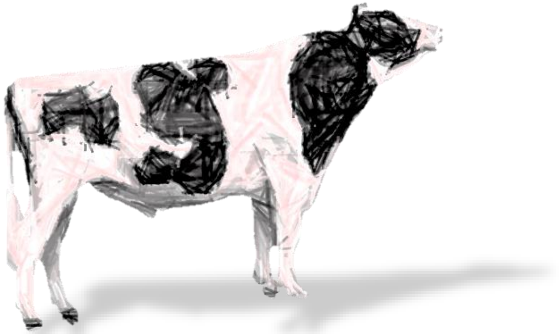
G. Molina, M.J. Carabaño, S. Karoui and C. Díaz

Identification of genomic regions associated with characters correlated with the fertilizing capacity of Holstein bulls



INIA
Instituto Nacional de Investigación
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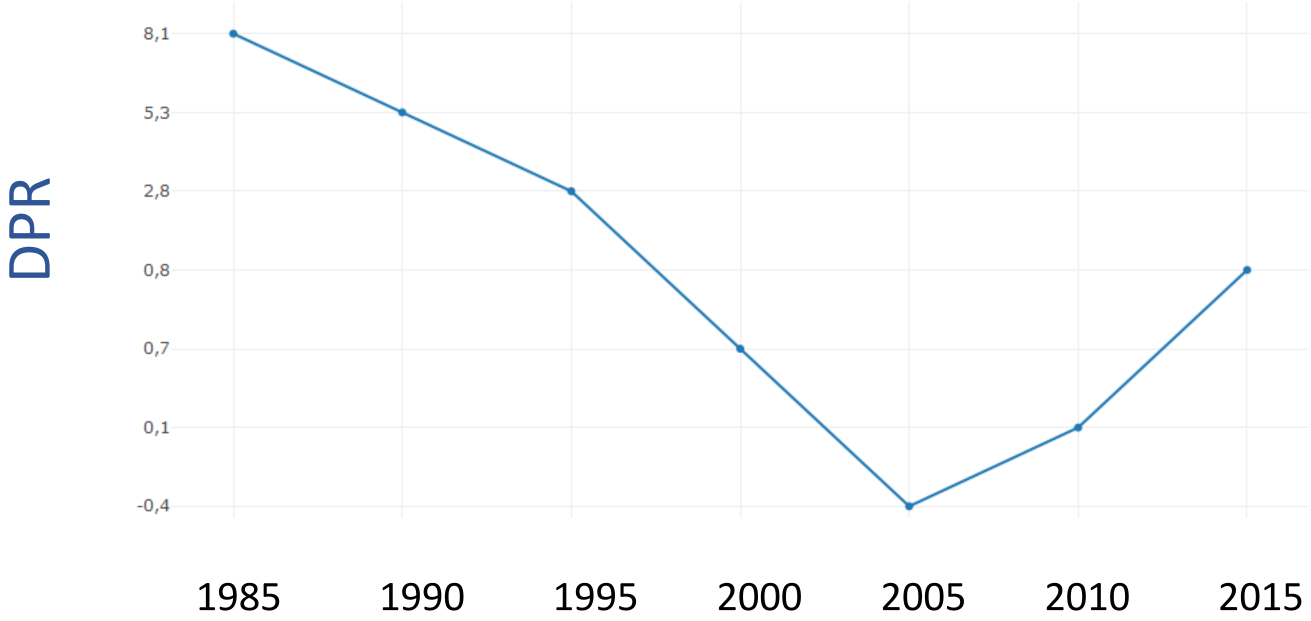
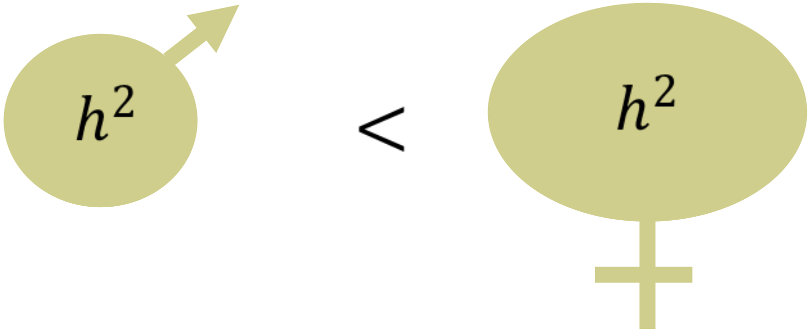
Introduction

