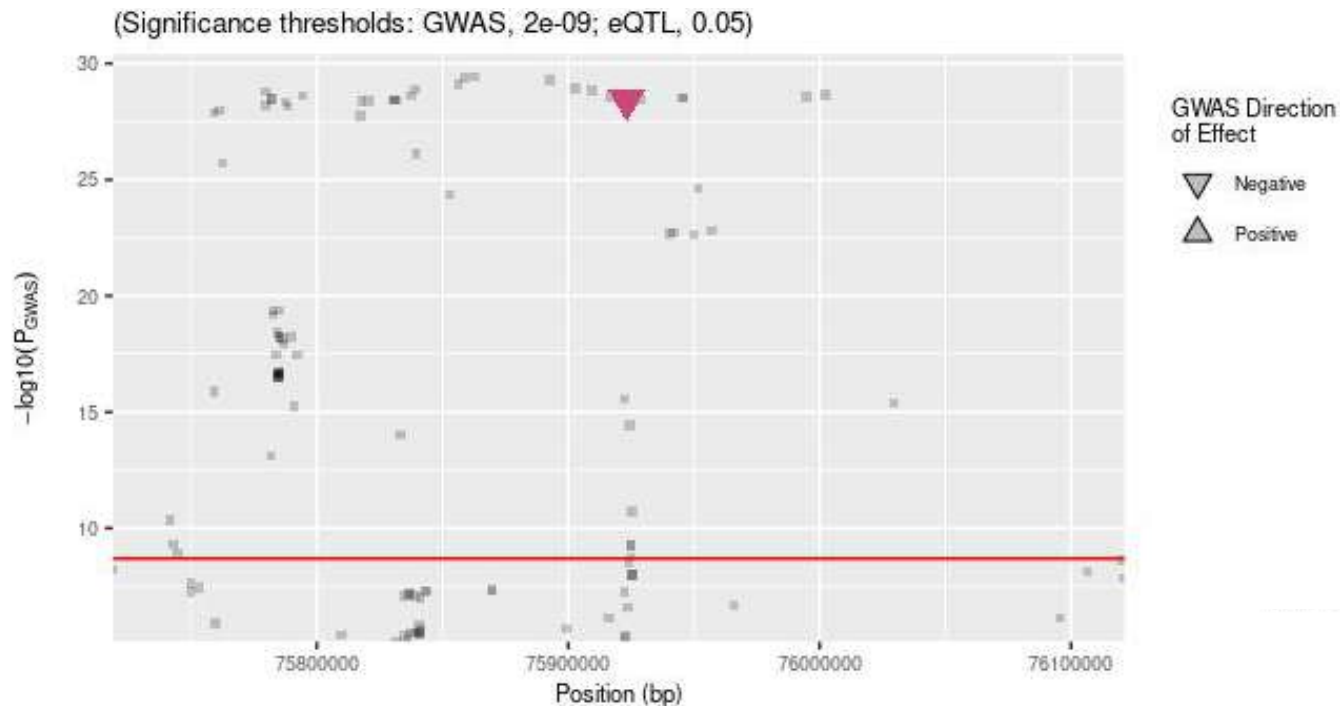
eQTpLot analysis for G1 and *SLIT2* MultiTissue analysis, eQTLs collapsed by minimum value



One of the TOP meta-GWAS variant is a cis-eQTL regulating the expression of *SLIT2*

Overlapping between QTL and cis e/sQTL

eQTpLot analysis for M5 and *MAPK8IP1* MultiTissue analysis, eQTLs collapsed by minimum value



Among a number of variants with the most significant effects, one is a cis-eQTL regulating the expression of *MAPK8IP1*

Conclusions

With almost 55,000 animals from 15 populations of various breeds, this study is the first meta-GWAS of this scale dedicated to beef production

Value of meta-GWAS compared to within-population GWAS, in identifying:

- A larger number of QTL
- A smaller number of target variants within the QTL
- A more significant enrichment of meat, carcass, and meat production QTL

Large-scale meta-GWAS conducted at the sequence level, coupled with post-GWAS analyses, significantly improved the identification of genes and causal variants associated with beef production traits

BovReg *PARTNERS*



Thank you for your attention

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Marie-Pierre SANCHEZ

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