OPTIMAL AND PRACTICAL STRATEGIES TO MANAGE AN OVULATION RATE MUTATION LOCATED ON THE X CHROMOSOME IN A FRENCH SHEEP BREED

J. Raoul[1,2,3], L. Bodin[2], J.M. Elsen[2] and A.A. Swan[3]

[1] Institut de l'Elevage, Castanet-Tolosan, France
[2] GenPhySE, INRA, Castanet-Tolosan, France
[3] Animal Genetics and Breeding Unit[*], University of New England, Armidale, NSW 2351

SUMMARY

In French sheep breeding programs, several mutations affecting ovulation rate have been discovered. For mutations located on the X chromosome, the optimal management of such genes is still a challenge because nucleus flocks are small compared to Australian or New Zealand ram breeding flocks. A deterministic model was developed, and using sequential quadratic programming methodology, the combination of mating types that maximized the profit across a range of genotype costs was determined. Results show that even if losses of genetic gain were quite high compared to the gain without the major gene, the optimal use of an ovulation rate mutation located on the X chromosome was beneficial. At the current costs, the optimal strategy that gave the maximal profit was based on four different mating types. A strategy based on only the use of carrier females mated to non-carrier males gave similar results to the optimal strategy in terms of profit and genetic gain. This strategy could be adopted by French breeding programs where this kind of mutation segregates.

INTRODUCTION

The number of lambs produced per female has a large impact on profitability in meat oriented sheep production. Several mutations affecting ovulation rate, and thus number of lambs, have been identified. For example, Booroola (Piper and Bindon 1982; Davis *et al.* 1982), BMP15-Inverdale (Davis *et al.* 1982) or BMP15-Grivette (Demars *et al.* 2013), and GDF9-Cambridge (Hanrahan *et al.* 2004). Most often, these polymorphisms have a positive effect on heterozygous carrier productivity. However, in homozygous ewes, these polymorphisms lead to sterility or excessive prolificacy and high rates of neonatal lamb mortality. Therefore homozygous females are undesirable for commercial production.

Several strategies can be implemented to manage these mutations, as outlined by Amer *et al.* (1998) for mutations carried by the X chromosome (i.e. Inverdale gene) and Raoul *et al.* (2017) for mutations carried by an autosomal chromosome: the proportion of each parental genotype is defined according to the sex and matings organised. These balance high frequency of heterozygous females with genetic gain. Increasing the frequency of heterozygotes leads to a change in the proportion of available candidates which affects the overall selection differential of parents and consequently genetic gain. Amer *et al.* (1998) assessed two strategies to manage the Inverdale gene and found that depending on the strategy implemented, the loss of genetic gain was either 24%, or less than 5% compared to the gain without major gene. In the case of an autosomal polymorphism, strategies that enhance either genetic gain or heterozygous female frequency gave equal profit (Raoul *et al.* 2017) and were affected by the genotyping cost per animal.

In the French meat sheep production context, the average number of ewes per nucleus flock is about 300. With such limited flock sizes implementing a strategy which comprises a small proportion of a given mating type (less than 10%) is difficult. It is not practical at a single flock level, but could be organized via specialization of several nucleus flocks in which different flocks

---

[*]AGBU is a joint venture of NSW Department of Primary Industries and the University of New England

focus on a specific mating. This is difficult to co-ordinate, so for practical reason, French breeders would much prefer strategies based on at most two mating types. Strategies outlined for autosomal mutation management have already been discussed for French breeding programs (Raoul *et al.* 2017). The aim of this study is, for the case of a mutation carried by the X chromosome, to determine the combination of mating types that provide the maximal profit (optimal strategy) according to various genotyping costs. This optimal strategy will be compared with more practical strategies in terms of profit and genetic gain.

MATERIALS AND METHODS

A nucleus population representative of a typical French breeding program based on natural mating was modelled. A maternal production trait expressed once per year during female's reproductive life was considered as the only selected trait (*e.g.* milk production estimated through lamb weight at 30 days). Each year, 8000 ewes were mated to 200 rams. Because homozygous carrier females were not used for reproduction, 2 genotypes, non-carriers and carriers were respectively considered for males ([+] and [m]) and females ([++] and [m+]) leading to 4 mating types: 1) ♀ [++] x ♂ [+], 2) ♀[++] x ♂ [m], 3) ♀ [m+] x ♂ [+] and 4) ♀ [m+] x ♂ [m]. As the flock management was assumed to be in a steady-state, the proportion of each mating type across time was constant. The newborn candidates were divided into categories according to their parental genotypes (*i.e.* 4 matings), their sex and their own genotype (2 genotypes for males and 3 genotypes for females). Generations were overlapping and the maximum reproductive life was 6 years for males and females, with a maximum parity of 5 (i.e., from 2 to 6 years of age), leading to a replacement proportion close to 24%.