Trends in fertility (DPR) genetic selection in US Holstein (USDA-ADC)





Introduction

Male ferlitity and Semen Quality traits

Heritabilities

Trait	h^2
EAI	0,01

David., et al 2011

Trait	h^2
VOL	0,22
CON	0,19
NSPZ	0,18
MM	0,16
IM	0,09
PTM	0,22
SDF_0	0,41
SDF_6	0,29

Genetic correlations with EAI

Trait	EAI
VOL	0,1
CON	0,22
NSPZ	0,26
MM	0,35
IM	0,29
PTM	0,34
SDF_0	-0,36
SDF_6	-0,38

Karoui., et al 2012

EAI (success in AI), VOL (volumen), CON (concentration), NSPZ (number of sperm), MM (mass motility), IM (individual motility), PTM (Post-thawing motility), SDF0/6 (sprem DNA fragmentation at 0 or 6 hours post-thawing)

Objectives

1. Identify genomic regions and propose candidate genes associated with male fertility and semen quality traits.

2. Analyse the genetic basis of the association between these traits through the genomic information from GWAS.

Material: *Phenotypes*

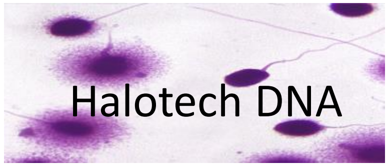
Data Pseudo-Phenotypes (environment free)

Federación Frisona
de Euskadi (EFRIFE).
1995-2008
511494 AI
136255 cows

Trait	N	Mean (S.D.)
EAI	715	0.35 (0,07)
VOL	431	4.97 (1,43)
CONC	431	1221 (310,25)
NSPZ	431	5.95 (1,97)
MM	431	4.11 (0,45)
IM	431	83.54 (6,16)
PTM	431	48.68 (9,44)
SDF_0	199	3.34 (2,32)
SDF_6	199	3.59 (2,33)

1990 – 2007
42348 ejaculates

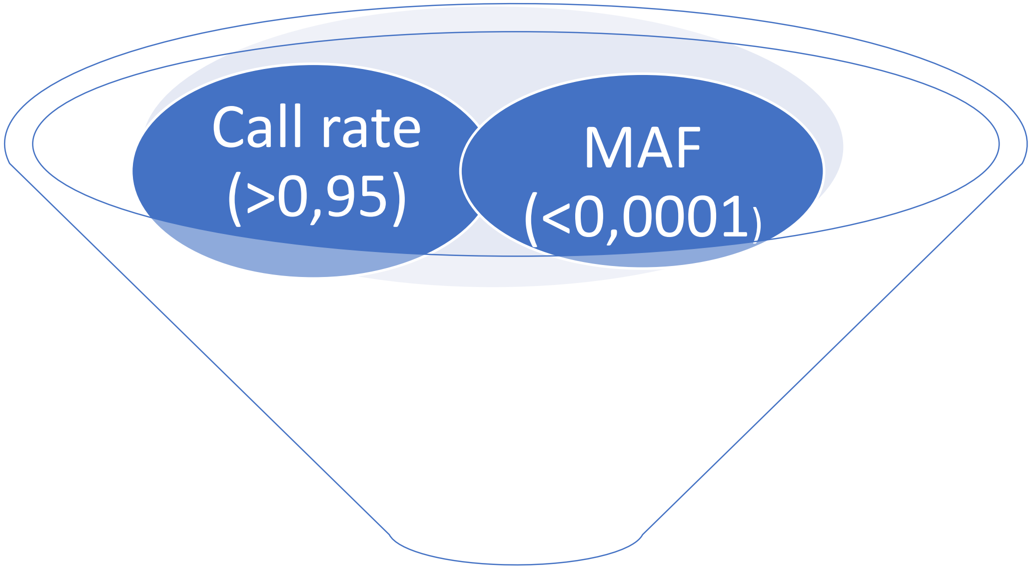
INIA, Madrid, Spain
Project RTA2007-0071



1206 straws

Material: *Genotypes*

Data – Genotypes: BovineSNP50 v3
DNA Analysis BeadChip (CONAFE)



51048 EAI
46648 SEMEN QUALITY TRAITS
45694 SDF

Methods: *Regions & candidate genes*

GWAS

- Linear mixed model association (MLMA).
- Leaving one chromosome out (LOCO).

$$y_{ij} = a + b_{ik}x_{jk} + g_{ij} + e_{ijk}$$

- GCTA Software (Yang et al., 2014).
- Significance (FDR<0,1).

