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Longitudinal analysis of the effects of *IGF1-SnaBI* genotypes on the growth curve of Angus bull calves

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ABSTRACT

The Insulin Growth Factor 1 (*IGF1*) has been proposed as a candidate gene for growth related traits as it plays a central role in growth and development of mammals. A relationship between serum IGF1 concentration and different growth traits in cattle has been documented. Furthermore, the *IGF1-SnaBI* SNP in the gene promoter region influences gene expression and IGF1 blood level. The current research was conducted to perform a genetic analysis of longitudinal data for growth curves through the evaluation of the influence of *IGF1-SnaBI* genotypes on the growth curve of beef cattle during highly anabolic stages. Data were taken on 275 Angus bull calves on two consecutive years, in two commercial cow–calf operations. Calves were weighed at birth, at weaning, and at 3 to 4 times before the year of age. A random regression animal model was employed for the analysis. Fixed effects were age of dam, herd-year, and age of calf (linear and quadratic terms nested within *IGF1-SnaBI* genotype). Random effects were age at measure (linear and a quadratic terms nested within animal). The analysis showed significant differences ($P < 0.01$) in the growth curves at ages in between 66 and 291 days for the *IGF1-SnaBI* genotypes. At 210 days of age, the effect of substituting a T by a C was estimated to be 5.21 kg. These results suggest that the effect of *IGF1-SnaBI* over growth in cattle take place mostly before puberty.

1. Introduction

The Insulin Growth Factor 1 (*IGF1*) has been proposed as a candidate gene for growth related traits in cattle and other farm animal species (Parmentier et al., 1999), as it plays a central role in growth and development of mammals. Associated with the Growth Hormone (GH), IGF1 participates in hormonal regulation of many anabolic processes like glucose and lipid metabolism, myogenesis, and in the development of puberty (Werner et al., 1994). Furthermore, a relationship has been demonstrated between serum IGF1 concentration and different growth traits in cattle (Anderson et al., 1988; Graml et al., 1994; Kitagawa et al., 2001). In this regard, Te Pas et al. (2004) indicated that the relationship between growth rate and IGF1 is mainly at the expression level. Noteworthy, Maj et al. (2008) have recently reported that a SNP (*SnaBI*) in

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the promoter region of the *IGF1* gene influences gene expression in cattle. They have also observed a significant association between the *IGF1* genotype and IGF1 blood level, and suggested that the polymorphism introduces a putative binding site (TCCA) for the Nuclear Factor I (NFI) transcription factor. Casas et al. (2003), Li et al. (2002), and McClure et al. (2010) have detected quantitative trait loci (QTLs) associated with growth traits in the region of BTA5 between 55 and 80 cM, where *IGF1* gene is located. Two polymorphisms have been described in the promoter region of the *IGF1* gene: a microsatellite (Kirkpatrick, 1992), and a SNP, identified as a C/T transition at position −472 (Ge et al., 2001). The microsatellite has been associated with birth and weaning weight (Andrade et al., 2008; Moody et al., 1996; Rogberg-Muñoz et al., 2011). A nearby SNP (named *IGF1-SnaBI*) was reported to affect animal growth rate and meat performance in Angus, Beefbooster, Holstein-Friesian and Charolais cattle (De la Rosa Reyna et al., 2010; Ge et al., 2001; Li et al., 2004; Siadkowska et al., 2006), even though these studies are not consistent in the period where the marker is associated.

Genetic evaluation programs for beef cattle employ three or four weight measurements as indicators of animal growth, and those usually are the weights at birth, at weaning (between 200 and 210 days), at 15 months (or 400 days) and at 18 months (or 600 days). Therefore, most of QTL detection and marker association tests on growth traits are performed at these particular ages (see QTL Data Base, 2012). Fitting growth models on different body weight data and extracting the relevant growth parameters provides a way to combine phenotypic information from multiple measurements into a biologically meaningful manner (Hadjipavlou and Bishop, 2009). There are several studies of genotype association with growth curves (or its parameters) in pigs, sheep or chickens (Buitenhuis et al., 2004; Hadjipavlou and Bishop, 2009; Podisi, 2011; Varona et al., 2005), and also in humans (Podolsky et al., 2007). Moreover, growth curve is affected by breed genotype (Lambe et al., 2006) and can be modified by selection (Köhn et al., 2008). However, little has been researched in cattle (Lusk, 2007). As the period between birth to 18 months includes different physiological stages, an analysis of the growth curve could be more informative in explaining the influence of the *IGF1* gene for animal growth than analyzing the data at individual ages.

