IMPLEMENTATION OF THE FRENCH BOVINE GENETIC DISEASE PROGRAMME

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INTRODUCTION

Morphological, neurological or metabolic abnormalities have been known and studied for several decades in cattle. Their causes and clinical consequences are diverse. Approximately 370 traits (mainly defects) of putative or proven hereditary origin are registered in the OMIA database for the bovine species (http://omia.angis.org.au/), including 31 for which the causal mutation has been identified. The frequency of the mutations responsible for these hereditary defects is generally low in field populations. However, due to the very particular genetic structure of some selected bovine populations (massive use of a few bulls generating severe genetic bottlenecks) the frequency of some specific mutations can increase over relatively short periods of time. In such situations, 1) early detection of the problem and 2) the rapid development of a molecular diagnostic test are necessary to avoid very important economic losses. The first condition can be fulfilled only if structured and efficient monitoring programmes exist. Several countries have developed such programmes. The most exemplary is probably the Danish Bovine Genetic Disease Programme (Agerholm *et al*., 1993). In France, the implementation of a national bovine genetic disease observatory (BGDO) was initiated in 2002 by the Department of Animal Genetics of INRA (National Institute for Agricultural Research) and its professional partners (federation of AI centres, national association of rural veterinary practitioners, performance recording organizations…). This paper presents the first results obtained within the French BGDO programme.

MATERIAL AND METHODS

Main actions carried out. Actions to date have been carried out in two main directions:

1) Monitoring of congenital defects: on-farm collection of detailed information concerning calves affected by congenital defects was initiated using a standardized description sheet widely distributed to AI technicians, veterinary practitioners and performance recording agents. This declaration sheet was also available on the UMR INRA-ENVT 898 website (http://www.cytogenetique.envt.fr) and could therefore be used by individual breeders. All the information was centralized in this laboratory and stored in a national database.

2) Management of emerging defects: as detailed in the following section, the monitoring programme carried out in 2002 allowed the identification of two emergent defects. Accurate clinical data were lacking for one of them, so affected animals were hospitalized at the national veterinary school of Toulouse for thorough clinical investigations (biochemical, haematological, histological, parasitological and infectiological analyses). Blood samples (or a small piece of ear for dead calves) were taken from affected calves and from their dams by veterinarians (or approved field-technicians) in order to initiate genetic mapping of putative deleterious gene(s) for both emergent defects.

RESULTS AND DISCUSSION

Four complete calving years have been monitored since the beginning of the BGDO programme. The total number of declarations received up to now is 1450 (January 16th, 2006 statistic). Almost 90% of the declarations were made by AI technicians. Thus the majority concerned dairy cattle breeds, and mainly the Holstein Friesian breed (80% of the total number of declarations). The number of declarations received doubled between the 2002-2003 and the 2003-2004 periods, then became stable at around 500 per year. The total number of different defects described was relatively high. For instance, 101 different defects were reported for the Holstein Friesian breed during the 2004-2005 calving campaign: 36 mainly concerned malformations of the head, 29 mainly the body and 17 mainly the limbs (plus 19 considered as "miscellaneous" malformations). Most of the defects seemed sporadic (only 1 to 5 cases reported annually). Only one defect was highly recurrent in the Holstein Friesian breed. It corresponded to declarations of "present but not functional anus". The birth weight and size of calves in this category was generally normal. The calves stood and suckled normally during the first hours, but did not excrete any faecal material ("blocked" calves, presence of a white/rosy mucus in the anus). Consequently, a swelling of the abdomen could be seen during the first days of life. The calves progressively lost appetite, became lethargic and generally died between 2 to 10 days after birth by self intoxication or septicaemia. These symptoms suggested that these declarations corresponded to a particular congenital defect, well studied in the past, called "atresia coli" (AC) (Syed and Shanks, 1992). The autopsies carried out on a number of cases confirmed the AC diagnosis. More than 470 AC cases have been reported since the beginning of the BGDO programme, i.e. ~30% of the total number of declarations received. The great majority (~90%) concerned purebred Holstein Friesian calves. The others were mainly Holstein crossbreds. Some rare cases were reported in the Normande and Montbéliarde breeds. Several authors considered that the rectal palpation for early pregnancy diagnosis (performed less than 42 days after AI) could strongly increase the risk of AC in calves (Syed and Shanks, 1993 ; Brenner and Orgad, 2003). In our study, this particular risk factor could be excluded with certainty in more than 70% of the cases. The 426 AC calves reported in the Holstein Friesian breed were sired by 200 different bulls. Only 6 bulls sired more than 10 reported AC calves (maximum 37 calves from the same sire). On the whole, 26% of these 426 reported AC calves had the same paternal grand-sire. Biological samples have been taken from 150 [calf + dam] pairs to date. This should allow us to initiate the genetic mapping of putative predisposition gene(s) soon, as has already been done for another genetic defect identified in the Montbéliarde breed (presented hereafter).

