A Capra Hircus Chromosome 19 Locus Linked to Milk Production Influences Mammary Conformation

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Abstract

Background:

Economically important milk production traits including milk volume, milk fat and protein yield vary considerably across dairy goats in New Zealand. A significant portion of the variation is attributable to genetic variation. Discovery of genetic markers linked to milk production traits can be utilised to drive selection of high-performance animals.

A previously reported genome wide association study across dairy goats in New Zealand identified a quantitative trait loci (QTL) located on chromosome 19. The most significantly associated single nucleotide polymorphism (SNP) marker for this locus is located at position 26,610,610 (SNP marker 19:26,610,610). This locus is associated with multiple milk production traits including fat, protein and volume. The predicted effect of selection for the beneficial haplotype would result in an average production increase of 2.2kg fat, 1.9kg protein and 73.6kg volume.

An outstanding question was whether selection for the beneficial allele would co-select for any negative pleiotropic effects. An adverse relationship between milk production and udder health traits has been reported at this locus. Therefore, a genome wide association study was undertaken looking for loci associated with udder traits

Results:

The QTL and production associated marker 19:26,610,610 was identified in this study to also be associated with several goat udder traits including udder depth (UD), fore udder attachment (FUA) and rear udder attachment (RUA). Our study replicates the negative relationship between production and udder traits with the high production allele at position 19:26,610,610 associated with an adverse change in UD, FUA and RUA

Conclusions:

Our study has confirmed this negative relationship between udder traits and production traits in the NZ goat population. We have found that the frequency of the high production allele is relatively high in the NZ goat population, indicating that its effect on udder conformation is not significantly detrimental on animal health. It will however be important to monitor udder conformation as the Chromosome 19 locus is progressively implemented for marker assisted selection. It will also be of interest to determine if the gene underlying the production QTL has a direct effect on mammary gland morphology or whether the changes observed are a consequence of the increased milk volume.

Background

Genetic gain focused on production for the dairy goat population in New Zealand is limited largely to within farm selection and some buck transfers between farms. This has resulted in considerable

unrealised marker driven selection potential which led to the search for and discovery of quantitative trait loci (QTL) for milk production traits in a subset of the population. In particular, the most significant QTL identified was located on chromosome 19 associated with all three production traits including fat yield, protein yield and milk volume (1). A QTL at the same location was also reported in the French (2, 3) and British dairy goat populations (4). A pleiotropic effect for this QTL has been described on a number of udder conformation traits including udder attachment and udder depth (3, 4). It appears that udders in animals with higher milk production determined by the chromosome 19 locus are characterised by greater udder depth with apparent weaker and narrower udder attachment. It is important to evaluate potential negative pleiotropic effects before large scale genetic selection. There are examples where the potential introduction of alleles may have or have resulted in the introduction of negative characteristics. For example, in cattle the non-synonymous A > C mutation in a splice enhancer region of the bovine Diacylglycerol O-Acyltransferase 1 (DGAT1) gene dramatically reduced milk fat content but caused scouring (non-bloody watery diarrhoea), impaired growth rate and flattened intestinal microvilli (5). Furthermore, the non-synonymous C636R mutation in bovine Mannose Receptor C Type 2 (MRC2) gene increased muscularity in meat breeds but caused Crooked Tail Syndrome (6, 7).

Goat udder traits and teat morphology plays important roles in milk quality (somatic cell count), milking ability/ease of milking (8) and overall milk production (9). Goat udder circumference (10, 11) and udder depth (12) have been positively correlated with milk volume. Goats with greater udder depth also had a higher somatic cell count, a negative indicator of milk quality, udder health and marker of mastitis (13). Teat size and shape was likewise indicative of mammary gland health with shorter and narrower teats associated with a lower somatic cell count (13, 14). These factors influence the animal's productive lifespan or longevity (15). Extensive selection pressure for milk production traits has been shown to exert a negative effect on udder and teat traits (3, 4, 16). It is thereby important to consider these traits in animal selection. Udder health and conformation traits have not been assessed at scale in the New Zealand goat herd. This paper reports for the first time a genome wide investigation for goat udder traits of the New Zealand goat population using Illumina GoatSNP50 BeadChip (Illumina Inc., San Diego, CA) and identifies caprine SNP marker 19:26,610,610 as a viable selection tool for future marker assisted breeding programmes.

