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Regional Heritability Mapping of Age-dependent Loci Affecting Growth Traits in Scottish Blackface Lambs

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ABSTRACT: Descriptors of growth derived from fitting the Gompertz curve to longitudinal live weights for 735 Scottish Blackface lambs were analysed using Regional Heritability Mapping to identify genetic regions with significant effects on growth. Evidence for loci affecting predicted growth rates and weights at distinct time points was seen on several chromosomes. Three loci on two chromosomes were mapped for age at maximum growth rate and seven regions on five chromosomes had significant associations with predicted growth rates and live weights at the suggestive level ($P<2.30x10^{-3}$). QTL significance and effects varied with age, with longitudinal QTL for growth rate often occurring earlier than for live weight. Irrespective of the methodology used to dissect loci affecting growth, the longitudinal nature of the trait, i.e. its evolution over time, needs to be taken into account, especially for genomic predictions at different growth stages.
Keywords: sheep; growth; growth curve; Regional Heritability Mapping; longitudinal traits

Introduction

Several studies in livestock have reported genetic loci that are associated with growth traits in terms of average daily gain, weight at a specific age, and days to reach a particular weight (e.g. Nagamine et al. (2003); Raadsma et al. (2009); Jonas et al. (2010)). The majority of studies used univariate approaches, either with sparse genotypic information to detect QTL, or dense genotypes in genome-wide association studies (GWAS). In both cases, weights at particular growth points are either analysed as separate traits (Raadsma et al. (2009) for sheep; Lu et al. (2013) for beef) or used to estimate the average body weight within a time range (Riggio et al. (2013)) or average daily gain at specific time points (e.g. Xu et al. (2012) for an overview on GWAS of growth phenotypes in chicken). This is despite the fact that live weights comprise a longitudinal trait that is a composite of growth rate phenotypes over time. Also, patterns of genetic correlations suggest additional complexity. For example, using sheep data, Riggio et al. (2008) showed that inter-age genetic correlations for live weight, whilst strongly positive, are often different from unity, with the correlation decreasing as the time between the weight measurements increases. Even though live weights have intermediate to high heritabilities in most livestock species, few loci have been found to be significantly associated with weights.

Hadjipavlou and Bishop (2009; 2010) examined a number of approaches to account for the longitudinal nature of growth in the process of mapping genetic loci that affect this trait in sheep. They successfully used a growth model approach to account for the correlation structure among weight measurements across time, and showed that distinct loci act on live weights at different growth stages in Scottish Blackface sheep (Hadjipavlou and Bishop (2009)). Additionally, QTL for growth rate were generally deemed significant at earlier time points than for live weight.

Recently, a novel methodology, Regional Genomic Heritability Mapping or Regional Heritability Mapping (RHM) (Nagamine et al. (2012)), has been employed for the analysis of univariate live weights and nematode resistance phenotypes for the same Scottish Blackface animals (Riggio et al. (2013)) that were studied in Hadjipavlou and Bishop (2009). The RHM approach was used to exploit dense SNP chip data in order to capture more of the underlying genetic effects, using genomic information derived from the Illumina Ovine 50k SNP BeadChip (50k SNP chip). Additionally, both Nagamine et al. (2012) and Riggio et al. (2013) showed that RHM facilitates heritability estimates attributable to small genomic regions and has the power to identify regions containing multiple alleles, each of which contributes too little variance to be detected by conventional GWAS.

In Riggio et al. (2013), even though the use of dense genomic information and the RHM approach led to the identification of various significant genetic loci associated with nematode resistance in sheep, only four regions on three distinct chromosomes were deemed significant for univariate live weight phenotypes, and certainly fewer than when the growth model approach, along with microsatellite information, was employed on the same dataset (Hadjipavlou and Bishop, 2009). This likely signifies the particularity of the underlying genetic profile of growth and the limitations of analysing growth indicators, such as live weights at particular time points, as distinct univariate traits.

In the current paper, we sought to examine whether the longitudinal effects of genetic loci, mapped using microsatellite genotypes in Hadjipavlou and Bishop (2009), could be further characterised using dense genotype information and the RHM approach, in an analysis of growth curve parameter estimates and predicted phenotypes (growth rates and live weights).

Materials and Methods

Data. Actual weight measurements at birth and at four-week intervals after birth (up to 24 weeks) for 735 Scottish Blackface lambs from nine half-sib families, with at least five records per lamb, were analysed using the Gompertz growth model (Hadjipavlou and Bishop (2009)). Lambs were genotyped using the 50k SNP chip and genotype data processed according to Riggio et al. (2013).

