LESSONS FROM THE USE, IN FRANCE, OF MAJOR GENES CONTROLLING PRODUCTION AND HEALTH TRAITS IN LIVESTOCK

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ABSTRACT

The gene assisted selection is currently used in France in a few cases. First lessons are drawn from our experience in this field: identification of the genes, estimation of their effects, definition of a new selection objective and of a breeding strategy including this genetic information, control of the negative effects of this strategy, genotyping of the animals, practical rules for the selection and mating.

KEY WORDS: Gene assisted selection, Marker assisted selection, Introgression, Genotyping.

INTRODUCTION

With the advance of molecular and computing technologies, an increasing number of genes controlling health and production traits were evidenced in livestock species. Among them, the Booroola (Mulsant *et al*, 2001; Wilson *et al*, 2001; Suza *et al*, 2001) and Lacaune (Bodin *et al*, 2002) genes (controlling ovulation rate in sheep), the RN gene (meat quality in pig) (Milan *et al*, 2000) , PrP gene (scrapie resistance in small ruminants) (Hunter *et al*, 1992; Elsen *et al*, 1997), Texel (conformation score in sheep) (Clop *et al*, 2006) and Syndactyly (a genetic defect in cattle) (Duchesne *et al*, 2006) have been extensively studied in France and are or will soon be currently used by the breeding organisations. Thus, we progressively built an expertise on the inclusion of this type of genetic information in the selection schemes, based both on theoretical considerations and on practical observations. The aim of this paper is to overview this expertise.

Identifying a gene of interest

The detection of a gene having a major effect is a versatile multistage process. Most often the starting point is a careful observation of mendelean-type inheritance of recorded traits by the breeders or applied geneticists exploring their data from the field. This was the case of the RN gene initially pointed out by J Naveau, who was selecting the cooked meat yield of his boar lines using a new approach he developed specifically (Le Roy *et al*, 1990). This was also the case for the Booroola and the Lacaune genes which were discovered respectively by L Piper (Piepr and Bindon, 1982) and L Bodin (Bodin *et al*, 2002) simply looking at their data files.

Alerted by this first signal of the segregation of a major gene, the researchers generally designed specific experiment to test mendelean segregation. The basic idea is to select (using already recorded data) reproducers which have a high chance of being heterozygous at the putative gene, and to observe if or not the distribution of the trait in their offspring is a mixture of sub distributions. As an example, the existence of the Lacaune gene (with the hyper ovulating L and wild type + alleles) was tested crossing rams from the prolific line, supposed to be L+ considering the high variability of their daughter performances, with ewes from a non prolific line (++) (Bodin *et al*, 2002). Their sons, either L+ or ++ sons were themselves progeny tested on non prolific ewes. Similarly, the existence of the Texel gene, suspected to have been selected in the Belgian Texel breed when looking at their extreme meat conformation was definitely proven in a crossbreeding (F2 and Back cross) experiment between Belgian Texel rams and Romanov ewes (Clop *et al*, 2006).

Sophisticated statistical procedures were imagined for a long time to add more formal proof in this hypothesis testing. The segregation and pedigree analyses (*e.g.* Elston and Stewart, 1971), which are considered as the gold standard in this field, are based on the likelihood theory which gives a nicely versatile framework for describing the various types of experiments which can be organised to test the segregation of a major gene, and the various genetic hypotheses which may be supposed (autosomal or sex linked locus, dominance, imprinting etc…). They were applied for instance to test the Lacaune, Texel, and RN genes.