Methods

Animals and phenotypic measurements

A total of 722 animals from 2 farms (298 animals from farm A, 424 animals from farm B) were scored for udder traits in February and March 2020. The New Zealand goat herd is a mixed breed population comprised of approximately 85% Saanen, 5% Toggenburg, 5% Nubian/Anglo-Nubian, 4.5% Alpine and 0.5% Sable (17). The udder traits measured included udder depth (UD), fore udder attachment (FUA), rear udder attachment (RUA), udder furrow (UF), teat placement (TP) and teat angle (TA). Udder traits were scored on a point system from 1 to 9 described in Table 1 with definition of traits as used in McLaren et al. (18). Additionally, the following milk production traits, milk volume, fat yield and protein yield were

measured for a subset of 336 animals out of the 722-animal cohort (141 animals from farm A, 195 animals from farm B) as part of standard herd testing procedures using Fourier transform infrared spectroscopy. Milk production traits were modelled by extrapolation to a 305-day lactation length period, restricted to animals with lactation length >200 days.

Table 1 Goat udder traits definitions

Trait	Description	Scoring system	Desired scores
Udder depth	Depth of udder measured relative to the hocks according to age	1 (deep) - 9 (shallow)	4,5,6
Rear udder attachment	Width at the top of the milk secreting tissue	1 (narrow) - 9 (wide)	9
Fore udder attachment	Attachment of udder to body wall	1 (weak) - 9 (strong)	9
Udder furrow	Strength and definition of medial suspensory ligament of udder	1 (weak) - 9 (strong)	7,8
Teat placement	Location of where teat attaches to udder	1 (wide) - 9 (close)	6,7,8
Teat angle	Teat angle from side view	1 (poor) - 9 (good)	8,9

Genotypes

The 722 phenotyped animals were genotyped with the Illumina Caprine 50K BeadChip with 54,241 SNP markers (Illumina Inc, San Diego, CA). Markers with ambiguous or missing genotypes in more than 5% of goats, or with minor allele frequency <0.01 were omitted. After filtering, 51,477 markers were retained.

Genome-wide association analysis

Genome wide association mapping with an applied mixed linear model accounting for differences in population structure was performed using genome-wide complex trait analysis tool (GCTA) v1.93.2 (19, 20). The following mixed linear model was used in our study:

$$y = a + bx + g - + e$$

y is the phenotype of interest, a is the mean term, b is the fixed (additive) effect of the SNP, x is the SNP genotype, $g -$ is the effect of population structure estimated by calculating genetic relationship matrices (GRM) between all animals (20). mixed linear model association analysis, leave one chromosome out (MLMA-LOCO) approach was used where the chromosome on which the significant candidate SNP is located are excluded from the GRM calculations to avoid double fitting of candidate variants. e is the residual effect.

A SNP was considered significantly associated to a trait of interest at the whole genome level if their -log10 p-values exceeded -log10($5x10^{-8}$). SNP marker trait association plots against the ARS1 goat reference were constructed using the ggplot R package (21).

Calculation of allelic effect sizes for marker 19:26,610,610

Allelic effect sizes for marker 19:266,610,610 were calculated for production and udder traits in the 722 animals Genome Wide Association Study (GWAS) population using a linear regression model adjusted for age and farm origin. A one-way analysis of variance (ANOVA) test between the means ($\alpha = 0.05$) was performed to characterise allelic effect differences between 19:26,610,610 genotype groups presented in figure 2. The Shapiro-Wilk normality assumption test was performed on all data presented. Multiple pairwise comparisons adjusted for false discovery rate were utilised to highlight statistically significant differences in the data presented.

