The *CHRNE* 470del20 mutation causing congenital myasthenic syndrome in South African Brahman cattle: Prevalence, origin, and association with performance traits[1]

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ABSTRACT: Genotyping of the South African, registered, Brahman cattle population for the 470del20 mutation in the *CHRNE* gene causing congenital myasthenic syndrome (CMS) was carried out in 1,453 animals. Overall prevalence of carriers was 0.97% (0.50 to 1.68%, 95% confidence interval). Carrier prevalence among breeding bulls in 2004 was 1.22% (0.65 to 2.15%, 95% confidence interval), and had not changed significantly since 2000. Using segregation analysis, CMS genotype probabilities were calculated for all 612,219 animals in the pedigree, leading to the identification of 2 founder animals as the most likely original carriers. Pedigree analysis revealed no ancestors common to all known carriers, but rather that the mutation had been introduced at least twice into the South African Brahman population, probably via animals imported from the United States. The effects of CMS genotype probability on adjusted birth, 200-d, 400-d, and 600-d BW, as well as on EBV for birth, 200-d, 400-d, and 600-d BW, and milk, were estimated, accounting for effects of sire. Heterozygosity for the *CHRNE* 470del20 mutation was associated with a 13.3-kg increase in adjusted 600-d BW ($P = 0.03$). Positive effects of CMS carrier status on all BW EBV were found, but no effect was found on milk EBV. We conclude that CMS carriers have a BW advantage at 600 d and possibly also at birth, 200 d, and 400 d. This may confer a selective advantage and tend to increase the frequency of the mutation.

Key words: Brahman cattle, congenital myasthenic syndrome, genotyping, heterozygote, pedigree analysis

INTRODUCTION

Congenital myasthenic syndrome (**CMS**) in Brahman cattle is caused by homozygosity for a 20 base pair deletion (**470del20**) in the *CHRNE* gene, resulting in absence of the epsilon subunit of the nicotinic acetylcholine receptor at the neuromuscular junction (Kraner et al., 2002). This results in a nonfunctional adult-type acetylcholine receptor, causing progressive muscle weakness and mortality in young calves (Thompson, 1998; Thompson et al., 2003b).

A PCR-based DNA test for the mutation has been developed and used for screening of breeding animals (Thompson et al., 2003b). Screening of a limited number of animals has revealed that the estimated prevalence of carriers in the South African pedigree Brahman population was 0.67% (95% confidence interval: 0.17, 2.1%; Thompson et al., 2003a). In the same report, a survey of 2,434 stored Australian Brahman DNA samples detected 2 carriers (0.08%), but none among 541 samples from foreign (mainly American) Brahmans tested before import to Australia from 1995 to 2003. It is not known whether the mutation is present in Brahman populations elsewhere in the world, although it is thought to have been introduced into the South African population by imported ancestors (Thompson et al., 2003b).

Although heterozygotes appear phenotypically normal (Thompson et al., 2003b), it is not known whether carrier status is associated with traits that are used in

the selection of breeding animals, and hence whether the frequency of the mutation is likely to increase or decrease due to selection on performance traits.

The objective of this study was to estimate more precisely the prevalence of carriers of the CMS mutation in the registered South African Brahman breeding population, to determine the origin of the mutation in the South African Brahman population by identifying common ancestors of known carriers, and to determine whether there is any association between CMS genotype and measured performance traits.

MATERIALS AND METHODS

Genotyping of Brahman cattle registered with the Brahman Cattle Breeders' Society of South Africa for the *CHRNE* 470del20 mutation was performed on a voluntary basis, together with compulsory DNA profiling for parentage verification, in accordance with breed society policy. Deoxyribonucleic acid was extracted from tail hair roots, and exon 5 of *CHRNE* was amplified as previously described (Thompson et al., 2003b). The DNA amplicons were size-separated by polyacrylamide gel electrophoresis, and cattle were classified as homozygous wild-type (noncarrier) or heterozygous (carrier). Results up to August 2005 were included in the analysis (n = 1,453). Animal care and use committee approval was not obtained for this study because the data were obtained from the breed society database.

The prevalence of carriers among bulls that sired at least 1 registered calf and the prevalence of carriers among registered calves born were calculated for each year from 2000 to 2004. Animals that had been purposively sampled were not included in these calculations. Exact hypergeometric confidence intervals (≥95%) for these prevalences were obtained using StatCalc 1.1 (Krishnamoorthy, 2000).

