Genome-Wide Association Study And Fine Mapping Of QTL On OAR 21 For Body Weight In Sheep

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Introduction

In sheep, growth rate and body mass represent economically important traits, which are under moderate genetic control and respond to directional selection (Safari (2005)). Relatively few QTL studies have been reported in sheep, furthermore many studies report on partial genome scans, which limit the option to discover new QTL. QTL for different body and carcass weight traits were identified on many chromosomes in sheep (Karamichou et al. (2006), Walling (2004), McRae et al. (2005), and Raadsma et al. (2009)). The advent of high-density genotyping platforms for Single Nucleotide Polymorphisms (SNP) has opened the possibility to under take high resolution mapping approaches exploiting between breed and within breed variation. In this paper, we report a high-density SNP marker association and linkage analysis using a paternal half-sib design within an Awassi × Merino resource population. Animals were genotyped using the 56k SNP array to map a genomic region with impact on body weight.

Material and methods

Animals and Phenotypes. A resource population from crosses between fat-tail Awassi (A) and small-framed Merino (M) sheep was established to exploit the extreme differences between these two types of sheep in a range of production characteristics (Raadsma et al. (2009)). In the genome-wide linkage and association study reported here, data from 319 backcross progeny of the first F_1 sire were analysed in detail. Body weights of animals were recorded at different time points including week 43 for which the genome scan analysis is reported specifically.

Genotyping. All 319 backcross animals and the F_1 sire were genotyped with the Ovine 56K SNP array generated by the ISGC hapmap project (http://www.sheephapmap.org). All markers were used for genome-wide association analysis (GWAS). The predicted map positions of each SNP were further used to select a subset of 679 SNP for fine mapping on OAR 21.

Quality control and analysis of SNP array data. Genotypes with a minor allele frequency < 0.05, a call rate < 0.95 were excluded from the final analysis. PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/) was used to check the gender and pedigree information and estimate the similarities between sire and offspring. Inheritance of the SNP was checked and corrected in 'R' using our own code.

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Association analysis. The probability of allele '1' derived from sire or dam was deducted from the dataset and used as fixed effect for the whole genome association analysis using a linear model in 'R'. A similarity score was set up for each animal by calculating the IBS matrix across all SNP in PLINK.

The following model was fitted to all data:

$$BWT_j = \beta_0 + \beta_1 SSim_j + \beta_2 SNP_i + \varepsilon_{ij} \quad [1]$$

The following model was also fitted to the data of chromosome 21:

$$BWT_j = \beta_0 + \beta_1 PDam_i + \varepsilon_{ij} \quad [2]$$

where BWT_j = Body weight of offspring *j*; $SSim_j$ = Similarity between offspring *j* and the sire, derived from the IBS matrix; SNP_i = *i*-th SNP; $PDam_{ij}$ = probability of allele 1 at SNP *i* transmitted from Dam *j*; and ε_{ij} = residual random error term.

LDLA analysis. LDLA analysis was performed as a preliminary fine mapping analysis on chromosome 21 only. The LDLA approach implemented in Grid-QTL was used (Hernandez-Sanchez and Knott (2009)). In their method, haplotypes are constructed using the minimum recombinant haplotype configuration method (Qian and Beckmann (2002)).

Results and discussion

Phenotypic data. The average body weight at week 43 was 26 kg. The pattern of growth in this flock was consistent for sheep maintained on semi-improved pasture in a temperate Australian tablelands climate (Raadsma et al. (2009)). The availability of pasture is reflected in the growth curve, with a rapid growth following birth in spring till the end of autumn, a period of no growth or decline coinciding with winter. The results of body weight in week 43 used in this study were in the peak of such a growth phase (Raadsma et al. 2009)).

Genotypes. The average call rate from all samples was > 0.98. The repeatability of positive control samples was >0.99. Samples were genotyped for a total of 54,241 loci. The final number of markers after quality check was 40,720 with coverage between 563 and 4,496 markers/chromosome. A total of 679 markers were retained for LDLA analysis on chromosome 21.

Genome-wide association. Along all chromosomes 2% of the markers were significantly ($P<0.01$) associated with body weight using both models. Consistent with findings in previous studies using European sheep, we have identified a number of significant QTL for body weight and growth rates on different chromosomes (Figure 1).

