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BUKTI KORESPONDENSI DENGAN PENGELOLA JURNAL JITAA Tahun 2021 dengan Judul: “"APPROPRIATE GROWTH MODELS TO DESCRIBE EARLY GROWTH OF KEJOBONG GOAT BASED ON GROWTH HORMONE (GH) GENE SEQUENCE ANALYSIS”.

No.	Tanggal	Keterangan
1	16 Januari 2021	[JITAA] Submission Acknowledgment from JITAA
2	1 Pebruari 2021	[JITAA] Manuscript #35852 We are sending herewith the comments of reviewers regarding your manuscript #35852. We give you 2 weeks to revise it. The parts of the manuscript revised should be given a different colour.
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Running Head : GH gene and growth model analysis on goat

Appropriate Growth Models to Describe Early Growth of Kejobong Goat Based on Growth Hormone (*GH*) Gene Sequence Analysis

ABSTRAK

Tujuan penelitian yaitu untuk menemukan model pertumbuhan yang tepat dalam mendeskripsikan pertumbuhan awal kambing Kejobong berdasarkan analisis sekuen gen *Growth Hormon* (GH). Materi penelitian menggunakan 35 sampel DNA dan 1.960 catatan sifat kuantitatif kambing Kejobong. Sampel DNA diamplifikasi dan disekuensing untuk mengidentifikasi SNP yang terdapat pada gen *GH* ekson 3. Pengukuran dan penimbangan bobot badan dan ukuran tubuh dilakukan pada umur 0-14 minggu. Empat model pertumbuhan non-linier diaplikasikan untuk menganalisis pertumbuhan guna membandingkan performan pertumbuhan dari berbagai genotipe dengan menggunakan Non-Linear Mixed model. Mutasi non-sinonim (g1170A→G) pada gen *GH* ekson 3 yang membentuk genotipe GG, AG dan AA secara signifikan berasosiasi dengan sifat pertumbuhan. Kambing Kejobong bergenotipe heterozigot AG menunjukkan sifat pertumbuhan yang lebih tinggi dibandingkan dengan kambing Kejobong bergenotipe homozigot AA. Meskipun demikian, kambing Kejobong bergenotipe homozigot GG memiliki sifat pertumbuhan yang sama dengan kambing Kejobong bergenotipe heterozigot AG dan homozigot AA. Model pertumbuhan yang paling tepat untuk mendeskripsikan bobot badan kambing Kejobong adalah model Von Bertalanffy, sedangkan untuk menggambarkan tinggi badan dan tinggi pinggul adalah model Brody.

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Dua analisis (model matematik) dan analisis sekuen masih terilihat dibahas satu per satu blm ada analisis dan diskusi integrasi antar keduanya.

Mohon diperjelas integrasinya dalam statement teori dan analisis methodologynya

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SNP pada gen *GH* ekson 3 dapat digunakan sebagai penanda genetik untuk perbaikan sifat pertumbuhan kambing Kejobong.

Kata Kunci : Analisis Pertumbuhan, GH, Kambing, Model Matematika, SNP

ABSTRACT

Objectives of this study were to reveal appropriate growth models describing early growth of Kejobong goat based on Growth Hormone (*GH*) gene sequence analysis. A total of 35 DNA samples and 1.960 records of quantitative traits of Kejobong goat were collected. The exon 3 of *GH* gene was amplified and was sequenced to determine the SNP. Body weight and body measurements of the goats were taken at 0-14 weeks of age. Four non-linear growth models were applied for analysis of growth to compare growth performance of different genotypes by Non-Linear Mixed Model. A non-synonymous mutation (g1170A→G) genotyped into GG, AG and AA was significantly associated with growth traits. Animals with heterozygous genotype AG showed higher growth traits than animals with homozygous genotype AA. Nonetheless, animals with homozygous genotype GG had the same growth traits with those animals with heterozygous genotype AG and homozygous genotype AA. The most fitted model for describing body weight was Von Bertalanffy model, while for describing wither height and hip height was Brody model. SNP at exon 3 of the *GH* gene can be used as genetic marker for improvement of growth traits of Kejobong goats.

Keywords: GH, Goat, Growth analysis, Mathematical models, SNP

INTRODUCTION

Commented [F5]: Bagaimana hasil evalusi dr pertumbuhan yang dibandingkan antara pertumbuhan menggunakan estimasi empat model pertumbuhan non-linier dan performan pertumbuhan dari berbagai genotype.

Mengapa saya tanyakan ini karena di atas penulis menyebutkan:
"Empat model pertumbuhan non-linier diaplikasikan untuk menganalisis pertumbuhan guna membandingkan performan pertumbuhan dari berbagai genotipe"

Kalimat ini sebenarnya yg menjadi core dari tulisan ini sehingga state of the art dr penelitian ini jadi terlihat jelas ada integrasi antara analisis model pertumbuhan dan analisis gen GH. Tapi seperti saya sebutkan diatas, manuskrip ini masih membahas *partially each analysis approaches* seolah-olah terspisah sehingga belum nampak *comprehensive (incoherens)*

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Kejobong goat is one of indigenous Indonesian breeds, which only exists in Purbalingga District, Central Java Province, Indonesia, and it is conventionally raised by local farmers. This goat belongs to Southeast Asian lineage and is confirmed to be descendant from crossbred of Kacang and Etawah Grade goats (Kurnianto *et al*., 2012; Kurnianto *et al*., 2013; Lestari *et al*., 2018[A]; Lestari *et al*., 2018[B]). As the meat animals, Kejobong goat had 41.30% carcass yield that comprised 67.06% meat and 32.94% bone, while its meat is known to have less cholesterol than meat of Kacang and Etawah Grade goat (Aqsa *et al*., 2011). Kejobong goat is popular at the district because of its high rate of growth, good reproductive performance, high resistance to local diseases and parasites and ability to survive and growing ability under poor feeding conditions (Kurnianto *et al*., 2012; Febriana *et al*., 2017). However, the breeders often have difficulty to satisfy the market demand on slaughtering weight. This is probably due to limited information of appropriate breeding strategy for Kejobong goat to accomplish the breeding goal of high meat productivity.

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Growth analysis can provide valuable information about mature weight, growth rate and mature time. Growth rate and body weight of animal at different ages influence productivity of meat and have deterministic effects on the profitability of meat production (Kheirabadi and Rashidi, 2019). Particularly, growth rate has large effect on meat producing efficiency up to slaughtering age which is crucial for economic success of animal production (Abbasi *et al*., 2012). According to Junior *et al*. (2013) and Ripoll *et al*. (2016), animals that have a large frame size of body tend to have higher potential of growth and have a higher proportion of meat. Therefore, besides body weight, body size is also important trait to be considered for performing animal selection. Study of growth analysis has been done by previous researchers (Waheed *et al*., 2011; Setiaji *et al*., 2013;

Zadeh *et al*., 2015; Raji *et al*., 2015; Lupi *et al*., 2016; Zadeh and Gorbani, 2018; Ghiasi *et al*., 2018; Rout *et al*., 2018; Kheirabadi and Rashidi, 2019), however they were only using phenotypic data into analysis. In this study, conventional growth analysis was modified by including genotype records to growth analysis.