The South African Brahman pedigree contained records of 310,320 males and 301,878 females, including 15,680 sires and 160,156 dams, tracing back to animals born in the early 1940s. Genotype probabilities for all animals in the pedigree were calculated using the GENEPROB program, which employs the segregation analysis algorithm of Kerr and Kinghorn (1996). The genotype probabilities were used to identify ancestors with a relatively high probability of being heterozygous for the 470del20 mutation. Using Pedigree Viewer (Kinghorn, 1994), the entire ancestor tree for each known carrier was extracted, and their common ancestors were identified.

Performance records (birth weight and 200-d, 400-d, and 600-d BW), adjusted for age at weighing and age of dam, were obtained from the Brahman Cattle Breeders' Society of South Africa. Contemporary groups were defined based on herd of origin, herd at time of weighing, calving year, sex, birth number (single/twin), birth type (natural/embryo transfer), breeder-defined management group, parity of dam (heifer/multiparous, for birth weight only), recipient dam breed (embryo transfer calves), and age (maximum age range in a group was 45 d for birth and weaning weights, and 60 d for 400-d and 600-d BW).

To estimate the effect of CMS carrier status on birth weight, and 200-d, 400-d, and 600-d BW, performance records were regressed on genotype probability, in a model that also accounted for contemporary group and sire. The sire effect was included to account for family effects possibly being confounded with genotype probabilities, through selection or drift. Relationships among sires were accounted for by tracing back sires to their ancestors, up to a maximum of 9 generations. The statistical model was

$$y = b.P(\text{het}) + \text{sire} + \text{cg} + e, \qquad [1]$$

in which y is the BW performance record; b is the effect of carrier status on this performance; $P(\text{het})$ is the probability of being heterozygous for the 470del20 mutation, calculated using GENEPROB; sire is a random effect with covariances proportional to their additive genetic relationships; cg is a fixed effect accounting for contemporary group; and e is the residual.

In addition, BREEDPLAN EBV based on BLUP (Henderson, 1984) were obtained, and the effect of an animal's CMS carrier status on its EBV for birth weight; 200-d, 400-d, and 600-d BW; and milk were estimated using a sire model. Only EBV with an accuracy >75% were used, except for milk EBV, where a cut-off of 65% was used because there were only 32 milk EBV with an accuracy >75%. The statistical model was

$$y = b.P(\text{het}) + \text{sire} + e, \qquad [2]$$

where y is the bull's EBV, and sire was fitted as in model 1. The residual variance was assumed homogeneous, which is partly justified through only using highly accurate EBV. Analysis was done using residual maximum likelihood as implemented in ASReml (Gilmour et al., 2002).

RESULTS

Prevalence of CMS Mutation

Genotyping results were available for 1,453 animals (1,102 males and 351 females), representing over 300 of the approximately 500 registered herds in South Africa. Of these, 210 animals had been purposively sampled, by virtue of their relationship to known carriers or during investigations of calf mortality. Of the 1,243 nonpurposively sampled animals genotyped, 12 (0.97%; 95% confidence interval 0.50 to 1.68%) were heterozygous for the 470del20 mutation. An additional 4 carrier bulls were detected as a result of the purposive sampling. No animals were found to be homozygous for the mutation. Table 1 shows, for each year from 2000 through 2004, the number of bulls that sired at least 1 registered calf, the number of registered calves born,

Table 1. Prevalence of *CHRNE* 470del20 carriers among registered South African Brahman breeding bulls and registered calves, 2000–2004

	Registered breeding bulls used				Registered calves born			
Year	Total[1]	Number tested	CMS carrier prevalence, %	95% confidence interval[2]	Total	Number tested	CMS carrier prevalence, %	95% confidence interval[2]
2000	1,515	201	1.00	0.13, 3.43	19,734	215	0.93	0.11, 3.30
2001	1,481	273	1.10	0.20, 2.97	19,072	202	0.50	0.01, 2.72
2002	1,433	370	2.43	1.26, 4.32	18,297	114	0.00	0.00, 2.59
2003	1,261	489	1.64	0.79, 2.85	14,426	56	0.00	0.00, 5.21
2004	1,069	574	1.22	0.65, 2.15	13,347	21	0.00	0.00, 13.29

[1]Bulls that sired at least one registered calf.
[2]Exact hypergeometric confidence interval (actual confidence level varies between 95 and 96.8%).

the number sampled from each, and the prevalence of CMS carriers. There were no significant differences in carrier prevalence between years, or between bulls used and calves born within each year.

