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## 440. Management of undesired alleles at multiple loci for a goat breeding program

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### Abstract

As the number of discovered loci carrying undesirable alleles continues to increase, culling carrier animals is not an option. Thus, we used a method that derives a genetic value for each genotype at a given locus. Using stochastic simulations, we assessed various strategies for a goat breeding program that combined two selection criteria used in a preselection step and four mating strategies between sires and dams to produce candidates for artificial insemination. Even without a strategy dedicated to reduce undesirable allele frequency, lethal alleles were purged and their frequencies slowly decreased whereas the average frequency of non-lethal alleles remained constant. Using, in a preselection step, an index including the genetic values for loci likely to carry an undesirable allele, was an efficient alternative to reduce the frequencies of non-lethal alleles and gave higher decrease for lethal alleles frequencies. After selection, the ability to control the frequencies of undesired alleles was similar across mating strategies. However, some mating strategies, based on optimizing an objective function including at least genetic values and increased inbreeding, enable to reduce undesired alleles at no or small cost for both genetic gain and increase in inbreeding.

### Introduction

In sheep and goat selected populations, the number of discovered loci carrying undesirable alleles is growing, both including lethal (e.g. Ben-Braiek *et al.*, 2021) and non-lethal (e.g. Martin *et al.*, 2016) alleles. The control of known undesired alleles can be operated at a preselection step by culling carrier animals. This method becomes difficult to adopt due to the increase in the number of undesired alleles to be included. A selection criterion that incorporates both the estimated genetic values for selected traits and a set of genetic values associated to genotypes at these specific loci can be applied (Boichard *et al.*, 2016). The undesirable effects can also be controlled by optimizing mating strategies to avoid producing homozygous carriers as in Cole (2015). In French goat breeding programs, only a few matings are optimized at the individual level, i.e. those to produce male candidates for artificial insemination (AI).

Focusing on a breeding program for goats, we performed stochastic simulations to assess the annual genetic gain, the increase in inbreeding and the control of undesired alleles (known and unknown i.e. genotyped and not genotyped) according to various designs combining a preselection step and strategies to select and optimize matings that produce male candidates for AI. Two cases have been separately considered: lethal and non-lethal alleles.

### Materials & methods

Using a stochastic model, we mimicked the Saanen goat breeding program of the French Breeding Society Capgenes, where around 70, 000 females divided in 196 flocks are recorded each year for a maternal trait.

To set up a reference population for genomic selection we first applied a classical design based on the progeny testing of AI sires over 10 years. The next fifteen years, we applied eight different genomic breeding program designs (2 types of selection index  $\times$  4 mating systems). The male candidates, elite dams and elite AI sires were selected based on: (1) on GEBV; or (2) an index  $ISp$  that combines GEBV and genetic values at five specific loci potentially carrying undesired alleles ( $R$ ).

For an individual  $i$ ,  $ISP_i = \alpha GEBV_i + \sum_{r=1}^R \hat{\beta}_{r,g_i}$  where  $\alpha$  denotes the relative emphasis put on both the selection trait and allele management, and  $\hat{\beta}_{r,g_i}$  the genetic value associated to the locus  $r$  given the genotype  $g$  of the individual  $i$ .

As proposed by Boichard *et al.* (2016),  $\hat{\beta}_{r,g}$  is  $2f^2c_r - f(1 - 2f)c_r$  and  $-2f(1 - f)c_r$  for  $g = ++$ ,  $g = m +$  and  $g = mm$ , respectively. Where  $f$  denotes the frequency of the deleterious allele  $m$ , and  $c_r$  the cost associated to the genotype  $mm$ . These genetic values assume that  $m$  is recessive.

Then, we considered 4 mating systems between elite dams and sires that produce male candidates for AI:

1. Elite dams and sires were randomly mated (RAND)
2. Elite dams and sires were mated according GEBV (assortative mating) but matings between animals with a common grandparent were excluded. (AM)
3. Matings were designed based on an objective function  $OPF_{ij}$  including the GEBV of a dam  $i$  and an elite sire  $j$  and their kinship coefficient  $F_{ij}$  (from Pryce *et al.*, 2012):  $OPF_{ij} = 0.5(GEBV_i + GEBV_j) - \lambda F_{ij}$ , where  $\lambda$  is a penalty coefficient (arbitrarily set to 0.1) and  $F_{ij}$  is the pedigree-based inbreeding coefficient of the offspring resulted from mating dam  $i$  and elite sire  $j$ .
4. Matings were designed based on the previous objective function plus the probability that a mating between a dam  $i$  and elite sire  $j$  produces an homozygous carrier  $g = mm$  for the locus  $r$  (from Cole *et al.*, 2014):  $OFC_{ij} = OPF_{ij} - \sum_{r=1}^R P(g = mm)_{ij,r} \times c_r$ .

