Identification of recessive genetic defects in the Abondance cattle breed using routine genotyping and life history information

Clémentine ESCOUFLAIRE[1,2], Chris HOZE[1], Mekki BOUSSAHA[2], Anne BARBAT[2], Sophie AGUERRE[2,3], Florian BESNARD[1,2], Maxime BEN-BRAIEK[2], Didier BOICHARD[2], Gilles FOUCRAS[4], Sébastien FRITZ[1,2], Aurélien CAPITAN[2]

[1] ELIANCE, 149 rue de Bercy, 75012 Paris, France, [2] Université Paris-Saclay, INRAE, AgroParisTech, GABI, 78350 Jouy-en-Josas, France

[3] IDELE, 149 rue de Bercy, 75012 Paris, France, [4] IHAP, Université de Toulouse, INRAE, ENVT, 31076 Toulouse, France

INTRODUCTION

Objective: Search for overlooked genetics defects in a regional breed to improve fertility, and minimize economic losses and unproductive periods

How:
Using two reverse genetics approaches designed to identify *loci* causing embryonic lethality and juvenile mortality without any specific or visible phenotype

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Screening of genetic defects in a local breed

MATERIAL AND METHODS

Homozygous Haplotype Deficiency: (Fritz *et al.,* 2013)

Compare the number of observed individuals homozygous for 20 markers window vs. expected based on ancestors' genotypes

Haplotype enrichment / depletion approach: (Besnard *et al.,* 2024)

An extension of the above, in which haplotypes are tested for both enrichment in a case group and depletion in a control group

Search for candidate variants:

Haplotype x variant correlation for 4,827 animals across 54 breeds
Annotation with *VEP* and effect prediction (MGI, OMIM, etc.)
Filter: breed specific damaging variant with R^2>0.5

Phenotype characterization:

Effect on fertility and survival in at-risk versus control mating

RESULTS AND DISCUSSION

Embryonic mortality
Haplotype deficiency analysis

Population: 28,791 genotyped with BovineSNP50K

Haplotype:
Chr19, 18 Mb

	Observed	Expected	Variation
Pop.	0	122	-100%

Causal mutation: a frameshift variant, position
Chr19 g.18244098_18244099insT in the *UTP6* gene
UTP6 interacts with APAF1
The apoptotic protease activating factor 1 is the main component of the apoptosome, and a crucial factor in the mitochondria-dependent death pathway

Mutation allele frequency: 0.07 (total animals: 21,253)

Large scale genotyping using custom probes:

Non-carriers	Carriers	Homozygous	Expected Homozygous
17,578	3,324	0	132

Phenotype characterization: Fertility traits

Trait	Number of matings		Effet on fertiliy	
	non-risk	At-risk	Loss	Pr >|t|
CR	16,381	400	-0.12	<.0001
NRR56	16,381	400	-0.15	<.0001

Two novel genetics defects identified and characterized

Juvenile mortality
Haplotype enrichment / depletion approach

Population: 559 dead heifers and
3,298 cows that survived 300 days after calving

Haplotype:
Chr4, 12Mb

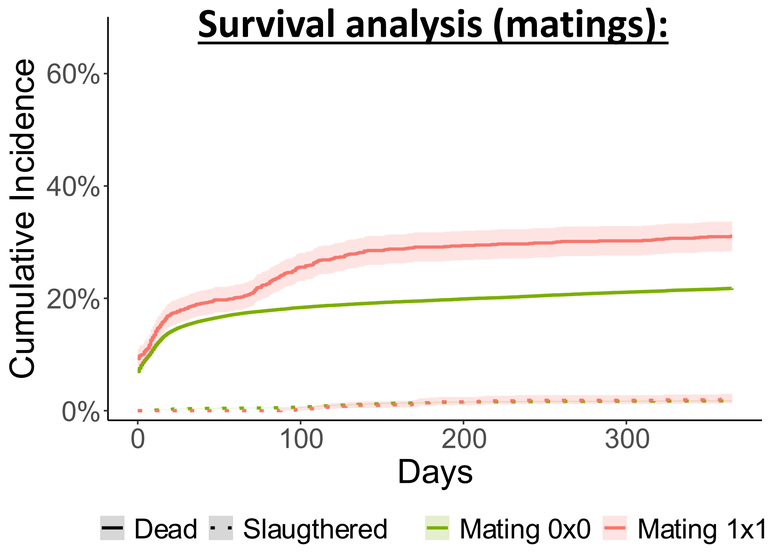
	Observed	Expected	Variation
Dead	41	10	+291%
Controls	5	18	-73%

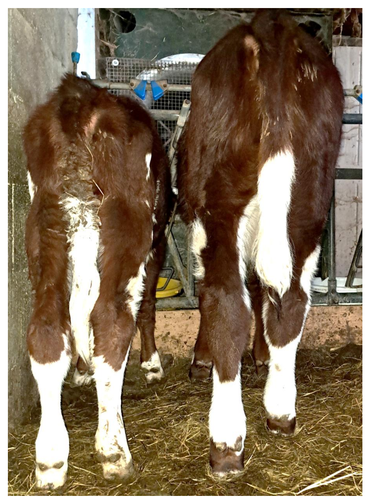
Causal mutation: a splice donor variant, position
Chr4 g.13551718delC in *SLC25A13* gene
Associated with Type 2 citrullinemia in humans

Mutation allele frequency: 0.08 (total animals: 14,290)

Phenotype characterization:
Death between 1-9 months of age
First examination of 5 cases shows coherent signs with severe hepatic dysfunction

Survival analysis (matings):





Case | Control

CONCLUSION

- **Genetic screening** is now routinely performed as part of genomic evaluation
- This work highlights the usefulness of a **reverse genetics** approach to identify genetic defects
- This is particularly critical in regional breeds, where higher inbreeding levels and smaller effective population sizes can make the impact of such defects can be more severe. Early detection and management are therefore essential to preserve genetic health and breed sustainability

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MINISTÈRE DE L'AGRICULTURE ET DE LA SOUVERAINETÉ ALIMENTAIRE

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