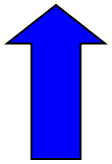
Towards novel selection strategies to improve production and fertility by integrating expression profiles and high throughput genotyping in cattle

Eduardo Pimentel, M. Tietze, H. Simianer, F. Reinhardt , S. Bauersachs, E. Wolf and S. König

Department of Animal Sciences
Animal Breeding and Genetics Group
Georg-August-University Göttingen, Germany




Motivation

 Production

 Fertility

- “Phenotypic” level:

  (e.g. Holtsmark *et al.* 2008, König *et al.* 2009)

- Genomic level:

  (e.g. ???)

Motivation

Gene expression profiling of bovine endometrium during the oestrous cycle: detection of molecular pathways involved in functional changes

S Bauersachs[1,2], S E Ulbrich[3], K Gross[1], S E M Schmidt[1], H H D Meyer[3], R Einspanier[4], H Wenigerkind[5], M Vermehren[6], H Blum[2], F Sinowatz[6] and E Wolf[1,2]

Dynamic changes in messenger RNA profiles of bovine endometrium during the oestrous cycle

Katrin Mitko[1,2], Susanne E Ulbrich[3], Hendrik Wenigerkind[4], Fred Sinowatz[5], Helmut Blum[2], Eckhard Wolf[1,2] and Stefan Bauersachs[1,2]

Candidate genes

→ Increased expression in luteal phase

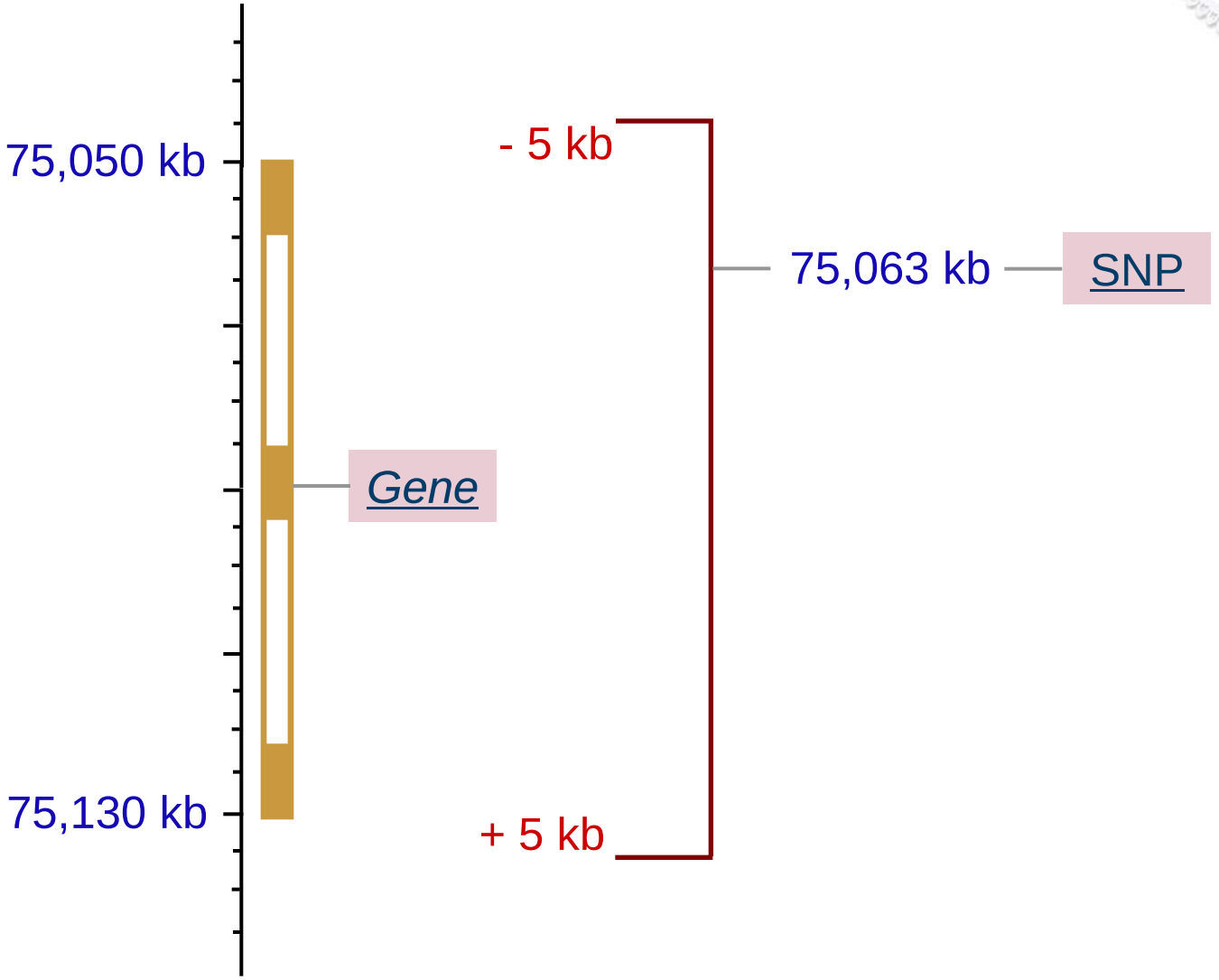
→ Regulation by progesterone (P4)

