

MINIREVIEW ARTICLES

The Important Candidate Genes in Goats - A Review

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ABSTRACT

A total of 271 candidate genes have been detected in goats. However, comprehensive investigations have been carried out on the polymorphism of some genes, involved in the control of economic traits. Candidate genes have an effect on the physiological pathway, metabolism and expression of phenotypes. For growth traits, growth hormone (*GH*), growth hormone receptor (*GHR*), insulin like growth factor I (*IGF-I*), leptin (*LEP*), caprine pituitary specific transcription factor-1 (*POU1F1*), caprine myostatin (*MSTN*) and bone morphogenetic protein (*BMP*) genes are necessary for bone formation, birth weight, weaning weight, body condition and muscle growth. For reproduction, forkhead box L 2 (*FOXL2*), melatonin receptor 1A (*MTNR1A*), sex determination region of Y chromosome (*SRY*) and amelogenin (*AMEL*) genes influence sex determination and proliferation. The major candidate genes for milk yield and milk composition traits are the casein gene and their family. Keratin associated protein (*KAP*) and melanocortin 1 receptor (*MC1R*) genes are candidate genes for wool traits. The major histocompatibility complex (*MHC*) gene is considered important for the immune system and disease resistance traits. The functions of these genes on economically important traits are different. Some genes have synergistic or antagonistic effects in nature for expression of phenotypic traits. On the other hand, some genes could control more than one trait. Also, the producers should be concerned with these effects because selection of a single trait by using only a gene could affect other traits. Therefore, the identification of candidate genes and their mutations which cause variations of gene expression and phenotype of economic traits will help breeders to search some genetic markers for these economic traits. It may be used as an aid in the selection of parent stock at an early age in the future.

Keywords: Candidate genes, goats

INTRODUCTION

The world goat population amounts to 550 million, 94 % of which are found in developing countries. Around the Mediterranean, in Asia and Africa, goats provide milk, meat and wool. Furthermore, in a few European countries (France, Germany and Netherlands), goats provide cheese, motivating the setting-up of genetic improvement programs for this species. Goat's meat is also consumed in many regions of the world. The number of goats for meat and milk in 2008 is approximately 344,516 and 29,513 heads. The total number of goats was estimated to be approximately 11 animals per household. About 80 % of the number of goats in Thailand were found mostly concentrated in center and southern part of Thailand. The demand for goat's meat tends to exceed the meat available [1]. Wool and conformation traits in goats have progressed by selection based on phenotype [2]. This selection is without any knowledge of the number of genes that affect the trait or the effects of each gene.

For the last decade, molecular genetics has lead to the discovery of individual genes or candidate genes with substantial effects on the traits of economic importance. Candidate gene strategy has been proposed by direct search for quantitative trait loci (QTL) [3]. In other words, the genetic variation in a gene affects the physiological pathways and phenotype. Moreover, the proportion of genetic and phenotypic variation would be likely to affect the breeding strategy for improvement of important traits in the future. Genetic markers associated with traits of interest can be searched directly by applying molecular biology techniques. These techniques can identify genetic variation at specific loci and analyze the relationship between genetic variation at QTL and production traits [4]. Application of molecular genetics for genetic improvement relies on the ability to genotype individuals for specific genetic loci. The information utility from candidate genes in breeding programs has potential to substantially enhance the accuracy of selection and increasing selection differences [5].

Many studies have reported that the candidate genes influence growth, reproductive, milk, wool and disease resistance traits in goats. In addition, some genes control more than one trait. For instance, the growth hormone (*GH*) gene influences expression of growth and milk traits. The important candidate genes for goats play a key role in productivity, metabolism, sex determination, reproduction and disease resistance [6-12]. Therefore, the aim of this article is to review the published candidate genes which have an influence on production traits such as growth, reproductive, milk, wool and disease resistance traits in goats. A study of the candidate genes for significant economic traits could be applied for a direct search of QTL in order to plan a breeding program in the future.