Early growth of kids is an economically important trait that affecting profitability in goat production (Baranzadeh *et al*., 2012; Moghbeli *et al*., 2013; Sadeghi *et al*., 2019). Physiologically, growth of an animal is a result from a complex process of metabolism including a coordinated action of several hormones that controlled by expression of their responsible genes (Mahrous *et al*., 2018). Growth Hormone (*GH*) gene is one of numerous genes which have large effect on growth performance of an animal. *GH* gene is encoding growth hormone that produces in anterior pituitary and is necessary for postnatal growth and metabolism in vertebrates (Ge *et al*., 2003). This hormone is known to have a broad impact on biological activity in all body cells, such as controlling and coordinating the flow rate of metabolic process, enhancing glycogen, protein, DNA and RNA biosynthesis and promoting the deposition of fat and the disintegration of fatty acids and glucose in the tissue (Gorlov *et al*., 2017; Wickramaratne *et al*., 2010; Othman *et al*., 2015; Seevagan *et al*., 2015; Singh *et al*., 2015). Therefore, *GH* gene is considered to be a prime factor which affects growth performance of an animal.

Based on these backgrounds, effect of *GH* gene on growth traits, especially from a point of genetic improvement is important to build breeding plan for high meat productivity. Prospectively, result of this study is not only suggesting appropriate management practice for improving production for the breeders, but also providing information of genetic marker in Kejobong goat for breeding selection in the future through Marker-Assisted Selection (MAS) and/or Marker-Assisted Introgression (MAI)

and appropriate mathematical growth models of Kejobong goat. Therefore, objective of this study was to reveal to reveal appropriate growth models describing early growth of body weight and body measurement of Kejobong goat based on the effect of Growth Hormone (*GH*) gene sequence analysis.

MATERIALS AND METHODS

Ethical approval

All procedure involving animals were based on the standard rule of animal treating as appointed in the Republic of Indonesia's law, number 41, 2014.

Sampling and data collection

A total of 35 blood samples and 1.960 quantitative traits records of Kejobong goat were collected from Purbalingga District, Central Java Province, Indonesia. Quantitative traits records comprised body weight (BW), wither height (WH), chest depth (CD), chest width (CW), hip height (HH), hip width (HW) and heart girth (HG) at 0, 2, 4, 6, 8, 10, 12 and 14 weeks of age.

DNA extraction, Polymorphism Chain Reaction (PCR) and sequencing

Blood samples for DNA analysis were taken by 3cc spuit from *jugular venous* that previously cleaned with alcohol. The blood was then collected in vacutainer blood collection tubes with an anticoagulant (EDTA). DNA was extracted from whole blood by gSYNC DNA mini kit (Geneaid Biotech, Taiwan) according to the manufacturer's standard protocol for PCR and sequencing analysis.

Forward primer F: 5'-TAGAAATGGGGGTGTGTGGGGT-3' and reverse primer R: 5'-CATCCTCCACTGCCATCCAACA-3' (Sigma-Aldrich, Japan) were used to amplify *GH* gene exon 3. PCR was carried out in total volume 50 µL comprising 1 µL

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KOD Plus (Toyobo, Japan), 5 µL buffer, 5 µL dNTP, 2 µL $MgSO_4$, 1.5 µL forward primer, 1.5 µL reverse primer, 32 µL PCR water and 2 µL DNA template. PCR amplification was running with an initial denaturation at 94°C for 2 min, followed by 40 cycles of denaturation at 94°C for 15 sec, primers annealing 66.8°C for 30 sec and extension at 68°C for 19 sec. PCR products were electrophoresed using 1.3% Agarose gel at 110 V for 20 min. PCR products were then visualized by UV trans-illuminator and was sequenced through Fasmac sequencing service, Japan.

Data analysis

Allelic and genotypic frequencies were directly calculated. Hardy-Weinberg Equilibrium (HWE) was tested using chi-square statistic (χ^2) as follows:

$$\chi^2 = \sum_{i=1}^{k} \frac{(o_i - e_i)^2}{e_i},$$

where χ^2 is the Chi square value; o_i the observed value of genotype frequency, e_i the expected value of genotype frequency, χ^2 the table using 5% significance level for HWE test.

Heterozygosity (H) was calculated as follows:

$$H = 1 - \sum_{i=1}^{k} p_i^2,$$

where H is the value of heterozygosity and p_i the frequency of the i^{th} of k alleles.

Sequencing result alignment was analyzed by Clustal W (Thompson *et al*., 1994) with Molecular Evolutionary Genetics Analysis (MEGA6.0) (Tamura *et al*., 2013) to find out the SNP within animals. Sequencing result then was translated into amino acids form by standard genetic code to identify amino acid alteration that caused by SNP.

Commented [F11]: This paper did not focus on the distribution of allele and genetic variability but focus on the comparation of growth based on two analysis with mathematical model and DNA approach, so I suggest to skip this analysis.
I think no relationship between allelic freq, HWE, heterozygosity (describing the genetic diversity of the population sample) with matemathical growth model?

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Linear Mixed Model (LMM) was used to analyze association between genotype with quantitative traits by MIXED procedure in Statistical Analysis System (SAS 9.3) (SAS Institute Inc, 2011). The model was:

$$y_{ijkl} = \mu + G_i + F_j + u_k + b_1\alpha_{ijkl} + b_2\alpha^2_{ijkl} + e_{ijkl},$$

where y_{ijkl} is the observed value of a dependent variable (body weight or body measurements); μ the overall mean of the population; G_i the fixed effect of i^{th} genotype (i = 1 for GG, 2 for AG, 3 for AA); F_j the fixed effect of j^{th} farm group (j = 1, 2, 3, 4); u_k the random effect of k^{th} animal; b_1 and b_2 the linear and quadratic coefficients of partial regression, respectively; l^{th} individual measurement, α_{ijkl} age in days of a covariate and e_{ijkl} the random residual for y_{ijkl}. Difference in the least square means of the genotypes was tested by the Tukey-Kramer (Tukey, 1949).

The nonlinear growth models comprised Brody (Brody, 1945), Von Bertalanffy (Bertalanffy, 1938), Logistic (Verhulst, 1838) and Gompertz (Gompertz, 1825) and they were compared by describing animal growth (Table 1). Growth models were analyzed using Nonlinear Mixed Model (NLMM) by NLMIXED procedure of SAS 9.3 (SAS Institute Inc, 2011). Body weight or body measurements as dependent variables are influenced by genotype and age. Therefore, dummy variables were created to assess the effect of qualitative variables on dependent variables according to the method by Filho *et al.* (2014). The NLMIXED procedure was used in this study due to its flexibility in engaging the variance covariance structure which could not be identified by traditional regression approach. Also NLMIXED has ability to handle unbalance data (Aggrey, 2009; Galeano-Vasco *et al*., 2014). This procedure can reduce potential biases despite selective sampling and supply supplemental parameters that characterize variation between individual animals (Craig and Schinkel, 2001).