Pedigree Analysis

There was insufficient information for the segregation analysis algorithm of GENEPROB to provide a stable estimation of base population allele frequency; therefore, the frequency of the dominant, wild-type allele in the base population was set at 0.98. This was slightly lower than the raw observed frequency of 0.994 in genotyped animals, on the assumption that the mutant allele frequency had been decreasing very slowly over generations. The distribution of CMS carrier probabilities in the Brahman pedigree is shown in Table 2. For the 5,883 half-founder or founder animals in the pedigree (defined as foreign-born animals, with one or both parents unknown), segregation analysis calculated P(het) to be <0.1 in all but 13; of these, 2 were markedly greater (0.19 and 0.22). No single carrier founder could be identified for all known carriers. However, 36 animals were identified, each of which was a common ancestor to all but one of the known carriers. Among these 36 animals were the 2 founder animals with the greatest P(het). One of the 36 was an imported American Brahman bull, whereas the others were all ancestors of animals or semen imported from the United States.

Effect on Performance

Performance records were available for 118,390 animals, descended from 4,583 sires. However, relatively few animals (n = 5,130) had all 4 BW records available, whereas the majority (n = 67,314) had only 1 of the BW recorded. Table 3 shows the number of animals for which each BW was available, the number of sires represented, and the effect of CMS carrier status on BW, using model 1. Heterozygosity for the 470del20 mutation was associated with a 13.3-kg greater 600-d BW (P = 0.03). No significant effects were detected for the other traits, although birth and 400-d BW also tended to be greater in carriers. Heritability estimates

obtained from the sire model were 0.32 for birth weight, 0.27 for 200-d BW, 0.28 for 400-d BW, and 0.27 for 600-d BW.

There were 35,549 animals, descending from 1,896 sires, with 1 or more EBV with accuracy >75% (>65% for milk EBV). However, very few animals (n = 270) had all 5 EBV available, whereas the majority (n = 29,860) had only 1 EBV available. Table 4 shows the number of animals for which each EBV was available, the number of sires represented, and the effect of CMS carrier status on each EBV, using model 2. Consistently positive effects of 470del20 heterozygosity on BW EBV were estimated, but no effect was found on milk EBV. The effect on 600-d BW using EBV (+14.9 kg) was comparable with that using own phenotype (+13.3 kg).

DISCUSSION

Prevalence of CMS Mutation

The 1.2% prevalence of carriers among 2004 breeding bulls was consistent with a previous estimate based on a smaller sample (Thompson et al., 2003a). The failure to detect any homozygous recessives was expected because it was assumed that this genotype results in early mortality. There was insufficient evidence to show any recent change in carrier prevalence. Because of the low numbers of younger animals tested since 2000, it is difficult to say whether the apparently clear downward trend in the prevalence of carrier calves born is real or due to random sampling error. However, due to the 3 to 4 yr lag period between birth and selection for breeding, it is possible that any downward trend in the frequency of carrier calves born has not yet resulted in significant change in the frequency of carriers among breeding bulls. For a lethal recessive mutation such as this, a decrease in carrier prevalence over successive generations is to be expected due to natural mortality of homozygous recessives. However, this decrease is slow: assuming random mating and no selective advantage or disadvantage of the heterozygote, a carrier prevalence of 1% is expected to decrease to 0.995% over 1 generation (Hedrick, 2000).

The animals were not sampled randomly because participation in the testing program was voluntary.

Table 2. Distribution of *CHRNE* 470del20 carrier probabilities in the South African registered Brahman pedigree, calculated by segregation analysis

	Frequency			
$P(het)^1$	Animals with performance records[2]	Animals with accurate EBV[3]	Founders and half-founders[4]	Total
0 to 0.01	54,364	22,688	1	123,478
>0.01 to 0.05	54,067	10,677	5,809	444,957
>0.05 to 0.1	4,104	949	60	25,294
>0.1 to 0.2	2,944	634	12	9,688
>0.2 to 0.3	1,770	358	1	5,760
>0.3 to 0.4	178	29	0	569
>0.4 to 0.5	844	186	0	2,187
>0.5 to 0.6	103	20	0	253
>0.6 to 0.99	5	3	0	17
>0.99	11	5	0	16
Total	118,390	35,549	5,883	612,219

[1]Probability of being heterozygous for the 470del20 mutation.
[2]Animals with 1 or more of the following records available: birth weight, or 200-d, 400-d, or 600-d BW.
[3]Animals with 1 or more of the following available: birth weight EBV (accuracy > 75%), 200-d BW EBV (accuracy > 75%), 400-d BW EBV (accuracy > 75%), 600-d BW EBV (accuracy > 75%), or milk EBV (accuracy > 65%).
[4]Defined as foreign-born, with 1 or both parents unknown.