→ Preparation of for implantation

Material

- 170 candidate genes
- 2294 Holstein bulls (call rate > 0.97)
- 39557 SNPs (Illumina BovineSNP50 BeadChip)
  - call rate > 0.95
  - MAF > 0.05
  - known position
  - no missing (imputed with fastPHASE)

Material



Material

- Production traits:
  - milk yield (Mkg)
  - fat yield (Fkg)
  - protein yield (Pkg)
  - fat percentage (Fpr)
  - protein percentage (Ppr)
  - somatic cell score (SCS)

Material

- Fertility traits:
  - non-return rate to 56 days:
    - in heifers (**NRh**)
    - in cows (**NRc**)
  - interval from first to successful insemination:
    - in heifers (**FLh**)
    - in cows (**FLc**)
  - interval from calving to first insemination (**CFc**)
  - days open (**DOc**)

Methods

- Statistical model: $\mathbf{y} = \mathbf{Xb} + \mathbf{Zu} + \mathbf{e}$

EBV

μ + marker effect

polygenic effect

$$\mathbf{e} \sim N(0, \mathbf{R}\sigma_e^2)$$

diag($1/r_i$)

$$\mathbf{u} \sim N(0, \mathbf{G}\sigma_a^2)$$

marker | pedigree

- Significance threshold: 5% FDR

Methods

- Marker-based kinship coefficients
  - Hayes & Goddard (2008)

$$S_{xy,l} = 1/4[I_{11} + I_{12} + I_{21} + I_{22}]$$

where I_{ij} is an indicator variable which is 1 when allele i on locus l in the first individual and allele j on the same locus in the second individual are identical, otherwise it is 0.

Methods

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The similarity index was averaged over loci.

