Prevalence of two inherited disorders in US Holstein cattle

J.L. ROBINSON AND R.D. SHANKS

Department of Animal Sciences, University of Illinois, 1207 West Gregory Drive, Urbana, IL 61801, USA.

ABSTRACT

The deficiency of uridine monophosphate synthase is a disorder of the de novo pathway for pyrimidine nucleotide biosynthesis. Inherited as an autosomal recessive, it results in early embryonic mortality for the homozygous recessive genotype. In the mid-1980's, heterozygotes were estimated at 1-2% among US Holstein cattle. The institution of a testing program for carriers and refusal by US artificial insemination companies to accept carriers into their progeny testing programs has eliminated the condition from the top 400 US Holstein bulls. Bovine citrullinaemia is a defect of the urea cycle. Also inherited as an autosomal recessive, it results in early postnatal mortality for the homozygous recessive genotype. In 1990, heterozygotes constituted 0.3% of US Holstein cattle. At present, no known carriers are among the top 400 US Holstein bulls. Carriers for either condition can be detected by convenient and inexpensive DNA based testing. To guard against these conditions reappearing, a modest testing program among prominent US bulls should be continued and importers should insist that imported Holstein germplasm have no evidence of these conditions.

Keywords: inherited disorders; dairy cattle; genetics.

INTRODUCTION

Because inherited disorders are found in all species and all breeds of cattle, discovery of new ones should not be the cause for undue alarm. On the other hand, controlling these conditions is one way of enhancing the productivity of animal agriculture. This paper reviews two inherited disorders in US Holstein cattle that we have studied. Their prevalence and implications are discussed.

DUMPS

The deficiency of uridine monophosphate synthase, known by the acronym DUMPS, was first described by Robinson *et al.* (1983). This inherited condition found in Holstein-Friesian cattle is transmitted as an autosomal recessive (Shanks *et al.*, 1984, 1987a); heterozygotes are asymptomatic, while the homozygous recessives suffer embryonic mortality around 40 days post-conception, (Shanks and Robinson, 1989; Shanks *et al.*, 1992.) The mortality is attributed to insufficient activity of UMP synthase, which catalyses the biosynthesis of pyrimidine nucleotides, which, as constituents of DNA and RNA, are essential for normal growth and development. The molecular basis for the mutation has recently been established as a point mutation in the gene for UMP synthase (Schwenger *et al.*, 1993).

Heterozygote detection for DUMPS has routinely been made by radiometric assay of UMP synthase activity in red cell haemolysates. Heterozygotes have half normal levels and with virtually no overlap with normal animals, 2/3 of normal is the cut-off between genotypes (Shanks *et al.*, 1987b). Recently, a DNA-based test has been developed for genotype detection (Schwenger *et al.*, 1993).

In 1982, the prevalence of DUMPS carriers among Holstein cows in the state of Illinois was estimated at 1.7% on the basis of a random survey of herds (Robinson *et al.*, 1984). A random survey of US Holstein bulls active in artificial insemination between 1982 and 1985 yielded an incidence of 1.4% (Shanks *et al.*, 1987b).

In late 1987, on the basis of embryonic mortality of the homozygous recessive, the Holstein Association of America acknowledged DUMPS as an undesirable recessive and initiated a testing program at the University of Illinois for Holstein cattle from North America. A comparable testing program was established in the Netherlands for European cattle. In the next 4 years, 3461 samples were tested in our laboratory, while 1226 were tested in Europe (Robinson *et al.*, 1993a), with a total of 999 carrier animals identified.

Since the DUMPS testing program was initiated, US artificial insemination companies have refused to accept carrier bulls into their sire proving schemes. As a result, carrier animals among proven sires have decreased as superior non-carrier bulls displace carrier sires. In 1987, three carrier bulls were present among the top 400 on the basis of Type-Performance Index, a linear index of predicted transmitting abilities for production and type traits (Holstein Association, 1987), as follows:

Happy-Herd Beautician, ranked #5
Riehlholm Mutual, ranked #117
Needle-Lane Jon-Red, ranked #218

Happy-Herd Beautician, despite being identified as a DUMPS carrier, was used extensively, having over 16,000 offspring registered by the Holstein Association of America. Riehlholm Mutual, while having been on the list for some years, was not used extensively. Needle-Lane Jon-Red, despite his low ranking, had been the most popular red and white Holstein sire in the US for several years. Accordingly, the incidence of DUMPS carriers was likely to be higher among US red and white Holsteins. In the years since 1987, only Happy Herd Beautician has remained among the top 400 and his ranking has fallen, as superior bulls have been proven. As

of 1992, he was no longer listed, and no DUMPS carriers are currently among the top 400.