Whole genome sequencing for variant identification

Whole genome sequencing was performed on 302 goats (including 48 animals included in the cohort used for GWAS) on the Illumina HiSeq XTen platform (Illumina Inc., San Diego, CA). For each animal, 700-1000 million paired end reads with read pair lengths of 150 nucleotides were generated. Read sequence quality was assessed using FastQC (FastQC v0.11.7). Reads were mapped to the ARS1 goat reference genome assembly using Burrows Wheeler aligner (22). Duplicate read pairs were marked using picard MarkDuplicates (Picard v2.1.0., https://broadinstitute.github.io/picard/). Reads aligned around small insertions/deletions were realigned using the Genome Analysis Toolkit (GATK v 3.8, RealignerTargetCreator and IndelRealigner tools) (23, 24). Probabilities for single nucleotide and indel variants were discovered individually in each alignment using GATK's HaplotypeCaller tool (25) and genotyped jointly across the entire cohort with GATK's GenotypeGVCFs tool. Pairwise linkage disequilibrium R^2 values between variants were calculated using PLINK software. The Ensembl Variant Effect Predictor (VEP v90.3) software (https://www.ensembl.org/vep) was used to annotate variants with their predicted effect on protein sequence.

Results

A chromosome 19 QTL associated with goat udder health traits in the NZ goat population

We report a single genome wide significant QTL for several udder health traits including udder depth, fore udder attachment and rear udder attachment (Table 2 & Fig. 1). The QTL extend from chromosome 19 positions 24–29Mb. A QTL signal was also detected for teat angle and udder furrow at the same locus but did not reach genome wide significance. No QTL association was observed for the teat placement phenotype. Fitting the most significant QTL SNP (19:26,610,610) as a covariate in the association

analysis resulted in the ablation of the entire QTL signal, indicative of a single haplotype responsible for the signal.

An overlapping locus was previously identified to be associated with milk production traits in the French (3), British (4) and New Zealand goat populations (1). The SNP most significantly associated with milk production in the New Zealand study (19:26,610,610) was also the most significantly associated SNP with the above udder traits in this study (Table 2 & Fig. 1).

Table 2
Genome wide significant SNPs for goat udder traits in the New Zealand goat population

Trait	SNP (Chr:Pos)	-log$_{10}$(P value)[1]	Annotation	Nearest gene	Distance to nearest gene (kb)
RUA	19:25,782,297	7.55	Intergenic	NLRP1	57.74
UD, RUA	19:25,823,025	8.76–10.10	Intergenic	NLRP1	40.73
UD, FUA, RUA	19:26,072,328	7.96–12.00	Intergenic	RABEP1	17.63
UD, RUA	19:26,115,456	8.06–11.26	Intergenic	ZNF232	23.45
UD, RUA	19:26,148,755	8.26–11.84	Downstream	ZFP3	1.30
UD, FUA, RUA	19:26,192,128	9.87–16.61	Downstream	KIF1C	3.80
UD, RUA	19:26,420,506	11.25–13.23	Intron	ZMYND15	Within gene
UD	19:26,542,254	8.68	Downstream	ALOX12	50.98
UD, FUA, RUA	19:26,578,775	8.86–13.69	Intergenic	ALOX12	14.46
UD, FUA, RUA	19:26,610,610	9.31–15.36	Synonymous	RNASEK	Within gene
UD, FUA, RUA	19:26,662,281	7.88–14.82	Intron	ASGR2	Within gene
UD	19:26,724,454	9.80	Intron	DLG4	Within gene
UD	19:26,780,952	8.83	Downstream	ELP5	0.19
UD, RUA	19:27,401,023	11.25–14.54	Intron	GUCY2D	Within gene
UD, RUA	19:27,480,793	8.06–11.17	Intron	ALOXE3	Within gene
UD, RUA	19:27,529,983	8.00–11.10	Intron	VAMP2	Within gene
UD	19:27,558,520	8.05	Intron	TMEM107	Within gene
UD	19:27,605,322	8.34	Intron	CTC1	Within gene
UD	19:27,646,998	7.57	Upstream	SLC25A35	1.18
UD, RUA	19:28,038,645	8.24–10.96	Intron	PIK3R6	Within gene
UD	19:28,202,268	8.11	Intergenic	NTN1	5.68
UD, RUA	19:28,953,102	7.48–7.91	Intron	GAS7	Within gene

[1]SNPs were considered significant if they exceed the genome wide significance threshold of -log$_{10}$(5x10^{-8})

RUA, Rear udder attachment; UD, Udder depth; FUA, Fore udder attachment

Whole genome sequence analysis revealed two candidate non-synonymous mutations in the Proteasome 20S Subunit Beta 6 (PSMB6) and the Sex Hormone Binding Globulin (SHBG) genes

