Small Ruminant Research 121 (2014) 232–243

Contents lists available at ScienceDirect

Small Ruminant Research

journal homepage: www.elsevier.com/locate/smallrumres

Determination of the novel genetic variants of goat *STAT5A* gene and their effects on body measurement traits in two Chinese native breeds

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ARTICLE INFO

Article history:
Received 5 December 2013
Received in revised form 15 July 2014
Accepted 5 September 2014
Available online 16 September 2014

Keywords:
Goat
Signal transducer and activator of transcription 5A (STAT5A) gene
Single nucleotide polymorphism (SNP)
Association
Body measurement traits

ABSTRACT

Signal transducer and activator of transcription 5A (STAT5A), previously known as mammary gland factor (MGF), belongs to the prolactin/JAK2/STAT5 pathway, and plays an important role in growth and development, milking, and lipid accumulation in mammals. The aim of this study was to identify novel genetic variants of the goat *STAT5A* gene, as well as to test the possible effects of these variants on body measurement traits in the Xinong Saanen dairy goat (XNSN, milking breed) and the Hainan black goat (HNBG, meat breed) that thrive in Northwest China and Southeast China, respectively, which concurrently need improvement in terms of growth. Three novel single nucleotide polymorphisms (SNPs) (IVS1+254C>T, SNP1; Tyr90Tyr, SNP2; and IVS3+303T>C, SNP3) within the goat *STAT5A* gene were identified in intron 1, exon 2, and intron 3, respectively, as well as a documented SNP (Pro268Pro, SNP4) was also detected in exon 7. These SNPs were genotyped using the amplification created restriction site-polymerase chain reaction-restriction fragment length polymorphism (aCRS-PCR-RFLP) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods; their minor allelic frequencies varied from 0.079 (SNP4) to 0.372 (SNP2) in the HNBG breed as well as from 0 (SNP1) to 0.362

Abbreviations: STATs, signal transducers and activators of transcription; JAKs, Janus kinase; JAK-STAT, Janus kinase-signal transducers and activators of transcription pathway; STAT5A, signal transducer and activator of transcription 5A; MGF, mammary gland factor; STAT5B, signal transducer and activator of transcription 5B; POU1F1(PIT1), POU class 1 homeobox 1; PROP1, PROP paired-like homeobox 1; LHX3, LIM homeobox 3; LHX4, LIM homeobox 4; GH, growth hormone; GHR, growth hormone receptor; PRL, prolactin; SNP, single nucleotide polymorphism; aa, amino-acid; bp, base pair; nt, nucleotide; MAS, marker-assisted selection; 5′-UTR, the five prime untranslated region; 3′-UTR, the three prime untranslated region; PCR-RFLP, polymerase chain reaction – restriction fragment length polymorphism; aCRS-RFLP, amplification created restriction site – polymerase chain reaction – restriction fragment length polymorphism; HWE, Hardy–Weinberg equilibrium; He, gene heterozygosity; Ne, effective allelic number; PIC, polymorphism information content; LD, linkage disequilibrium; LSM, least squares mean; GLM, general linear model; BW, body weight; BH, body height; BL, body length; ChC, chest circumference; ChD, chest depth; ChW, chest width; HW, hip width; HuW, hucklebone width; CaC, cannon circumference; BLI, body length index; ChCI, chest circumference index; CaCI, cannon circumference index; TI, trunk index; HuWI, hucklebone width index.

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http://dx.doi.org/10.1016/j.smallrumres.2014.09.002
0921-4488/

(SNP4) in the XNSN breed, respectively. The PIC values of these loci varied from 0 to 0.358. Haplotype analysis uncovered only 8 haplotypes; the major haplotypes were Hap1 (CCCC), Hap2 (CCTC), and Hap4 (CTTC). During linkage disequilibrium analysis, only SNP1 and SNP3 loci showed strong linkage ($r^2 = 0.999$) in the HNBG breed. Statistical analyses indicated that only the known variant (SNP4, Pro268Pro) was significantly associated with body measurement traits in the two breeds when analyzed separately or in combination ($P < 0.05$ or $P < 0.01$), implying that this SNP significantly affected goat body measurement traits. Therefore, the *STAT5A* gene is a candidate gene affecting goat body measurement traits and could contribute to goat breeding improvement programs through marker-assisted selection (MAS).