Methods

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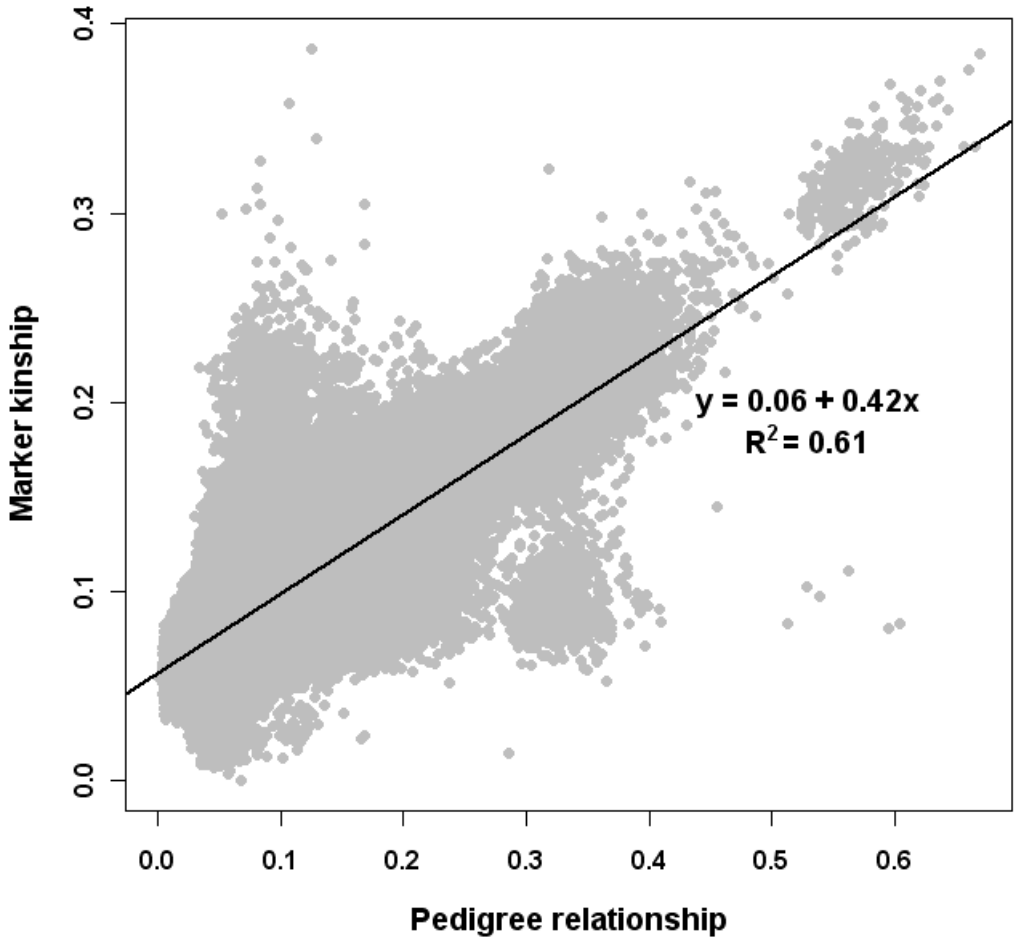
where I_{ij} is an indicator variable which is 1 when allele i on locus l in the first individual and allele j on the same locus in the second individual are identical, otherwise it is 0.

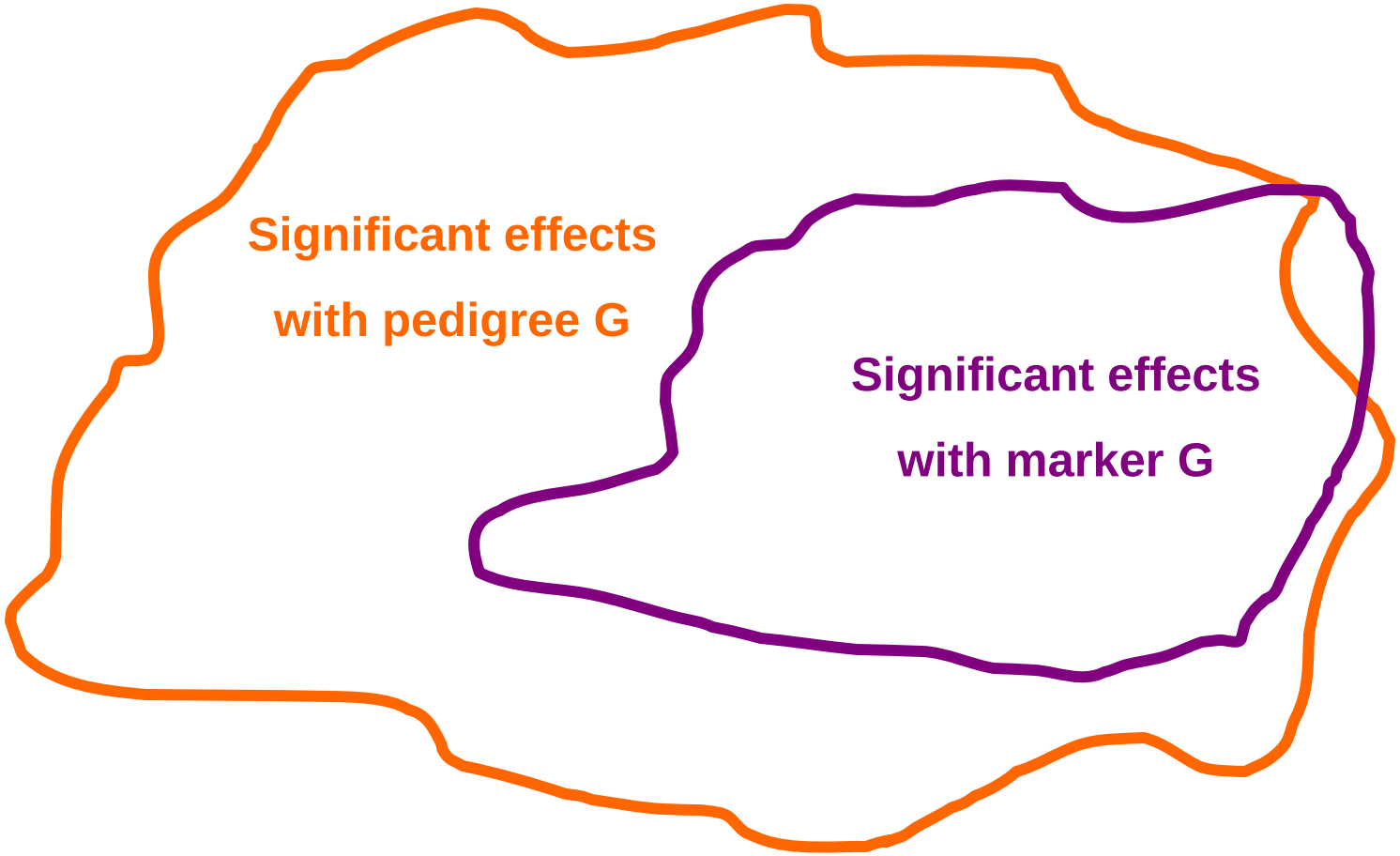
The similarity index was averaged over loci.