At each generation, new parents were selected within sex*genotype categories by truncation selection on EBVs: 4 truncation thresholds (2 per parental genotype) were determined across the candidate EBV distributions. For example, [++] female replacement were selected from progeny of mating types 1 and 3. Considering dam parity, these female were selected across 10 EBVs distributions. Whatever their parental genotype or dam's age, we selected females whose EBV was above the unique truncation threshold. Given those thresholds, selection differential and genetic contribution to the next generation (*i.e.* probability of gene origin) were calculated for each candidate category. Evolution of genetic values of parents and their progeny across time for the maternal trait was derived using the gene flow methodology proposed by Hill (1974): a transition matrix representing the gene flow from categories at year t to categories at year t+1 was built from genetic contributions to newborns and accounting for ageing of parents.

Discounted revenues and costs were computed for each cycle (year). The revenues were proportional to the number of lambs sold per year which was equal to the number of live lambs produced minus the number selected for replacement, and the number of live lambs produced by ewes transferred to a commercial flocks. The costs included genotyping costs made at the nucleus level and proportional breeding costs per ewe (nucleus and transferred ewes). It was assumed that 50% of newborn females would still be available after parent selection, and these surplus females would be transferred to a commercial flock where they could be retained for up to 5 parities. These female were not genotyped and only females from mating types 1, 2 and 3 were transferred. It was assumed that independently of their genotype, the selected maternal trait was related to the cost per ewe, because the trait was determined based on milk production, with higher production levels reducing feed costs per lamb. The overall profit was computed as the sum of discounted revenues minus costs over a long-term time horizon (year 5 to year 30). This overall profit was assessed for the following sets of parameters: number of lambs produced = 1.5 for non-carrier females, and +0.5 additional lambs for heterozygous females. Given the fertility, the lamb viability (higher for lambs born from non-carrier), the number of lambs weaned per ewe joined for non-carrier and carrier ewes were 1.22 and 1.44 respectively. The income per lamb sold was assumed to be constant and the

production cost per lamb depended on the dam's genetic value for the selected trait and genotype. Three genotyping costs were tested: no cost, 10 and 20 € per genotyped animal.

For a given genotyping cost, the relative proportion of mating types that gave the maximum profit (the optimal strategy) was determined using an algorithm based on sequential quadratic programming methodology. The gain in the absence of the major gene and two simplified strategies was also assessed based on 1 mating only, ♀ [m] x ♂ [++] (S1, corresponding to the "self-sustaining scheme" outlined by Amer (1998)) or 2 mating types, ♀ [++] x ♂ [m] and ♀ [m+] x ♂ [+], (named S2). The proportion of each mating types of these strategies is shown in Table 1.

Table 1. Proportion (%) of each mating type of alternative strategies assessed for the management of an ovulation rate mutation[1] located on the X chromosome

Mating type	♀[++]x♂[+]	♀[++]x♂[m]	♀[m+]x♂[+]	♀[m+]x ♂[m]
Gain without major gene	100	0	0	0
S1	0	0	100	0
S2	0	60	40	0

[1] Biallelic locus (X chromosome) influencing the number of lambs per female (1.5 for [++] and 2.0 for [m+]).

RESULTS AND DISCUSSION

Table 2 gives the proportion of each mating type in the nucleus that maximizes profit according to the genotyping cost. Results show that when genotyping costs were not included (cost=0), the best strategy was to bred only carriers females and mate them to non-carrier males.

Table 2. Percentage of each mating type in the optimal strategy to manage an ovulation rate mutation[1] located on the X chromosome, according to three genotyping costs (€)

		Mating type			
	genotyping costs	♀[++]x♂[+]	♀[++]x♂[m]	♀[m+]x♂[+]	♀[m+]x ♂[m]
optimal strategy	0	0	0	100	0
	10	21	49	12	18
	20	39	57	0	4

[1] Biallelic locus (X chromosome) influencing the number of lambs per female (1.5 for [++] and 2.0 for [m+]).

For a genotyping cost equal to 10 €, the optimal strategies combined the 4 mating types. The main mating type was non-carrier females mated to carrier males (49% of all matings). In this strategy 30% of the nucleus females were carriers. For a genotyping cost equal to 20, the proportion of non-carrier females mated to carrier males reached 57%. The proportion of carrier females in the nucleus reduced to 4% which corresponded to the minimum requirement to replace carrier males and produced heterozygous females transferred to commercial flocks.