1. Introduction

The Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway is responsible for promoting a variety of cytokines, growth factors, and hormones in numerous genes, and thus, it plays an important role in development and homeostasis in various animal species, from humans to flies (Richard and Stephens, 2011; Kaplan, 2013; Liongue and Ward, 2013; Oliver and Watson, 2013). This pathway has a very close relationship with the growth hormone (GH) (Herrington et al., 2000; Trovato et al., 2012), growth hormone receptor (GHR) (Herrington and Carter-Su, 2001), and prolactin (PRL) (Gouilleux et al., 1994; Boutinaud and Jammes, 2004). Compared to the JAK family, including JAK1-3 and Tyk2, the STAT family has more members, e.g., STAT1-4, STAT5A, STAT5B, and STAT6 (Kaplan, 2013; Liongue and Ward, 2013). Since phosphorylated STATs enter the nucleus to bind to specific regulatory sequences to activate or repress the transcription of target genes (Gouilleux et al., 1994; Richard and Stephens, 2011; Jiang et al., 2012), these play a prominent role in the regulatory process of GH by the association between GH and JAKs (Herrington et al., 2000). Furthermore, several STATs are indispensable in the regulation of obesity and/or insulin resistance, and immunity (Kaplan, 2013).

As one of the members of the STAT family, STAT5 is responsible for sexually dimorphic gene expression in the liver as determined by the secretory pattern of GH and its importance in body weight and body measure traits (Herrington et al., 2000; Herrington and Carter-Su, 2001; Trovato et al., 2012). STAT5 occurs in various species and comprises two kinds of hypotypes (STAT5a and STAT5b), which share a high degree of sequence homology (>90%) (Kanai et al., 2014). However, these hypotypes demonstrate significant differences in the DNA binding specificities and tissue expression profiles (Kanai et al., 2014). Thus, STAT5A seems to be more important in various functions. Previously, STAT5A was known as the mammary gland factor (MGF), and transduced PRL sends signals to the milk protein genes (Gouilleux et al., 1994; Boutinaud and Jammes, 2004), suggesting that the PRL/JAK2/STAT5 pathway is essential for alveologenesis and milk protein gene expression (Oliver and Watson, 2013). Subsequently, several studies have focused on the influence of STAT5A on breast growth (Boutinaud and Jammes, 2004), immunity (Kaplan, 2013), lipid accumulation and metabolism of adipocytes (Richard and Stephens, 2011), and development of myeloid cell types in animals. STAT5A serves as an important downstream gene of GH and PRL, which significantly affects the body measurement traits in large livestock animals; thus, the *STAT5A* gene has been hypothesized to become the important candidate gene affecting the body measurement traits in goats.

In large livestock animals, the *STAT5A* gene has been mapped to chromosome 19 in cattle, chromosome 11 in sheep, and chromosome 19 in goat (Goldammer et al., 1997). Compared with a few genetic variants of this gene in bovine and sheep, however, a few mutations have been reported, except for one single nucleotide polymorphism (SNP) in exon 7, which was genotyped using the *Ava*I polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method (An et al., 2013). However, the existence of other novel genetic variants within the goat *STAT5A* gene is in unclear. Moreover, whether the novel and documented goat SNPs (if present) significantly affect body measurement traits remains elusive.

The Xinong Saanen dairy goat (XNSN), which is mainly reared in Northwest China, is a famous breed with excellent milk performance, but has slow growth. The Hainan black goat (HNBG) that thrives in Southeast China is a well-known meat breed with delicious meat flavor and is characterized to undergo slow growth. To improve the Chinese goat industry, marker-assisted selection (MAS) can be used to increase the rearing size of these breeds by overcoming its negative traits. Therefore, the aim of this study was to detect novel genetic variants of the goat *STAT5A* gene, as well as to test the possible effect of these variants on body measurement traits in the XNSN and HNBG breeds in order to extend the spectrum of the goat *STAT5A* gene and provide a useful DNA marker for breeding improvement programs of the Chinese goat industry through the use of the MAS strategy.

2. Materials and methods

2.1. Animals and data recording of body measurement traits

A total of 707 samples were collected from unrelated female goats belonging to the two well-known Chinese native goat breeds, including 284 ear tissues of 2–3-year-old HNBGs and 423 blood samples of XNSNs. The HNBG breed represented the meat breed and was reared in native breeding farms in the Zanzhou country of Hainan province, PR China. A the total of 284 healthy and unrelated female HNBG goats was investigated and measured in seven growth traits, which were reared in native breeding farms, in Zanzhou County (East Longitude 109.5°; North Latitude