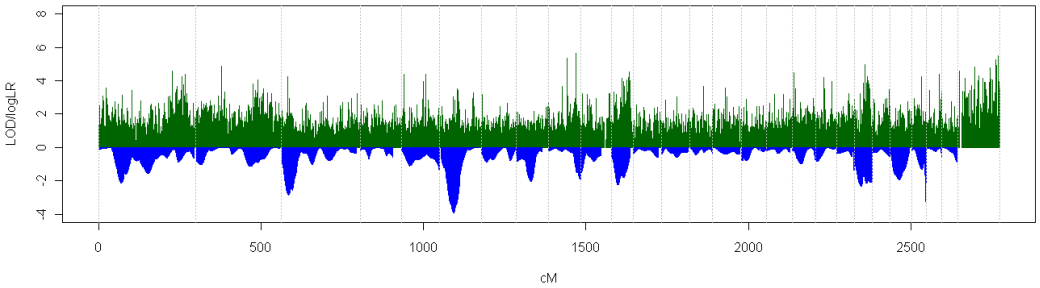

Figure 1: Results of the genome-wide association study using model [1] for body weight (green, above), and genome-wide QTL analysis using QTL-MLE (blue, below) (Raadsma et al. (2009)); grey vertical lines indicate the chromosomes and SNP classified for chromosome un-known in the last column

The comparison between the association study using SNP markers and the linkage analysis using QTL-MLE previously published (Raadsma et al. (2009)) showed that both are in reasonable agreement. Especially on chromosome 11 and 21 significant linkage was previously identified and confirmed by the genome wide association analysis. To demonstrate utility of the SNP data in fine mapping and LDLA approaches, results from chromosome 21 were analysed in detail. For model [2] probabilities of allele 1 derived from dam were incorporated as fixed effect. The results off this model were in good agreement with SNP information using the first model. Results of association analysis with body weight are shown in Figure 2.

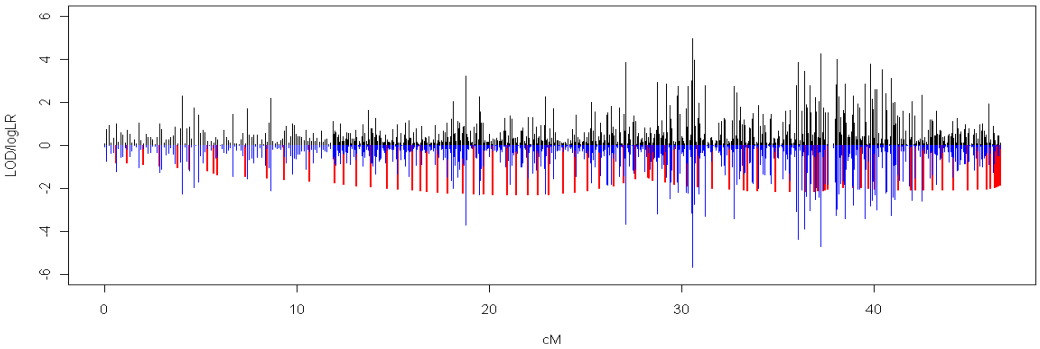

Figure 2: Results of the association analysis for body weight using model [1] (black, above) and model [2] (blue, below) for chromosome 21. LOD scores of the QTL mapping (Raadsma et al. (2009)) are shown (red, below)

LDLA analysis. To confirm the results from the association analysis, LDLA analysis was performed on chromosome 21. A significant QTL was identified between 15 and 20 cM on this chromosome (Figure 3) which did not correspond to the region of the most significant SNP effects (30-35 cM and 40-50 cM , Figure 2)

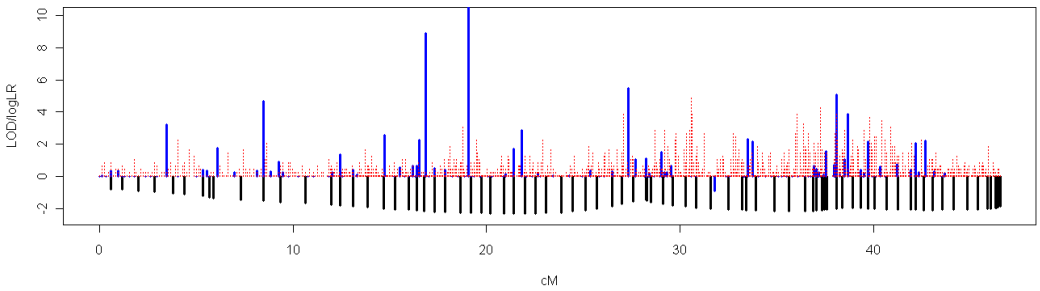

Figure 3: Results of the LDLA analysis for body weight using 679 markers (blue) and for linkage mapping using five microsatellite markers (black) (Raadsma et al. (2009)) on chromosome 21, additional the results of the WGAS is shown in red dotted lines above the x-axis

The results of both association analysis and LDLA mapping did not align on chromosome 21. Furthermore, the LDLA mapping provided a narrow single location for the QTL between 15 and 20 cM compared to the chromosome wide confidence interval obtained from linkage analysis by means of the microsatellite data. Fine mapping this QTL supports findings for a QTL for body weight in a population of Scottish Blackface sheep on chromosome 21 (Karamichou et al. (2006)).

Conclusion

The application of high-density SNP assays to genotype animals of an ovine resource population showed high utility to provide high-resolution mapping information allowing both LALD mapping and SNP association approaches. Both methods showed the importance of a QTL for body weight in the region 15-40 cM on chromosome 21. In future studies we will implement population data and genetic similarity among offspring into the analysis. This study showed result using different models in one half-sib family only; results will be tested using more families of the same sheep population.

References

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