166 The models were tested for goodness of fit using -2 log likelihood, Akaike
167 Information Criterion (AIC) (Akaike, 1974), Bayesian Information Criterion (BIC)
168 (Schwarz, 1978) and the residual variances (σ^2_e). AIC and BIC were calculated by the
169 following formula:

170 $$AIC = n\, ln\left(\frac{SSE}{n}\right) + 2k$$

171 $$BIC = n\, ln\left(\frac{SSE}{n}\right) + k\, ln\,(n)$$

172 where n is the number of observation; SSE the Sum Square Errors and *k* the number of
173 parameters. Smaller values of AIC, BIC or σ^2_e indicate the best fit of the model to the
174 observations.
175
176 **RESULTS**
177 Result showed that a total 117 bp of *GH* gene exon 3 encoding 38 amino acid
178 sequence were well amplified. Sequencing result revealed 5 SNPs as transition mutation
179 in parsimonious form, which were g1121A→G (SNP1), g1148T→C (SNP2),
180 g1160A→G (SNP3), g1170A→G (SNP4) and g1178C→T (SNP5). Genotype
181 frequencies of Kejobong goats were not different from HWE, and the frequency of
182 heterozygosity was 49% (Table 2). The estimated allele of the *GH* gene exon 3 in this
183 study was 57% and 43% for G and A, respectively. Frequencies of genotypes GG, AG
184 and GC were 37%, 40% and 23%, respectively, so that G allele and heterozygous
185 genotype AG were predominant in this locus.
186 Test of significance showed that the fixed effect of genotype together with effect
187 of farm and linear and quadratic coefficients of age were statistically significant (P<0.05)
188 in BW while the fixed effect of genotype and linear and quadratic coefficients of age were

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189 statistically significant (P<0.05) in WH, and the fixed effect of genotype, age of doe and
190 linear and quadratic coefficients of age were statistically significant (P<0.05) in HH.
191 Conversely, the fixed effect of genotype was not significant in CD, CW, HW and HG
192 (Table 3).

193 Animals of genotype AG demonstrated the highest BW, HW and HH then it
194 followed with animals of genotype GG and AA (Table 4). Comparing genotypes at
195 different periods, BW0 and BW6 in animals of genotype AG (4.35 kg and 8.40 kg) were
196 significantly heavier (P<0.05) than animals of genotype AA (3.40 kg and 6.59 kg), while
197 animals of genotype GG (3.84 kg and 6.97 kg) showed no significant difference with
198 genotype AG and AA. However, there were no significant effect of genotype at BW2,
199 BW4, BW8, BW10, BW12 and BW14.

200 Significant difference between genotypes for body measurements were observed
201 in wither height (WH6, WH10, and WH14) and hip height (HH12 and HH14). Similar to
202 body weight, animals of genotype AG had significantly (P<0.05) higher wither and hip
203 heights than those animals of genotype AA, but there was no significant difference
204 between animals of genotype GG with animals of genotype AG and AA (Table 5).

205 Estimated parameters for body weight, wither height and hip height are presented
206 in Table 6, respectively. Growth analysis showed that Von Bertalanffy model had the
207 lowest -2 log likelihood, and two criteria AIC and BIC compared with the other models
208 indicating this model as the best model for describing growth of body weight in Kejobong
209 goat. On the other hand, the highest -2 log likelihood, AIC and BIC were obtained in
210 Logistic model. Brody model in this study showed fit to wither height and hip height well
211 according to its value of -2 log likelihood, AIC and BIC, which was lower than Gompertz,
212 Logistic and Von Bertalanffy model.

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Von Bertalanffy model fitted best to body weight, estimated 23.01 kg mature body weight (a), 0.39 integration constant (b) and 0.01389 growth rate (k). The best estimated for wither height and hip height by Brody model were 54.65 cm and 58.91 cm for parameter a; 0.37 and 0.36 for parameter b; 0.01577 and 0.01647 for parameter k. In this study, the estimated parameter b for body weight, wither height and hip height were 0.39, 0.37 and 0.36 respectively.

Furthermore, estimated parameter k of body weight in Von Bertalanffy model was 0.01389. Negative correlation was found between parameter k and parameter a (Table 7). This result was confirmed by the fact that Brody model in this study had the slowest parameter k (0.006948) in body weight, yet it had the highest estimated parameter a (25.29 kg) among the others. Similarly, the highest parameter k in wither height (0.2606) and hip height (0.02341) had the lowest estimated parameter a (50.78 cm, 56.26 cm) in Von Bertalanffy and Logistic models respectively.

Representing variability among individual animals, estimated animal variance (σ^2_u) of the body weight in this study was 5.78. The higher the variance, the greater the difference is realized among animals. Furthermore, residual variance (σ^2_e) of the body weight in this study was 0.31 that indicated the gap between predicted value and observed value. Repeatability of body weight by intra-class correlation was 0.95 this study.

DISCUSSION

SNP2 of this study was also found in a report analyzing *GH* gene of Chinese goat (An *et al*., 2010). Among five SNPs in this study, translation result showed SNP4 causing amino acid alteration which changes amino acid sequence in *GH* gene exon 3. SNP4 as non-synonymous mutation changed the first triplet codon of AGC encoding Serin to GGC

encoding Glycine (Figure 1) and we used it to distinguished as GG, AG and AA genotypes, whereas the other SNPs were silent mutation (SNP1 CAG>CAA(Gln); SNP2 TCT>TCC(Ser); SNP3 CCA>CCG(Pro); SNP5 AAC>AAT(Asn)). According to Nei and Kumar (2000), most of synonymous amino acid was found due to substitution of nucleotides in the third codon, while substitution of nucleotides in the first and second codon generate non-synonymous amino acid. Therefore, non-synonimous mutation that change amino acid sequence in exon region may change the peptide sequence of the encoded protein and influence the function of the protein, which was growth hormone in this study. This hormone has substantial metabolic effects on somatic growth, stimulation of protein synthesis and cellular uptake of amino acids and development of body composition (Hjortebjerg *et al*., 2017).

Result in this study agreed with a result by Dayal *et al*. (2016), in which goats with heterozygous genotype AC had the heaviest body weight among five observed genotypes in Black Bengal goat. Gorlov *et al*. (2017) reported their study in Salsk sheep that sheep with AB genotype significantly had heavier body weight, average daily gain and carcass weight than sheep with AA genotype. A contradictory result was reported by An *et al*. (2011) that goats with homozygous genotype AA significantly had higher body weight than those of heterozygous genotype AB at age of one and three months old in Chinese goat, however, wither height showed no significant difference. The different results seem to be due to genetic difference that leads to different structure of *GH* gene and limited number of observations. Therefore, further study is necessary to validate the predominant effect of heterozygote of *GH* gene with a larger number of animals and more sampled observations.

Commented [F16]: Did the authors compare with the sama SNP loacation? If not, then the comparation are bias

The best model for describing growth of body weight in this study was different with previous study by Kheirabadi and Rashidi (2019), reported that Logistic model fitted worst to body weight, while Brody model fitted most accurately to body weight of Markhoz goat. In this study, estimated mature body weight (a) was 23.01 kg implying that Kejobong goat had heavier mature body weight than Raeini Cashmere goat (17.97 kg) (Ghiasi *et al*., 2018) and Nondescipt goat (6.42 to 10.55 kg) (Raji *et al*., 2015) but lighter body weight than Beetal goat (23.39 kg) (Waheed *et al*., 2011). Those values of parameter b for body weight, wither height and hip height in this study were described to represent the proportion of mature weight attained after birth, calculated by the initial weight and age value (Lupi *et al*., 2016). On the other hand, Ghiasi *et al*. (2018) stated that parameter b is a scale parameter that has no biological interpretation. Waheed *et al*. (2011) reported higher estimated values of parameter k (0.1077) in Beetal goat by Brody model. Other researchers estimated parameter k as much as 0.017 in Cashmere goat (Ghiasi *et al*. 2018) and 0.0108 in Repartida goat (Pires *et al*., 2017) by applying Gompertz model, so that Kejobong goat in this study is considered to attain mature weight later than Beetal and Cashmere goats but earlier than Repartida goat.