Once the gene experimentally and statistically proven, the next step is to locate its corresponding locus on the genome, to progressively refine its position and finally to identify the mutation which causes the phenotypic variability. The animals needed for the first step (primo location) may generally be found in the population used to test the existence of the gene. Refining the position needs an extension of the family size since the precision of the localisation is proportional to the number of "informative meioses" (*e.g.* the Texel experiment), the research of linkage disequilibrium coherently found in diverse populations (e.g. the RN gene), and the research of genes which both are located in the locus confidence interval and are known to be involved in the physiological mechanisms underlying the phenotype of interest (*e.g.* the Booroola discovery). The causal mutation may be very difficult to detect, as this was the case for the Texel gene, where a silent mutation in an intron of the myostatin (GDF8) locus was demonstrated to create a target for a miRNA which causes a translational repression of the GDF8 transcripts (Clop *et al*, 2006).

The discovery process, as described above, may be tedious and costly, but works. So far, the very large majority of the genes which are used in selection schemes were identified following this model.

However, the availability of genetic markers such as microsatellites and SNP (Single Nucleotide Polymorphism) made realistic and efficient the direct search of QTL (Quantitative Trait Loci) controlling the animal traits, without any *a priori* on the segregation of major gene. The first application of this technique in livestock concerned the pig (Andersson *et al*, 1994) and cattle (Georges *et al*, 1995) species. They were followed by a large number of experiments, in all species and looking at many traits. From the very big number of detected QTL, only a few have been fully elucidated. The reason of this discrepancy probably comes

from the smaller effect of the QTL on the trait, as compared to the "major gene" as described above, and thus the big difficulty of exact individual genotyping.

Basing the decision of selecting a known gene

A gene detected either directly or after a QTL approach is primarily known through its effect on a single trait such as the ovulation rate or meat yield ("the primary trait"). Before implementing a selection scheme which considers explicitly the polymorphism of this gene, its global value must be evaluated, *i.e.* the effects of its different genotypes on the various traits of interest.

As an example, the possibility that the PrP allele (identified as ARR) which gives a high resistance to scrapie in sheep may have negative consequences on production traits has been extensively studied in a large panel of countries and breeds. The authors looked at reproduction (ovulation rate, fertility, and litter size), body weight and growth rate, carcass conformation, muscle and fat scores, milk quality and quantity, mastitis resistance etc…and found nearly no unfavourable effects of this "ARR" allele (*e.g.* Vitezica *et al*, 2005; Vitezica *et al*, 2006). On the opposite, it is now clearly established that the Booroola gene has a negative effect on the birth weight and survival of the lambs, simply caused by the competition between foetuses during the pregnancy (e.g. Teyssier *et al*, 1998). It has been also shown that the RN- allele which decreases the yield of the cooked meat in pig is favourable in terms of carcass fatness (Le Roy *et al*, 2000).

The negative effect on some other traits of the allele which is favourable for the primary trait may come from a real pleitotropic phenomenom (*e.g.* the susceptibility to the stress of the n allele of the RYR gene (Ollivier, 1980)) or may be due to linkage disequilibrium between the major gene and a QTL located in its vicinity. An extensive review of the available QTL information is thus a good mean for checking possible adverse effects of a planed selection on the gene of interest. As an example, QTL affecting conformation score were evidenced at less than 10cM of the PrP gene in cattle (Heindleder *et al*, 2003), suggesting that such genes could segregate in the equivalent region in sheep, and should be monitored.

The interaction between the genotype and the environment, in a very large sense, is an other matter of interest. For instance, the negative effect of the Booroola gene on the lamb survival is critical in extensive condition, but may be overcome if the feeding and care are of high value, *e.g.* using artificial milking. However, the genotype x husbandry is not the unique interaction to be considered. The effect of the genotype at the major locus, on the primary trait, as well as on the other traits, may vary from breed to breed. As an example, this genotype x breed interaction was studied for the Booroola gene in France. The hyper ovulating allele B was introgressed in the Mérinos d'Arles (non prolific) and Romanov (prolific) breeds, to look at the effects of the gene on ovulation rate, litter size, and any physiological underlying traits. It was shown that the effect of the B allele on the ovulation rate is much higher in the Romanov (++: 2.55 vs. B+: 5.05) than in the Mérinos d'Arles (++: 1.05 vs. B+: 1.93) (Elsen *et al*, 1994).