POSITIONAL CANDIDATE GENES

- Bovine assembly UMD 3.1
- 1 Mb regions around each significant SNPs

FUNCTIONAL ANALYSIS

- (DAVID v6.7)

Methods: *Association between traits*

LINKAGE DISEQUILIBRIUM (LD)

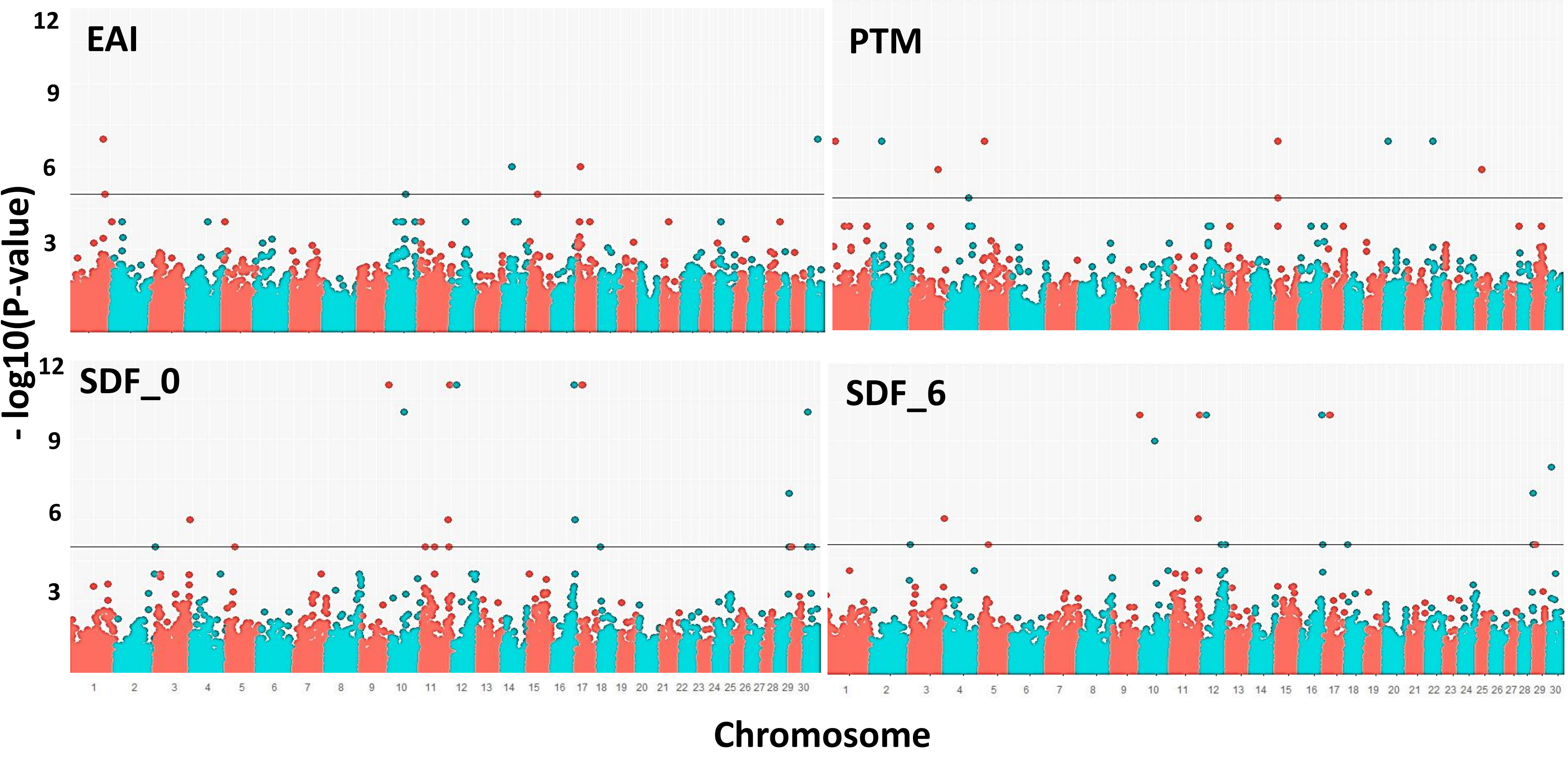
- PLINK 1.9 toolset (Purcell et al., 2014).