In a first approach all  $c_r$  were arbitrarily set to 1 for all loci  $r$  (genetic values and  $OPF$ ).

In (3) and (4), a score based on the objective function was computed for all potential matings between elite AI sires and female candidates for AI (around 80% of adult females). Then 1,050 matings were sequentially selected based on the best score and under constraints (one female is mated with only one male and a maximum of 3,000 females per male are inseminated along his reproductive life).

In addition, to assure the replacement of females, 46% of the breeding females were selected on (G)EBV and mated to an AI sire. Other females and females that did not conceive with AI (fertility after AI was set to 60%) were mated to a natural mating sire. Natural mating sires were all self-replaced within flocks and born from AI sire. The number of progenies per dam depended on the mode of reproduction and parity. Some dams were randomly culled after each reproductive cycle and the maximum parity was five. Around 30% of dams were replaced per year by females that were preferentially chosen among newborn progeny from AI matings. No selection step was considered for newborn females before they were mated.

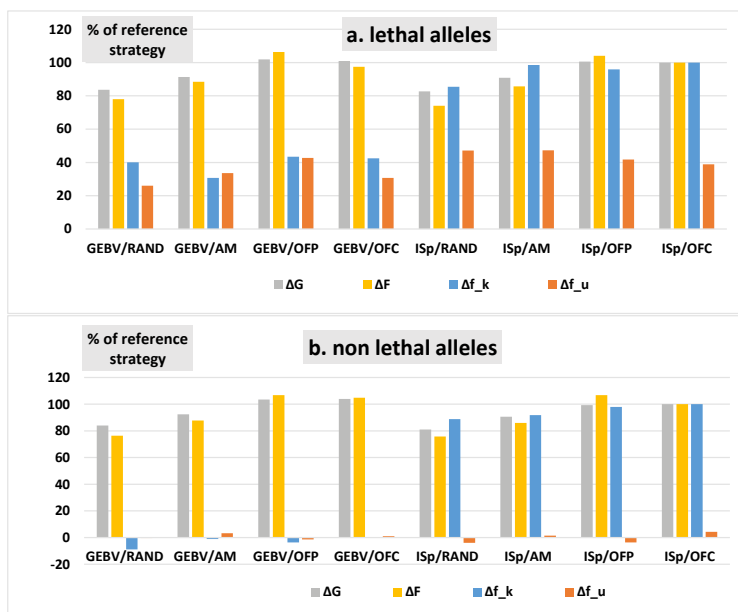
We simulated individuals and their genome based on a real goat 50 K SNPs chip, as in Raoul *et al.* (2017). In addition, we simulated  $5 \times 2 = 10$  loci (5 known and 5 unknown) with a starting frequency respectively equal to 1, 4, 7, 10 and 13%. These loci are independent (no linkage disequilibrium) from the rest of the genome (i.e. 50 K SNPs). Within simulations, undesirable alleles are all lethal (homozygous carriers were stillborn) or all non-lethal (no effect on fitness). In both cases, they did not have any effect on the main selected maternal trait ( $h^2=0.3$ ,  $rep=0.5$ ). The model included: (1) the establishment of the founder population; (2) the simulation of 1000 QTL picked from the 50K SNPs and their effect drawn from a Gamma distribution; (3) the simulation of phenotypes and genotypes based on the 50K SNP panels (SNPs selected as QTL were excluded from genotypes); (4) and the estimation of both breeding values and pedigree inbreeding respectively. The last estimations were performed with single step GBLUP using the Blupf90 software developed by Misztal *et al.* (1999) and inbugf90 software developed by Aguilar *et al.* (2008).