In the case of genes controlling resistance / susceptibility to a disease, a very crucial issue is the possibility that a given genotype may be resistant to some pathogen strains and susceptible to others. This is a real worry in the case of selection for the resistance to scrapie. The PrP homozygous ARR/ARR animals were considered as fully resistant from observations made in many locations and breeds, thus probably facing a large range of prion agents. The discovery of a very limited number of diseased ARR /ARR (less than 5 at the world level) did not change the picture dramatically. However, the systematic survey of cullen stocks using biochemical tests (Elisa) to detect the presence of the prion protein in its scrapie form in the brain (a signature of the scrapie disease) have shown that all genotypes, including ARR/ARR, may be hit by a particular, called atypical, form of scrapie (Moum *et al*, 2005; Moreno *et al* 2006). Even if the importance, in term of animal health, of those atypical scrapie is still a matter of debate (*e.g.* its between animal transmission is not proven), this is a clear example of pathogen strain x host genotype interaction.

Even if such inversion is not found, it is often hypothesized that a strong selection for a resistant allele may induce a selection of the pathogen population for particles (parasites, bacteria, viruses or prions) which attack the "resistant" animals, similarly to the antibio-resistance which is largely observed in Human or animal diseases. Thus a long term surveillance of the genotypes of the diseased animals is essential to control the efficiency of the selection programme.

Defining the objective of the selection scheme

Depending on the value of the different genotypes at the major locus, the objective when organising an explicit selection at this gene may vary.

When one of the allele is clearly showing a negative effect on the health or production level of the carriers, the selection will aim to eliminate it. This is the case for the allele of the LRP4 gene which was identified as the cause of the syndactyly abnormality and should now be directly eliminated from the cattle populations (Duchesne *et al*, 2006). This was also the case for the BoLA-DRB3*09 allele of the Major Histocompatibily Complex which is strongly linked to susceptibility to dermatophilosis, and which was successfully counterselected in a small population in the French West Indies (Maillard *et al*, 2003). A last example is the n allele of the RYR gene which produces both a loss of meat quality and stress problem in the pig (Ollivier, 1980).

The situation is a little bit more complicated when the entity showing a negative value is a genotype rather than an allele. For instance, the sheep with the VRQ/VRQ genotype at the PrP locus are highly susceptible to scrapie. This is not the case for the ARR/VRQ carriers which are rather resistant (not fully). In this situation, the selection must consider both in the short term the elimination of the animals carrying the genotype, and to prevent its occurrence in the future, the elimination of the unfavourable allele.

In the opposite situation, a particular allele displays a positive value as compared to the others and could be explicitly selected for. The mutation of the GDF8 gene creating the double muscling of the Texel sheep, the A allele of the casein gene in goat (Barbieri *et al*, 1995), the ARR allele of the PrP gene (forgetting the recent discovery of the atypical cases)

are clear examples of this situation. If the allele, detected in a "source" population, is not present in the breed of interest (say the target), it is necessary to organise an introgression from the source to the target, through F1 production and repeated backcrossing to recover the target blood. Such introgressions were organised for the Booroola gene (Source: Australian Merino, Target: Mérinos d'Arles, Romanov, Border Leicester, Romney etc…,) and nowadays the Texel gene (Target: Lacaune). This is a long process which may be accelerated using molecular information (see below). If the allele is already present in the target population, its frequency will be increased by the selection of carriers.

The final objective may not be the fixation of the favourable allele in the population, but the increase of its frequency up to a sufficient level. This objective has been suggested for the ARR allele of PrP gene. The underlying hypothesis, tested using the concept of basic reproduction number (Matthews *et al*, 1999), is that the scrapie epidemic should stop if a sufficient proportion of the animals are resistant and thus do not spread the prion agent. The additional interests of this strategy are (i) the cost and time saving since the finalisation of a fixation process needs the genotyping of all the reproducers – males and females – (ii) the preservation of a genetic diversity at the PrP locus, which may be useful if a new scrapie agent targeting ARR carriers appears.

