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Analisis Polimorfisme Gen LEPR (*Reseptor Leptin*) pada Spesies Ruminansia Domba, Kambing, dan Sapi Berdasarkan Basis Data Bank Gen

(Gene Polymorphism Analysis of LEPR (Leptin Receptor) in Ruminant Species of Sheep, Goat and Cattle Based on Gene Bank Database)

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ABSTRAK

Domba mempunyai morfologi yang mirip dengan kambing dibandingkan dengan sapi. Persamaan dan perbedaan morfologi ketiga spesies tersebut tidak selalu diikuti dengan perbedaan dan persamaan fenotip ciri reproduksinya. Oleh karena itu, ciri-ciri reproduksi antara ketiganya perlu dikaji pada level genetik. Gen LEPR merupakan kandidat kuat gen pengatur sifat reproduksi. Penelitian ini bertujuan untuk membandingkan profil gen LEPR antara domba, kambing dan sapi. Metode yang digunakan dalam penelitian ini adalah analisis statistik deskriptif induktif. Profiling dilakukan dengan menggunakan program BLAST (local lignment) dalam NCBI. Polimorfisme yang diperoleh kemudian dianalisis jenis mutasinya. Melalui local lignment diketahui adanya perubahan SNP dan perubahan asam amino. Profil gen domba, kambing, dan sapi ditemukan berbeda, dengan hasil polimorfisme nukleotida tunggal (SNP) menunjukkan bahwa terdapat 37 SNPs pada domba dan kambing, 79 SNPs pada domba dan Sapi, serta 78 SNPs pada kambing dan sapi. Selanjutnya, jumlah polimorfisme nukleotida tunggal pada spesies tersebut diikuti oleh 15, 42, dan 39 perubahan asam amino secara berurutan. Perubahan asam amino menghasilkan silent mutation, neutral mutation, dan missense mutation dengan proporsi yang berbeda. Berdasarkan hasil penelitian secara keseluruhan, dapat disimpulkan bahwa gen LEPR ketiga spesies tersebut memiliki profil yang berbeda. Perbedaan tersebut dapat menegaskan mengapa domba, kambing dan sapi mempunyai ciri reproduksi yang berbeda.

Kata kunci: Gen LEPR, Domba, Kambing, Sapi, SNP.

ABSTRACT

Sheep have a closer morphology to goat than cattle. The morphological similarities and differences between the three species are not always accompanied by phenotypic differences and similarities in their reproductive characteristics. Therefore, reproductive characteristics between the three need to be studied at the genetic level. The LEPR gene is a strong candidate for a gene regulating reproductive traits. This study aims to compare LEPR gene profiles between sheep, goats and cattle. The method used in this research is inductive descriptive statistical analysis. Profiling was carried out using the BLAST (local alignment) program in NCBI. The polymorphisms obtained were then analyzed for the type of mutation. Through local alignment, it is known that there are SNP changes and amino acid changes. Gene profiles of sheep, goat, and cattle were found to be different, with the result of single nucleotide polymorphism (SNP) that there are 37 SNPs of sheep and goat, 79 SNPs of sheep and cattle, 78 SNPs of goat and cattle. Furthermore, the number of single nucleotide polymorphisms of those species is followed by 15, 42, and 39 amino acid changes, consequently. Amino acid changes produce silent mutations, neutral mutations, and missense mutations in different proportions. Based on the overall research results, it can be concluded that the LEPR genes between the three species have different profiles. These differences can explain why sheep, goats and cows have different reproductive characteristics.

Keywords: LEPR Gene, Cattle, Goat, Sheep, SNP.

INTRODUCTION

Ruminant species are important for livestock production, including sheep, goat, and cattle. Those species produce animal products such as milk and meat as the main products. The livestock production is a complex process that involves genetic, environment, and the interaction of genetic and environment. To this, the genetic factor can play an important role as one of the main factors in determining livestock production (Rauw and Gomez-Raya, 2015).

Sheep, goats, and cattle own similarities in the physiological aspects of livestock production. On the other hand, the morphology of sheep is closer to goat than cattle (Tomar et al., 2024). Moreover, when viewed from the phenotype of reproductive traits, each of these livestock have different reproductive traits. Livestock reproductive traits are composed of different parameters such as calving interval, days open, pregnancy rate, and litter size (Hafez and Hafez, 2013).