Statistical analyses. The Gompertz growth curve equation was fitted to actual live weight measurements and curve parameters were estimated separately for each lamb. Subsequently, these parameter estimates were used to predict live weight and growth rate phenotypes at weekly intervals and at maximum growth for all lambs. The Gompertz equations and estimated parameters are further described in Hadjipavlou and Bishop (2009).

To map loci associated with growth model parameters and predicted phenotypes, RHM was used to estimate the variance attributable to windows of specific numbers of SNP on each chromosome (OAR). The window size was 100 adjacent SNPs and the window shifted every 50 SNPs. A mixed model was employed, accounting for fixed effects (sex, year, management group, litter size, age of dam, and day of birth as covariate, with residual and additive genetic (both regional and whole genomic) effects fitted as random. The whole genomic additive effect was estimated using the genomic relationship matrix constructed from all SNPs, whereas the regional genomic additive effect from the SNPs within each window, i.e. region (for more details, see Riggio et al. (2013)). Regional significance was assessed using a Likelihood Ratio Test (LRT) of the full (both whole-genome and region-specific additive variance fitted) against the null hypothesis of no variance in that window (whole-genome additive variance only). The test statistic was assumed to follow a mixture of $1/2\chi^2_{(1)}$ and $1/2\chi^2_{(0)}$ distributions (Self and Liang (1987)). After Bonferroni correction to account for multiple testing, the LRT thresholds for 5% genome-wide and suggestive significance levels were 13.56 ($P<1.15x10^{-4}$) and 9.29 ($P<2.30x10^{-3}$), respectively. Nominal significance threshold for a single test was set at an LRT of 2.00.

Results and Discussion

By combining the growth model and RHM approaches, one or more genetic regions on several autosomal chromosomes were found to be significant at distinct growth stages. Additionally, QTL significance and effects varied with age, with longitudinal QTL for growth rate generally occurring earlier than for live weight. This had been previously observed when microsatellite information was used to map growth QTL in the same sample (Hadjipavlou and Bishop (2009)).

More specifically, the analysis of growth model parameter estimates and, subsequently, growth rate and live weight predictions over time, led to the identification of three loci on two chromosomes for age at maximum growth rate (parameter C of the Gompertz model) and of seven genomic regions on five chromosomes whose association with predicted growth phenotypes was deemed significant at the suggestive level ($P<2.30x10^{-3}$) (Table 1). On OAR1, two loci appeared to have an effect on age at maximum growth rate. On OAR4, at least one locus was found to be significant for early growth phenotypes and for age at maximum growth rate. On the same chromosome, a nominally significant region was mapped for intermediate to late predicted growth rate. A region mapped on OAR6 had longitudinal effects on growth, and was also identified as significant in univariate analyses of actual weight at 16 weeks using RHM in Riggio et al. (2013). In the current study, loci were found for the first time to be significant at the suggestive level; on OAR 7 and 15 for predicted growth rates and weights at early ages, and on OAR12 for intermediate growth rates and weight around 20 weeks of age. These loci need to be further investigated. On OAR14, a QTL was mapped as nominally significant for 1-week growth rate (LRT=8.94) and for 1 to 12-week weight (suggestive significance for predicted weight at 4 weeks; i.e. LRT=10.56). A QTL on OAR14 had also been mapped in Hadjipavlou and Bishop (2009) for actual weight at birth and 8 weeks and for age at maximum growth rate (parameter C of the Gompertz equation).

Table 1. Summary of windows deemed significant at the suggestive level using RHM on each chromosome (OAR) for predicted growth rates and live weights across time.

Trait	OAR	SNP Window	LRT[#]	Age at max LRT[§]
Age at max GR (days)	1	58	10.40	-
Age at max GR (days)	1	67	9.60	-
Age at max GR (days)	4	30	10.06	-
1-4 week WT (kg)	4	40	12.12	1 week
1 week WT (kg)	4	44	11.24	-
12-20 week GR (kg/d)	4	44	6.02	16 weeks
8 week GR (kg/d)	6	13	6.56	-
4-20 week WT (kg)	6	13	9.40	16 weeks
4-8 week WT (kg)	7	16	10.62	4 weeks
1 week GR (kg/d)	7	16	5.06	-
8-20 week WT (kg)	12	15	10.44	20 weeks
8-12 week GR (kg/d)	12	15	6.90	8 weeks
1-12 week WT (kg)	14	17	10.56	4 weeks
1 week GR (kg/d)	14	17	8.94	-
1-20 week WT (kg)	15	28	9.56	8 weeks
1-4 week GR (kg/d)	15	28	6.14	4 weeks

Age at max GR=Age at maximum growth rate (parameter C of the Gompertz curve fitted to actual live weights over time), WT=predicted live weight, GR=predicted growth rate

[#]5% suggestive significance threshold= 9.29 ($P<2.30x10^{-3}$)

[§]Lamb age at which the Likelihood Ratio Test (LRT) was maximum, in cases when a SNP window was significant over a time range for a particular trait.