Citrullinaemia

Citrullinaemia is another inherited disorder found in Holstein-Friesian cattle. It was discovered in Australian Friesians by Harper *et al.* (1986). Affected calves for this autosomal recessive condition are born at term, but, shortly thereafter, begin to exhibit neurological dysfunction, which becomes progressively worse. Depression is observable within a day, followed by unsteady gait, aimless wandering, apparent blindness, head pressing, collapse, convulsions and death within 1 week. (Harper *et al.*, 1986; Healy *et al.*, 1990). Citrullinaemia results from a deficiency of argininosuccinate synthetase, an enzyme of the urea cycle, which converts ammonia to urea. In the absence of a functional urea cycle, ammonia accumulates in blood and tissues, with nervous tissue particular sensitive to it.

The mutation responsible for this disorder has been characterised as a single-base substitution in the gene for argininosuccinate synthetase (Dennis *et al.*, 1989) A → T substitution converts a CGA codon for arginine 86 to TGA, a translation - termination codon, resulting in a truncated, inactive peptide product (85 amino acids) rather than the normal active protein (412 amino acids). This mutation also eliminates a restriction site for AvaII; this forms the basis for detecting genotypes for this disorder.

In the late 1980's, it was estimated that in Australia 1 of every 250 Friesian calves born was affected and that more than 10% of Friesian cattle were carriers (Healy *et al.*, 1990; Healy, personal communication). The progenitor of most, if not all, Australian cases was Linmack Kriss King, a Canadian bull transferred at 1 month of age to the Milk Marketing Board in the United Kingdom. His semen was used extensively in Australia and other countries in the British Commonwealth. His US sire, Gray-View Crisscross, was also shown to be a carrier (Healy *et al.*, 1991). Because Crisscross was the sire of less than 2,000 offspring registered by the Holstein Association of America, citrullinaemia was expected to be less prevalent in the US than in Australia. Nevertheless, a study of the incidence among prominent US Holstein bulls was conducted (Robinson *et al.*, 1993b). Focus was on proven bulls among the top 400 for Type-Performance Index as of July 1990. A total of 273 from this group, including 90 of top 100 were tested as well as 94 sires-in-waiting. Only one heterozygote for the citrullinemia locus was identified, corresponding to 0.3% of all bulls tested. While the lone carrier bull, Exranco Triad, was among the top 400, he was ranked in the lower quartile of the group and was culled for other reasons before his citrullinaemia status was known. As he sired fewer than 2000 offspring registered by the Holstein Association of America, he was not widely used. Because he was distantly related to Gray-View Crisscross, appropriate sequencing of his DNA was performed and showed that he was a carrier of the same mutation. Of his daughters tested, 26 were carriers and 25 were normal, which is fully consistent with the 1:1 ratio expected for autosomal recessive inheritance.

IMPLICATIONS

At the present time, no carriers of DUMPS or citrullinaemia are known to be present among the top 400 US Holstein bulls. A high degree of confidence can be attached to the absence of DUMPS carriers because of the extensive testing for this condition since 1987. A good degree of confidence is attached to the absence of citrullinemia carriers because, while the testing has not been as extensive, the only bull identified on the 1990 list was of low impact and removed from service. The risk of lethal recessives for either condition is very low in populations mated to elite US Holstein bulls.

However, it is possible that carriers of these mutations could reappear among these leading sires in the US or other countries. This reappearance could arise from a new mutation, or more likely, from a distantly related and untested carrier, as via the maternal lineage. To guard against this, a modest program to monitor the leading bulls in each country should be maintained. In addition, any imported Holstein-Friesian germplasm should be checked to ensure freedom of these conditions for which effective and inexpensive tests exist.

It is argued that removing carriers for such inherited disorders from the breeding population of Holstein-Friesians could decrease the genetic progress being made in the breed. This may indeed be the case. In fact, DUMPS carrier cows do have higher production than their normal siblings (Healey and Shanks, 1987; Shanks and Greiner, 1992). Accordingly, it may be necessary to consider the costs and benefits of retaining carriers for inherited disorders among breeding sires. The summary culling of proven sires of the highest merit is generally unwarranted in view of the high cost of proving such bulls and their contribution to increased genetic progress. However, the long term retention of carrier animals among breeding sires is probably unwise. It is unlikely that dairy cows in most countries will be genotyped for such conditions on a wide scale in the foreseeable future. If carrier sires are retained, matings between heterozygotes will occur, with resultant generation of affected offspring. Concerns for animal welfare, both within and outside the dairy industry, may place a heavy cost on any policy that does not minimize the generation of affected offspring. Inexpensive, effective genotype testing does permit screening prospective young sires and salvaging normal offspring and most of the genetics of carrier sires.