This other defect, initially called "sheep head" or "roe deer head" was later renamed "caprine-like generalized hypoplasia syndrome", or, in French, SHGC for "syndrome d'hypoplasie généralisée capréoliforme". This particular defect is inherited as a recessive trait. From a clinical point of view, SHGC calves generally presented a low birth weight (30 to 35kg) and a lifelong developmental delay (Figure 1a). Their viability and vitality were normal, and a particularly good resistance of these calves to digestive pathologies was observed. The pronounced amyotrophy mainly concerned the rear limbs. The affected animals generally presented a particular head morphology (thin and long), and partial depigmentation of the red coat areas. In particular, the presence of white and apparently large ears was one of the main differential diagnostic elements (Figure 1b). Nevertheless, the clinical characteristics were quite variable from one animal to the other.

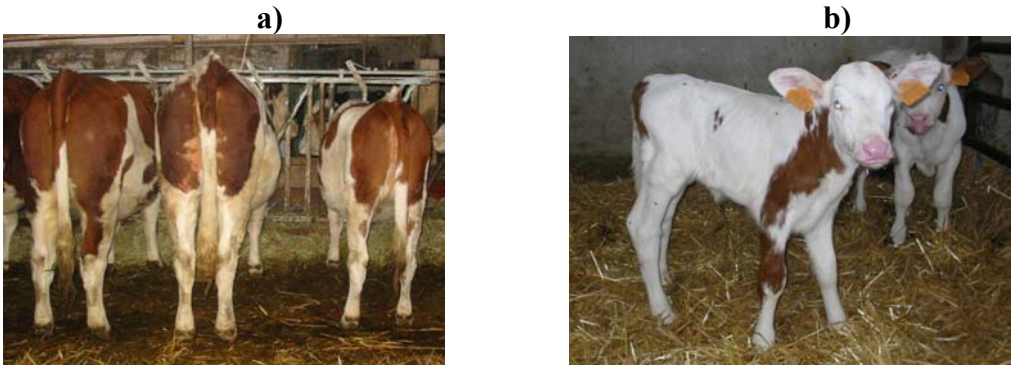

Figure 1. SHGC affected animals: a) 3 animals of the same age, the SHGC one is on the right; b) the presence of large depigmented ears is characteristic of the defect.

Reproduction of SHGC females was normal. On the other hand, milk production of adult SHGC cows was decreased (by about 1000kg per lactation) but these cows generally presented particularly good udder morphology. Even though the biological modifications could be considered as minor, the economic repercussions of the SHGC genetic defect were important due to the very low commercial value of affected animals. From 2002 to 2005, 161 SHGC cases were recorded, thanks to the effective involvement of the AI organizations (UMOTEST and CEIA 25/70). The estimated overall incidence was low: 7 cases in over 10000 cows inseminated at least once during the 2004-2005 year. At the end of year 2003, an experimental group of 6 animals (3 female calves, 2 heifers and one adult pregnant cow) was housed for thorough clinical investigations at the National Veterinary School of Toulouse. The only finding of diagnostic interest was a major selenium deficiency in the affected calves. This was later confirmed by on farm comparisons of SHGC and normal calves. In parallel, biological samples were collected from affected calves as well as from their dams. A full genome scan with a subpanel of 117 animals (11 sires and 53 pairs of affected calves and dams) and 143 polymorphic microsatellite markers revealed a single locus localized within a 35 cM region on bovine chromosome 13 (Figure 2). Genotypes of all available animals (>250) for 18 new microsatellite markers from the region confirmed the localization of the disorder and refined the position to a 6 cM interval.

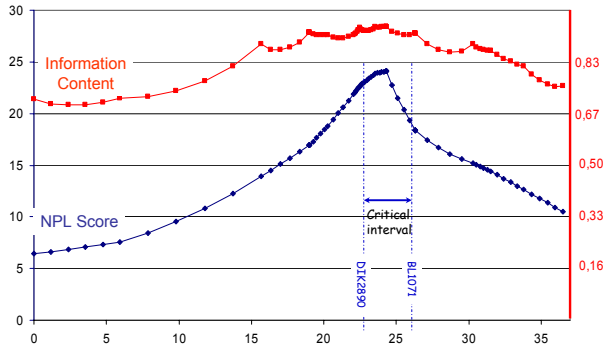

Figure 2. Non-parametric linkage analysis of the 35 cM interval of BTA13 isolated after the genome scan. The red curve represents the information content and the blue curve the NPL score as calculated by the GeneHunter software. With the addition of new markers, linkage to BTA13 is confirmed, and the localization of SHGC is refined.

Complementary fine mapping experiments and estimation of the frequency of the deleterious haplotype in different population samples (service bulls, candidate bulls, random sample of the general population) are in progress. These results should allow us to define an optimal management strategy for this genetic defect in the Montbéliarde breed.

CONCLUSION

The French BGDO was implemented in 2002 with limited resources. The first results obtained (identification of two emergent defects and development of a molecular diagnostic test for one of these) illustrate the efficiency of this kind of policy. In the short term, the monitoring efforts must be increased, and genetic analysis of the *atresia coli* defect will definitely be implemented. In addition, international cooperation between the different national programmes will be sought. Such a cooperation will enhance the efficiency of detection of emergent defects for widely distributed breeds, facilitate the collection of biological samples and mutualize the costs of molecular genetics programmes.

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