Whole genome sequence analysis of 302 animals which included 48 animals in the GWAS cohort highlighted 340 variants within the 24–29Mb chromosome 19 QTL interval with high linkage disequilibrium, $R^2 > 0.8$ with the most significant SNP marker 19:26,610,610. Of these, two variants were predicted to alter protein sequence. A non-synonymous variant in the candidate gene *PSMB6* at position 26,370,181 (NC_030826.1:g. 26,370,181C > T), observed at an alternative allele frequency of 0.434 and linkage disequilibrium R^2 value of 0.887 with the most significant SNP marker encodes a substitution of highly conserved valine 221 to isoleucine (XP_005693520.1:p.V222I) (Supplementary 1). A G > T transversion at position 27,087,979 in the *SHBG* gene (NC_030826.1:g. 27,087,979G > T) exists at an alternative allele frequency of 0.445 and linkage disequilibrium R^2 value of 0.87 with the most significant SNP marker in the genome-sequenced animals. This variant encodes a substitution of serine 301 to isoleucine (XP_013827697.1:p.S301I).

An adverse relationship between milk production traits and udder conformation

Allelic effect sizes for marker 19:26,610,610 adjusted for age and farm origin were calculated in our GWAS population. An average difference of 3.66kg fat (p value = $3.09x10^{-4}$), 4.12kg protein (p value = $2.58x10^{-8}$) and 159.52L volume (p value = $7.22x10^{-10}$) was recorded when comparing opposing homozygotes (Fig. 2 & Table 3). The production gains were accompanied by a decrease of 1.14 score points in udder depth (p value = $9.31x10^{-18}$), 0.99 score points in fore udder attachment (p value = $5.05x10^{-7}$) and 1.19 score points in rear udder attachment (p value = $1.08x10^{-12}$) when selecting for the high production T allele (Fig. 2 & Table 3).

Table 3
Allelic effect sizes for 19:26,610,610 SNP marker

Phenotypic Trait	19:26,610,610 marker genotype		
	CC	CT	TT
Milk production traits			
Milk fat (kg) [1]	37.78 (34.87–40.69)	39.55 (36.64–42.47)	41.44 (38.25–44.63)
Milk protein (kg) [1]	32.31 (30.16–34.46)	34.66 (32.52–36.81)	36.43 (34.08–38.78)
Milk volume (L)[1]	1033.76 (958.75-1108.78)	1116.52 (1041.5-1191.54)	1193.28 (1111.12-1275.44)
Udder traits			
Fore udder attachment[1]	3.69 (2.24–5.13)	3.44 (2.01–4.87)	2.70 (1.25–4.14)
Rear udder attachment[1]	6.32 (4.99–7.64)	5.89 (4.58–7.20)	5.13 (3.80–6.46)
Teat angle	5.11 (4.05–6.18)	4.96 (3.91–6.01)	4.75 (3.68–5.81)
Teat placement	3.92 (3.07–4.77)	4.03 (3.18–4.87)	4.03 (3.18–4.88)
Udder depth[1]	5.21 (4.13–6.29)	4.60 (3.53–5.66)	4.07 (2.99–5.15)
Udder furrow	6.57 (5.70–7.45)	6.48 (5.61–7.34)	6.23 (5.36–7.11)
Phenotypic values were taken as averages of animals (95% confidence intervals in brackets) with each corresponding genotype. Values were adjusted for birth year and farm origin.			
[1]Traits associated with marker 19:26,610,610.			

Discussion

A genome wide association study with an applied mixed model to account for differences in population structure was performed in 722 dairy goats in New Zealand. The study highlighted a QTL located on chromosome 19 (24-29Mb) associated with udder depth, fore udder attachment and rear udder attachment. This QTL was also identified in a previous study of the dairy goat population in New Zealand to be associated with milk production traits; fat yield, protein yield and milk volume (as described in Scholtens et al., 2020). Our findings are in agreement with trait effects of an overlapping QTL previously reported in French dairy goats for milk fat content, milk protein content, udder depth and rear udder attachment (2, 3) and British dairy goats for milk volume, udder depth and udder attachment (4). The pleiotropic effect of this locus on both production and udder phenotypes combined with a high density of genes within the region (22.5 genes/Mb) has made it difficult to nominate candidate genes for the observed traits. Martin and colleagues suggested several fatty acid and lipid metabolism pathway genes

including *Phospholipase D2 (PLD2)* Gamma-Glutamyltransferase 6 (*GGT6)* and the arachiodonate lipoxygenase (*ALOX*) family of genes (3). Mucha and colleagues also noted a potential role for protein stability and lipid homeostasis gene, Asialoglycoprotein Receptor 2 (*ASGR2)* in udder formation (4). Our analysis from 302 whole genome sequenced animals showed no protein-altering variants for *PLD2*, *GGT6*, *ASGR1/ASGR2* and *ALOX* genes.