Negative correlation between parameter k and parameter a indicated the slower growth rate, the larger mature weight, *vice versa*. Previous studies supported this results. Kurnianto *et al*. (1998) reported that animals with slower growth rate tended to have estimated heavy body weight at maturity. Brown *et al*. (1976) stated that selection for increasing growth rate tended to decrease mature weight, yet its antagonistic association could be minimized by cross-breeding and improving feed quality. On other hand, previous study by Ghiasi *et al*. (2018) showed lower animal variance (1.29) and higher residual variance (8.01) on growth analysis of Raeni Cashmere goat using Gompertz

model than the present study. Repeatability of body weight in this study was higher than repeatability value of South African Angora goat (Snyman and Olivier, 1999) and Boerawa goat (Beyleto *et al*., 2010). The high repeatability in this study may be resulted by the fact that systematic factors affecting body weight were fitted as many as possible in NLMM and that earlier body weight was a component of latter body weight.

The NLMIXED procedure used in this study has flexibility in engaging the variance covariance structure which could not be identified by traditional regression approach. Also NLMIXED has ability to handle unbalance data (Aggrey, 2009; Galeano-Vasco *et al*., 2014). This procedure can reduce potential biases despite selective sampling and supply supplemental parameters that characterize variation between individual animals (Craig and Schinkel, 2001). Therefore, this procedure can facilitate growth analysis by including genotype information and estimates accurately the growth performance of Kejobong goats.

Please add one section to discuss the integrasion between molecular analysis and growt model analysis

CONCLUSION

SNP g1170A→G in *GH* gene is associated with growth traits and can be used as genetic marker for animal selection to improve goat's growth performance. Animals with heterozygous genotype AG showed higher growth performance than homozygous genotype AA. Nonetheless, animals with homozygous genotype GG showed no difference with either heterozygous genotype AG or homozygous genotype AA. Model ($y = 23.01\ (1 - 0.39\ e^{-0.01389age})^3$) by Von Bertalanffy, $y = 54.65\ (1 - 0.37\ e^{-0.01577age})$ and $y = 58.91\ (1 - 0.36\ e^{-0.01647age})$ by Brody were fitted well to describe body weight, wither height and hip height of Kejobong goat, respectively.

Acknowledgement???

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TABLE

Table 1. Growth equations used to construct the growth model

Model	Function[A]	Inflection weight	Inflection age
Brody	$y = a (1 – b \exp^{-kt})$	-	-
Von Bertalanffy	$y = a (1 – b \exp^{-kt})^3$	$y_i = 8a/27$	$t_i = \ln(3b)/k$
Logistic	$y = a / (1 + b \exp^{-kt})$	$y_i = a/2$	$t_i = \ln(b)/k$
Gompertz	$y = a \exp (– b \exp^{-kt})$	$y_i = a/\exp$	$t_i = \ln(b)/k$

[A]y, observed body weight/body measurements; a, the estimated of mature body weight/body measurements; b, the integration constant; k, the growth rate constant; t, the animal age in day and exp, Napier's constant the base of natural logarithm.

462 Table 2. Estimated allele and genotype frequency

Variable Measured	Genotype			Allele		H	χ^2
	GG	AG	AA	G	A		
Frequencies	0.37	0.40	0.23				
Observation	13	14	8	0.57	0.43	0.49	1.18
Expectation	11.43	17.14	6.43				

463 H, Heterozygosity; χ^2, Chi square value.

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465

466 Table 3. Significance analysis of factor affecting body weight and body measurements

Traits	Effect	Degree of freedom	f-value	p-value
BW[A]	Genotype	2	3.44	0.0335
	Age of doe	3	1.43	0.2355
	Farm	3	5.33	0.0050
	Age (linear)	1	224.97	<0.0001
	Age (quadratic)	1	17.98	<0.0001
WH[B]	Genotype	2	4.14	0.0171
	Age of doe	3	2.59	0.0537
	Farm	3	2.27	0.1021
	Age (linear)	1	238.66	<0.0001
	Age (quadratic)	1	50.99	<0.0001
CD[C]	Genotype	2	0.14	0.8677
	Age of doe	3	0.54	0.6541
	Farm	3	1.00	0.4081
	Age (linear)	1	40.44	<0.0001
	Age (quadratic)	1	10.58	0.0013
CW[D]	Genotype	2	2.41	0.0920
	Age of doe	3	2.66	0.0491
	Farm	3	5.48	0.0043
	Age (linear)	1	36.02	0.0001
	Age (quadratic)	1	9.05	0.0029
HH[E]	Genotype	2	4.25	0.0153
	Age of doe	3	2.64	0.0499

	Farm	3	1.71	0.1879
	Age (linear)	1	267.39	<0.0001
	Age (quadratic)	1	59.44	<0.0001
HW[F]	Genotype	2	1.74	0.1775
	Age of doe	3	0.71	0.5496
	Farm	3	2.27	0.1023
	Age (linear)	1	62.34	<0.0001
	Age (quadratic)	1	13.53	0.0003
HG[G]	Genotype	2	1.69	0.1873
	Age of doe	3	1.62	0.1852
	Farm	3	3.89	0.0192
	Age (linear)	1	347.92	<0.0001
	Age (quadratic)	1	70.55	<0.0001

[A]Body weight; [B]Wither height; [C]Chest depth; [D]Chest width; [E]Hip height; [F]Hip width; [G]Heart girth.

471 Table 4. Average of body weight and body measurements

Traits	Genotype		
	GG	AG	AA
Body weight (BW)			
BW0	3.75±0.76	4.26±1.02	3.51±1.06
BW2	4.91±0.75	5.39±1.20	4.87±1.20
BW4	6.12±0.89	6.57±1.38	5.84±1.95
BW6	7.39±1.01	7.91±1.63	6.74±2.15
BW8	8.24±1.14	8.87±1.89	7.85±2.62
BW10	9.07±1.21	9.72±2.26	8.64±2.89
BW12	9.87±1.33	10.52±2.56	9.19±3.08
BW14	10.64±1.49	11.36±2.78	9.80±3.10
Wither height (WH)			
WH0	33.93±3.21	35.08±2.49	31.69±4.63
WH2	37.85±2.84	37.72±4.45	36.63±2.92
WH4	40.63±2.55	40.57±4.12	39.33±4.43
WH6	42.34±2.30	43.28±2.48	40.77±5.35
WH8	44.29±2.40	45.09±3.30	42.51±4.88
WH10	45.42±1.85	45.65±3.47	42.85±5.24
WH12	46.35±2.52	47.54±3.29	44.49±4.88
WH14	47.61±2.67	49.06±3.07	45.39±4.98
Hip height (HH)			
HH0	36.57±3.19	37.60±3.40	34.23±4.73
HH2	40.09±3.30	40.78±2.55	38.34±3.55