The potential prolific or litter size traits of sheep and goat is better when compared to cattle. The litter size value of sheep is 1.56 Rahman and Sembiring (2013), goat 1.83 Rahmah et al. (2023), and cattle 1.01 Piper et al. (2015). Meanwhile, the age of puberty of sheep is 6-8 months (Rusdiana and Adiati, 2020). According to Feradis (2010), the age of puberty of goat is 6-8 months and the average age of cattle is 9-11 months. The duration of the estrous cycle of sheep is 16-17 days Larsen (2021), goat 20-24 days Edwards (2015), and the average cattle is 21 days with a range of 18-24 days (Karisch, 2016). Based on time, the estrous cycle of goat has almost the same duration as cattle. Morphological differences and similarities between species will not ensure similar reproductive performance.

One gene that is considered a candidate gene for regulating reproductive traits is the Leptin Receptor (LEPR). LEPR gene are expressed in several traits such as puberty, estrous cycle, lactation, litter size, and early stages of embryonic development Moschos et al. (2002),Taheri and Parham (2016). According to Israel and Chua (2010), Lakhssassi et al. (2020); Liefers et al. (2004), LEPR is a leptin receptor that can effect reproductive traits in sheep and cattle.

Polymorphism or variations in the nucleotide sequence of the LEPR gene can effect to gene expression and receptor function if the amino acid structure is different. This statement is same with the opinion of Schaefer and Rost (2012), that changes in Single Nucleotide Polymorphism (SNP) can change protein structure and protein function. According to research by Liefers et al. (2004) and Israel and Chua (2010), the results showed that LEPR gene SNP are associated with reproductive traits. This study aims to compare profile LEPR gene between sheep, goat and cattle. Through LEPR gene profiling, it is expected to know the genetic pattern of reproductive traits in sheep, goat and cattle so that the differences can be easy to understand more clearly

MATERIALS AND METHODS

The material used was three LEPR gene DNA sequences, that are sheep, goat, and cattle taken from the Nationa Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/). The database sheep (*Ovis aries*) with Acc No. NM_001009763.1, goat (*Capra hircus*) with Acc No. XM_018045220.1, and cattle (*Bos taurus*) with Acc No. XM_010803431.4. Data analysis was performed with an inductive descriptive statistical model. Identifying single nucleotide polymorphism (SNP) and changes in amino acid composition by alignment the DNA sequence of the LEPR gene using the BLAST Nucleotide GenBank NCBI program. SNP identification was analyzed after gene alignment was manually performed by viewing nucleotides that differed in each base pair. The results of SNP changes were grouped again based on the type of mutation. SNP changes were classified and categorized in mutation groups for further analysis. The grouping of mutations from SNP changes followed by amino acid changes based on the grouping of amino acid properties by Elofsson (2019).

RESULTS AND DISCUSSION

The LEPR gene is a receptor for leptin. Leptin is a polypeptide hormone synthesized and secreted by adipose cells (Forhead and Fowden, 2009). Leptin is a protein composed of 167 amino acids (Pamungkas, 2018). Leptin will be active if it binds to receptor in the target tissue. According to Tartaglia (1997), the effect of leptin is exerted through 6 receptor isoforms, but the one that serves as the physiological function of the hormone is LEPR-b. According to Trakovická et al. (2013), because leptin concentration is influenced by adipose tissue, leptin is considered a signalling molecule that links nutritional status with reproductive function. Leptin which is associated with reproductive traits, is thought to be active when associated with receptors located on hypothalamic neurons. Therefore, its may be associated with reproductive hormones.

Table 1. Base Pair (bp) Length and Nucelotide Composition of LEPR Gene

Livestock	LEPR gene (bp)	Composition Nucleotide (%)			
		A	T	G	C
Sheep	2757	30.6	30.6	19.8	19
Goat	5026	31.6	33.8	18.1	16.5
Cattle	5037	31.1	33.2	18.3	17.4

LEPR gene that is candidate for reproductive traits in sheep, goat, and cattle was obtained from a search in the Gen Bank. The result of the gene obtained was analysed use BLAST Nucleotide Gen Bank NCBI available in Table 2. This is same with the opinion of Healy (2007), that BLAST is one of the programs that can be used to find SNP. The BLAST of local alignment programme applies the Smith-Waterman logarithm that aligns sequences from end to end while the global alignment applies the Needleman-Wunsch logarithm that alignment based on the highest similarity. In addition, compositional identification was carried out using Mega software version 11 which is available in Table 1.

