

THE “SNPLAIT” PROJECT
*TOWARD AN EXTENSION OF THE FRENCH
MAS PROGRAM TO SMALL POPULATION
SIZE DAIRY CATTLE BREEDS*

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INTRODUCTION

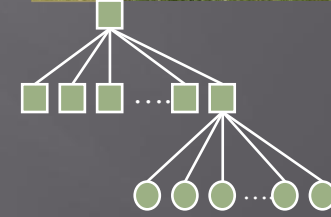
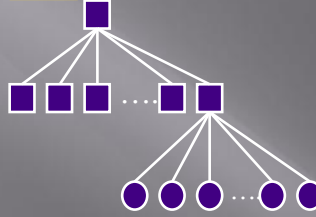
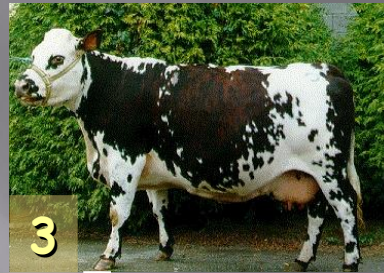
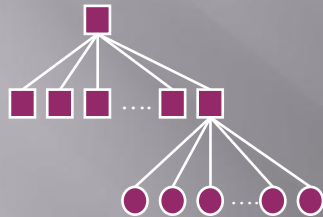
- ▣ The promise of genomics in assisting selection
- ▣ Identification of loci underlying traits of interest
 - Difficulties in small size breeds to define powerful mapping experiments
- ▣ Some solutions:
 - Identify regions on which selection has acted (signatures of selection):
 - ▣ Need to relate observed signals to a phenotype
 - Validate « candidate QTL »
 - ▣ From results in breeds where powerful design are available

Rationales for the « candidate QTL » approach

- ▣ Cattle breeds share a common history until very recently
- ▣ Common variant hypothesis:
 - QTL are underlied by common variants *i.e.* rather old (before breed formation)
- ▣ Variants identified in one breeds are expected to segregate in several others breeds
 - For neutral variant: most SNP polymorphic in one breed are in several other even distantly related (*e.g. Gautier et al., 2007a*)
 - This might also be true for a causal variant:
 - ▣ ex: DGAT1 K232A polymorphism has been characterized in several cattle breeds (*e.g. Grisart et al., 2004; Kaupe et al., 2006; Gautier et al., 2007b*)

The French QTL program starting point

(Boichard et al., 2003)



