



Molecular marker heterozygosities and genetic distances as correlates of production traits in F_1 bovine crosses

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Abstract

Several studies have investigated the relationship between heterozygosity, genetic distance and production traits. The objective of the present study was to evaluate the influence of the degree of heterozygosity and genetic distance on growth, carcass and reproductive related features in F_1 bovine crosses. We tested 10 polymorphic markers in 330 purebred cattle (Nelore, Canchim, Aberdeen Angus and Simental) and 256 crossbred cattle belonging to four crossbred groups. Individual heterozygosities (H_i) and multilocus genetic similarity (D_m) were estimated and used in correlation analysis against individual phenotypic measurements. Significant ($p < 0.05$) H_i effects occurred for birth weight, 15 to 18 month weight, hot carcass weight and *longissimus* rib eye area. The extent to which increased heterozygosity (ΔH) in F_1 crosses can be predicted from the genetic distance of parental breeds was also investigated using Nei's standard genetic distance (D_s) and standard heterozygosity (H_s). High correlations were found between ΔH_i , ΔH_s and the D_s of the parental breeds. Our results suggest that heterozygosity of the ten molecular markers used in this study may affect live weight during at least one growth phase. Parental genetic distance was a suitable predictor of the degree of progeny heterozygosity.

Key words: bovine crosses, molecular markers, heterozygosity, genetic distance, production traits.

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Introduction

The selection of suitable sires for the production of the first filial generation (F_1) is an important prerequisite for the success of any breeding program, but this is complicated by the fact that classic sire selection relies on the evaluation of the phenotypic value of the progeny which is time-consuming for large farm animals. An essential assumption underlying the prediction of hybrid performance is the correlation between heterozygosity and heterosis and in recent years molecular markers have been proposed for the prediction of heterosis and genetic relationship studies of both animal and plant species.

Several studies have investigated the relationships between genetic distance, degree of heterozygosity and production traits in populations of both feral and domesti-

cated animal and plant species. Many of these studies have shown positive correlations between heterozygosity at a small number of marker loci and traits related to fitness (Pierce and Mitton, 1982; Garton *et al.*, 1984; Stuber *et al.*, 1992; Xiao *et al.*, 1995), although negative correlations have also been reported (Zhang *et al.*, 1996). When the correlation involves heterozygosity based on allozymes it is difficult to distinguish between the direct effects of the allozyme loci and their influence as neutral markers (Pogson and Zouros, 1994), because of which polymorphisms such as microsatellites and blood groups, that are not subject to direct selection, are normally used. This approach is consistent with the associative overdominance hypothesis that predicts that the cause of correlation is not specific to the type of genetic marker used. The use of markers associated with production traits (*i.e.* commercially desirable traits) has been proposed by Charcosset *et al.* (1991) to strengthen the accuracy of prediction because any correlation would arise from the associated effect of

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each marker locus. Regarding allele number, monomorphic or nearly monomorphic loci should be avoided due to the low probability that they will affect individual heterozygosities and the fact that a lower number of polymorphic systems can provide the same information (Cepica *et al.*, 1995). If microsatellites are used, it is important to verify that Mendelian allele segregation is occurring, due to the high occurrence of null alleles (Eggleston-Stott *et al.*, 1997) and preferential amplification (Rodriguez *et al.*, 2001), and in both cases the non-detectable alleles must be considered in the heterozygosity estimate.

As far as we know there have been no previous reports of studies on bovines concerning parental genetic distance, heterozygosity and production traits. The objective of the work presented in this paper was to rectify this lack of information by investigating the relationship among parental genetic distance, heterozygosity and production traits (growth, carcass and reproductive related features) in F1 bovine crosses.