Additional QTL for predicted growth traits, identified in Hadjipavlou and Bishop (2009) using linkage analyses within half-sib families, were also mapped on OAR 3, 5, 18 and 20 as being nominally significant, using the RHM analysis of the same growth model predictors. In all instances, the regions deemed significant for growth over time using both approaches, were mapped with greater resolution with the RHM analysis, likely due to the different model fitted to the data and to the denser marker information that was available.

The shape of the QTL profiles across time is also informative. Loci with significant effects on predicted growth phenotypes were observed to often persist across an extended time range for live weights, whereas to have significant effects only at a specific age for growth rates (see Figures 1, 2, 3). In other words, a temporary effect on growth rate translates into a longer-term subsequent effect on live weight. Also, loci that were significant for live weights early in life (e.g. birth to four weeks) were not mapped for predicted growth rate. This would be expected based on the observed pattern, as they would be likely to act on embryonic growth rate. An analogous situation is observed for loci deemed significant for late growth rates; these were not mapped for live weights within the recorded range of 20-24 weeks, since they probably exert their effects on live weight at a later stage in the animal's life.

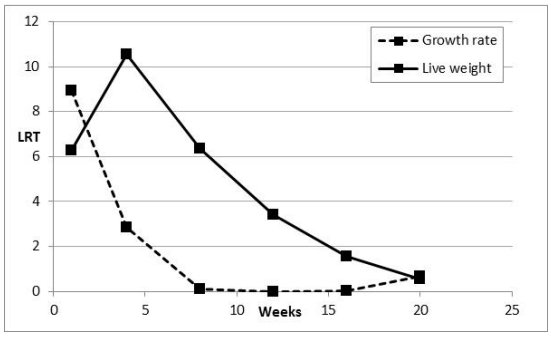

Figure 1: Across-age significance of SNP window 17 on OAR14 for growth rates and live weights, predicted at weekly intervals using the Gompertz curve

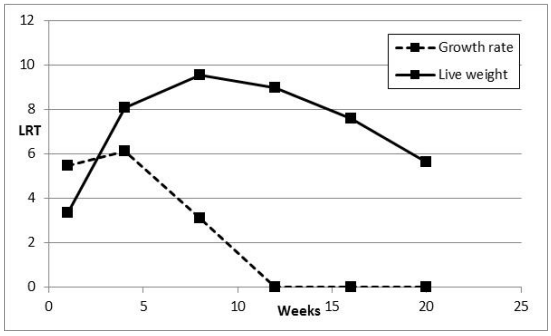

Figure 2: Across-age significance of SNP window 28 on OAR15 for growth rates and live weights, predicted at weekly intervals using the Gompertz curve

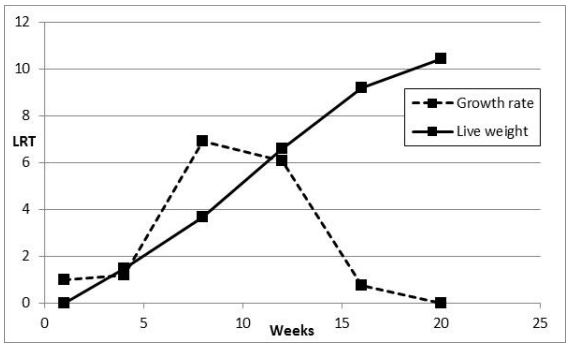

Figure 3: Across-age significance of SNP window 15 on OAR12 for growth rates and live weights, predicted at weekly intervals using the Gompertz curve

Conclusion

The genetic architecture of growth changes over time. Irrespective of the methodology used to dissect loci associated with growth, the longitudinal nature of the trait needs to be taken into account, especially for the purpose of genomic predictions at different growth stages. Further, growth rates and live weights, although correlated, represent different components of the trait. Growth rate QTL seem to be age-specific since they manifest their effects temporarily and prior to live weight QTL effects being detected. Integration of growth rate QTL effects with those of live weight QTL would allow more comprehensive genomic evaluations for growth and a better description of the genetic loci affecting such an economically important trait through GWAS, RHM or other approaches.

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