The most apt approach to the genetic analysis of longitudinal data for growth curves is random regression—repeated measures by means of mixed models (Little et al., 1998). In words of (Diggle et al. 1994) the analysis is characterized by "its effectiveness for studying change". This is due to: (1) all information is used to produce tests of hypothesis at given time points; (2) the number of degrees of freedom for the error term in hypothesis testing greatly increases. This is even true after correcting degrees of freedom for the lack of independence of error terms and/or random effects (Kenward and Rogers, 1997); and (3) estimable functions of fixed effects are Best Linear Unbiased Estimators (BLUE), which is not the case with the analysis at individual time points. Therefore, the goal of this research was to estimate the additive and dominance effects of *IGF1-SnaBI* genotypes on the growth curve of Angus bull calves by a random regression animal model for longitudinal data. Animals were fed on a pasture based system during highly anabolic stages.

2. Materials and methods

The experimental population consisted of 275 Angus bull calves belonging to two herds located in Buenos Aires Province, Argentina. Groups of half-sib calves sired by 24 related bulls, which were born between July and September of 2008 and 2009. The animals were bred in an extensive pasture system with *ad libitum* access to cultivated grass. The average daily gain in the whole period (birth to year) was 0.739 kg/day; with a maximum value of 1003 kg/day and a minimum of 0439 kg/day. Calves were weighed at birth; at weaning (range of age = 170 to 240 days); and at 3 to 4 additional times before one year of age. DNA was extracted from blood samples using Wizard Genomic kit following manufacturer instructions (Promega, Madison, WI, USA). The *IGF1-SnaBI* promoter SNP, previously reported by Ge et al. (2001), was genotyped by the pyrosequencing technique (Lirón et al., 2012; see Supplementary materials—Appendix A, for further detail).

The trait analyzed was weight gain between birth up to one year of age. A random regression animal model for repeated measures using either 5 or 6 weights per animal was employed for the analysis. Fixed effects were the classification variables of age of dam (4 levels: 2–3 years old, 4 years old, 5–7 years old and more than 8 years old), and herd-year (3 levels), and linear and quadratic effects of the covariate age of calf nested within *IGF1-SnaBI* genotype (CC, CT, and TT). Random effects were the covariate age at measure, with a linear and a quadratic term, nested within animal. Let $\boldsymbol{A}$ be the additive relative matrix of order 275×1, and $\boldsymbol{H}$ be the 2×2 matrix:

$$\boldsymbol{H} = \begin{bmatrix} Var(\hat{\boldsymbol{\beta}}_{Li}) & Cov(\hat{\boldsymbol{\beta}}_{Li}, \hat{\boldsymbol{\beta}}_{Qi}) \\ Cov(\hat{\boldsymbol{\beta}}_{Qi}, \hat{\boldsymbol{\beta}}_{Li}) & Var(\hat{\boldsymbol{\beta}}_{Qi}) \end{bmatrix}$$

where $\hat{\boldsymbol{\beta}}_{Li}$ and $\hat{\boldsymbol{\beta}}_{Qi}$ are the linear and quadratic random regressions of growth on age for animal I, respectively. Then, the variance of age effects for all animals was equal to $\boldsymbol{H} \otimes \boldsymbol{A}$.

To detect the age at which the maximum value of the additive effect was observed, the contrast CC vs. TT was formed, the first derivative of the resulting function was set to 0, and the value was solved for. Other appropriate linear contrasts were used to test for differences between genotypes and to estimate additive and dominance effects (Falconer and Mackay, 1996) at the usual average age at weaning of 210 days. To this purpose, allelic frequencies were calculated as suggested by McPeek et al. (2004), to avoid the effects of genetic drift and non-random mating on the gene frequency across generations. Let $\boldsymbol{s}$ be a vector of order 275×1, with element s_i being equal to 1, 0.5, or 0, if the genotype of individual i is CC, CT, or TT, respectively. Then, the allelic frequency for C was calculated as $f_C = (\boldsymbol{s}'\boldsymbol{A}\boldsymbol{s})/(2n)$ where $n = 275$.