PLEIOTROPY

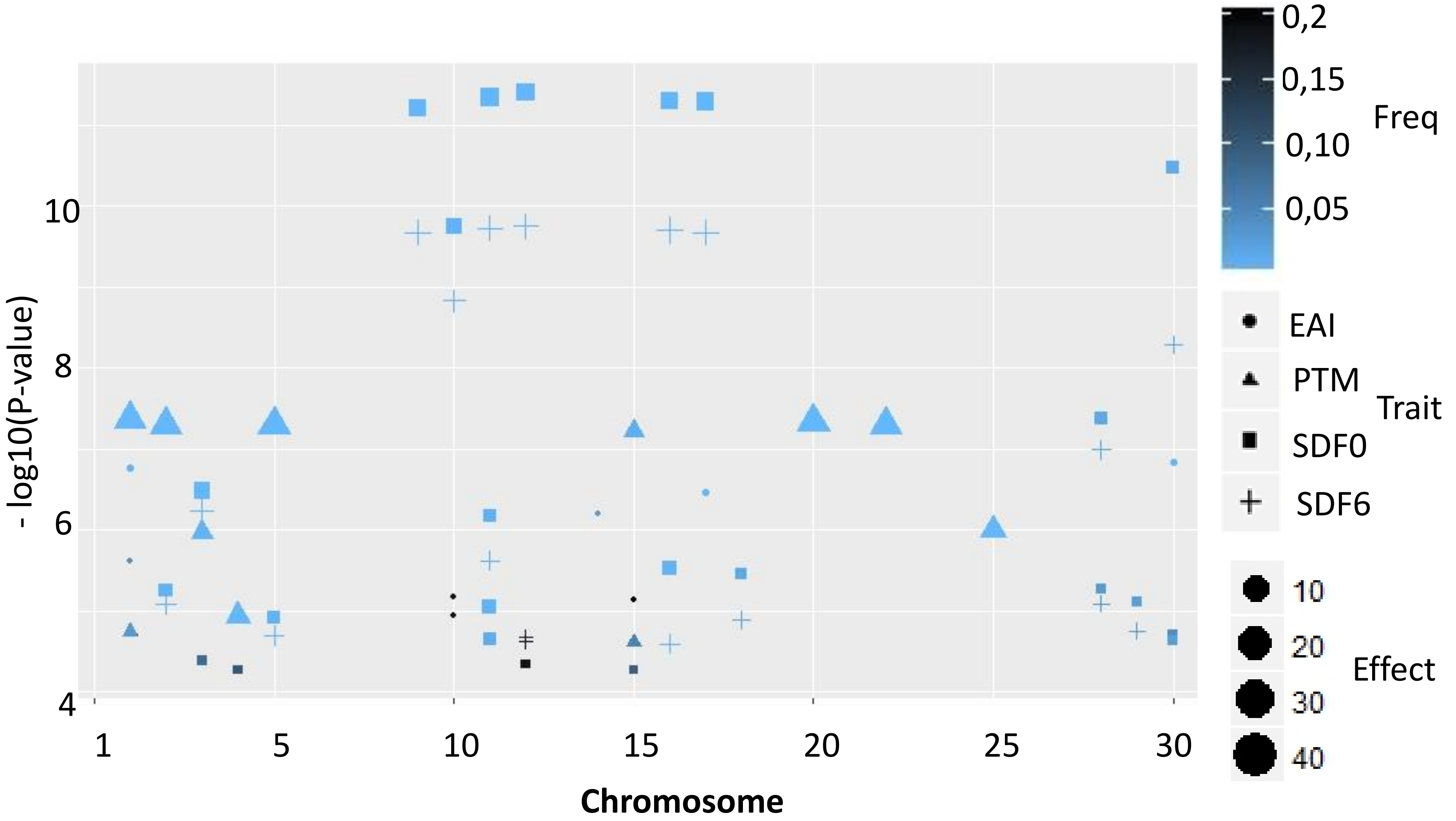
- Mendelian randomization. Test the putative causal associations (Zhu et al., 2018).