Material and Methods

Experimental conditions

The animals used in this study resulted from the following crosses: Nelore (NE) cows mated to five Aberdeen Angus (AN) bulls (TA crossbred group, number of progeny ($N_p = 72$), five Canchim (CN) bulls (RC crossbred group, $N_p = 74$), four Simmental (SI) bulls (TS crossbred group, $N_p = 65$) and two Nelore (NE) bulls (NI crossbred group, $N_p = 44$), totaling 256 progeny. Offspring belonging to the TA, RC and TS genetic groups were born in 1998 and 1999 while NI offspring were born in 1999 only. The Nelore cows used in the crosses were from several farms and represented a sample of the Brazilian herd. The same cows were used in both reproductive periods (except for some replacements) and their ages at calving ranging from 3.4 to 17.6 years (average 6.6 years). Cows grazed on fertilized *Brachiaria brizantha* pastures and received supplementary sugarcane during the winter. Calves received a concentrate ration limited to 1.5 kg per day and were weaned between 5 and 8 months of age. After weaning the calves grazed fertilized *Cynodon dactylon* (coastcross) grass during the raining season, supplemented with 3 kg concentrate per day plus a complete mineral mixture or with only a complete mineral mixture. During the dry season, twelve-month old males were divided into two blocks according to body weight and fed in feedlot while heifers grazed on fertilized *Cynodon dactylon* and received sugarcane and concentrate as a supplement.

The restriction fragment length polymorphisms (RFLPs) used were as follows: κ -casein (LGB)-*Hinf*I (35.5 cM on *Bos taurus* chromosome 6 - BTA 6) (Medrano and Cordova, 1990); β -lactoglobulin (LGB)-*Hae*III (108.7 on BTA 11) (Ron *et al.*, 1994); growth hormone (GH)-*Alu*I (65.7 cM on BTA19) (Lucy *et al.*, 1993); and the

microsatellites *BM8246* (76.2 cM on BTA 1) (Stone *et al.*, 1995), *BM1224* (51.2 cM on BTA4) (Bishop *et al.*, 1994), *BM1329* (35.5 cM on BTA 6), *BM7160* (0 cM on BTA 7), *BM6026* (6.7 cM on BTA 5), *CSFM50* (23.0 cM on BTA 2) (Barendse *et al.*, 1997) and *TEXAN15* (77.2 cM on BTA 5) (Burns *et al.*, 1995). Except for *BM6026*, *TEXAN15*, *BM1329* and *CSN3* all the markers were on different chromosomes.

Statistical analysis

Allele frequencies were obtained by direct counting (Weir, 1996) and heterozygosity measured as the mean standard heterozygosity (H_s) calculated over all loci (Weir, 1996) and the individual heterozygosity (H_i), estimated as the proportion of heterozygote loci over the ten loci in an individual animal (Mitton and Pierce, 1980). Since there was evidence for at least one null allele at the *BM1224* locus segregating in the Nelore population (Tambasco *et al.*, 2000), segregation analysis was employed to detect whether homozygotes should or should not be considered heterozygotic for the null allele. The increase in heterozygosity (Cepica *et al.*, 1995) of the progeny in relation to the mean heterozygosity of the two parental populations (ΔH_s) or individuals (ΔH_i) were calculated as $\Delta H\% = (H_{F1} - H_p) \times 100/H_p$, where H_{F1} is either the H_s or the mean of H_i in the progeny of a given cross and H_p is the arithmetic mean of H_s or H_i of the parental populations. Nei's standard genetic distance (Nei, 1972), based on allele frequencies estimated from 50 unrelated animals of each breed (Vasconcellos *et al.*, In press), was used to determine the genetic distances between breeds (D_s). The genetic distance between individuals was calculated using the method developed by Bowcock *et al.* (1994) and Ciampolini *et al.* (1995) based on pair wise inter-individual comparisons resulting in a multilocus genetic similarity value complementary to the multilocus genetic distance (D_m). The H_i and D_m parameters allowed the correlation of each individual heterozygosity and genetic distance value with the corresponding phenotypic measure. These measures were: birth weight (BW); weaning weight (WW); twelve subsequent weight measurements from 230 days (W1) to about 580 days (W12); body weight at first calving (W1C) and estrus (W1E); and the carcass traits hot carcass weight (HCW), backfat thickness (RFT), *longissimus* rib eye area (REA) and carcass yield (CY). For both sexes, heterozygosity effects on body weight (BW, WW and W1 to W12) were analyzed using the SAS (Statistical Analysis System) program (Carry, 2000) and the GLM (General Linear Models) procedure using the statistical model $Y_{ijklmn} = \mu + GG_i + S_j + T_k + A_l + YB_m + b(H_i) + e_{ijklmn}$, where Y_{ijklmn} represents the trait evaluated on the $ijklmn^{\text{th}}$ animal; μ is the overall mean for each trait; GG_i , S_j , T_k , A_l , and YB_m are classificatory fixed effects associated with the i^{th} genetic group, the j^{th} sex, the k^{th} nutritional treatment, the l^{th} age and the m^{th} year of birth; b is the linear regression for the individual degree of