$(S_{xy} - \min) / (1 - \min)$, where min is the minimum relationship in the matrix

Results


Marker kinship
Pedigree relationship
0.0
0.1
0.2
0.3
0.4
0.5
0.6
y = 0.06 + 0.42x
R2 = 0.61

Results


Significant effects
with pedigree G
Significant effects
with marker G

Results

- 111 markers located within gene regions
- 16 significantly associated with at least one production plus one fertility trait
- 15 significantly associated with Mkg, Fpr and Ppr

Results

Chr	Gene symbol	Trait					
		Mkg	Fkg	Pkg	Fpr	Ppr	SCS
2	*CYP27A1*	52.025	NS	1.101	-0.020	-0.007	0.878
2	*IDH1*	-37.881	-0.763	-1.046	0.009	0.002	NS
3	*UGT1A6*	-18.877	0.870	NS	0.019	0.006	NS
4	*MRPL32*	21.533	NS	NS	-0.012	-0.009	NS
5	*ACO2*	-38.976	NS	NS	0.023	0.008	NS
5	*BCAT1*	65.064	NS	1.062	-0.038	-0.011	NS
5	*GABARAPL1*	-93.189	-0.796	-1.848	0.035	0.015	NS
5	*MGP*	52.051	-3.505	NS	-0.063	-0.016	1.241
13	*TGM2*	-29.947	NS	-0.712	0.016	0.004	NS
17	*MTMR3*	-18.565	-1.815	-1.050	-0.013	-0.005	NS
17	*OAS1*	-51.017	NS	-1.121	0.019	0.007	NS
21	*LGMN*	-37.049	NS	NS	0.019	0.008	NS
21	*SERPINA14*	30.829	NS	NS	-0.014	-0.006	NS
26	*LIPA*	35.818	1.046	NS	-0.007	-0.010	NS
28	*ARID5B*	-65.214	NS	-1.641	0.023	0.006	NS

Results

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4	*MRPL32*				012	-0.009	NS
5	*ACO2*				023	0.008	NS
5	*BCAT1*				038	-0.011	NS
5	*GABARAPL1*				035	0.015	NS
5	*MGP*				063	-0.016	1.241
13	*TGM2*				016	0.004	NS
17	*MTMR3*				013	-0.005	NS
17	*OAS1*				019	0.007	NS
21	*LGMN*				019	0.008	NS
21	*SERPINA14*				014	-0.006	NS
26	*LIPA*	35.818	1.046	NS	-0.007	-0.010	NS
28	*ARID5B*	-65.214	NS	-1.641	0.023	0.006	NS

+ is ‘good’

- is ‘bad’