Nevertheless, most samples submitted for the mandatory DNA profiling for parentage verification were also elected to be genotyped for CMS. It is possible that breeders who suspected the presence of the mutation in their herd and wished to avoid the risk of negative publicity may have been unwilling to have their bulls genotyped, resulting in an underestimate of the true carrier prevalence. Another possible source of bias is the fact that carrier prevalence among breeding bulls and calves for each year was not measured during that year, but mainly between 2003 and 2005; thus, only those animals that survived until then were sampled. If there had been a difference in survival between carriers and noncarriers (i.e., differential genotype fitness) due to natural or artificial selection, or both, prevalence estimates may have been biased.

Nevertheless, the presence of the 470del20 mutation in the Brahman population at a frequency of this order of magnitude is unlikely to be economically significant for the breed as a whole. Assuming random mating, and that carrier prevalence among breeding cows is equal to that among bulls, a carrier prevalence of 1.22% (95% confidence interval 0.65 to 2.15%) in the breeding population will result in the birth of 0.004% homozygous recessive calves (95% confidence interval 0.001 to 0.012%). For the South African pedigree Brahman population of approximately 15,000 cows, this would mean only between 0.16 and 1.73 affected calves per year. However, carriers are not randomly distributed throughout the population, and the condition may become economically significant for individual breeders. In the herd in which the mutation was originally detected, 12% of the animals were found to be carriers (Thompson et al., 2003b). Inadvertent use of a carrier bull on all cows in this herd would have resulted in 3% of the calves being affected with CMS. An increase in the frequency of the mutation might occur when the carrier animals have a selective advantage due to a favorable effect of the mutation on a performance trait or to its linkage with a beneficial QTL allele. The associations between carrier status and performance traits were estimated in this study and are discussed below.

Pedigree Analysis

It is unlikely that a similar size deletion has occurred more than once in the same region of the *CHRNE* gene because it shows no obvious features of a mutation hotspot (Thompson et al., 2003b). Therefore, assuming that there are no errors in the pedigree, the absence of a

Table 3. Effect of heterozygosity for the *CHRNE* 470del20 mutation on growth phenotypes in South African Brahmans, using a sire model

	Number of records				95% confidence	
Phenotype	Animals	Sires	b	SE(b)	interval	*P*-value
Birth weight	70,099	3,265	0.66	0.48	−0.28, 1.60	0.17
200-d BW	62,760	3,133	−0.50	2.87	−6.13, 5.13	0.86
400-d BW	38,980	2,528	5.66	4.75	−3.65, 14.97	0.23
600-d BW	27,079	2,154	13.30	5.94	1.66, 24.94	0.03

Table 4. Effect of heterozygosity for the *CHRNE* 470del20 mutation on growth and milk EBV in South African Brahmans, using a sire model

| | Number of records | | | | 95% confidence | |
EBV	Animals	Sires	*b*	SE(*b*)	interval	*P*-value
Birth weight	32,468	1,755	1.13	0.24	0.66, 1.60	<0.001
200-d BW	3,143	519	9.08	3.26	2.69, 15.47	0.005
400-d BW	5,519	595	12.12	3.97	4.34, 19.90	0.002
600-d BW	4,862	556	14.93	5.11	4.91, 24.95	0.004
Milk	349	99	−1.55	1.86	−5.20, 2.10	0.41

single common ancestor leads to the conclusion that the 470del20 mutation was introduced at least twice into the South African Brahman population. This was most likely by the importation of carrier animals or semen from the United States because the most likely carrier founders, identified by segregation analysis, were American ancestors. However, to our knowledge, no disease similar to CMS has previously been described in American Brahmans or in any other breed of cattle. The Brahman breed was developed in southern United States during the late 19th and early 20th centuries, mainly from the Ongole, Kankrej, Gir, and Krishna Valley breeds from India (Porter, 1991). Whether the mutation event occurred in the United States, or in one of the ancestral Indian breeds, would require further investigation.

Effect on Performance

Regression on genotype probability, rather than on known genotype, allows utilization of records from non-genotyped animals, thus increasing the power of the analysis. This approach has been used in an animal model for QTL detection (Weller et al., 2003), producing similar estimates to a model utilizing information from genotyped animals only.