heterozygosity H_i ; and $e_{ijklmno}$ is the random error associated with the $ijklm$ th observation. The same model was used to assess the influence of multilocus genetic distance.

For reproductive traits (W1C and W1E), the GLM procedure used a model comprising all the effects described above with the exception of the sex effect. Carcass composition traits were analyzed considering genetic group, nutritional treatment, year of birth and feedlot block with the heterozygosity or multilocus genetic similarity as sources of variation. Pearson correlation coefficients were calculated for the ΔH_s , ΔH_i , D_s and D_m variables using the CORR procedure of the SAS program (SAS, 2001).

Results

Heterozygosity and genetic distance

Segregation analysis revealed the presence of null alleles for the *BMI224* microsatellite in the Nelore females and this had to be taken into account when calculating the heterozygosity, the individual heterozygosity (H_i) ranging from 0.2 to 0.9 and the multilocus genetic distance (D_m) values from 0.2 to 0.7. The mean standard heterozygosity (H_s) and H_i along with the increase in these values in the crosses (ΔH_i and ΔH_s) are presented in Table 1.

The Pearson correlation analysis of the relationship between the genetic distances of the parental breeds (D_m , D_s) and the increase in heterozygosity (ΔH_s , ΔH_i) of their crosses is summarized in Table 2. Despite their high values the correlation coefficients between the multilocus genetic distance (D_m) and ΔH_s and ΔH_i were not significant, although high correlation values were detected between the genetic distances between breeds (D_s) and ΔH_s and ΔH_i ($p < 0.05$). These results were to be expected because the correlation between ΔH_s and ΔH_i was 0.97 ($p < 0.05$). No correlation was found between the D_m and D_s genetic distances.

Effect of individual heterozygosity and multilocus genetic distance on phenotypic traits.

The H_i data comprised only animals known to be heterozygotes or homozygotes as confirmed by segregation analysis. Results of the ANOVA for the various weight measures and carcass composition traits are summarized in Tables 3, 4 and 5. With the exception of body weight (BW) and carcass yield (CY), significant genetic group effects ($p < 0.01$) were verified for all traits but this was to be expected because the four sire breeds used in the crosses are different in body size and weight. At each phenotypic measure both the age and sex of the animal significantly affected all weights except for BW ($p < 0.01$). When included in the analysis, nutritional supplementation had a significant effect ($p < 0.01$) on all characteristics except for body weight at first calving (W1C) and carcass composition traits. A birth year effect was observed for most traits ex-

Table 1 - Standard (H_s) and individual (H_i) heterozygosity for all the genetic groups and the increase in percentage for these parameters ($\Delta H_s\%$, $\Delta H_i\%$) in the progeny compared with the mean of the two parental populations.