Results: *Manhattan plots for male fertility traits*

EAI	PTM	MM	IM	SDF_0	SDF_6
8	12	1	3	26	19



Results: *Freq & Effect of significant SNPs*



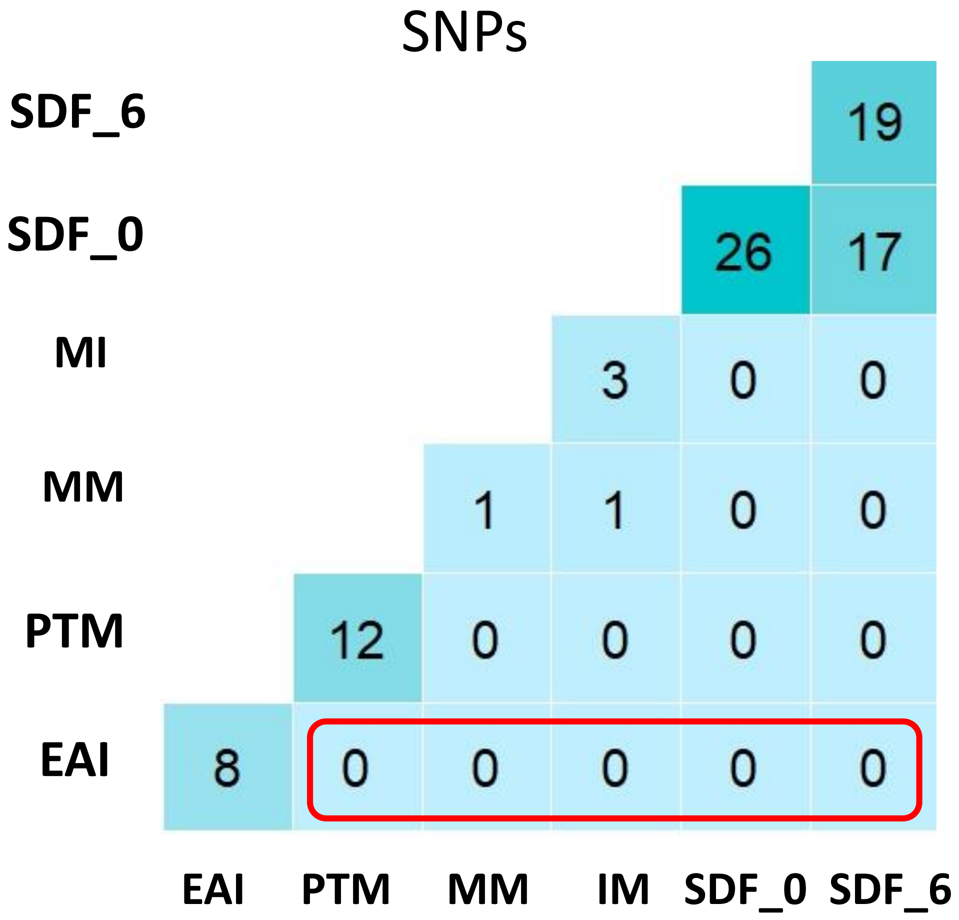
Results: *Genes and Pathways of male fertility*