Another situation where the objective is not the fixation of one of the alleles occurs when the optimum genotype is a heterozygous, say AB. This is the case with the Booroola and Lacaune genes which create a considerable increase of the ovulation rate, causing high embryonic losses and lamb mortality, making the homozygous carriers non profitable. Within breed, the only way is to select for the two alleles A and B which are present in the heterozygous animals, with the aim of minimising the proportion of homozygous individuals (AA + BB). The situation is simpler when specialised lines or different breeds may be used as parents of the heterozygous animals (*e.g.* The dwarf gene in poultry (Mérat and Ricard, 1974), the myostatin gene in beef cattle (McPherron and Lee, 1997)).

Monitoring the negative effects of the gene selection

These effects are of three natures.

The first, described in the part 2, is a negative effect of the favourable (for the primary trait) allele on any other characteristic. When such a negative effect is demonstrated, the solution for solving it depends on its origin.

If this is a direct (pleiotropy) effect, the only way is to consider the global value of the gene, for instance weighting the value of the different genotypes considering all the traits of economical importance:

$EBV_i\ (G_i) = \Sigma_k\ w_k\ .\ (EBV_{ik} + f_k(G_i))$, where w_k is the value of the k^{th} trait, $EBV_i\ (G_i)$ is the Estimated Breeding Value of the individual i which is carrying the genotype G_i, EBV_{ik}, its EBV for the k^{th} trait and $f_k(G_i)$, the effect of the genotype G_i on the k^{th} trait.

When the effect is indirect (linkage), the solution should be a selection of gametes carrying all the positive features. Let + / - be the alleles at the major locus (+ favourable, - unfavourable) and P / N at the linked QTL controlling the secondary trait (P : favourable for

this trait, N : unfavourable). The individuals displaying the [- -] or [N N] genotypes should be excluded from the reproduction. The ([+ +] and [P P]) animals are ideal candidates. The phase of the double heterozygous ([+ -] and [P N]) should be checked with an exclusion of the [+ N / - P] and a selection, within the offspring of [+ P ; - N] reproducers of the progeny which inherited the + P allele. The control of this genotypic information will first come from a biochemical genotyping at both loci, and progressively be replaced by ancestral information and a careful control of the pedigree.

The second possible negative effect is a lower control of the genetic variability due to the extensive selection of the favourable allele at the major locus.

Breeding has always been a balance between short term improvements obtained by a vigorous selection of the best animals and long term improvements, only possible if the genetic variability is preserved through a careful management of the diversity, within and between breeds or lines. The Marker Assisted Selection and the Gene Assisted Selection did not change the nature of this short *vs.* long term conflict, but, being more efficient than the previous methods, are more susceptible to create difficulties if the balance is not carefully controlled.

The deleterious effects of intense selection, which decreases the number of reproducers, are the inbreeding which reduces the general performances of the animals (growth, reproduction etc..) and reveals congenital defects, the loss of genetic variability which reduces the possibilities of further improvement, and the drift. Those phenomena are closely linked. Different criteria were proposed to evaluate the level of danger (see Baumung and Sölkner, 2003): some are based on pedigree information (mean coefficient of relationship, number of ancestor contributing to 50pcent of the origins…), others on molecular information, most often from neutral markers spread over the genome (average molecular coancestry, Hardy Weinberg heterozygosity, average number of observed alleles …). The effect of selection may also be monitored by regular estimations of the characteristics of the traits distributions: genetic variances, mean genetic levels. To organise such monitoring, it is needed (i) to have a long term control of the pedigree with ad hoc animal identification in the breeding flocks (ii) to use adequate panel of genome markers.