	H_s	$\Delta H_s\%$	H_i	$\Delta H_i\%$
Sire breeds				
Canchim (CN)	0.596	-	0.570	-
Simental (SI)	0.558	-	0.560	-
A. Angus (AN)	0.530	-	0.520	-
Nelore (NE)	0.459	-	0.480	-
Dam breed				
Nelore (NE)	0.459	-	0.480	-
Crossbred groups				
CN x NE (RC)	0.596	13.09	0.620	18.1
SI x NE (TS)	0.607	19.49	0.630	21.2
AN x NE (TA)	0.643	30.16	0.650	30.0
NE x NE (NI)	0.469	2.18	0.480	0

cept BW, W1, W12, W1C, backfat thickness (RFT), *longissimus* rib eye area (REA) and carcass yield (CY).

At about 15 to 18 months H_i had a significant effect ($p < 0.05$) on BW, W10, W11 and W12, but it should be noted that at these ages the sample was composed mainly of heifers because bulls were gradually slaughtered for carcass composition analysis during the experiment and this is also the reason why the number of phenotypic measurements declined during the course of the study. Despite this, the fitness model (R^2) for these traits was high (0.77 to 0.85). The H_i regression coefficient for BW, W10, W11 and W12 indicated that each heterozygote locus in the 10 analyzed contributed with an increase of 0.437 kg for BW, 4.42 kg for W10, 4.22 kg for W11 and 4.53 kg for W12, as calculated from the regression analysis. For carcass composition traits, H_i showed a significant effect on hot carcass weight (HCW) and REA ($p < 0.05$), with the regression coefficient indicating an increase of 63 g for HCW and 1.89 cm² for REA for each heterozygote locus.

Although both genetic group and age significantly affected weight at estrus W1E and W1C ($p < 0.05$) these re-

Table 2 - Pearson correlation coefficients among the multilocus genetic distance (D_m), Nei's standard genetic distance (D_s), the increase in individual and standard heterozygosities of the crosses (ΔH_i , ΔH_s).

	D_m	D_s	ΔH_s	ΔH_i
D_m	-			
D_s	0.85	-		
ΔH_s	0.84	0.95*	-	
ΔH_i	0.94	0.96*	0.97*	-

* $p < 0.05$.

Table 3 - Summary of analysis of variance (ANOVA) for birth weight (BW), weaning weight (WW) and the five subsequent weights (W1, W2, W3, W4 and W5).

Source of variation	Df	Mean square						
		BW	WW	W1	W2	W3	W4	W5
Genetic group	3	36.97	9143.80**	10255.28**	12027.67**	12797.04**	14858.48**	17068.57**
Sex	1	19.14	11342.96**	38.07**	26472.97**	35353.96**	36930.88**	50414.98**
Nutritional treatment	1	-	-	-	8469.03**	35404.41**	72417.67**	109171.80**
Age	1	-	69214.99**	84872.36**	73099.23**	100673.77**	120009.39**	112348.48**
Year of birth	1	19.81	10298.91**	38.08	4503.75**	25031.80**	36199.98**	74025.34**
Individual heterozygosity	1	71.08*	83.01	684.84	734.21	43.51	20.99	3.60
Error (Df) ^{&}	-	14.80 (236)	458.67 (228)	427.71 (210)	407.08 (209)	436.29 (207)	488.01(207)	617.12(204)

[&]Degrees of freedom.
*p < 0.05. **p < 0.01.

Table 4 - Summary of analysis of variance (ANOVA) for weights W6, W7, W8, W9, W10, W11 and W12.

Source of variation	Df	Mean square						
		W6	W7	W8	W9	W10	W11	W12
Genetic group	3	20441.18**	24594.55**	26536.19**	31331.68**	18265.84**	16009.52**	18160.82**
Sex	1	146717.43**	281891.84**	580376.73**	718789.31**	320447.77**	294161.66**	61937.16**
Nutritional treatment	1	99783.93**	89449.63**	57271.79**	32020.80**	30011.20**	23273.44**	21170.66**
Age	1	93915.05**	105659.95**	102313.28**	80632.71**	47035.22**	28299.83**	21498.17**
Year of birth	1	36934.81**	30912.89**	27303.24**	3520.40*	2736.13	11452.53**	777.08
Individual heterozygosity	1	167.92	356.51	1534.70	2534.19	3741.26*	3119.85*	3107.84*
Error (Df) ^{&}	-	777.47 (180)	852.99 (180)	957.56 (177)	833.43 (162)	739.62 (119)	674.76 (110)	620.74 (98)

[&]Degrees of freedom.
*p < 0.05. **p < 0.01.