EAI	PTM	MM	IM	SDF_0	SDF_6
52	28	1	7	228	166

Pathway	GENES
Aquaporin-like	*AQP10, AQP2, AQP5, AQP6*
Calcium-binding	*S100A1, S100A1 , CLSTN2, CRB2, DYSF, PCDH18, SYT14, SYT15*
Ion transport	*ATP6V1B1, FXYD6, ASIC1, CHRNB2, GRID1, KCNH1, SCN2B, SCN4B, SLC39A1, SLCO2A1, TF*
RNA-binding	*ADAR, MTRF1, STRBP*
Ubiquitin	*HERC1, ANAPC13, UBE2F, UBE2Q1 UBE4A*
Embryonic development	*ADAR, BMPR1A, CCNB1, FLVCR1, SLC39A1, TMEM231*
Zinc finger	*WBP4, ZNF638*

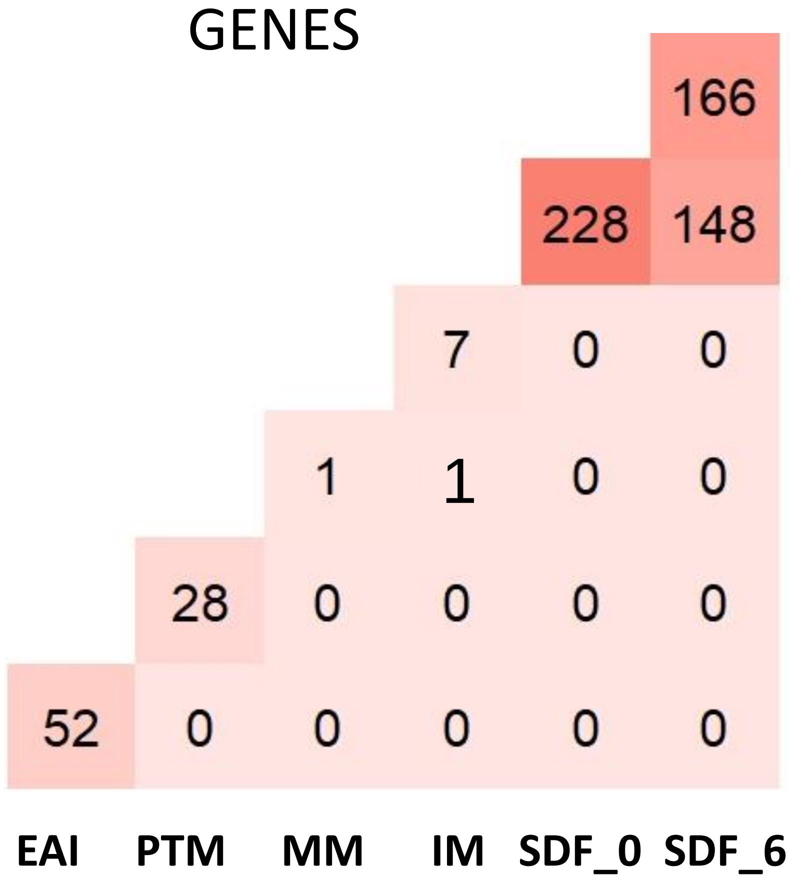
Results: *Association between traits*

Number of significant SNPs and GENES associated with each trait (diagonal) and shared between traits (off-diagonal).