Goat Production

The world goat population is 550 million, 94 % of this total is found in the Mediterranean, Asia and Africa [10]. Furthermore, in a few European countries such as Italy and Hungary, the making of goat cheese is of major interest and has motivated the setting-up of a genetic improvement program. Goat's meat is also consumed in many regions of the world. In the USA, the demand for goat's meat exceeds availability [13]. Similarly in Thailand, goat production has increased steadily during the past 5 years because of the increased demand for goat's meat by ethnic groups who prefer goat's meat in their diet. The number of goats is highest in southern of Thailand, especially Yala province while the number of goats is lowest in northeast Thailand [1]. Economic traits in goats can be divided into 4 main types; growth, reproduction, meat and milk traits. In addition, disease resistance is an important trait in small ruminant herds. These traits are controlled by polygenes and are affected by environmental factors. The breeding improvement for these economic traits of goats in the past had been achieved by selection based on only phenotypic expression.

Genetic Selection of Goat

Genetic progress for quantitative traits in livestock production, especially for goats have been made by selection based on phenotypes and estimated breeding value derived from phenotypes. These strategies do not require any knowledge of genes that influence the traits or the effect of each gene because utilization of advances in molecular genetics in the past decade for selection processes is expensive. Therefore, the substantial rates of genetic improvement have been achieved and continue to be achieved on this quantitative genetic approach [3]. The success of this approach depends on accurate information concerning data or data structure and genetic evaluation methods.

For several years, many hopes have been raised for genetic improvements in goats by using molecular genetics. The current advances in molecular genetics are leading to the discovery of individual genes or candidate genes with substantial effects on the traits of economic importance. Studying the genetic make-up of individuals at the DNA level and molecular genetics has given scientists the tools for opportunities for genetic improvement. Currently, molecular genetic techniques have already resulted in the discovery of several genes that have a major effect on some interesting quantitative traits and of genetic markers that are linked to QTL [3]. Marker assisted selection (MAS), employed in conjunction with traditional selection methods, could accelerate the rate of change in economically important traits [14]. Two approaches of MAS have been pursued to identify genetic markers for economic traits. Firstly, genome scans employing anonymous DNA markers like microsatellites have been used to identify QTL. Secondly, a candidate gene approach as a direct gene assay has been employed in order to find genes or regions with an impact on traits of interest [15]. Indeed, the total detected genes in the goat genome at present are 271 genes and 423 microsatellite markers [16]. The identification of powerful polymorphic markers, essentially

microsatellites has led to the construction of low resolution linkage maps and to the mapping of genes and QTL. Therefore, the candidate gene strategy has been proposed as a direct search for QTL in order to improve quantitative traits [3].

Since 1989, when the growth hormone gene was investigated with regard to its influence for the evolution of vertebrates, this gene has been found to affect growth traits and milk yields in goat [17]. Several candidate genes and QTL analyses have been performed to find genes or regions with an impact on growth, reproductive, milk, fiber and disease resistant traits [14]. Nevertheless, no gene has been detected with a causative mutation for traits through linkage analyses because many genes contribute a small amount to economic trait parameters. There are 2 ways in which a gene can affect the production performance. Firstly, mutation in coding regions of a gene may modify the quality of the encoded protein. In this case, if a mutation causes amino acid exchange, premature stop of translation or alternative splicing will occur. The change in the primary protein structure could cause failure of the protein function. Secondly, mutations in regulatory regions of the gene which influence the amount of the transcripts of the gene in the cell and the amount of produced functional protein with unchanged quality. Also, these mutation situations are expected to cause phenotypic changes [18].

Candidate Gene Affecting on Economic Traits

Candidate genes can be separated into 6 economic traits such as growth, reproductive, meat, milk, fiber and disease resistant traits. The location and function of these genes are presented in **Table 1**.

Candidate Genes on Growth Traits

1) Growth Hormone (*GH*) Gene

GH gene is encoded by 1,800 base pairs (bp). It consists of 5 exons and it is separated by 4 intervening sequences [5,17]. This gene produces *GH*. This hormone is a peptide hormone that is produced from the anterior pituitary. *GH* is necessary for postnatal growth and metabolism in vertebrates [19]. Many publications have reported that polymorphism of this gene has been identified in the regulatory region, untranslated regions and exons. Indeed, a few of these polymorphic sites have been precisely characterized for nucleotide and amino acid changes [5,17,19,20]. In addition, 2 polymorphic sites were located in each of exon 1 and exon 2, 4 sites in exon 3, 7 sites in exon 4 and 5 sites in exon 5 [5]. Moreover, these sites could be associated with birth weight and weaning weight of their offspring. Similar results have been found by Yu and co-workers [20]. They stated that 5 substitution mutations of the *GH* gene influenced birth weight and weaning weight.