In retrospect, our assumption of a base population wild-type allele frequency of 0.98 may not have been accurate because it was based on the assumption that the mutant allele frequency had slowly been decreasing over generations. A possible BW advantage in the heterozygote may instead have caused the frequency to remain stable or increase slightly. However, only animals born since 1984 had performance records, whereas the pedigree extended back to the 1940s. The assumed base population allele frequency would therefore have had only very little effect on the calculated genotype probabilities of the animals included in the analyses. Consequently, this is unlikely to have affected the results of the regression of performance on genotype probability. In addition, *P*(het) calculated using base population allele frequencies of 0.98 and 0.994 (or slightly greater) would be almost perfectly correlated and would therefore yield similar effect estimates.

In the analysis of the effects of carrier status on phenotypes or EBV, genetic relationships between sires were taken into consideration to avoid overestimation

of levels of significance (Kennedy et al., 1992). A sire model was used for the analysis because it is computationally much easier, and dams usually have only 1 or a few offspring. Sire model results were compared with those from an animal model for 400-d and 600-d BW (data not shown) and agreed closely, although the sire models tended to yield more conservative and less significant estimates. The heritability estimates obtained from the sire model for birth and 200-d, 400-d, and 600-d BW were within ranges reported elsewhere (Davis, 1993). We consider the sire model to be an acceptable alternative to the animal model because selection is mainly among sires. Most of the potential confounding due to family will therefore be due to sire family, which is accounted for in the sire model.

It is interesting that the models of EBV showed consistently significant positive effects of CMS carrier status on BW, which increased with increasing age. Although the effect on 600-d BW EBV was similar to the effect on 600-d BW (own phenotype), it is unclear why the effects at lower ages differed between models. The 2 analyses used different subsets of animals, which may explain the difference in estimates between the 2 approaches. The EBV used in the analysis had an accuracy of >75% (65% for milk EBV), and consequently, the residual variance for the EBV was substantially lower than that of a single phenotype, which had a positive effect on the accuracy of the estimates. However, this was counterbalanced by the lower number of animals with EBV of high accuracy. The exclusion of animals with low accuracy EBV meant that animals of the poorer performing genotype were less likely to be included in the analyses, due to their having insufficient progeny. This could have resulted in underestimates of the effect of genotype on EBV.

An EBV is an estimate of the additive or transferable genetic merit for a given trait compared with the breed average, incorporating the animal's own phenotype, adjusted for age at weighing and age of dam and compared within contemporary groups, as well as the performance of relatives. Because of inclusion of the latter, EBV of related animals are not regarded as independent observations, and regression models of EBV may therefore result in underestimation of standard errors. However, only using EBV of high accuracy, which are based mainly on progeny, will tend to minimize this

effect because correlations between EBV should be lower.

We conclude that there is strong evidence that CMS carriers have greater 600-d BW, and possibly greater birth, 200-d, and 400-d BW. This effect may be due to linkage or pleiotropy. The *CHRNE* gene has not been mapped on the USDA-MARC linkage map (USDA-ARS, 2006) but is located in a poorly mapped region of BTA 19 between X82261 at 19.4 cM and BMS2142 at 44.7 cM. Known or suspected QTL for growth traits on BTA 19 include one for birth weight and ADG on feed at 67.4 to 98.4 cM (Taylor et al., 1998) and ones for preweaning ADG at 4.8 to 15.9 cM and ADG on feed at 52 to 52.7 cM (Kneeland et al., 2004). It is possible that linkage may exist between *CHRNE* and one of these or other unknown QTL.

A BW advantage conferred by the carrier state may have resulted in a selective advantage for animals heterozygous for the CMS mutation, which would tend to increase the frequency of the mutant allele in the population. However, with the availability of a screening test for the mutation, many of the carriers still present in the population are likely now to be identified and excluded from breeding, and the frequency is expected to drop considerably. Alternative strategies for the control of a recessive disease allele such as this, where there is differential fitness between genotypes, have recently been modeled and discussed (Thompson et al., 2006). Studies such as the present one can assist in determining appropriate relative genotypic fitness values for input into such models.

IMPLICATIONS

The *CHRNE* 470del20 mutation causing congenital myasthenic syndrome is segregating in the South African Brahman cattle population at a low frequency, with approximately 1.2% of breeding bulls heterozygous for the allele. The allele frequency did not change markedly between 2000 and 2004. With the possible exception of individual herds, with a relatively high frequency of carrier cows, in which bulls of unknown congenital myasthenic syndrome genotype are used, the mutation is unlikely to have a significant economic impact on the breed. However, there is evidence that carriers have greater 600-day body weight, and possibly greater birth, 200-day, and 400-day body weight, which may confer a selective advantage. Selection on these traits may tend to increase the frequency of the mutation. Nevertheless, continued genotyping of breeding animals should allow breeders to virtually eliminate the disease.

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