Whole genome sequence analysis revealed 340 variants within the 5Mb QTL with linkage disequilibrium $R^2 > 0.8$ with the most significant SNP marker 19:26,610,610. After removing markers not predicted to change protein sequence, we propose two novel candidate variants including a valine to isoleucine non-synonymous variant (V222I) in the proteasome 20S subunit 6 (*PSM6B*) gene, and a serine to isoleucine non-synonymous variant (S301I) in the sex hormone binding globulin (*SHBG*) gene. Genetic variation in human PSM6B was associated with LDL cholesterol and total cholesterol levels in a meta-analysis of 617,303 individuals of multi-ethnic backgrounds with 32 million genotyped and imputed variants (26). PSMB6 encodes a core component of the 20S proteasome complex involved in intracellular protein degradation. However, its role in lipid metabolism is unclear. In the same GWAS study, genetic variants in SHBG were associated with triglyceride levels (26). SHBG regulates the plasma metabolic clearance rate of steroid hormones such as oestrogen (27–29), although like PSMB6 a strong functional link with lipid metabolism is not yet determined. Attributing causality to either of these mutations will require further genotyping of these variants within a study population that contain sufficient meioses to separate out causative haplotypes and appropriate functionality testing.

Selection on the chromosome 19 QTL for milk production traits will hold economic value in dairy industries. Markers capturing the QTL effect may be utilised in marker-assisted breeding programmes to drive selection of the next generation of high-performance animals. Employing selection with the most significant marker at chr19:26,610,610 was predicted to increase fat yield, protein yield and milk volume in our study population. However, a potential adverse relationship between production traits and udder conformation has been indicated for this locus (3, 4). Our study replicated the observations of a shift in the negative direction for udder depth, fore udder attachment and rear udder attachment scores. It is unclear whether the negative correlation between production and udder traits are a consequence of increased milk production and udder volume retention giving rise to a perceived increase in udder depth with weak and narrow udder attachment or a true biological deterioration of udder morphology independent to the production increase. In the future, it will be interesting to determine whether the gene underlying the QTL has a direct effect on mammary gland morphology. Both alleles at the chr19:26,610,610 locus are common in the dairy goat population, with the high-milk production allele approaching fixation on some farms after long-term phenotypic selection for both milk production and conformation traits. These observations imply that the magnitude of the udder effects may be well-balanced with the increase in milk production. A comprehensive analysis of udder shape deterioration versus the production increase across the wider population will be required to optimise selection and breeding programmes for marker 19:26,610,610 as these traits affect production (9), milk quality (somatic cell count) (13), milking ability (8) and total number of days in production (15).

The overarching goal of this research is development of a marker-assisted breeding programme that can be implemented to accelerate productivity gain. This study identified use of the 19:26,610,610 SNP as a viable selection marker for marker assisted breeding programmes to increase production.

Conclusion

Genome wide association analyses across the dairy goat population in New Zealand have discovered a 24-29Mb QTL on caprine chromosome 19 that has a pleiotropic effect on milk production and udder conformation traits. A negative correlation between production and udder conformation traits was observed in the New Zealand goat population which corroborates reports in French and British dairy goat herds. Close monitoring of udder health is recommended for future selection programmes involving this locus. Marker assisted breeding programmes with markers effectively identifying this QTL can be utilised to select the next generation of high-performance animals to accelerate productivity gain.