In addition, *GH* plays an important role in lactation. Some *GH* secretion parameters and peak frequency are associated with dairy animals of high genetic value. It has been demonstrated that those animals with high milk yield reveal superior *GH*

average levels when compared to those observed in animals with lower production [21]. It has also been reported that genetic polymorphisms of the *GH* gene were associated with milk, fat and protein production ($p < 0.05$) [5].

Table 1 Location of important candidate genes of goat on economic traits.

Candidate genes	Location ¹	Function	References
<i>GH</i>	19q22	Growth and milk yield	[5,20,21]
<i>GHR</i>	20q17	Milk yield, content of the major milk components and somatic cell count	[23,24]
<i>IGF-I</i>	5q31	Growth, metabolism and reproduction	[9,27,30,31]
<i>LEP</i>	3q33	Growth development, feed conversion efficiency and milk	[32-35]
<i>POUIF1</i>	1q21-q22	Growth, carcass, milk and wool	[10,36-38]
<i>MSTN</i>	-	Muscle growth	[7,39,40]
<i>BMP</i>	-	Embryonic development, homeostasis, repairing of various tissue patterning, cell differentiation, apoptosis and female fertility	[11,45-47]
<i>FOXL2</i>	-	Cell growth, proliferation, differentiation longevity and reproduction in female	[12, 48-50]
<i>MTNR1A</i>	-	Reproductive seasonality	[55-61]
<i>SRY</i>	Y	Sex determination	[62,63]
<i>AMEL</i>	-	Sex determination	[67,68]
Casein	6q32	Milk yield and milk composition	[69-71,73,76,77]
<i>KAP</i>	5q25	Fiber/ wool textile	[79,80]
<i>MC1R</i>	-	Fiber/ wool color	[81,82]
<i>MHC</i>	23q22	Immune system	[88]
<i>PrP</i>	13q17	Scrapie resistance	[89,90,92,93]

Note: ¹Reference of gene locations comes from Cribiu and Weiss [16], - = no report, growth hormone (*GH*), growth hormone receptor (*GHR*), insulin like growth factor I (*IGF-I*), leptin (*LEP*), caprine myostatin (*MSTN*), caprine pituitary specific transcription factor-1 (*POUIF1*), bone morphogenetic protein (*BMP*), forkhead box L 2 (*FOXL2*), melatonin receptor 1A (*MTNR1A*), Sex determination region of Y chromosome (*SRY*), amelogenin (*AMEL*), keratin associated protein (*KAP*), melanocortin 1 receptor (*MC1R*), major histocompatibility complex (*MHC*) and prion protein (*PrP*) genes.

2) Growth Hormone Receptor (*GHR*) Gene

GH actions on target cells depend on the *GHR*. This hormone binding to *GHR* causes its dimerization. This binding could activate the *GHR*-associated Janus kinase 2 (*JAK2*), tyrosine kinase and tyrosyl phosphorylation of *JAK2* and *GHR* [22]. These events activate a variety of signaling molecules, including mitogen activate protein (*MAP*) kinases, insulin receptor substrates, phosphatidylinositol 3'-phosphate kinase, diacylglycerol, protein kinase C, intracellular calcium and signal transduction and

transcription (STAT) factors [22]. The *GHR* is a member of the cytokine/hematopoietin superfamily of receptors. The gene coding for *GHR* of most mammalian species consists of 9 exons in the translated part and of a long 5'-noncoding region that includes several alternative untranslated exons [22]. The researchers found polymorphism in a TG-repeat microsatellite in the promoter of the bovine *GHR* gene [23]. This 11-TG-repeat allele commonly occurred in *Bos indicus* cattle while alleles with 16 - 20 consecutive TGs are most common. They reported that this polymorphism was related with growth traits. Only a review paper of *GHR* in goats has been reported. TG-repeat polymorphism in the 5'noncoding region of *GHR* gene in dairy goats was observed. This polymorphic site had no associations with milk yield, content of the major milk components and somatic cell count in dairy goats [24].