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REFERENCES

Dennis, J.A.; Healy, P.J.; Beaudet, A.L.; O'Brien, W.E. (1989). Molecular definition of bovine argininosuccinate synthetase deficiency. *Proceedings of the National Academy of Sciences (USA)* **86**:7947 - 7950.

Harper, P.A.W.; Healy, P.J.; Dennis, J.A.; O'Brien, J.J.; Hayward, D.G. (1986). Citrullinaemia as a cause of neurological disease in neonatal Friesian calves. *Australian Veterinary Journal* **63**:378 - 380.

Healey, M.H. and Shanks R.D. (1987). Performance of females heterozygous for deficiency of uridine monophosphate synthase. *Journal of Dairy Science* **70**:945 - 951.

Healy, P.J.; Dennis, J.A.; Camilleri, L.M.; Robinson, J.L.; Stell, A.L.; Shanks, R.D. (1991). Bovine citrullinaemia traced to sire of Linmack Kriss King. *Australian Veterinary Journal* **68**:155.

Healy, P.J.; Harper, P.A.W.; Dennis, J.A. (1990). Bovine citrullinaemia: a clinical, pathological, biochemical and genetic study. *Australian Veterinary Journal* **67**:255 -260.

Holstein Association of America (1987). Registered Holstein Type - Production Sire Summaries. Vol.2. Holstein-Friesian Association of America, Brattleboro, VT.

Robinson, J.L.; Burns, J.L.; Magura, C.E.; Shanks, R.D. (1993b). Low incidence of citrullinemia carriers among dairy cattle of the United States. *Journal of Dairy Science* **76**: 853 - 858.

Robinson, J.L.; Dombrowski, D.B.; Harpestad, G.W.; Shanks, R.D. (1984). Detection and prevalence of UMP synthase deficiency among dairy cattle. *Journal of Heredity* **75**:277 - 280.

Robinson, J.L.; Drabik, M.R.; Dombrowski, D.B.; Clark, J.H. (1983). Consequences of UMP synthase deficiency in cattle. *Proceedings of National Academy of Sciences (USA)* **80**:321-323.

Robinson, J.L.; Popp, R.G.; Shanks, R.D.; Oosterhof, A.; Veerkamp, J.H. (1993a). Testing for deficiency of uridine monophosphate synthase among Holstein-Friesian cattle of North America and Europe. *Livestock Production Science* **36**:287 - 298.

Schwenger, B.; Schober, S.; Simon, D. (1993). DUMPS cattle carry a point mutation in the uridine monophosphate synthase gene. *Genomics* **16**:241 - 244.

Shanks, R.D.; Bragg, D.S.A.; Robinson, J.L. (1987a). Deficiency of uridine monophosphate synthase in Holstein dairy cattle: Inheritance and body measurements. *Journal of Animal Science* **64**: 695 - 700.

Shanks, R.D.; Bragg, D.S.A.; Robinson, J.L. (1987b). Incidence and inheritance of uridine monophosphate synthase in Holstein bulls. *Journal of Dairy Science* **70**:1893 -1897.

Shanks, R.D.; Dombrowski, D.B.; Harpestad, G.W.; Robinson, J.L. (1984). Inheritance of UMP synthase in dairy cattle. *Journal of Heredity* **75**:337 - 340.

Shanks, R.D. and Greiner, M.A. (1992). Relationships between genetic merit of Holstein bulls and deficiency of uridine monophosphate synthase. *Journal of Dairy Science* **75**:2023 - 2029.

Shanks, R.D. and Robinson, J.L. (1989). Embryonic mortality attributed to inherited deficiency of uridine monophosphate synthase. *Journal of Dairy Science* **72**: 3028 -3032.

Shanks, R.D.; Popp, R.G.; McCoy, G.C.; Nelson, D.R.; Robinson, J.L. (1992). Identification of the homozygous recessive genotype for the deficiency of uridine monophosphate synthase in 35 - day embryos. *Journal of Reproduction and Fertility* **94**:5 - 10.