HH4	42.89±2.85	43.56±3.67	42.00±4.72
HH6	44.84±2.68	46.39±2.52	43.92±5.37
HH8	46.63±3.01	47.67±3.12	45.39±5.02
HH10	48.01±2.00	48.33±2.91	46.03±5.62
HH12	48.99±2.41	50.56±3.08	45.96±4.76
HH14	50.55±2.57	52.15±2.99	47.82±5.75

472

473

474 Table 5. Estimated genotypic effect for body weight and body measurements for each
475 measurement

Traits	Genotypes		
	GG	AG	AA
Body weight (BW)			
BW0	3.84±0.22^{AB}	4.35±0.20^{A}	3.40±0.27^{B}
BW2	4.84±0.28	5.67±0.26	4.82±0.36
BW4	5.87±0.37	6.97±0.34	5.75±0.46
BW6	6.97±0.43^{AB}	8.40±0.40^{A}	6.59±0.55^{B}
BW8	7.80±0.52	9.43±0.47	7.71±0.66
BW10	8.57±0.59	10.35±0.54	8.54±0.75
BW12	9.29±0.65	11.17±0.60	9.17±0.84
BW14	10.03±0.69	12.03±0.63	9.71±0.88
Wither height (WH)			
WH0	34.27±0.94	35.03±0.87	32.64±1.20
WH2	37.38±1.18	38.41±1.08	36.03±1.51
WH4	39.89±1.07	41.44±0.98	39.08±1.37
WH6	41.88±0.90^{AB}	44.25±0.83^{A}	40.45±1.16^{B}
WH8	43.41±1.04	46.15±0.95	42.14±1.33
WH10	44.15±1.01^{AB}	46.83±0.93^{A}	42.33±1.29^{B}
WH12	45.59±1.03	48.53±0.95	44.34±1.32
WH14	46.69±1.04^{AB}	49.95±0.95^{A}	45.29±1.33^{B}
Hip height (HH)			
HH0	36.95±1.01	37.71±0.93	34.59±1.30
HH2	36.95±1.01	41.11±0.89	38.16±1.23

HH4	42.61±1.12	43.85±1.03	42.02±1.43
HH6	44.55±1.03	47.21±0.94	43.87±1.32
HH8	45.57±1.14	48.65±1.05	44.96±1.46
HH10	46.94±1.00	49.31±0.96	45.48±1.28
HH12	48.58±1.05^{AB}	51.28±0.97^{A}	45.82±1.35^{B}
HH14	49.59±1.09^{AB}	53.08±1.00^{A}	47.57±1.39^{B}

476 ^{A,B} In the same row, values with different superscripts are significantly different (P<0.05).

477

478

479 Table 6. Estimated parameters of growth and goodness of fit for four different growth
480 models

Parameter	Model			
	Brody	Von Bertalanffy	Logistic	Gompertz
Body weight				
a	25.29±1.01	23.01±0.47	21.65±0.30	22.48±0.39
b	0.83±0.01	0.39±0.01	2.56±0.07	1.42±0.03
k	0.006948±0.001019	0.01389±0.001097	0.0277±0.001309	0.01735±0.001143
y_i	-	6.82	10.83	8.27
t_i	-	11.75	33.93	20.10
σ^2_u	9.08±2.67	5.78±1.48	4.17±1.03	5.13±1.29
σ^2_e	0.32±0.03	0.31±0.03	0.32±0.03	0.31±0.03
GG	-3.6±0.79	-4.2±0.59	-4.64±0.49	-4.37±0.55
AG	-2.01±0.85	-3.03±0.061	-3.63±0.50	-3.26±0.56
AA	-4.53±0.95	-5.06±0.75	-5.3±0.63	-5.18±0.70
-2 Log Likehood	606.6	605.8	609.5	606.1
AIC	630.6	629.8	633.5	630.1
BIC	649.6	648.8	652.5	649.1
Wither height				
a	54.65±0.94	50.78±0.31	53.59±0.71	55.54±0.81
b	0.37±0.01	1.96±0.08	0.53±0.02	0.44±0.01
k	0.01577±0.002084	0.2606±0.01207	0.02292±0.002268	0.01934±0.002171
σ^2_u	9.93±2.56	0.0014±0.5954	9.39±2.40	9.62±2.47
σ^2_e	3.95±0.36	29.44±1.63	3.97±0.36	3.96±0.36
GG	-3.3±0.82	-6.82±0.50	-3.67±0.77	-5.02±0.79
AG	-2.76±0.81	-6.78±0.47	-3.14±0.76	-4.48±0.78
AA	-5.59±0.92	-11.91±0.64	-5.90±0.88	-7.27±0.90

-2 Log Likehood	1274.3	2217.3	1276.0	1275.1
AIC	1290.9	2233.3	1292.0	1291.1
BIC	1303.0	2246.0	1304.6	1303.8
Hip height				
a	58.91±0.72	57.73±0.73	56.26±0.56	56.61±0.62
b	0.36±0.01	0.13±0.01	0.50±0.01	0.42±0.01
k	0.01647±0.002009	0.01839±0.002112	0.02341±0.002187	0.01994±0.002092
σ^2_u	8.40±2.20	12.99±0.64	7.91±2.04	8.09±2.10
σ^2_e	3.72±0.34	3.71±0.33	3.75±0.34	3.73±0.34
GG	-2.24±0.77	-2.12±0.94	-1.56±0.73	-1.44±0.75
AG	-0.60±0.78	-0.81±0.93	0.12±0.74	0.25±0.75
AA	-4.55±0.89	-4.63±1.08	-3.60±0.86	-3.50±0.87
-2 Log Likehood	1254.6	1258.2	1256.5	1255.4
AIC	1278.6	1282.2	1280.5	1279.4
BIC	1297.6	1301.2	1299.5	1298.4

a, the estimated of mature body weight/body measurements; b, the integration constant; k, the growth rate constant; y_i, body weight (kg) at the point at inflection; t_i, age (weeks) at the point at inflection; σ^2_u; additive genetic variance; σ^2_e, error variance; AIC, akaike information criterion; BIC, bayesian information criterion.