Results

Chr	Gene symbol	Trait							
			Mkg	Fkg	Pkg		**Fpr**		**Ppr**	SCS
2	*CYP27A1*	+	52.025	NS	1.101	-	0.020	-	0.007	0.878
2	*IDH1*	-	37.881	-0.763	-1.046	+	0.009	+	0.002	NS
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17	*OAS1*	-	51.017	NS	-1.121	+	0.019	+ 0.007	NS
21	*LGMN*	-	37.049	NS	NS	+	0.019	+ 0.008	NS
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Results

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Results

Chr	Gene symbol
1	*TNFSF10*
2	*IFIH1*
2	*IGFBP2*
3	*HFM1*
4	*PARP12*
4	*SCRN1*
6	*IGFBP7*
8	*APBA1*
10	*IRF9*
17	*KSR2*
18	*CNOT1*
18	*NDRG4*
19	*BAIAP2*
20	*CCNB1*
23	*CCND3*
24	*NPC1*

NDRG4:

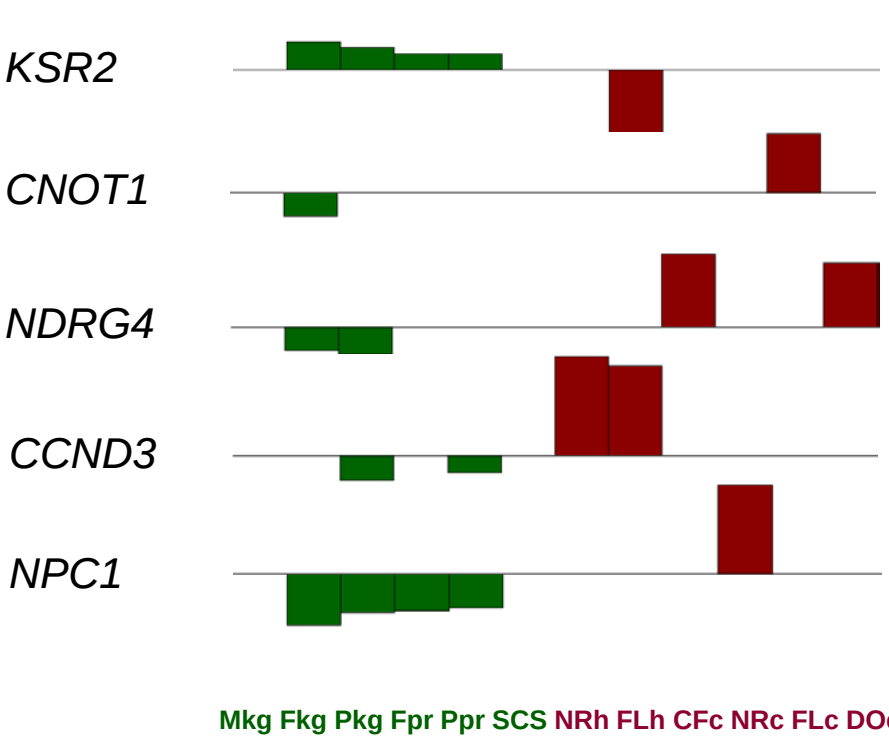
Fkg	Pkg	CFc	DOc
-0.831	-0.747	+0.945	+0.867

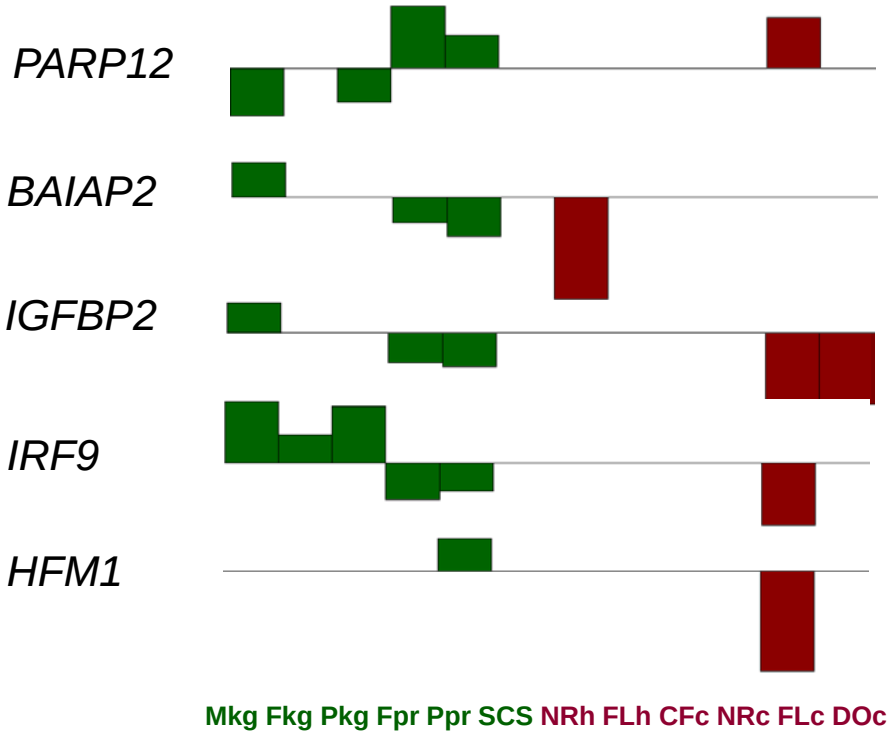
(in units of standard deviations of the trait)