The $\boldsymbol{A}$ matrix was calculated using PROC INBREED, and the covariance components were estimated by Restricted Maximum Likelihood (REML) using PROC MIXED. Both

procedures are built into SAS 9.3 (SAS, 2012). The α-level for all tests of significance was set equal to 0.01, and degrees of freedom were corrected by the method of Kenward and Roger (1997).

3. Results and discussion

The association between *IGF1-SnaBI* (SNP in the 5′-non-coding region of the *IGF1* gene) and gain of weight was tested in Angus bull calves. The rough estimate of allelic frequencies gave a value of 0.55 for C and 0.45 for the T allele. After adjusting for non-random mating and genetic drift (McPeek et al., 2004), the corresponding frequencies of C and T for the Angus resource population used herein were 0.52 and 0.48, respectively. In a previous work, Ge et al. (2001) had found rough estimates of frequencies for the C allele equal to 0.52 and 0.75, in two divergent Angus populations. Underwood et al. (1994) demonstrated that nutritional restrictions affect the expression and the action of the *IGF1* gene and hormone. In our experiment, animals were constantly gaining weight: the ADGs were 0.740, 0.739 and 0.735 kg/day, for the genotypes CC, CT and TT, respectively. Using a longitudinal (multivariate) mixed animal model for analyzing the effects of change, differences among linear functions of estimated fixed effects for the three genotypes were deemed significant for weight gain (third column in Table 1). Estimated weight gain at 210 days was larger for CC than for CT, and the latter was larger than TT. At 210 days, the estimated difference between the genotypes CC and TT was 10.47 kg ($P < 0.01$). This is displayed by the growth curves in Fig. 1. The magnitude of the estimated effects suggests that growth of these calves was mostly linearly related with age. Age of dam and herd-year were also significant ($P < 0.01$). The additive effect (a, Falconer and Mackay, 1996) for CC at 210 days of

Table 1
Predicted average weight for each *IGF1-SnaBI* genotype at 210 days age, and the contrast between them, are presented. Additive (a), dominant (d) and substitution (α) effects for each age calculated as suggested by Falconer and Mackay (1996) are also showed.

Genotype (*N*)	Weight at 210 days (kg)	Genotype contrast (kg)		*a* (kg)	*d* (kg)	Substitution effect α (kg)
CC (50)	197.38 ± 3.06	CC vs. TT	10.47 ± 3.50**			
CT (141)	192.27 ± 2.43	CT vs. TT	5.36 ± 3.20	5.24 ± 1.75**	0.13 ± 2.38	5.21
TT (80)	186.91 ± 3.39	CC vs. CT	5.11 ± 2.67			