Table 5 - Summary of analysis of variance (ANOVA) for weight at first calving (W1C), weight at first estrum (W1E), hot carcass weight (HCW), backfat thickness (RFT), *longissimus* rib eye area (REA) and carcass yield (CY).

Source of variation	Df	Reproductive traits		Carcass traits			
		W1C	W1E	HCW	RFT	REA	CY
Genetic group	3	10291.85**	7962.18**	5754.88**	12.78**	497.14**	0.95
Treatment	1	910.87	31023.48**	533.31	9.89	44.56	0.97
Age	1	9096.35***	86771.49**	-	-	-	-
Year of birth	1	20.94	16492.69**	272.28	63.86**	495.13*	4.39
Block	1	-	-	162.08	26.48**	39.45	15.27
Individual heterozygosity	1	1427.20	279.56	4398.55**	0.84	401.97*	2.11
Error (Df) ^{&}	-	1365.17(89)	630.70(95)	842.33(78)	2.92(78)	82.93(78)	7.59(78)

[&]Degrees of freedom.
*p < 0.05. **p < 0.01.

productive characteristics were unaffected by H_i or D_m . Multilocus genetic distance (D_m) did not affect any of the traits examined.

Discussion

Two different measures of genetic diversity were used, the standard heterozygosity (H_s) representing the fre-

quency of heterozygotes observed in one population or sample over all loci analyzed (Weir, 1996) and the individual heterozygosity (H_i) as estimated by the proportion of heterozygote loci over the ten loci analyzed (an individual measure). The Nelore breed showed the lowest H_s and H_i genetic diversity of the parental breeds, possibly related to the small number of founder animals in the Brazilian herd,

whereas the highest H_s and H_i genetic diversity was observed with the Canchim breed, probably because this is a composite breed consisting of 5/8 Charolais plus 3/8 Zebu. Despite the infrequent use of H_i , the high correlation value between ΔH_s and ΔH_i indicates that the individual heterozygosity (H_i) is a suitable measure of genetic diversity.

We used two methods to calculate the genetic distance between the breeds, Nei's standard genetic distance (D_s ; Nei, 1972) which is widely used in the literature and takes into account evolutionary forces, and the multilocus genetic distance (D_m ; complementary to the multilocus genetic similarity) which is based on pair wise inter-individual comparisons (Bowcock *et al.*, 1994; Ciampolini *et al.*, 1995) and which dispenses with the need to calculate previous allele frequencies and thus allows the assessment of the genetic distance between individuals of the same breed. Ciampolini *et al.* (1995) used 17 microsatellites to analyze the inter and intrapopulation genetic variability of four Italian cattle breeds and confirmed the utility of D_m and its agreement with classical genetic distances but we did not find the same agreement in our study because although the Pearson's correlation coefficient was high it was not significant. To increase the sensitivity of the method and enable a better estimate the number of loci examined should be as high as possible. In our study the H_i and D_m parameters were chosen to investigate the effects of heterozygosity and genetic distance on production traits since these parameters allow for regression analysis for individual animals. This approach was considered better than working with the average values for these parameters in the populations studied.