Table 3 shows the genetic gain achieved by the nucleus for all strategies assessed, the genotyping requirements, the frequencies of heterozygous females (nucleus and transferred) and the profit. Apart from the heterozygous frequencies, all results are expressed relative to values obtained for the optimal strategy when there was no genotype cost (=100 in the first row of Table 3).

Results show that when genotyping costs were not included, the optimal strategy maximized the heterozygous female frequency in the nucleus. In this case, a proportion of m+ females were selected for the nucleus, whereas all ++ females were available for transfer. This lead to a reduction in the heterozygous frequency of transferred females to 24%. When genotyping costs were included, the strategy maximized the heterozygous frequency of transferred females. In this case, mating type 2 (♀[++]x ♂[m]) which produces m+ females without genotyping was used, allowing production of heterozygous females to be transferred to a commercial flock. For a moderate genotyping cost (10€),

the number of genotyping remained at a significant level and allowed implementation of a strategy providing a substantial genetic gain. For a high genotyping cost, the number of genotypes was very low and limited to genotyping male progeny of the mating ♀[m+]x ♂[m] only, implemented to replace male carriers. Even if this mating produced homozygous carrier females which were culled, it allowed a higher genetic value of carrier males and a higher genetic gain compared to the use of the mating ♀[++]x ♂[m] This strategy maintained the high proportion of heterozygous females transferred to a commercial flock and limited losses in genetic gain.

Table 3. Genetic gain, genotyping needs, heterozygous female frequencies and profit of various strategies according to the genotyping costs (€)

	Geno. Costs	Genetic gain[1]	Genotyping requirements[2]	Het. freq (nucleus)	Het. freq (transferred)	Profit[3]
	0	100.0	100	1.00	0.24	100.0
Optimal strategy	10	100.4	27	0.29	1.00	79.1
	20	85.1	4	0.04	1.00	74.6
Gain without major gene	-	125.4	0	0.00	0.00	72.5
S1[4]	0	100.0	100	1.00	0.20	100.0
	10	100.0	100	1.00	0.20	77.1
	20	100.0	100	1.00	0.20	54.2
S2[5]	0	103.5	59	0.40	1.00	85.8
	10	103.5	59	0.40	1.00	72.4
	20	103.5	59	0.40	1.00	58.9

[1] 100=genetic gain obtained for the optimal strategy at null genotyping costs
[2] 100=number of genotype for the optimal strategy at null genotyping costs
[3] 100= profit obtained for the optimal strategy at null genotyping costs
[4] Simplified strategy based on one mating type ♀ [m] x ♂ [++]
[5] Simplified strategy based on two mating types ♀ [++] x ♂ [m] and ♀ [m+] x ♂ [+]

The genetic gains for the S1 and S2 strategies were similar to those obtained for optimal strategies, and losses of genetic gain ranged from 22 to 25%, compared to gain without the major gene, similar to the results obtained by Amer *et al.* (1998). Profit obtained for S1 was higher than S2 except at the high genotyping cost. In this case, simple management of the mutation gave lower profit than its eradication. Given the current genotyping cost, approximately 10 €, S1 is a strategy which could be considered for French breeding programs. This strategy has quite high genotyping requirements (two genotyped animals per selected replacement) but results in profitability similar to the optimal strategy and a high productivity in the nucleus flocks. The use of a tool combining parentage assignment and mutation genotyping, which is available in France, would decrease the genotyping cost and make application the S1 strategy more attractive.

REFERENCES
Amer P.R., McEwan J.C., Dodds K.G. and Davis G.H. (1998) *Proc. NZ Soc. Anim. Prod.*, **58**: 157
Piper L.R. and Bindon B.M. (1982) *In the Booroola Merino*, **9**:20. CSIRO, Melbourne
Davis G.H., Montgomery G.W., Allison A.J., Kelly R.W. and Bray A.R. (1982) *NZ J. Agric. Res.* **25**: 525.
Demars J., Fabre S., Sarry J., Rossetti R., Gilbert H., Persani L., Tosser-Klopp G., Mulsant P., Nowak Z., Drobik W., Martyniuk E. and Bodin L. (2013) *PLoS Genetics* **9**:4
Hanrahan J.P., Gregan S.M., Mulsant P., Mullen M., Davis G.H., Powell R., Galloway S.M (2004) *Biol. Reprod.* **70**:900
Hill W.G. (1974). *Ani. Prod.*, **18**:117
Raoul J., Palhière I., Astruc J.M., Swan A.A. and Elsen J.M. (2017) submitted to *Animal*