3) Insulin Like Growth Factor I (*IGF-I*)

Growth is a complex process that involves the regulated coordination of a wide diversity of neuroendocrine pathways. *IGF-I* is an important component of the somatotrophic axis that plays a key role in postnatal growth and metabolism in mammals [25]. The *IGF-I* gene consists of 6 exons [26]. The researchers stated that *IGF-I* can stimulate anabolic processes such as cell proliferation, skeleton growth and protein synthesis [27]. Mutation of *IGF-I* in mice resulted in a lower skeletal growth rate [28]. Moreover, single nucleotide polymorphisms (SNPs) have been described in bovine and buffalo which was associated with production traits [29]. In addition, the insulin like growth factor binding protein-3 (*IGFBP3*) gene is a subfamily of *IGF-I*. *IGFBP3* is a structural gene. It is responsible for multiple effects of insulin like growth factors (*IGFs*) playing a key role in mammalian growth, development and reproduction [30,31]. Only one report of SNPs in exon 2 and intron 2 of *IGFBP3* gene in goats has been published [9]. The authors found that 4 point mutations influenced average litter size, birth weight, weight at 6 and 12 months of age ($p < 0.05$).

4) Leptin (*LEP*) Gene

LEP is a 16-kilodalton protein secreted from adipocytes involved in several physiological functions, including regulation of feed intake, energy expenditure, body temperature regulation and whole body metabolic balance [32-35]. *LEP* is produced by fat cells but is also found in the placenta [32]. Furthermore, some reports [33,34] indicate that *LEP* plays an important role in the regulation of growth, development and feed conversion efficiency. The possible effects of *LEP* on growth traits of goat kids are unknown and little research has been conducted involving *LEP* in goats. In addition, *LEP* is also found in goat's milk that may be related to the birth weight and body condition of does [35]. Similar reports have revealed that *LEP* has been found in the milk of human and livestock species and it influenced birth weight [32].

5) Pituitary Specific Transcription Factor-1 (*POU1F1*) Gene

The *POU1F1* gene is also named *PIT-1* or *GHF-1* gene. It is a positive regulator for *GH*, prolactin and thyroid-stimulating hormone and itself in mammalian animals [10]. Mutations on this gene possibly result in deficiency of *GH*, prolactin, thyroid-stimulating hormone and *POU1F1* [36]. The published reviews have reported that genetic polymorphisms of *POU1F1* gene were significantly associated with growth, development and lactation in mammalian animals such as swine, bovine and goats [10, 36-38]. Furthermore, the genetic variation of this gene in exon and flanking regions is associated with economic traits and production performance such as growth, carcass, milk and wool in meat, dairy and cashmere industries, respectively [10].

6) Caprine Myostatin (*MSTN*) Gene

The *MSTN* gene has been considered as an important candidate gene for growth and development of domestic animals because of its key role in muscle growth and its potential application in animal husbandry. This gene is studied in not only ruminant but also non-ruminant animals. The researchers reported that 9 base variations affected amino acids in cattle [39]. These changes gave rise to double muscling. Moreover, point mutations of the *MSTN* gene in swine influenced improvement of average daily gain [40]. In chickens, [41] found 5 SNPs in the 5' and 3' untranslated region. These polymorphic sites were strongly associated with production traits ($p < 0.05$). Research identified SNPs of this gene in goats [7], the authors found 8 polymorphic sites and 2 haplotypes in a part of intron 2 and exon 3. However, the association between these SNPs and production traits was not reported.

7) Bone Morphogenetic Protein (*BMP*) Gene

BMPs are members of the transforming growth factor-beta (*TGF- β*) superfamily which are multifunctional cytokines with a 2-fold function and are expressed in a variety of cells. *BMPs* were originally identified on the basis of their ability to produce ectopic bone formation when implanted within soft tissue *in vivo*. They also play roles in embryonic development, homeostasis, repairing of various tissue patterning, cell differentiation and apoptosis [42].

Besides, *BMPs* consist of subfamilies such as the *BMP4* and *BMP15* genes that influence growth and reproduction. The genetic variations of the *BMP4* gene in intron 2 by using Polymerase Chain Reaction-Single Strand Conformational Polymorphism (PCR-SSCP) were significantly associated with body height, chest circumference and trunk index ($p < 0.05$) [11]. The *BMP15* regulates granulosa cell proliferation and differentiation by promoting granulosa cell mitosis, suppressing follicle-stimulating hormone receptor expression and stimulating kit ligand expression. This protein plays a pivotal role in female fertility in mammals [43,44]. Polymorphisms of the *BMP15* gene were associated with both increased ovulation rate and litter size in heterozygous carriers and sterility in homozygous carriers in sheep and goats [45-47].