Sires

Sons

Granddaughters

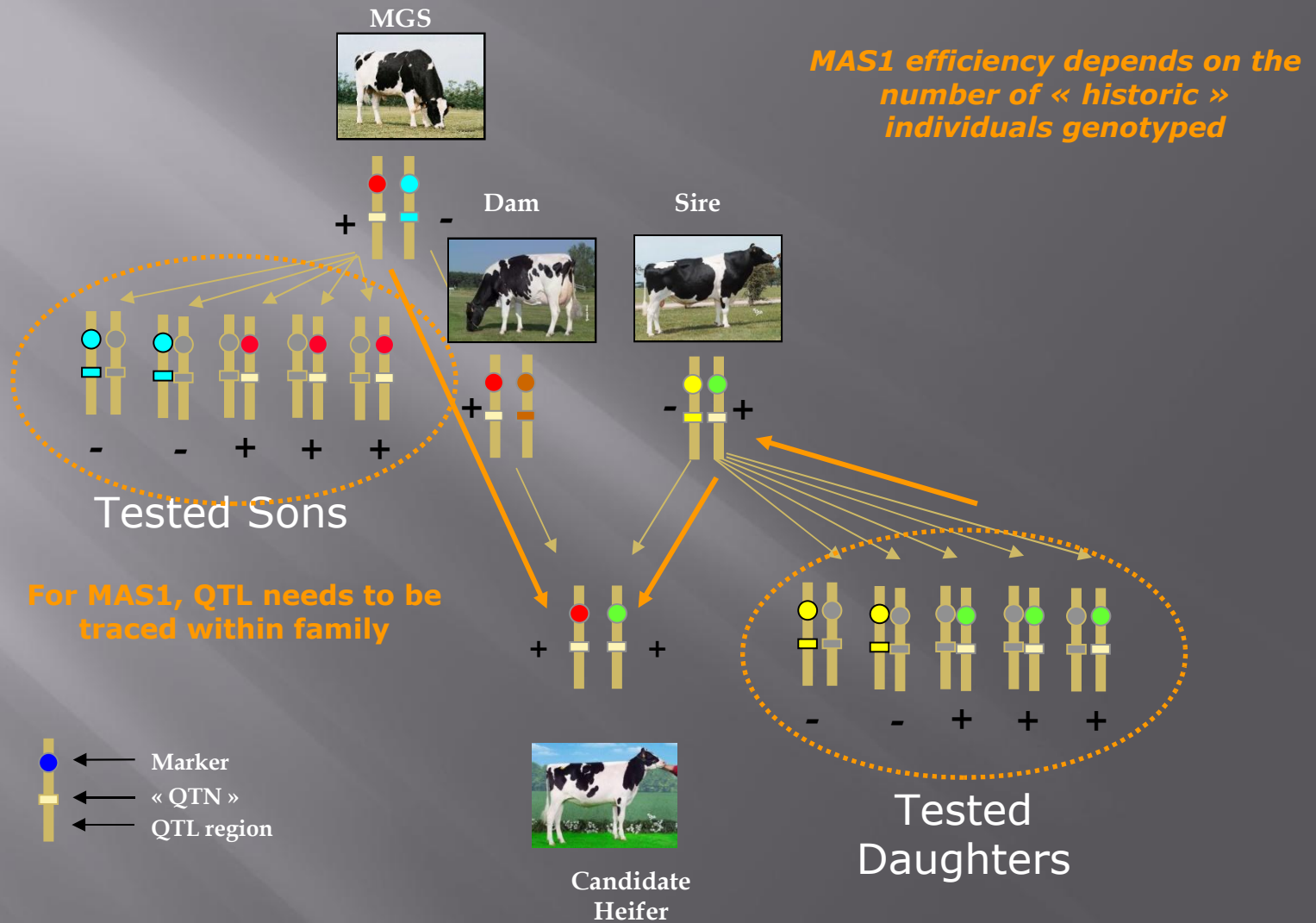
- 14 families, 1568 AI bulls
- 25 traits : production, fertility, mastitis resistance, milking speed, persistency, type ...
- Genome scan with 169 markers
- Analysis performed by Interval mapping using regression of bulls performances on their genotypes
- ↳ QTLs detected for all traits
- ↳ 120 QTLs were detected

<u>Trait</u>	<u>Chromosome</u>
• Production	7, 11, 14, 19, 26
• Milk Composition	3, 6, 14, 18, 20
• Persistency	11
• Mastitis resistance	10, 15, 21
• Fertility	1, 7
• Milking speed	6, 8, 13
• Udder shape	2, 9, 11, 12, 13, 14, 17, 18, 19, 20, 28
• Teat length	2, 21, 27, 28
• Stature	2, 5, 6, 9, 11, 13, 24
• Legs	7, 15
• Pump	1, 5, 6, 8, 13, 19, 20