Table 7. Correlation among growth parameter within traits based on their best model

Growth Parameter	Mature weight (a)		
	BW[A]	WH[B]	HH[C]
Integration constant (b)	0.5564	0.7038	0.6652
Growth rate (k)	-0.7833	-0.8755	-0.8636

[A]Body weight; [B]Wither height; [C]Hip height

FIGURE

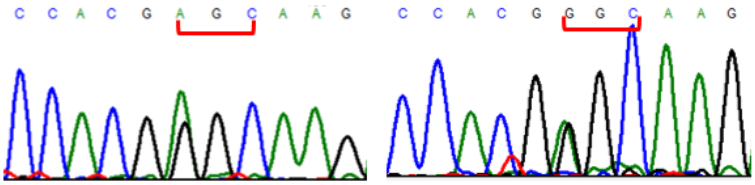


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Figure 1. Amino acid alteration caused by SNP g1170A

Running Head : GH gene and growth model analysis on goat

Appropriate Growth Models to Describe Early Growth of Kejobong Goat Based on Growth Hormone (*GH*) Gene Sequence Analysis

ABSTRAK

Tujuan penelitian yaitu untuk menemukan model pertumbuhan yang tepat dalam mendeskripsikan pertumbuhan awal kambing Kejobong berdasarkan analisis sekuen gen *Growth Hormon* (GH). Materi penelitian menggunakan 35 sampel DNA dan 1.960 catatan sifat kuantitatif kambing Kejobong. Sampel DNA diamplifikasi dan disekuensing untuk mengidentifikasi SNP yang terdapat pada gen *GH* ekson 3. Pengukuran dan penimbangan bobot badan dan ukuran tubuh dilakukan pada umur 0-14 minggu. Empat model pertumbuhan non-linier diaplikasikan untuk menganalisis pertumbuhan guna membandingkan performan pertumbuhan dari berbagai genotipe dengan menggunakan Non-Linear Mixed model. Mutasi non-sinonim (g1170A→G) pada gen *GH* ekson 3 yang membentuk genotipe GG, AG dan AA secara signifikan berasosiasi dengan sifat pertumbuhan. Kambing Kejobong bergenotipe heterozigot AG menunjukkan sifat pertumbuhan yang lebih tinggi dibandingkan dengan kambing Kejobong bergenotipe homozigot AA. Meskipun demikian, kambing Kejobong bergenotipe homozigot GG memiliki sifat pertumbuhan yang sama dengan kambing Kejobong bergenotipe heterozigot AG dan homozigot AA. Model pertumbuhan yang paling tepat untuk mendeskripsikan bobot badan kambing Kejobong adalah model Von Bertalanffy, sedangkan untuk menggambarkan tinggi badan dan tinggi pinggul adalah model Brody.

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SNP pada gen *GH* ekson 3 dapat digunakan sebagai penanda genetik untuk perbaikan sifat pertumbuhan kambing Kejobong.

Kata Kunci : Analisis Pertumbuhan, GH, Kambing, Model Matematika, SNP

ABSTRACT

Objectives of this study were to reveal appropriate growth models describing early growth of Kejobong goat based on Growth Hormone (*GH*) gene sequence analysis. A total of 35 DNA samples and 1.960 records of quantitative traits of Kejobong goat were collected. The exon 3 of *GH* gene was amplified and was sequenced to determine the SNP. Body weight and body measurements of the goats were taken at 0-14 weeks of age. Four non-linear growth models were applied for analysis of growth to compare growth performance of different genotypes by Non-Linear Mixed Model. A non-synonymous mutation (g1170A→G) genotyped into GG, AG and AA was significantly associated with growth traits. Animals with heterozygous genotype AG showed higher growth traits than animals with homozygous genotype AA. Nonetheless, animals with homozygous genotype GG had the same growth traits with those animals with heterozygous genotype AG and homozygous genotype AA. The most fitted model for describing body weight was Von Bertalanffy model, while for describing wither height and hip height was Brody model. SNP at exon 3 of the *GH* gene can be used as genetic marker for improvement of growth traits of Kejobong goats.

Keywords: GH, Goat, Growth analysis, Mathematical models, SNP

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INTRODUCTION

Kejobong goat is one of indigenous Indonesian breeds, which only exists in Purbalingga District, Central Java Province, Indonesia, and it is conventionally raised by local farmers. This goat belongs to Southeast Asian lineage and is confirmed to be descendant from crossbred of Kacang and Etawah Grade goats (Kurnianto *et al*., 2012; Kurnianto *et al*., 2013; Lestari *et al*., 2018[A]; Lestari *et al*., 2018[B]). As the meat animals, Kejobong goat had 41.30% carcass yield that comprised 67.06% meat and 32.94% bone, while its meat is known to have less cholesterol than meat of Kacang and Etawah Grade goat (Aqsa *et al*., 2011). Kejobong goat is popular at the district because of its high rate of growth, good reproductive performance, high resistance to local diseases and parasites and ability to survive and growing ability under poor feeding conditions (Kurnianto *et al*., 2012; Febriana *et al*., 2017). However, the breeders often have difficulty to satisfy the market demand on slaughtering weight. This is probably due to limited information of appropriate breeding strategy for Kejobong goat to accomplish the breeding goal of high meat productivity.

Growth analysis can provide valuable information about mature weight, growth rate and mature time. Growth rate and body weight of animal at different ages influence productivity of meat and have deterministic effects on the profitability of meat production (Kheirabadi and Rashidi, 2019). Particularly, growth rate has large effect on meat producing efficiency up to slaughtering age which is crucial for economic success of animal production (Abbasi *et al*., 2012). According to Junior *et al*. (2013) and Ripoll *et al*. (2016), animals that have a large frame size of body tend to have higher potential of growth and have a higher proportion of meat. Therefore, besides body weight, body size is also important trait to be considered for performing animal selection. Study of growth analysis has been done by previous researchers (Waheed *et al*., 2011; Setiaji *et al*., 2013;

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Zadeh *et al*., 2015; Raji *et al*., 2015; Lupi *et al*., 2016; Zadeh and Gorbani, 2018; Ghiasi *et al*., 2018; Rout *et al*., 2018; Kheirabadi and Rashidi, 2019), however they were only using phenotypic data into analysis. In this study, conventional growth analysis was modified by including genotype records to growth analysis.

Early growth of kids is an economically important trait that affecting profitability in goat production (Baranzadeh *et al*., 2012; Moghbeli *et al*., 2013; Sadeghi *et al*., 2019). Physiologically, growth of an animal is a result from a complex process of metabolism including a coordinated action of several hormones that controlled by expression of their responsible genes (Mahrous *et al*., 2018). Growth Hormone (*GH*) gene is one of numerous genes which have large effect on growth performance of an animal. *GH* gene is encoding growth hormone that produces in anterior pituitary and is necessary for postnatal growth and metabolism in vertebrates (Ge *et al*., 2003). This hormone is known to have a broad impact on biological activity in all body cells, such as controlling and coordinating the flow rate of metabolic process, enhancing glycogen, protein, DNA and RNA biosynthesis and promoting the deposition of fat and the disintegration of fatty acids and glucose in the tissue (Gorlov *et al*., 2017; Wickramaratne *et al*., 2010; Othman *et al*., 2015; Seevagan *et al*., 2015; Singh *et al*., 2015). Therefore, *GH* gene is considered to be a prime factor which affects growth performance of an animal.

Based on these backgrounds, effect of *GH* gene on growth traits, especially from a point of genetic improvement is important to build breeding plan for high meat productivity. Prospectively, result of this study is not only suggesting appropriate management practice for improving production for the breeders, but also providing information of genetic marker in Kejobong goat for breeding selection in the future through Marker-Assisted Selection (MAS) and/or Marker-Assisted Introgression (MAI)

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and appropriate mathematical growth models of Kejobong goat. Therefore, objective of this study was to reveal to reveal appropriate growth models describing early growth of body weight and body measurement of Kejobong goat based on the effect of Growth Hormone (*GH*) gene sequence analysis.

MATERIALS AND METHODS

Ethical approval

All procedure involving animals were based on the standard rule of animal treating as appointed in the Republic of Indonesia's law, number 41, 2014.