A limited number of studies have already been published giving such information in the case of the selection for scrapie resistance (Palhière *et al*, 2006, Brochard *et al*, 2004, Alfonso *et al*, 2006). These first studies did not show a big impact of the selection on PrP on the pedigree based criteria. However, breeds of limited size proved to be more fragile when facing important reduction of their genetic variability (Palhière *et al*, 2006, Brochard *et al*, 2004), an observation fully consistent with the theoretical considerations of Windig *et al* (2004). The molecular based criteria gave very different results depending on the chromosome (Palhière *et al*, 2006). Due to hitchhiking effects, an important loss of variability (in terms of Hardy Weinberg heterozygosity but not for the average number of observed alleles with the exception of the smaller breed) was observed on the chromosome 13 carrying the PrP gene. On the contrary, the effect on the other chromosomes was quasi null, even with a slight increase of variability of the breeds of large size.

Beyond the surveillance of the evolution of the genetic variability, it is possible to adapt the selection schemes to limit inbreeding and loss of variability.

The third negative effect to be monitored is possible decrease of the genetic gain for the other traits than the "primary" one. Again, this is a quite general tendency in artificial selection: each time an additional trait is put in the list of characteristics to be selected for, the progresses on the components of the global objective are lowered. This phenomenon was observed when implementing the selection on PrP in France (Brochard *et al*, 2004), even if it may be temporary (Barillet *et al*, 2004). It was also a real issue when organising the introgression of the Texel mutation of the GDF8 gene in the Lacaune breed. However, the implementation of the selection of PrP in France revealed that the cost of including a new objective in an existing breeding plan may be largely reduced simply through the optimisation of the current practices, suppressing the pressure put on the secondary traits of low economical value such as the coat colour or ear shapes.

Choosing a strategy

Introgressing the gene from the source population to the target population is the only way when the allele is not segregating in the target (part 3). The introgression process may be designed following different schemes (*e.g.* Boomarov, 1991). In any case, a number of backcrosses from the F1 to the target breed are needed. Without the control of the genotypes at the major locus, the chance of loosing the favourable allele during this backcrossing increases with the number of generations. Depending on the source of information (phenotypes if the gene is not mapped on the genome, genetic markers when it is located, genotypes at the mutation point when the gene is fully identified) the genotyping and selection of the reproducers is more or less easy. When the only available information is the phenotype, the procedure for genotyping animals depends on the type of trait (sex limited expression or not, measurement late in the life or in the early ages, precision of the genotyping linked to the effect of the gene on the measured trait). For instance the introgression of the Booroola gene in the Mérinos d'Arles breed made use, at each generation, of a progeny test of the rams to infer their genotype (B+ or ++) from the ovulation rate of their daughters.

The practical design of the introgression is complicated by the overlapping between generations, which induces a need for optimising the process in terms of resource allocation (mostly the total number of animals which can be bred at the same moment). A theoretical support for optimising the introgression process in terms of resource and time is the linear programming, as explored by Elsen *et al* (1985).

The availability of molecular information deeply changes the efficiency of the introgression. This is obvious for the gene itself (the carriers can be identified soon after birth and in both sexes), but is also fruitful to accelerate the recovery of the target genome. Market Assisted Introgression has been proposed and the possible strategies (number of markers / chromosome, definition of the selection criteria for each generation) explored (Hospital *et al*, 1992).

If the favourable allele is already present in the target population, different strategies may be proposed.

The simplest is to leave the favourable mutation to be implicitly selected within the current selection scheme. This will be the case as soon as the selection criterion considers the trait which is affected by the gene of interest. The main advantage of the solution is the absence of cost. The drawbacks are: the total inefficiency of the selection if the gene controls a trait which is not considered in the selection process, a situation which may be encountered for functional or health traits (resistance to scrapie, syndactyly), or when the trait is not routinely measured (meat quality); a too slow evolution of the favourable allele frequency when a rapid change of the population structure is desirable (*e.g.* solving a human health risk); a too rapid evolution of this frequency, with a concomitant unacceptable loss of genetic progress on the main traits.