Candidate Genes on Reproduction and Sex Determination Traits

1) Forkhead Box L 2 (*FOXL2*) Gene

FOX proteins are a family of transcription factors that play important roles in regulating the expression of genes involved in cell growth, proliferation, differentiation and longevity [48]. A sequence of FOX proteins consists of 80 to 100 amino acids forming a motif that binds to DNA [49]. FOX proteins are divided into many subclasses (*FOXA* to *FOXK*). Only the *FOXL2* subclass has been reported in goats [50].

FOXL2 is a transcription factor essential for proper reproductive function in females. This gene was first identified in 1998 [50]. *FOXL2* is a novel member of the winged helix or forkhead family of transcription factors involved in pituitary gland development. The goat *FOXL2* protein consists of 375 amino acids and so far has no predicted functional domains apart from the DNA binding domain and a 14 amino acids polyalanine tract [48]. This gene is necessary for the establishment of the body axis, the development of tissue from all 3 germ layers and metabolic processes as well as cell cycle control [49]. Human carrying mutations in *FOXL2* gene display blepharophimosis/ptosis/epicanthus in versus syndrome (BPES) [48]. An autosomal dominant disease associated with eyelid defects and premature ovarian failure in females [50]. Mutations upstream of the *FOXL2* gene in goats may be deleted in the goat polled syndrome (PIS) because of the reduction in *FOXL2* expression [50]. The PIS syndrome leads to the absence of horns or polliness in male and female goats and is inherited in a dominant fashion. Intriguingly, it also causes XX female to male sex reversal in a recessive manner [12].

2) Melatonin Receptor 1A (*MTNR1A*) Gene

Melatonin synthesis by the pineal gland occurs only during the hours of darkness and gates photoperiodic information in mammals. Melatonin regulates circadian rhythms and reproduction changes in seasonally reproductive mammals [51]. The circadian effects of melatonin appear to be mediated by melatonin receptors in the hypothalamic suprachiasmatic nucleus [52]. Moreover, melatonin receptors (*MTNRs*) influenced the reproductive effect meditation in the hypophyseal pars tuberalis [53]. Melatonin exerts its reproductive and circadian effects through the binding to pharmacologically specific, high-affinity, G-protein-coupled receptors [54]. *MTNR1A* is a high affinity melatonin receptor that mediates reproductive functions in mammals. Researchers reported that 2 polymorphic sites by Restriction Fragment Length Polymorphism (RFLP) within the *MTNR1A* gene provided an opportunity to evaluate the influence of this gene on seasonal reproduction in goats [55]. The polymorphic site of the *MTNR1A* gene in exon 2 was associated with reproductive seasonality in ewes [55-60]. This is in contrast with Migaud and co-workers [61] who reported that no relationship could be detected between the polymorphic site in exon 2 of the *MTNR1A* gene and the expression of reproductive seasonality in goats.

3) Sex Determination Region of Y Chromosome (*SRY*) Gene

Sex determination and differentiation are controlled by sex chromosomes that induce the embryonic gonad into testes or ovaries [62]. *SRY* is a major candidate gene responsible for initiating genital development leading to testis formation. It has been equated with the testis-determining factor (TDF) [62,63]. The *SRY* gene encodes a protein with a DNA-binding motif known as the high-motility group (HMG) box. This box is a conserved motif for minor groove DNA recognition which has the ability to recognize the DNA binding motif with highest affinity [63]. The authors indicated that mutations of the *SRY* gene that give rise to male-to-female sex reversal almost always occur in the HMG box in mammals [63]. The goat *SRY* contains a 61-amino acid high-motility-group box [62]. Similarly, researchers carried out amplification of the HMG box of the *SRY* gene with a specific *SRY* primer in goats by using the PCR technique. Only males showed bands for an *SRY* band. It indicated that the *SRY* gene in goats was male specific [63].