A first application of the QTL program results

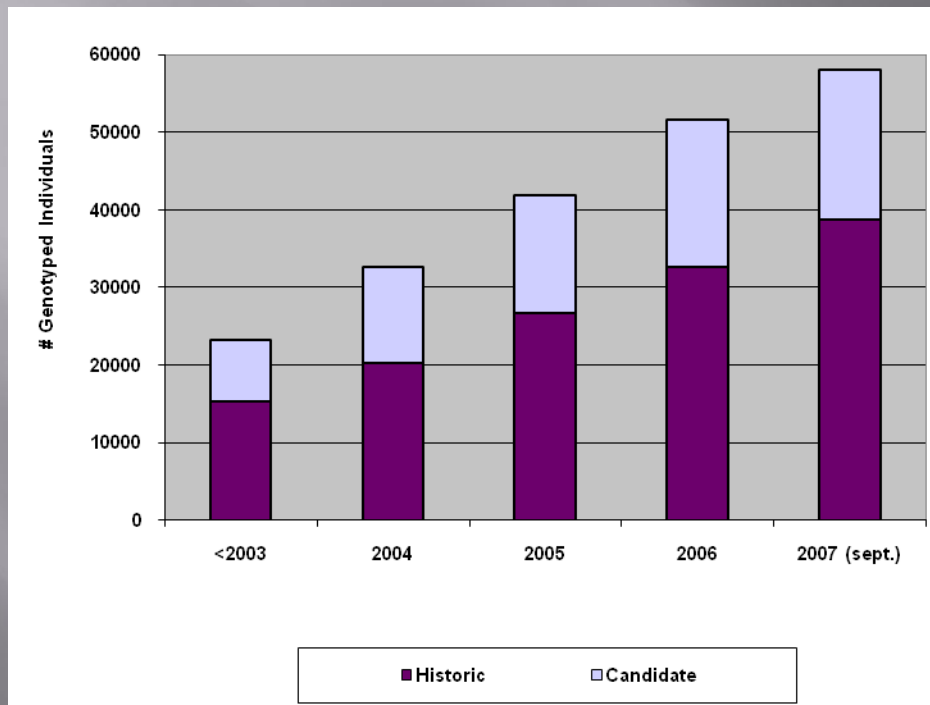
- ▣ The French MAS program :
 - Begun in 2000 (Boichard et al., 2002)
 - Second 3 year contract (between INRA, Labogéna and AI industry)
- ▣ 14 chromosomal regions selected
 - According to previous studies (mainly French QTL program)
 - Containing at least one QTL underlying production, milk composition, mastitis resistance (~SCS), female fertility
 - traced with 45 microsatellite markers
- ▣ Individual genotyped (10,000 genotypes per year) :
 - Candidates (young bulls, females before first lactations)
 - “Historic animals” to better estimate QTL allele transmission and effects

MAS1 Principle



MAS1 BV = Polygenic Effect + ● effect + ● effect

The French MAS1: First Results (2001-2007)



- **60000** genotyped individuals (coordination among the partners of the program has continuously improved)
- **45** microsatellite markers (14 QTL regions ~20% of the genome)
- **1/3** individuals without phenotypes
- Most QTL confirmed: 30 to 40% of the genetic variance is explained by 3-5 QTLs
- **8** traits evaluated each month (MAS BV)

Gain in Efficiency: An example

of tested AI candidate bulls to obtain the same genetic improvement as compared to a classical genetic selection program (150 sires in MON, 130 in NOR and 500 in HOL)

	MO		NO		PH	
Trait	#	%	#	%	#	%
MY	138	-8.0	109	-16.2	415	-17.0
FY	130	-13.3	108	-16.9	404	-19.2
PY	128	-14.7	111	-14.6	438	-12.4
FP	120	-20.0	102	-21.5	421	-33.0
PP	131	-12.7	114	-12.3	436	-18.0

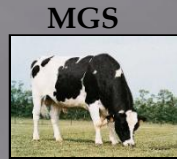
The 1st Generation MAS: some limits...

- ▣ Only 14 regions considered
 - (<20% of the genome)
 - What about not yet characterized regions?
- ▣ QTL are very broadly characterized (CI>20 cM)
 - It is necessary to use within-family information (genotyping a lot of related individuals)
- ▣ Implemented only in large cattle breeds
 - Large families are needed to validate QTL effects
 - Difficult to extrapolate results to small size breeds