The implementation of a gene assisted selection scheme is based on the genotyping of the candidates, with different options as describer below (part 6). The scheme includes procedures for the ways the animals are selected, considering all the available information and traits of interests, and are mated, depending both on their major locus genotype and estimated breeding values (part 7).

The general frameworks of the optimum contribution selection (Sonesson and Meuwissen, 2000), the optimal control theory (Dekkers and Van Arendonk, 1998) or the dynamic truncation selection (Larzul *et al*, 1997) give solutions for a long term maximisation of the genetic progress in the situation of the co-selection of an identified locus and a polygenic background (the production traits). Those theories may be difficult to apply in the field (in particular when the breeding plan is in the hands of many actors with a low background in modern genetics, *e.g.* the sheep industry) and more practical rules must be proposed. An example may be found in Windig *et al* (2004) who suggested the choice between three levels of selection for sheep scrapie resistance (mild: ARR carrier rams are used indiscriminately, moderate: preference for the ARR/ARR, sever: ARR/ARR rams only) depending on the size of the population and the ARR allele frequency.

Genotyping the candidates

The genotypes at the major locus are primarily obtained through biochemical techniques which explore the variability of the DNA. A panel of techniques are available. Some are adapted to large scale genotyping, when thousands of animals have to be examined (PCR-RFLP, TaqMan, allele specific amplification, sequencing). Others are more appropriate when the numbers are limited (DGGE, SSCP, CFLP). In some case, Elisa kits are developed to genotype the candidate on the protein rather than on the DNA itself (PrP).

A noteworthy difficulty with most of those techniques is their allele specific spectrum. The archetype is the PrP genotyping. Most of the currently used methods are only able to classify the animals on their genotype at the three most studied codons (136, 154 and 171) of this gene. The information from the genotyping tells us if the candidate is an ARQ, ARH, VRQ, AHQ or ARR carrier (ARQ means Alanime at the 136 codon, Arginine at the 154 and Glutamine at the 171). This was considered as sufficient during years, since most of the

variability in scrapie resistance was identified as depending on this specific polymorphism. The discovery of the atypical scrapie pointed out the role of the codon 141 which may encode either a phenylalanine (F) or a leucine (L) amino acid (Moum et al, 2005). The AFRQ allele confers a very high susceptibility to this type of scrapie while the ALRQ allele seems rather resistant. Thus, (i) it is now needed to extend the genotyping methods to deal with this polymorphism at the 141 codon (ii) the genotypes obtained in the past are not informative within the new context. More generally, this evolution suggests that a full sequencing of the gene of interest is a long term solution, insuring that any new information coming from the labs will be directly usable in the field.

This demonstrated existence of alleles not yet found for a given gene is a general situation which opens additional prospects in terms of application. The knowledge of the role of BMPR-1B as the locus of the Booroola gene suggests for instance that other variants of this gene may have a positive but moderate effect on the prolificacy, which could be more useful in practice. Similar approaches were followed for the RN gene in pig and myostatine gene in cattle (Dunner *et al.*, 2003). It must also be noted that any discovery of a new allele should be followed by a careful examination of its effects, as described in part 2.

With the increase of the number of genotyped animals in a population, it becomes possible to infer the genotype of new candidates from information collected in their pedigree. The simpler situation corresponds to the progeny of two homozygous parents (say AA and BB), the genotype of which is reliably known (AB). Thus, in some instance (as the previous example), the genotype is perfectly known. An other example could be an ungenotyped dam mated to AA rams and which gave birth to AB and AC progeny, proving its BC genotype. Quite often it is only possible to assign probabilities to the possible genotypes, fully excluding some of them, giving chance to others. This information is still useful. For instance, if the objective is the eradication of an unfavourable allele, knowing that the parents were non carriers is sufficient to keep the candidate.