Mkg Fkg Pkg Fpr Ppr SCS NRh FLh CFc NRc FLc DOc

Results

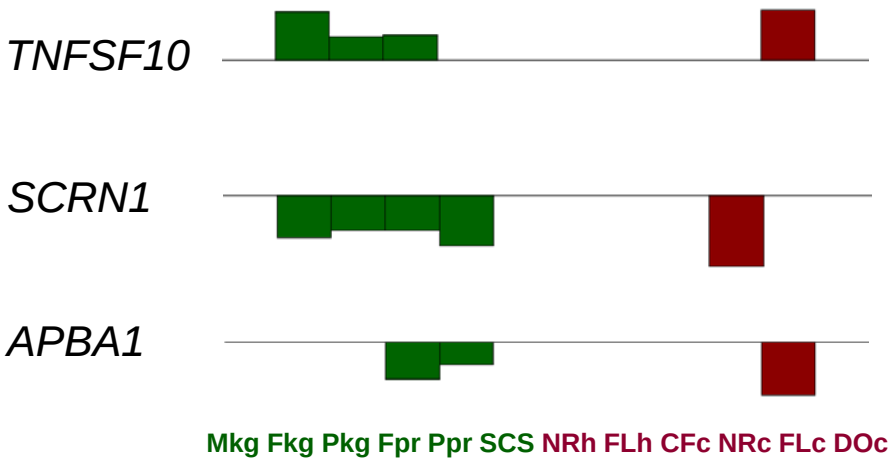
Production and fertility in opposite directions:

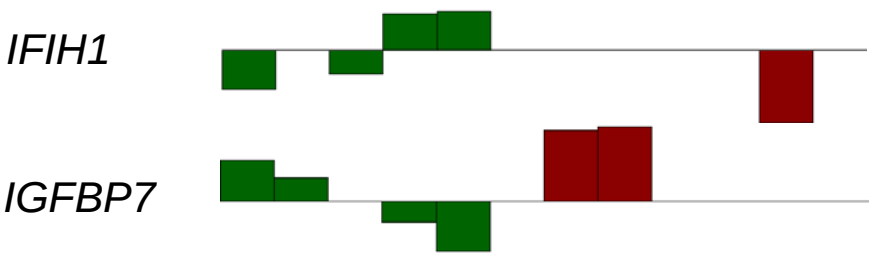




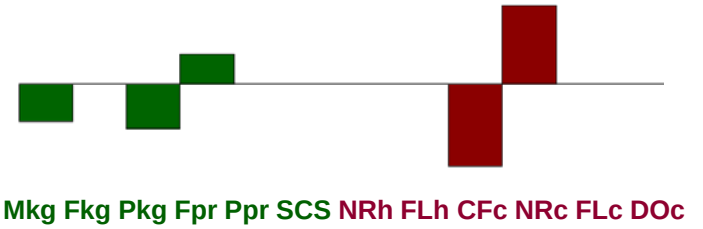
Results

Production and fertility in the same direction:





-CFc and +NRc:



Conclusions

- The majority of the SNP with effects on both classes of traits showed antagonism between production and fertility

- Antagonistic relationships were also observed between milk yield and percentage traits

Conclusions

- Selection strategies enhanced by focus on specific SNP may help finding a compromise between production and fertility

- Input from gene expression studies may be useful in identifying such markers

Acknowledgments

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