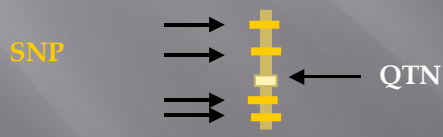
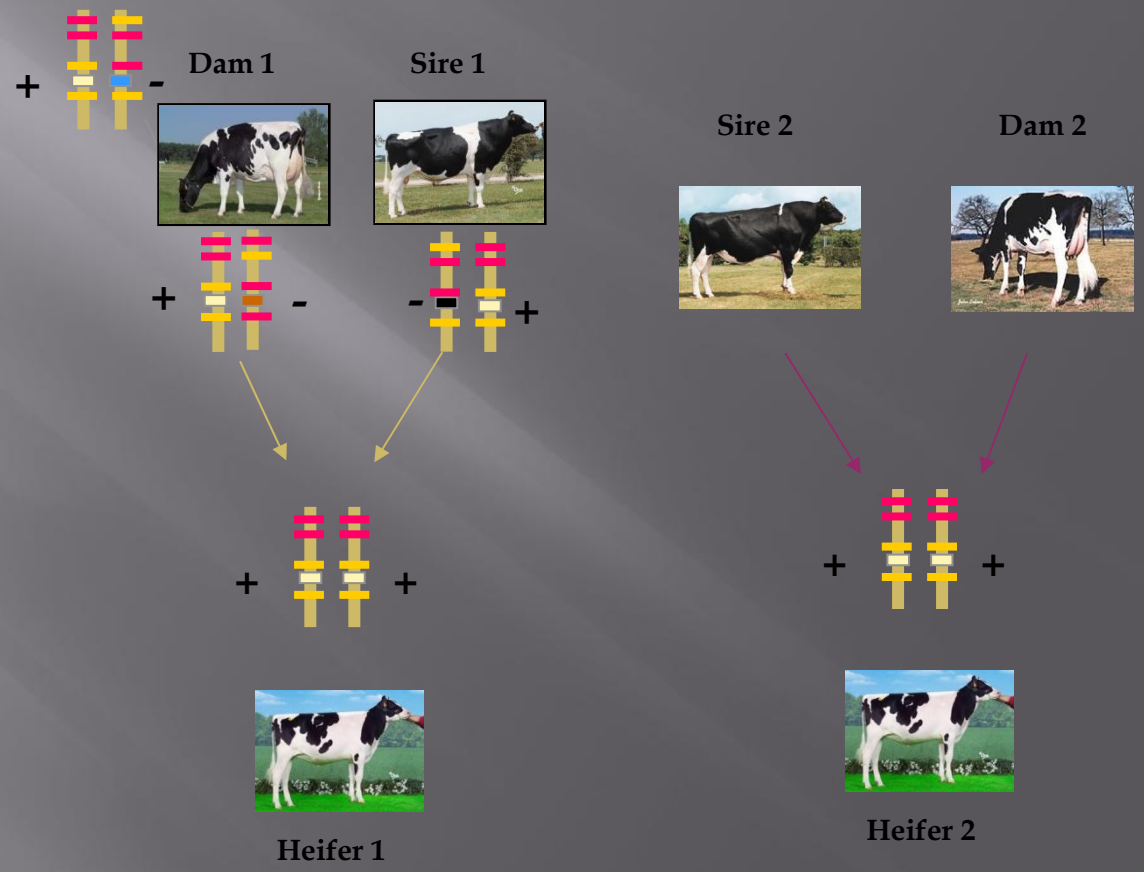
Towards a 2nd Generation MAS

- ▣ Prerequisite:
 - Refining QTL locations to identify and characterize the effects of haplotype on a population-wide basis
 - Technically: high throughput genotyping methods available
- ▣ MAS2 Principle:
 - Direct selection of haplotype of interest according to their effects
- ▣ Advantages
 - Gain in efficiency: Less individuals need to be genotyped (no need to genotype related « historical » individuals)
 - Extension to other breeds is now possible

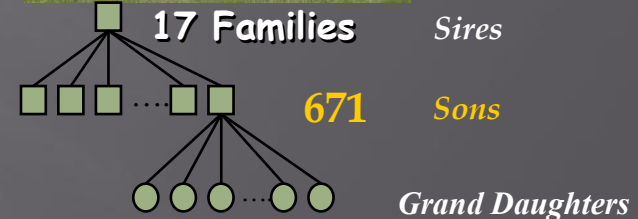
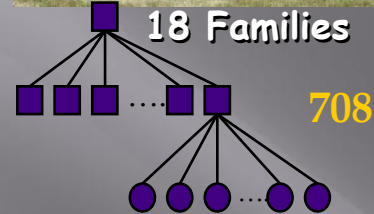
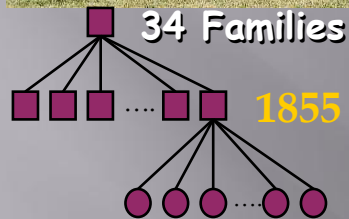
MAS2 principle



MAS2 is much more simple and efficient in particular within small families



The French Fine Mapping Project (2006-2008)



- ▣ ~3200 sons originating from the MAS1 program
- ▣ >50000 SNP genotyped
 - ▣ *Illumina Bovine50K chip + 50 SNPs within 18 candidate genes*
- ▣ (Fine) Mapping of QTL underlying >20 traits
 - ▣ *Milk, disease resistance, conformation, fertility...*
- ▣ MAS2 Application:
 - ▣ *The MAS2 SNP chip: Selection of the 1536 most relevant SNPs*
 - ▣ *Tracing the most informative haplotypes*