** $P < 0.01$.

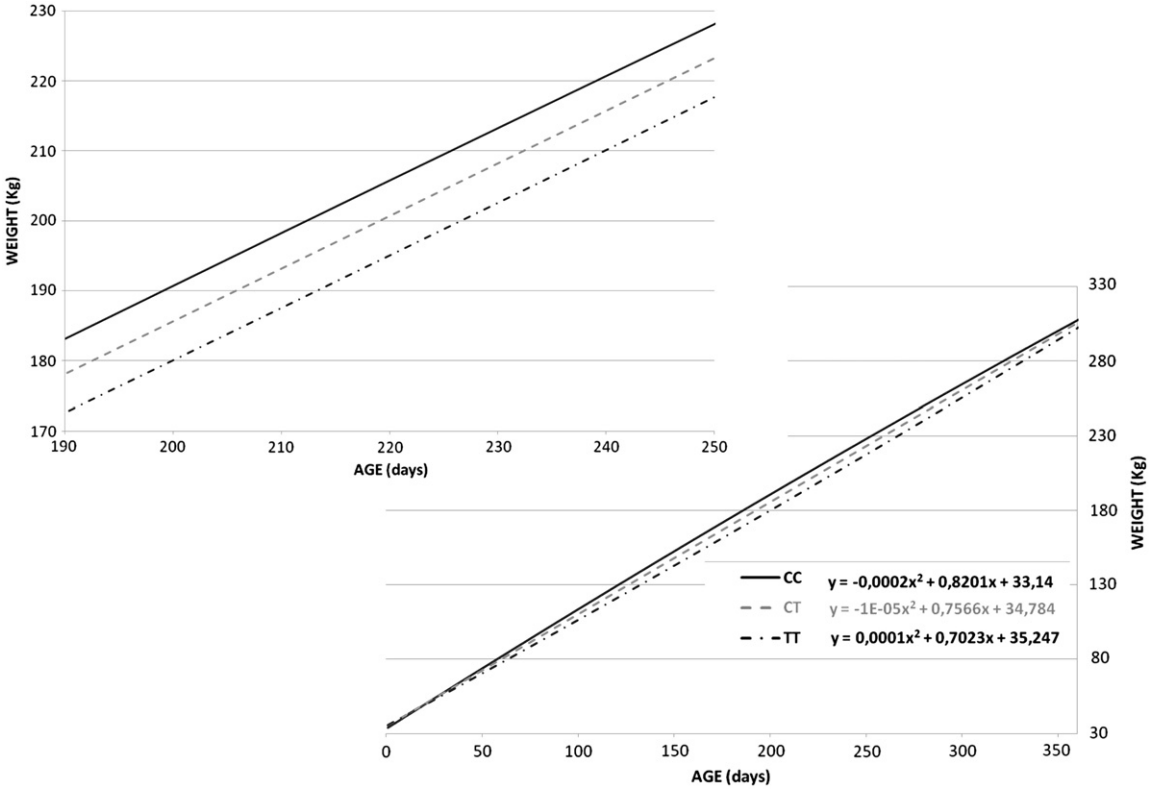

Fig. 1. Growth curves (weight-age) for the three *IGF1-SnaBI* genotypes (CC, CT and TT). The obtained quadratic regression equation for each genotype is presented in the plot on the right. The graph in the left is an enlargement from the first graph showing the period between 190 and 250 days.

age was equal to 5.24 kg ($P < 0.01$), whereas the estimated value of *d* was equal to 0.13 kg and non-significant. Therefore, the substitution effect was equal to 5.21 kg. These results agree with those of Maj et al. (2008) who found increased blood IGF1 concentration with the number of C alleles, in a gene expression analysis of Holstein-Friesian cattle.

In a different analysis using the same Angus calves that were employed in the current study, Lirón et al. (2012) found that the average age at puberty was 290 days. In the current study the differences between homozygous genotypes were significant between 66 and 291 days of age, a period of high anabolism in mammals. The observation that *IGF1-SnaBI* mostly affects early stages of growth in bull calves (*i.e.* the period before and closely after weaning), whereas later on differences between *IGF1-SnaBI* genotypes become smaller and eventually vanish, is consistent with the findings in mice of Lupu et al. (2001). These authors found that after weaning and few days after reaching puberty the contribution of the GH/IGF1 system to growth was practically terminated. In the same direction, Curi et al. (2005) compared the growth of cattle with CC and CT after 110 days of confinement. They found that CC genotype animals have a superior final (1 year old) weight, but the same daily weight gain during the test period. They observed that CC genotype animals had entered confinement (240 days age) with a larger body weight, indicating that animals would have been heavier at weaning. The fact that the effect of *IGF1-SnaBI* was significant, and hence detectable, in a restricted period before weaning and little after puberty could support those findings. Furthermore, the present results expand the ones obtained in the previous association tests of *IGF1-SnaBI* genotypes with growth traits in different beef cattle breeds. Ge et al. (2001) detected a significant additive effect between genotypes in the growth rate 20 days after weaning. Interestingly, the effect was detected in an Angus herd selected for a low concentration of circulating IGF1, but no effect was observed in a herd selected for a high concentration of circulating IGF1. Furthermore differences in growth were not significant in both herds in the off-test weight. Siadkowska et al. (2006) found that the daily weight gain during the 8th month (post-weaning) was superior in CC genotype Holstein young bulls and heifers, but there was no difference in the weight at 15 months between genotypes. In both studies, differences in the period close to weaning were detected but no effect was detected in the post year weight.

4. Conclusions

The analysis of longitudinal data detected a possible effect of the marker *IGF1-SnaBI* on the early growth of cattle. The substitution effect at 210 days of age of a C by a T in the SNP *IGF1-SnaBI* was estimated to be 5.21 kg, in Angus bull calves. The effect was significant at about the time of weaning whereas it vanished later: the maximum difference was detected around 217 days of age, and it became not significant 74 days after. These results suggest that the effect of *IGF1-SnaBI* over growth in cattle takes place mostly before puberty.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.livsci.2013.03.016.

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