Previous studies have investigated the relationship between production traits, parental genetic distance and heterozygosity, and it is accepted that such relationships are related to heterosis, with several reports suggesting a strong correlation between molecular-marker heterozygosity and hybrid performance (Garton *et al.*, 1984; Stuber *et al.*, 1992; Xiao *et al.*, 1995) although, according to Zhang *et al.* (1996), this relationship can be variable depending on the genetic material in question and the complexity of the genetic basis of heterosis. Numerous reports of both positive and negative correlations between heterozygosity and fitness-related traits have been published for many different organisms. Pierce and Mitton (1982), for example, observed significant and positive correlations between individual heterozygosity and the size of tiger salamanders while Smith *et al.* (1990) suggested that it was possible to use genetic distance to predict combinations of maize lineages that would result in high grain-yields, although Melchinger *et al.* (1990) found that in maize the correlations were too small to be of predictive value. Cepica *et al.* (1995) found a high correlation between increased heterozygosity in pig crosses and the genetic distance between the parental lines while Gregory *et al.* (1994) demonstrated that in beef cattle crossbreeding systems the

retention of heterosis was approximately proportional to the expected retention of heterozygosity for most traits.

The molecular basis of heterosis could be related to overdominance or dominance events. If overdominance was the cause the superior performance of heterozygotes could be described as a manifestation of physiological differences between heterozygotes and parental homozygotes which cause variations in their metabolic rates (Trehan and Gill, 1987). The correlation between heterozygosity and phenotype can not arise from single-locus dominance because homozygotes for the dominant allele would share the same phenotype as heterozygotes (Deng and Fu, 1998). If multiple-loci were involved a correlation might exist because it is unusual to have two parental lines homozygotes for alternate alleles at each *locus*, with one line harboring all the dominant alleles and the other harboring all the recessive alleles.

In a simulation study using natural populations, Mitton and Pierce (1980) found that the estimation of individual heterozygosity obtained from as few as a dozen randomly chosen loci may reflect the heterozygosity determined by 100 independent loci, while Cepica *et al.* (1995) found that in polymorphic systems a smaller number of polymorphic loci would be sufficient to detect differences in heterozygosities between populations.

Body weight traits can be considered as essentially additive traits since they usually have high heritability and low heterosis resulting from crosses. However, growth at different ages may be the result of the action of different genes that could differ in average gene action, which could account for the fact that H_i was significant during only one growth period (W10-W12). In marine bivalves, David *et al.* (1995) found that there was a significant positive correlation between heterozygosity and the rate of weight gain in the first half of the growth curve but no correlation with mature weight. While Cheverud (2002), investigating quantitative trait loci affecting growth in mice, found that variability in different growth periods and physiological status are controlled by independent sets of genes. In our study, the positive and significant H_i effect on hot carcass weight (HCW) and longissimus rib eye area (REA) supports the result obtained for live weight because live weight affects carcass weight. To assess whether the effect of H_i on REA was related to carcass weight we corrected REA to account for carcass weight (REA/HCW) and when this was done the effects of H_i on REA did not remain, indicating that H_i affected total growth and not just REA. Similar results were obtained when carcass weight was the covariant for carcass composition traits (data not shown). The regression coefficients for BW, W10-W12 and REA showed a high weight increment per heterozygote locus. In addition, the percentage of phenotypic variation due to the level of heterozygosity ranged from 0.6% (W10 and W11) to 2% (BW) for live weights and was about 4% for REA and HCW. This is an interesting finding when considering the

limited number of loci and it is hard to predict what the results would be if more markers had been used.

Our results suggest that heterozygosity at a limited number of polymorphic markers may affect live weight in at least one growth period. Whether this is an effect of general heterozygosity or the effect of heterozygosity at specific loci is still unclear since at least one direct effect has been detected for the analyzed loci (Tambasco *et al.*, 2003). The H_i parameter has shown to be a powerful tool for regression analysis and previous and present work points to the possibility of pre-selecting individuals for commercial crosses according to their heterozygosity. Also, despite the fact that multilocus genetic distance (D_m) was not significant the hypothesis of its positive correlation with growth related traits should be investigated using a larger number of animals (increased sample size) and a greater number of markers. Moreover, our study also indicates that the genetic distance between parents is positively correlated with increased heterozygosity in the progeny and could be used, as in the present crosses, as a predictive measure for heterozygosity.

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