Different techniques are developed to estimate the genotype probabilities from the pedigree. Some are purely heuristic, other are based on sophisticated theories such as the iterative peeling or the Monte Carlo Markov Chain (Vitezica, 2003 for a review). This has been utilised to assign possible PrP genotype of sheep populations (Vitezica *et al*, 2005).

It must also be emphasized that the quality of the inference of genotype from relatives is strongly dependant on the reliability of the pedigree information. Any error in the filiations may have dramatic consequences on the genotype assignation

Selecting and matting the candidates

A number of practical questions must be considered when designing a gene assisted selection programme. They concern the choice of the animals to be genotyped, as well as the way their selection will be organised.

Due to their reproduction capacity, the males are the first choice for the genotyping, and in many programmes, the only choice: rapid progresses in terms of allele frequencies are made when considering the major genotype of the future sires. However, genotyping the females must be considered in two instances. The first is the set up of mate selection (see below) and the second the full eradication or selection of a particular allele. This objective is desirable

when the resources are time limited, inducing the need of getting a full homozygous state before the end of the programme. This is the case for the French national selection for scrapie resistance, which is founded over a given period of time by the ministry of agriculture.

The selection on the genotype may occur at different moments in the life of the animals. An early selection (say, at birth) avoids the maintenance of uninteresting animals, but may be very costly since it needs the genotyping of large numbers of candidates. If the unfavourable allele frequency is low, a cheaper solution could be to genotype preselected animals considering their general genetic value and to discard the few carriers of the undesired type. Thus the organisation of the selection scheme is optimally dynamic, and should change with the progress on the major gene frequency distribution. Efforts are still needed to provide suitable tools for this optimisation to the breeders.

The balance between major gene and polygenic selection is an other very hot topic when setting up the programme. The global EBV as described above (part 4) is an option, which needs a full knowledge of the economical weights of the traits and the effects of the major gene on each of them. More simply, the selection on the polygenic values (which generally concern more than one characteristic) may be organised within major genotype, the question being the selection pressure to put on each group (if Q is the global selection rate, the question is the choice of the Q_k, for the k^{th} genotype, with $Q=\Sigma_k Q_k f_k$, with f_k the proportion of genotype k within the candidates) (Larzul *et al*, 1997) .

When the reproducers are genotyped, it is possible to organise a mate selection, *i.e.* the way the animals are mated depending on their genotype. The allele frequencies will not be change by the mating plan, but the genotype frequencies may be modified. To give a simplistic example, if we consider a biallelic gene, with frequencies ¼, ½ and ¼ for the AA, AB and BB genotype in males and females, a random mating will not change the genotype frequencies in the following generation, whereas a homogametic (mates are from the same genotype) will give ¾ of AB progeny. This change of the genotypes distribution may increase the efficiency of the selection. However, the most important application of the mate selection is the co optimisation of the major gene frequencies and polygenic value. The idea is to produce animals which assemble interesting characteristics of their parents, for instance AA male of low polygenic value with AB or BB females of high merit. Here again theoretical modelling is still needed to provide useful advices to the breeders.

CONCLUSION

Even if the principles of the gene assisted selection are established for a long time, its practical implementation is recent. The few applications we had in France evidenced the variety of situations encountered, each of them needing specific organisation and tools. A number of problems are still unsolved and should be given attention in the future. The theoretical and practical optimisation of the within breed and across breeds (introgression) plans, the production of algorithms and softwares to explore pedigree and infer genotypes, the invention of efficient genotyping techniques, are on the list.

In the mean time, the number of known gene and QTL increases. The real challenge for the future will be this multidimensionality. The genomic selection may be a solution to face those difficulties (Meuwissen *et al*, 2001). However all the questions open in the "simple" case of single gene assisted selection will still to be considered within this global approach.

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