Table 2. SNP (Single Nucleotide Polymorphism), Amino Acid Changes, and Mutation

Alignment	SNP	*Local Alignment* (%)	Amino Acid Changes	Mutation		
				Silent	Neutral	Missense
Sheep-Goat	37	99	15	22	6	9
Sheep-Cattle	79	97	42	37	19	23
Goat-Cattle	78	97	39	39	17	22

Based on the reproductive performance of sheep, goat and cattle, it can be seen that sheep and goats have similarities in the value of litter size and age at sexual maturity, but are different when compared to cattle. Furthermore, the duration of the estrous cycle of sheep and cattle is relatively the same, but different when compared to the duration of the estrous cycle of sheep. The differences in phenotypic traits are supported by differences in genetic pattern. When the LEPR gene sequences between the three species are alignment, sheep with goats have a 2% higher similarity value compared to the alignment results of sheep with cattle, and goats with cattle (Table. 2). Based on Table 2, it was found that the SNP and amino acid changes in sheep-goat were 37 SNP and 15 amino acids, in sheep-cattle 79 SNP and 42 amino acids, and in goat-ccattle 78 SNPs and 39 amino acids. Table 6 present mutation group data with details of 22 silent mutations, 6 neutral mutations, and 9 missense mutations in sheep-goat. Sheep-cattle identified 37 silent mutations, 19 neutral mutations, and 23 missense mutations. Goat-cattle identified 39 silent mutations, 17 neutral mutations, and 22 missense mutations. According to Warmadewi (2017), silent mutation is a mutation that causes changes in the genetic code but does not cause changes in amino acids while missense mutation is a mutation that causes changes in the genetic code that causes changes in amino acids. Change of SNP which followed by amino acid change will be grouped into missense mutation and neutral mutation. Neutral mutation is a mutation that causes changes in amino acids but is not followed by changes in the properties of these amino acids. Based on the grouping of amino acid properties by Elofsson (2019), the results are present in Table 2 and Table 3.

Table 3. Analysis of SNP and Amino Acid Change

Sheep-Goat				Sheep-Cattle				Goat-Cattle			
Exon	Location	SNP	Amino Acid	Exon	Location	SNP	Amino Acid	Exon	Location	SNP	Amino Acid
-	113	A>T		1	167	A>T	S>C	-	149	T>A	
1	131	A>T	S>C		177	T>C	F>S	1	177	T>C	F>S
	150	T>C	V>A		186	T>C	V>A		216	C>T	T>I
	168	C>T			216	C>T	T>I		263	T>G	L>V
2	247	T>C			259	C>T		2	283	C>T	
	312	C>A	S>A		263	T>G	L>V		387	A>C	N>T
	364	T>C		2	348	C>A	S>Y		409	A>C	
	378	C>T	T>I		387	A>C	N>T		414	T>C	I>T
	462	T>C	I>T		400	T>C			439	T>C	
3	580	C>T			409	A>C			467	G>A	A>T
	597	A>C	K>T		439	T>C			523	A>G	
	652	C>T			467	G>A	A>T		536	C>A	H>N
	670	C>G	H>Q		498	T>C	I>T	3	587	T>A	Y>N
	754	C>T			523	A>G			616	T>C	
6	867	T>C	I>T		536	C>A	H>N		633	C>A	T>K
	874	C>T		3	587	T>A	Y>N		662	C>G	
7	1012	C>T			662	C>G			664	A>G	L>V
	1094	G>A	A>T		664	A>G	L>V		688	T>C	
	1155	T>C	V>A		689	G>C	E>Q		689	G>C	E>G