4) Amelogenin (*AMEL*) Gene

The *AMEL* gene exists on both X- and Y- chromosomes [64-68]. They are called *AMELX* on the X-chromosome and *AMELY* on the Y-chromosome. The *AMEL* gene encodes an important protein in developing mammalian teeth and enamel matrix that has been conserved during the evolution of vertebrates [64-68]. *AMEL* amplification by PCR is a reliable method for sex determination in humans [64], cattle [65], sheep and deer [66]. Although, sexing embryo in farm animals such as karyotyping, H-Y antigen detection, X-linked enzymatic determination and identification of the gene on the Y chromosome are favorable techniques at the present moment in farm animals. The use of the *AMEL* gene has made the sex determination much less complicated [68]. This gene could be applied for sex determination in goats. Only a pair of primers is required to amplify the different size fragment of the *AMEL* gene. A pair of primers was utilized and the system of PCR was established to amplify a 262 bp fragment from the X-chromosome in female goats and a 202 bp fragment from the Y-chromosome in male goats [67]. The researchers stated that the PCR sexing protocols based on the *AMEL* gene is highly reliable and suitable for sex determination of goats [67,68].

Candidate Genes on Milk Production Traits

1) Casein (*CSN*) Gene

In goat's milk, 4 casein (α 1, α 2, β and κ -casein) coded by 4 tightly linked autosomal genes namely *CSN1S1*, *CSN1S2*, *CSN2* and *CSN3* genes, respectively were identified [69]. The 4 caseins represent about 80 % of milk proteins. They are characterized by specific properties which are of low solubility at pH 4.6 and an organization in clusters of protein chains called micelles. These genes that encode the major milk proteins are thought of as candidate genes for the observed variation in protein composition [69-71]. As an example, cheese yield is related to the casein

content in milk, particularly the ratio of casein to the total protein [70]. The *CSN1S1*, *CSN1S2*, *CSN2* and *CSN3* genes influenced sensitivity for calcium precipitation. They have been mapped with 250 kilobases (kb) [69]. In both cattle and goats, the *CSN1S1* and *CSN2* genes are convergent transcribed. There were 20 and 12 kb in these 2 genes [71]. The *CSN1S2* gene shows a relative large transcription unit. It is approximately 18.5 kb but the protein size of *CSN3* was not reported.

The *CSN1S1* gene is the most complex and has highly polymorphic sites. This gene is reported to have strong variation determined by at least 15 alleles. The researchers reported that the polymorphisms of this gene are associated with different efficiencies of protein synthesis. This gene is spread over 16.7 kb and consists of 19 exons varying in length from 24 to 385 bp on exon 5 - 8, 10, 13, 16 and 19 and 18 introns varying in length from 90 to 1,685 [72].

The *CSN1S2* gene in goats is characterized by 7 alleles (*A*, *B*, *C*, *D*, *E*, *F* and *O*) [73]. This gene is associated with a high content of casein to produce milk characterized by a minor diameter of micelles, a significantly higher percentage of protein, fat, total calcium and better parameters for curd firming time, curd firmness and cheese yield [70,73].

The *CSN2* gene is a half the size of the other calcium (Ca)-sensitive casein genes [71]. The Ca-sensitive caseins of goats exhibit both quantitative and qualitative variations. It arises from genetic polymorphism in encoded genes [70]. The *CSN2* gene is composed of 3 protein variants that were found to be associated with a normal β -casein content: *A*, *B* and *C*. The genetic polymorphisms of the *CSN2* gene at the promoter region have been associated with the level of β -casein expression in milk. *CSN2^A*, *CSN2^{A1}*, *CSN2^B*, *CSN2^C*, *CSN2^D* and *CSN2^E* alleles were associated with normal content that was approximately 5 grams of β -casein per liter. On the other hand, some publications reported that the variants of *CSN2* are associated with no protein expression [74,75].

The *CSN3* gene has been identified with 13 polymorphic sites in domesticated goats. Genetic polymorphisms of this gene were associated with protein and casein content ($p < 0.05$) [76,77]. In Chiatti and co-workers [78], they reported 3 genotypes in exon 4 of this gene that were associated with protein and casein expression ($p < 0.05$).