Sampling and data collection

A total of 35 blood samples and 1.960 quantitative traits records of Kejobong goat were collected from Purbalingga District, Central Java Province, Indonesia. Quantitative traits records comprised body weight (BW), wither height (WH), chest depth (CD), chest width (CW), hip height (HH), hip width (HW) and heart girth (HG) at 0, 2, 4, 6, 8, 10, 12 and 14 weeks of age.

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DNA extraction, Polymorphism Chain Reaction (PCR) and sequencing

Blood samples for DNA analysis were taken by 3cc spuit from *jugular venous* that previously cleaned with alcohol. The blood was then collected in vacutainer blood collection tubes with an anticoagulant (EDTA). DNA was extracted from whole blood by gSYNC DNA mini kit (Geneaid Biotech, Taiwan) according to the manufacturer's standard protocol for PCR and sequencing analysis.

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Forward primer F: 5'-TAGAAATGGGGGTGTGTGGGGT-3' and reverse primer R: 5'-CATCCTCCACTGCCATCCAACA-3' (Sigma-Aldrich, Japan) were used to amplify *GH* gene exon 3. PCR was carried out in total volume 50 µL comprising 1 µL

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KOD Plus (Toyobo, Japan), 5 µL buffer, 5 µL dNTP, 2 µL $MgSO_4$, 1.5 µL forward primer, 1.5 µL reverse primer, 32 µL PCR water and 2 µL DNA template. PCR amplification was running with an initial denaturation at 94°C for 2 min, followed by 40 cycles of denaturation at 94°C for 15 sec, primers annealing 66.8°C for 30 sec and extension at 68°C for 19 sec. PCR products were electrophoresed using 1.3% Agarose gel at 110 V for 20 min. PCR products were then visualized by UV trans-illuminator and was sequenced through Fasmac sequencing service, Japan.

Data analysis

Allelic and genotypic frequencies were directly calculated. Hardy-Weinberg Equilibrium (HWE) was tested using chi-square statistic (χ^2) as follows:

$$\chi^2 = \sum_{i=1}^{k} \frac{(o_i - e_i)^2}{e_i},$$

where χ^2 is the Chi square value; o_i the observed value of genotype frequency, e_i the expected value of genotype frequency, χ^2 the table using 5% significance level for HWE test.

Heterozygosity (H) was calculated as follows:

$$H = 1 - \sum_{i=1}^{k} p_i^2,$$

where H is the value of heterozygosity and p_i the frequency of the i^{th} of k alleles.

Sequencing result alignment was analyzed by Clustal W (Thompson *et al*., 1994) with Molecular Evolutionary Genetics Analysis (MEGA6.0) (Tamura *et al*., 2013) to find out the SNP within animals. Sequencing result then was translated into amino acids form by standard genetic code to identify amino acid alteration that caused by SNP.

Linear Mixed Model (LMM) was used to analyze association between genotype with quantitative traits by MIXED procedure in Statistical Analysis System (SAS 9.3) (SAS Institute Inc, 2011). The model was:

$$y_{ijkl} = \mu + G_i + F_j + u_k + b_1\alpha_{ijkl} + b_2\alpha^2_{ijkl} + e_{ijkl},$$

where y_{ijkl} is the observed value of a dependent variable (body weight or body measurements); μ the overall mean of the population; G_i the fixed effect of i^{th} genotype ($i = 1$ for GG, 2 for AG, 3 for AA); F_j the fixed effect of j^{th} farm group ($j = 1, 2, 3, 4$); u_k the random effect of k^{th} animal; b_1 and b_2 the linear and quadratic coefficients of partial regression, respectively; l^{th} individual measurement, α_{ijkl} age in days of a covariate and e_{ijkl} the random residual for y_{ijkl}. Difference in the least square means of the genotypes was tested by the Tukey-Kramer (Tukey, 1949).

The nonlinear growth models comprised Brody (Brody, 1945), Von Bertalanffy (Bertalanffy, 1938), Logistic (Verhulst, 1838) and Gompertz (Gompertz, 1825) and they were compared by describing animal growth (Table 1). Growth models were analyzed using Nonlinear Mixed Model (NLMM) by NLMIXED procedure of SAS 9.3 (SAS Institute Inc, 2011). Body weight or body measurements as dependent variables are influenced by genotype and age. Therefore, dummy variables were created to assess the effect of qualitative variables on dependent variables according to the method by Filho *et al.* (2014). The NLMIXED procedure was used in this study due to its flexibility in engaging the variance covariance structure which could not be identified by traditional regression approach. Also NLMIXED has ability to handle unbalance data (Aggrey, 2009; Galeano-Vasco *et al*., 2014). This procedure can reduce potential biases despite selective sampling and supply supplemental parameters that characterize variation between individual animals (Craig and Schinkel, 2001).

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166 The models were tested for goodness of fit using -2 log likelihood, Akaike
167 Information Criterion (AIC) (Akaike, 1974), Bayesian Information Criterion (BIC)
168 (Schwarz, 1978) and the residual variances (σ^2_e). AIC and BIC were calculated by the
169 following formula:

170 $$AIC = n\, ln\left(\frac{SSE}{n}\right) + 2k$$

171 $$BIC = n\, ln\left(\frac{SSE}{n}\right) + k\, ln\,(n)$$

172 where n is the number of observation; SSE the Sum Square Errors and *k* the number of
173 parameters. Smaller values of AIC, BIC or σ^2_e indicate the best fit of the model to the
174 observations.
175
176 **RESULTS**

177 Result showed that a total 117 bp of *GH* gene exon 3 encoding 38 amino acid
178 sequence were well amplified. Sequencing result revealed 5 SNPs as transition mutation
179 in parsimonious form, which were g1121A→G (SNP1), g1148T→C (SNP2),
180 g1160A→G (SNP3), g1170A→G (SNP4) and g1178C→T (SNP5). Genotype
181 frequencies of Kejobong goats were not different from HWE, and the frequency of
182 heterozygosity was 49% (Table 2). The estimated allele of the *GH* gene exon 3 in this
183 study was 57% and 43% for G and A, respectively. Frequencies of genotypes GG, AG
184 and GC were 37%, 40% and 23%, respectively, so that G allele and heterozygous
185 genotype AG were predominant in this locus.

186 Test of significance showed that the fixed effect of genotype together with effect
187 of farm and linear and quadratic coefficients of age were statistically significant ($P<0.05$)
188 in BW while the fixed effect of genotype and linear and quadratic coefficients of age were

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189 statistically significant (P<0.05) in WH, and the fixed effect of genotype, age of doe and
190 linear and quadratic coefficients of age were statistically significant (P<0.05) in HH.
191 Conversely, the fixed effect of genotype was not significant in CD, CW, HW and HG
192 (Table 3).

193 Animals of genotype AG demonstrated the highest BW, HW and HH then it
194 followed with animals of genotype GG and AA (Table 4). Comparing genotypes at
195 different periods, BW0 and BW6 in animals of genotype AG (4.35 kg and 8.40 kg) were
196 significantly heavier (P<0.05) than animals of genotype AA (3.40 kg and 6.59 kg), while
197 animals of genotype GG (3.84 kg and 6.97 kg) showed no significant difference with
198 genotype AG and AA. However, there were no significant effect of genotype at BW2,
199 BW4, BW8, BW10, BW12 and BW14.