The annual genetic gain  $\Delta G$  and annual increase in inbreeding  $\Delta F$  were estimated as the regression slope of the average true breeding value and inbreeding coefficients of first parity females on time for years 10 to 25,

respectively. As well the annual decrease in frequency for known (i.e. genotyped)  $\Delta f_k$  and unknown (i.e. not genotyped)  $\Delta f_u$  loci were estimated from years 10 to 25 and averaged across known and unknown loci separately. The means and standard deviations presented are based on 30 replicates.

## Results

Figure 1 gives the annual genetic gain  $\Delta G$ , increase in inbreeding  $\Delta F$  and changes in the frequencies of known  $\Delta f_k$  and unknown  $\Delta f_u$  alleles according to 8 breeding strategies. In Figure 1a (lethal alleles) we observed that the selection based on *ISp* gave faster decrease in known undesired alleles frequencies than GEBV only, regardless of the mating design. The frequencies of unknown lethal alleles decreased in all breeding strategies without significant differences on average across breeding strategies. The frequencies tended to converge below 6% at time 10 and below 5% at time 25 for GEBV based strategies (results not shown). For *ISp* based strategies, the trend is the same until time 10 but the frequencies of genotyped lethal alleles tended to converge below 2% at time 25 (results not shown). No significant difference across strategies was observed for the frequencies of ungenotyped alleles. For non-lethal alleles we observed on Figure 1b that ungenotyped alleles are subject to genetic drift and their frequency remains, on average across loci, constant over time. For genotyped alleles, decrease in frequency is significantly higher for *ISp* than GEBV strategies regardless of the mating optimization. The decrease in frequency of the undesired allele at specific loci is poorly influenced by the mating system. We observed a slightly better result for OFP



**Figure 1.** Annual genetic gain ( $\Delta G$ ), increased in inbreeding ( $\Delta F$ ) and changes in the frequencies of known ( $\Delta f_k$ ) and unknown ( $\Delta f_u$ ) alleles according to the selection criteria  $\times$  mating design (30 replicates) for lethal (a) and non-lethal (b) alleles.  $\Delta G$ ,  $\Delta F$  and both  $\Delta f_k$  and  $\Delta f_u$  are respectively expressed as the % of  $\Delta G$ ,  $\Delta F$  and  $\Delta f_k$  obtained for the reference strategy = *ISp/OFC*. a. Reference strategy:  $\Delta G=0.180 \sigma_a$ ,  $\Delta F=0.33\%$  per generation,  $\Delta f_k = -0.15\%$  per year. b. Reference strategy:  $\Delta G=0.179 \sigma_a$ ,  $\Delta F=0.32\%$  per generation,  $\Delta f_k = -0.38\%$  per year. Selection criteria: GEBV or *ISp* (index combining GEBV and genetic values at five specific loci potentially carrying undesired alleles). Mating designs: RAND (random mating), AM (assortative mating), OFP (objective function including GEBV and penalty to F), OFC (OFP + penalty to probabilities to produce homozygous carriers at five specific loci potentially carrying undesired alleles).

and OFC compared to RAND and AM for non-lethal alleles (significant) and even smaller differences for lethal alleles (non-significant). Avoiding the production of homozygous individuals at specific loci had no or a small effect on the control of the allele frequencies. However, the optimization of matings had significant consequences on the genetic gains and the increase in inbreeding. OFP and OFC gave higher  $\Delta G$  (but also higher  $\Delta F$ ) than RAND and AM. A better adjustment of  $\lambda$  (penalty coefficient applied to  $\Delta F$  in OFP and OFC strategies) would be necessary to fairly compare  $\Delta G$  across strategies.

## Discussion

These preliminary results show that including a genetic value at specific loci is an efficient alternative to reduce their frequencies in a goat breeding scheme especially for non-lethal alleles. The genetic architecture simulated in this study, based on an independent segregation of specific loci and other markers as well as the use of a penalization on a pedigree based  $\Delta F$ , do not enable to assess the apparent contradiction between a general maximization of the SNP heterozygosity and the fixing of favourable alleles at the level of specific loci and QTLs. To go further it is necessary to simulate specific loci which are in linkage disequilibrium with markers and QTLs, use a penalization on a genomic based  $\Delta F$  and analyse the sensitivity of the result to the value of both  $\lambda$  and  $c_r$ .

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