	1348	C>T			696	G>A	G>D		696	G>A	G>D
8	1479	A>G	N>S		706	C>G	H>Q		707	A>G	I>V
	1555	A>G			707	A>G	I>V		728	T>G	F>V
	1559	G>A	V>I		728	T>G	F>V		731	A>C	N>H
	1579	T>C			731	A>C	N>H		763	A>G	
10	1972	A>G			763	A>G			772	A>G	
11	2251	A>G			772	A>G			779	A>G	N>D
12	2293	C>T			779	A>G	N>D	4	819	T>C	V>A
	2344	C>T			790	C>T			821	A>G	I>V
	2359	C>T		4	819	T>C	V>A	5	891	A>G	H>R
	2379	C>G	T>S		821	A>G	I>V	6	928	C>G	
14	1509	T>C		5	891	A>G	H>R		944	T>C	
	2564	G>A	V>I	6	903	T>C	I>T		974	A>C	K>Q
	2647	G>A			910	T>C			998	A>T	N>Y
	2656	C>A			928	C>G			1003	G>A	M>I
	2698	A>G			944	T>C			1005	A>G	K>R
	2709	C>T			974	A>C	K>Q		1010	G>A	A>T
	2710	A>G	S>L		998	A>T	N>Y		1025	A>T	T>S
					1003	G>A	M>I		1048	T>C	
					1005	A>G	K>R		1069	A>G	
					1010	G>A	A>T		1074	A>G	
					1025	A>T	T>S		1075	T>C	D>G
					1069	A>G			1077	T>C	
					1074	A>G			1078	G>A	V>A
					1075	T>C	D>G		1088	A>T	S>C
					1077	T>C			1123	C>T	
					1078	G>A	V>A		1129	C>T	
					1088	A>T	S>C		1130	A>G	T>A
					1123	C>T			1191	C>T	A>V
					1129	C>T			1240	T>C	
					1240	T>C			1438	C>T	
					1384	C>T		7	1515	G>A	S>N
					1438	C>T		8	1740	T>C	V>A
				7	1591	A>G			1849	T>C	
					1595	G>A	V>I	9	1924	G>A	
					1615	T>C			2008	G>A	
				8	1740	T>C	V>A		2059	T>C	
					1849	T>C		10	2060	G>A	
				9	1924	G>A			2102	A>C	I>L
				10	2060	G>A		11	2234	C>T	
					2102	A>C	I>L		2251	T>C	
				11	2234	C>T			2287	G>A	
				12	2302	T>G		12	2302	T>G	
					2329	C>T			2353	A>C	L>F
					2353	A>C	L>F		2360	T>G	S>A
					2360	T>G	S>A		2380	T>C	
					2389	C>A			2389	C>A	
					2395	C>T		13	2449	T>C	
					2415	C>G	T>S	14	2545	C>T	
				13	2449	T>C			2558	C>T	H>Y
				14	2558	C>T	H>Y		2578	G>A	
					2578	G>A			2645	A>G	T>A
					2600	G>A	V>I		2692	A>T	
					2645	A>G	T>A		2707	C>T	
					2683	G>A			2733	C>T	T>1
					2692	C>T			2734	G>A	
					2707	C>T			2743	A>G	
					2733	C>T	T>I		2745	T>C	
					2743	A>G			2746	G>A	L>S
				15	2842	A>T					

Count	37	37	15	Count	79	79	42	Count	78	78	39

Proportion of silent mutation, neutral mutation, and missense mutation can effect the expression of a trait. In the research of Ma et al. (2022), the value of litter size was influenced by a combination of silent mutation and missense mutation. Silent mutations can change the stability of mRNA and can change the secondary structure of mRNA, while missense mutations can effect the tertiary structure mRNA of the LEPR gene. The proportion of silent mutation, neutral mutation and missense mutation between the three alignments in this study show different results. This may explain why differences in the phenotypes of reproductive traits in the three species can happen.

CONCLUSIONS

Based on the results of this study, it can be concluded that local alignment shows SNP changes at several locations, that there are 37 SNPs of sheep and goat, 79 SNPs of sheep and cattle, 78 SNPs of goat and cattle. Furthermore, the number of single nucleotide polymorphisms of those species is followed by 15, 42, and 39 amino acid changes, consequently. These changes cause changes in amino acids. Changes in amino acids produce silent mutations, neutral mutations, and missense mutations with different proportions. Based on the overall results, it can be concluded that the LEPR gene between the three species has a different profile. These differences can explain why sheep, goats and cattle have different reproductive traits. However, further molecular research is required to support this initial gene profile result.

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