SNPs

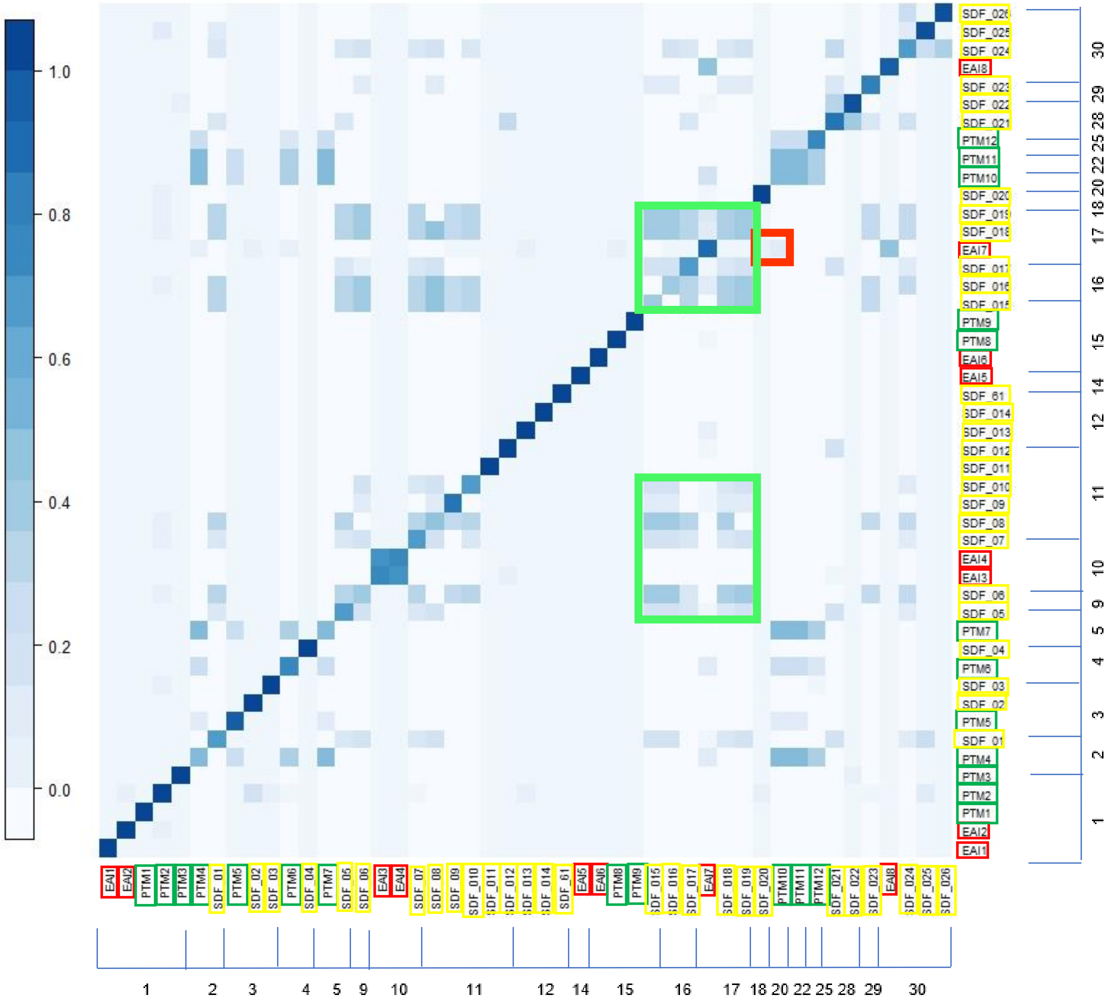
	EAI	PTM	MM	IM	SDF_0	SDF_6
SDF_6						19
SDF_0					26	17
MI				3	0	0
MM			1	1	0	0
PTM		12	0	0	0	0
EAI	8	0	0	0	0	0



GENES

	EAI	PTM	MM	IM	SDF_0	SDF_6
						166
					228	148
				7	0	0
			1	1	0	0
		28	0	0	0	0
	52	0	0	0	0	0

Results – *Linkage disequilibrium?*



Results – *Pleiotropy?*

MR analysis by exploiting GWAS summary data.

Trait*	***p* (x)** **<5e-4**	***p* (x+y**)** **<5e-4**	**LD** **<0,1**	**Pleiotropy** **< 0,05**	**analysis**	**b $_{xy}$**	**se $_{xy}$**	***p* $_{xy}$**
PTM	334	58	28	0	28	0.14	0.05	0.003
IM	294	28	22	1	21	0.03	0.05	0.454
MM	308	37	10	1	26	0.14	0.04	0.001
SDF_0	312	62	22	1	21	-0.04	0.05	0.443
SDF_6	258	46	17	0	17	-0.116	0.07	0.105

* Semen quality traits (x), ** Male fertility (y)

Conclusions

- We have found SNPs associated with the fertility of the male located in or near genes directly involved in the process of spermatogenesis and fertilization.
- A functional analysis has helped to propose functional candidate genes for bull fertility.
- The results suggest the existence of both pleiotropy and LD as background for the estimated correlations between EAI and semen traits, although more information would be needed to obtain more knowledge about the relation between these traits .

Acknowledgments

efrife

euskadiko frisoi federakuntza

aberekin

CONFEDERACION DE ASOCIACIONES DE FRISONA ESPAÑOLA

CONAFE

MEDGAN

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