Candidate Genes on Wool Traits

1) Keratin Associated Protein (*KAP*) Gene

KAP is a major component of the matrix between hair keratins and form intermediate filaments (KIFs) which generate cells of the central hair-forming compartment. *KAP* form the rigid hair shaft through a cross-linked network with KIF. Hair keratins and their associated proteins are important in the formation of cashmere fiber [79,80]. *KAP* are encoded by a large number of multigene families. The *KAP* gene consists of a single exon of less than 1,000 bp. It is classified into 3 groups on the basis of their amino acid composition: high sulfur (16 - 30 % cysteine content), ultra-high

sulfur (> 30 % cysteine content) and high glycine/tyrosine protein content [79]. The *KAP6.2* gene, one of *KAP*'s families, is a necessary part of high glycine/tyrosine protein that is the smallest among the keratin proteins. Also, this gene is an important structural gene responsible for wool in cashmere goats [79,80]. Furthermore, Zhao and co-workers [80] reported genetic polymorphisms of this gene by SSCP in Mongolia White and Shaanbei White cashmeres. The results showed that 2 alleles such as O and X alleles were detected at the locus. The O allele mostly appeared in Mongolian White cashmere. Indeed, the sequencing of this allele represented no deletion but the other allele represented a 24 bp deletion. The results indicated that deletion mutation was predicted as a possible cause for the multiple patterns of cashmere wool.

2) Melanocortin 1 Receptor (*MC1R*) Gene

This gene influences fleece or wool color. Quantitative variation of fleece color has been studied in the context of the chemical properties of melanins and morphology of melanosomes because of the commercial value of fleece [81]. *MC1R* plays an important role in melatonin synthesis and the differentiation of coat color phenotypes. In many mammals, a gain of function of *MC1R* variants is associated with an increase in the production of eumelanin, while loss of function variants is associated with an increase in red/yellow pheomelanin production [82]. Also, this gene is hypothesized to be a candidate gene for variation in coloration patterns [81-83]. The researchers reported 11 point mutations of the *MC1R* gene. At this point of mutation was a 4 bp deletion. Four point mutations were silent mutations and 6 point mutations were single nucleotide polymorphism. These mutations of the *MC1R* gene were not correlated completely with fleece color [83]. In fact, the researchers expected that no association may be due to the epistatic relationship of *MC1R* with other coat color genes. However, Wu and co-workers [82] reported that genetic polymorphism of this gene influenced coat color traits in Boer goats. They stated that the red head and neck of Boer goats may be controlled by the recessive nature of this gene.

Candidate Genes on Disease Resistant Traits

1) Major Histocompatibility Complex (*MHC*) Gene

Major histocompatibility complex (*MHC*) is a gene family found in most vertebrates. It plays an important role in the immune system, autoimmunity and reproductive success [84-88]. The proteins from this gene encoded by the *MHC* are expressed on the surface of cells and these proteins display antigen to a type of white blood cell [84]. This white blood cell has the capacity to kill or co-ordinate the killing of pathogens, infected or malfunctioning cells [84]. *MHC* is divided into 3 subgroups such as *MHC* class I, *MHC* class II and *MHC* class III. *MHC* class I and class II encode heterodimeric peptide binding proteins but *MHC* class II can encode proteins that modulate antigen loading in lysosomal compartments. *MHC* class III encodes other immune compartments such as complement components, cytokines and heat shock

proteins [85]. The length of *MHC I* in goats is 1,077 bp encoding a mature protein with 337 amino acids [86]. *MHC* class II molecules can be separated into *DQ* and *DR* subtypes that are the most polymorphic sites in both human and domestic species and probably play a major role in the development of *MHC* restricted immune responses [87]. The polymorphic sites of *MHC* class II in goats have been found with amino acid substitutions at positions 70, 71, 73, 74 and 78 by using PCR-RFLP [87]. The authors concluded that the structural organization and polymorphisms of the caprine *MHC* provided the possibility for existence of close associations between restriction sites and amino acid substitution at positions with disease resistance [88].

2) Prion Protein (*PrP*) Gene

Scrapie is a fatal and infectious neurodegenerative disease affecting sheep and goats. It belongs to the group of transmissible sub-acute spongiform encephalopathies (TSEs) along with bovine spongiform encephalopathy (BSE) in cattle [89,90]. A feature common to all TSE diseases is the accumulation of an aberrant isoform of the normal *PrP* [89]. The abnormal configuration is considered to be infectious and resistant to proteolysis [90]. The occurrence of natural scrapie is strongly influenced by alterations in the host gene that encodes *PrP* [91]. The susceptibility or resistance to scrapie is varied among sheep and goats depending on genotype of the host and infectious strain. The polymorphic sites of the *PrP* gene in goats at 142, 143, 154, 222 and 240 bp have been used to describe scrapie susceptibility [89,92]. Only the polymorphic site at 142 bp was associated with an altered disease incubation period. It is conceivable that the different periods of *PrP* polymorphisms reported for sheep and goats could lead to a differential phenotypic expression of individual scrapie strains [93].