Abbreviations

QTL; quantitative trait loci, SNP; single nucleotide polymorphism, GWAS ; Genome Wide Association Study, UD ; udder depth , FUA; fore udder attachment, RUA; rear udder attachment, UF; udder furrow, TP; teat placement, TA; teat angle, DGAT1; Diacylglycerol O-Acyltransferase 1, MRC2; Mannose Receptor C Type 2, GCTA; genome-wide complex trait analysis tool, GRM; genetic relationship matrices , MLMA-LOCO ; mixed linear model association analysis, leave one chromosome out, ANOVA; analysis of variance, *PSMB6;* Proteasome 20S Subunit Beta 6, *SHBG* ; Sex Hormone Binding Globulin, *PLD2;* Phospholipase D2, *GGT6;* Gamma-Glutamyltransferase 6, *ALOX* ; arachiodonate lipoxygenase, *ASGR2;* Asialoglycoprotein Receptor 2

Declarations

Ethical approval and consent to participate

Animal genotyping were approved by The University of Auckland animal ethics committee (Auckland, New Zealand) ethics permit 001763. Collection of animal phenotypes and milk sampling were approved by AgResearch ethics committee (Hamilton, New Zealand) ethics permits 14828 and 14889.

Consent for publication

N/A

Availability of supporting data

Supporting data is available through contact with the authors.

Competing interests

KL and AA-U received compensation from the Dairy Goat Co-operative (DGC) and RGS obtained research funding from the DGC. S-AT is an employee of the DGC. AJ was supported by the DGC Russ Moroney scholarship.

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Authors contributions

RGS, KL, S-AT and CGP considered the study and obtained funding. AA-U measured on farm phenotypes. AJ, KL, MDL and RGS performed phenotype and genotype analysis. AJ wrote the manuscript. AA-U, S-AT, MS, MDL, NL-V, CGP, RGS, and KL revised and approved of the final manuscript.

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Figures

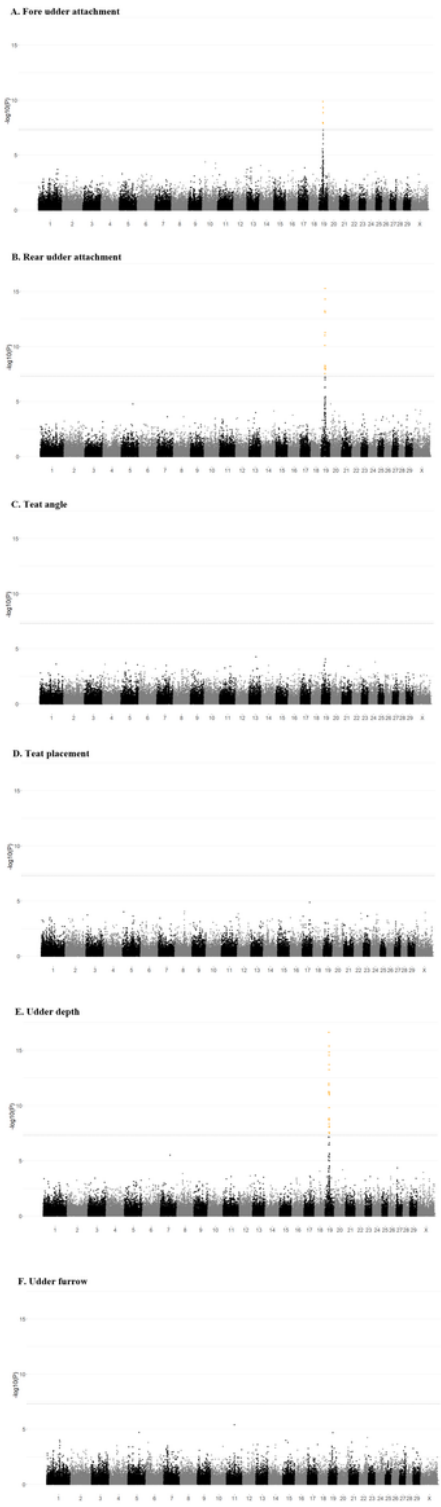

Figure 1

Manhattan plots of SNP marker association across chromosomes 1 to 29 plus X for Fore udder attachment (A), Rear udder attachment (B), Teat angle (C), Teat placement (D), Udder depth (E) and Udder furrow (F) for 722 animals. Population structure accounted for by estimating genetic relationship matrices (GRM) between all animals. Genome wide significance threshold is indicated by a dashed line at P value of 5.0 x 10-8. SNP markers of genome wide significance are coloured in orange.