« SNPLAIT » Project

- ▣ 5 local breeds selected to validate the MAS2 chip:
 - ~250 (phenotyped) cows sampled (~25 per sire) per breed:
 - ▣ Milk collected (50 mL)
 - ▣ DNA extracted from somatic cells (~1 μ g)
 - ▣ Whole Genome Amplification (GenomiPHI)
- ▣ Genotyping of the 1536 MAS2 SNPs
- ▣ Analysis
 - Haplotype characterization
 - Identification of original haplotypes
 - Association analysis to evaluate within breed effects

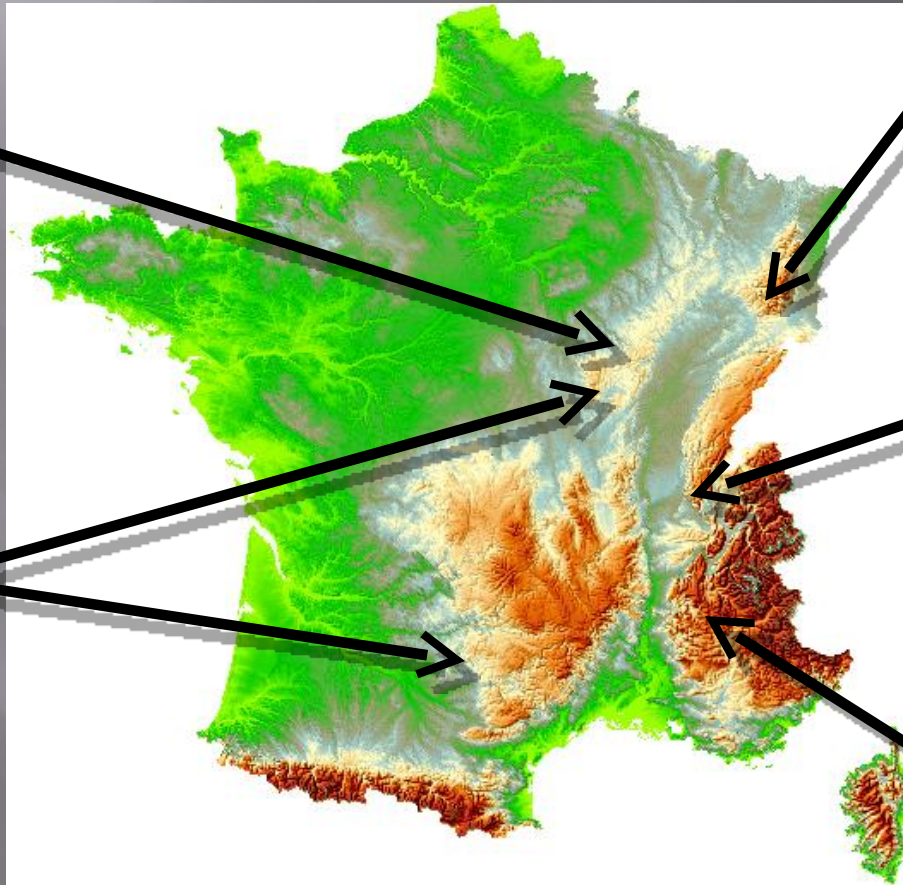
Characterization of the MAS regions in 5 local french dairy breeds



Simmental Française



Brune



Vosgienne



Abondance



Tarentaise

Breed characteristics

Breed	# Cows (x1000)	Milk Production (kg)	Fat Percentage (‰)	Protein Percentage (‰)
<i>Holstein</i>	2,850	10,300	40.0	33.5
<i>Normande</i>	810	6,200	43.4	35.4
<i>Montbéliarde</i>	710	6,200	38.6	34.1
Abondance	65	6,100	37.3	34.8
Brune	32	7,200	39.3	34.5
Simmental	30	6,900	40.2	34.9
Tarentaise	14	4,700	36.1	33.7
Vosgienne	8.5	3,500	37.5	33.3

CONCLUSIONS

- ▣ For small size breeds:
 - Difficult to design powerful QTL mapping design
 - Possible to benefit from history of the breeds and close relationships with large size breeds
- ▣ Phenotype based approach:
 - Validation of the fine mapping experiment performed in 3 breeds
 - Association based analysis of candidate regions
- ▣ Another promising approach (« phenotype-free »)
 - Identification of signatures of selection...
 - 50000 SNPs chip is currently genotyped on a sample of more than 30 breeds

Acknowledgements

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