CONCLUSION

Improvement of goat production is composed of 2 main points such as feeding and management under farm conditions and selection of the parent stock in order to increase the economical efficiency. Certainly, most genetic progress for economic traits in goats would consider candidate genes because major genes and other genes that influence the physiological pathways of phenotypic traits control these traits. For instance, *GH*, *GHR*, *IGF-I*, *LEP* and *POU1F1* genes are translated into important hormones for growth traits. The *MSTN* and *BMP* genes are translated for development of muscle and bone. Moreover, the *FOXL2* and *MTNR1A* genes affect reproductive traits in females and reproductive seasonality. The *SRY* and *AMEL* genes control sex determination. These genes could be applied for embryo sexing by PCR. Genetic improvement of goat's milk may be achieved by considering the casein gene and its family because they have an effect on milk yield and milk compositions. On the other hand, the *KAP* and *MC1R* genes could be major genes for the development of desirable fiber in the textile industry. The *MHC* gene is a necessary gene for the immune system

for the killing of pathogens, infected or malfunctioning cells. The *PrP* gene is associated with the scrapie disease that is a fatal and infectious neurodegenerative disease. The analysis of the polymorphism of regulatory fragments of these genes will bring important data on gene expression regulation. This genetically controlled variation of quantitative traits may affect phenotypic performance. Nowadays, the sophisticated use of molecular and quantitative information on an industry-wide scale will require robust systems that can cope with imperfect data as well as the development of selection indices to take full advantage of the information. However, selection by genetic polymorphism of candidate genes could be concerned with the function of some genes which would have synergistic or antagonistic effects in nature for expression and pleiotropy among candidate genes that would affect other traits.

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บทคัดย่อ

จินา สุภากรณ์

ยื่นเป้าหมายที่สำคัญในแพะ

Candidate genes ถูกค้นพบทั้งหมด 271 ยีน ซึ่งมียีนจำนวนหนึ่งที่มีความสำคัญต่อลักษณะสำคัญทางเศรษฐกิจในแพะ ยีนดังกล่าวจะเกี่ยวข้องกับระบบสืบพันธุ์ เมแทบอลิซึม และการแสดงออกของลักษณะปรากฏ เช่น ลักษณะการเจริญเติบโต ได้แก่ ยีน growth hormone (*GH*), growth hormone receptor (*GHR*), insulin like growth factor I (*IGF-I*), leptin (*LEP*), caprine pituitary specific transcription factor-1 (*POUIF1*), caprine myostatin (*MSTN*) และ bone morphogenetic protein (*BMP*) ลักษณะทางการสืบพันธุ์ ได้แก่ ยีน forkhead box L 2 (*FOX L2*), melatonin receptor 1A (*MTNR1A*), sex determination region of Y chromosome (*SRY*) และ amelogenin (*AMEL*) ลักษณะปริมาณน้ำนม ได้แก่ กลุ่มของยีน casein ลักษณะคุณภาพขน ได้แก่ ยีน keratin associated protein (*KAP*) และ melanocortin 1 receptor (*MC1R*) นอกจากนี้ ยีน major histocompatibility complex (*MHC*) และ prion protein (*PrP*) gene จะส่งผลต่อระบบภูมิคุ้มกันและการต้านทานโรค ยีนดังกล่าวจะมีหน้าที่แตกต่างกัน แต่ส่งผลโดยตรงต่อลักษณะที่ควบคุมอยู่ในขณะเดียวกันบางยีนจะส่งผลต่อการแสดงออกได้มากกว่าหนึ่งลักษณะ โดยอาจส่งผลให้อีกลักษณะหนึ่งดีขึ้นหรือแย่ลง ดังนั้น การประยุกต์ใช้ยีนเป้าหมาย เพื่อเป็นเครื่องหมายทางพันธุกรรม สำหรับปรับปรุงลักษณะต่างๆ ในแพะ จึงอาจเป็นแนวทางหนึ่งในการคัดเลือกพ่อแม่พันธุ์เมื่ออายุยังน้อย แต่ทั้งนี้จำเป็นต้องพิจารณาผลของยีนใดยีนหนึ่งต่อลักษณะไม่พึงประสงค์ด้วย