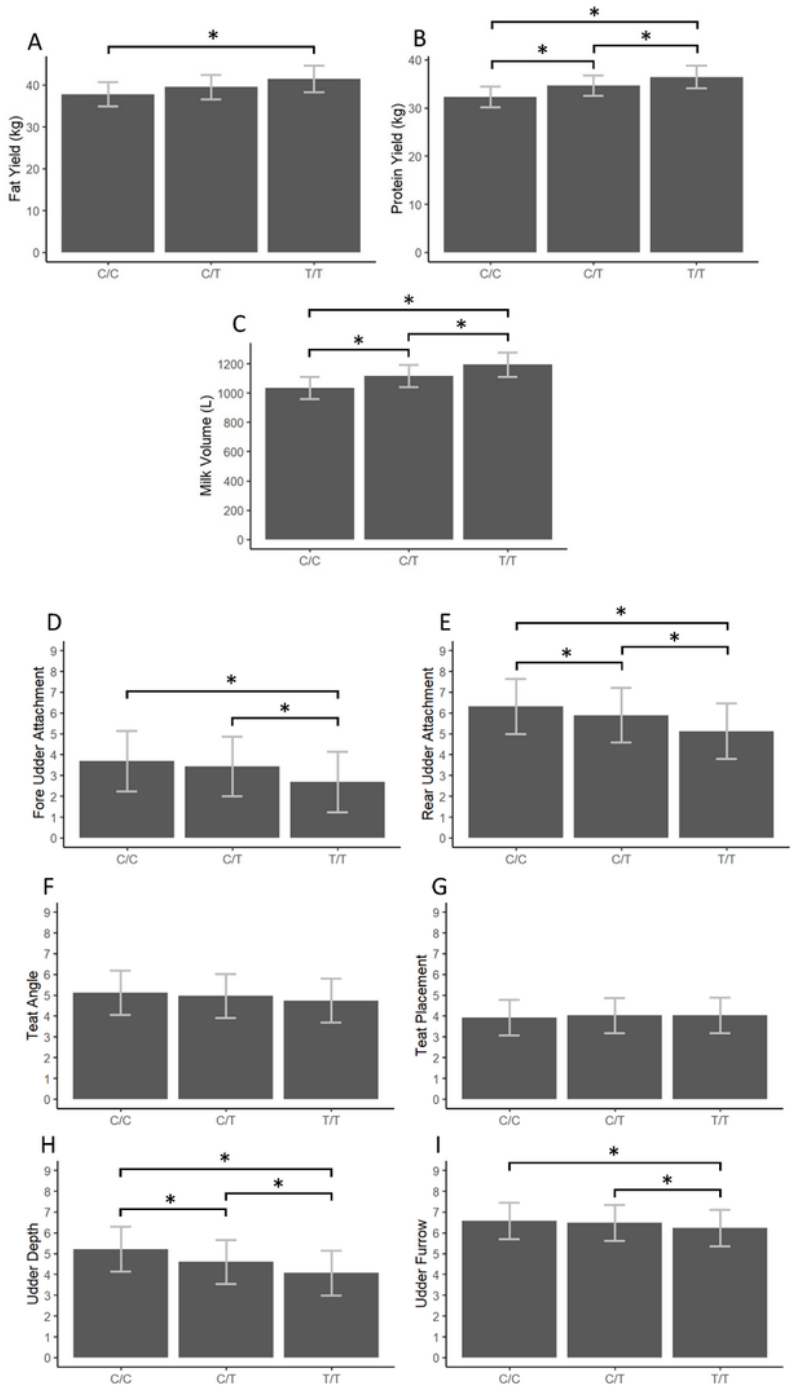

Figure 2

Allelic effect sizes for marker 19:26,610,610 genotype groups. Production traits, Milk Fat (A), Milk Protein (B), Milk volume (C) and udder traits, Fore udder attachment (D), Rear Udder Attachment (E), Teat Angle (F), Teat Placement (G), Udder Depth (H), Udder Furrow (I) were plotted as least squared means with 95% confidence intervals. Asterisks indicate pairwise significant differences between genotype groups (p value < 0.5, multiple pairwise comparisons adjusted for false discovery rate; α=0.05)

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