200 Significant difference between genotypes for body measurements were observed
201 in wither height (WH6, WH10, and WH14) and hip height (HH12 and HH14). Similar to
202 body weight, animals of genotype AG had significantly (P<0.05) higher wither and hip
203 heights than those animals of genotype AA, but there was no significant difference
204 between animals of genotype GG with animals of genotype AG and AA (Table 5).

205 Estimated parameters for body weight, wither height and hip height are presented
206 in Table 6, respectively. Growth analysis showed that Von Bertalanffy model had the
207 lowest -2 log likelihood, and two criteria AIC and BIC compared with the other models
208 indicating this model as the best model for describing growth of body weight in Kejobong
209 goat. On the other hand, the highest -2 log likelihood, AIC and BIC were obtained in
210 Logistic model. Brody model in this study showed fit to wither height and hip height well
211 according to its value of -2 log likelihood, AIC and BIC, which was lower than Gompertz,
212 Logistic and Von Bertalanffy model.

Von Bertalanffy model fitted best to body weight, estimated 23.01 kg mature body weight (a), 0.39 integration constant (b) and 0.01389 growth rate (k). The best estimated for wither height and hip height by Brody model were 54.65 cm and 58.91 cm for parameter a; 0.37 and 0.36 for parameter b; 0.01577 and 0.01647 for parameter k. In this study, the estimated parameter b for body weight, wither height and hip height were 0.39, 0.37 and 0.36 respectively.

Furthermore, estimated parameter k of body weight in Von Bertalanffy model was 0.01389. Negative correlation was found between parameter k and parameter a (Table 7). This result was confirmed by the fact that Brody model in this study had the slowest parameter k (0.006948) in body weight, yet it had the highest estimated parameter a (25.29 kg) among the others. Similarly, the highest parameter k in wither height (0.2606) and hip height (0.02341) had the lowest estimated parameter a (50.78 cm, 56.26 cm) in Von Bertalanffy and Logistic models respectively.

Representing variability among individual animals, estimated animal variance (σ^2_u) of the body weight in this study was 5.78. The higher the variance, the greater the difference is realized among animals. Furthermore, residual variance (σ^2_e) of the body weight in this study was 0.31 that indicated the gap between predicted value and observed value. Repeatability of body weight by intra-class correlation was 0.95 this study.

DISCUSSION

SNP2 of this study was also found in a report analyzing *GH* gene of Chinese goat (An *et al*., 2010). Among five SNPs in this study, translation result showed SNP4 causing amino acid alteration which changes amino acid sequence in *GH* gene exon 3. SNP4 as non-synonymous mutation changed the first triplet codon of AGC encoding Serin to GGC

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encoding Glycine (Figure 1) and we used it to distinguished as GG, AG and AA genotypes, whereas the other SNPs were silent mutation (SNP1 CAG>CAA(Gln); SNP2 TCT>TCC(Ser); SNP3 CCA>CCG(Pro); SNP5 AAC>AAT(Asn)). According to Nei and Kumar (2000), most of synonymous amino acid was found due to substitution of nucleotides in the third codon, while substitution of nucleotides in the first and second codon generate non-synonymous amino acid. Therefore, non-synonimous mutation that change amino acid sequence in exon region may change the peptide sequence of the encoded protein and influence the function of the protein, which was growth hormone in this study. This hormone has substantial metabolic effects on somatic growth, stimulation of protein synthesis and cellular uptake of amino acids and development of body composition (Hjortebjerg *et al*., 2017).

Result in this study agreed with a result by Dayal *et al*. (2016), in which goats with heterozygous genotype AC had the heaviest body weight among five observed genotypes in Black Bengal goat. Gorlov *et al*. (2017) reported their study in Salsk sheep that sheep with AB genotype significantly had heavier body weight, average daily gain and carcass weight than sheep with AA genotype. A contradictory result was reported by An *et al*. (2011) that goats with homozygous genotype AA significantly had higher body weight than those of heterozygous genotype AB at age of one and three months old in Chinese goat, however, wither height showed no significant difference. The different results seem to be due to genetic difference that leads to different structure of *GH* gene and limited number of observations. Therefore, further study is necessary to validate the predominant effect of heterozygote of *GH* gene with a larger number of animals and more sampled observations.

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The best model for describing growth of body weight in this study was different with previous study by Kheirabadi and Rashidi (2019), reported that Logistic model fitted worst to body weight, while Brody model fitted most accurately to body weight of Markhoz goat. In this study, estimated mature body weight (a) was 23.01 kg implying that Kejobong goat had heavier mature body weight than Raeini Cashmere goat (17.97 kg) (Ghiasi *et al*., 2018) and Nondescipt goat (6.42 to 10.55 kg) (Raji *et al*., 2015) but lighter body weight than Beetal goat (23.39 kg) (Waheed *et al*., 2011). Those values of parameter b for body weight, wither height and hip height in this study were described to represent the proportion of mature weight attained after birth, calculated by the initial weight and age value (Lupi *et al*., 2016). On the other hand, Ghiasi *et al*. (2018) stated that parameter b is a scale parameter that has no biological interpretation. Waheed *et al*. (2011) reported higher estimated values of parameter k (0.1077) in Beetal goat by Brody model. Other researchers estimated parameter k as much as 0.017 in Cashmere goat (Ghiasi *et al*. 2018) and 0.0108 in Repartida goat (Pires *et al*., 2017) by applying Gompertz model, so that Kejobong goat in this study is considered to attain mature weight later than Beetal and Cashmere goats but earlier than Repartida goat.

Negative correlation between parameter k and parameter a indicated the slower growth rate, the larger mature weight, *vice versa*. Previous studies supported this results. Kurnianto *et al*. (1998) reported that animals with slower growth rate tended to have estimated heavy body weight at maturity. Brown *et al*. (1976) stated that selection for increasing growth rate tended to decrease mature weight, yet its antagonistic association could be minimized by cross-breeding and improving feed quality. On other hand, previous study by Ghiasi *et al*. (2018) showed lower animal variance (1.29) and higher residual variance (8.01) on growth analysis of Raeni Cashmere goat using Gompertz

model than the present study. Repeatability of body weight in this study was higher than repeatability value of South African Angora goat (Snyman and Olivier, 1999) and Boerawa goat (Beyleto *et al*., 2010). The high repeatability in this study may be resulted by the fact that systematic factors affecting body weight were fitted as many as possible in NLMM and that earlier body weight was a component of latter body weight.

The NLMIXED procedure used in this study has flexibility in engaging the variance covariance structure which could not be identified by traditional regression approach. Also NLMIXED has ability to handle unbalance data (Aggrey, 2009; Galeano-Vasco *et al*., 2014). This procedure can reduce potential biases despite selective sampling and supply supplemental parameters that characterize variation between individual animals (Craig and Schinkel, 2001). Therefore, this procedure can facilitate growth analysis by including genotype information and estimates accurately the growth performance of Kejobong goats.

CONCLUSION

SNP g1170A→G in *GH* gene is associated with growth traits and can be used as genetic marker for animal selection to improve goat's growth performance. Animals with heterozygous genotype AG showed higher growth performance than homozygous genotype AA. Nonetheless, animals with homozygous genotype GG showed no difference with either heterozygous genotype AG or homozygous genotype AA. Model ($y = 23.01\ (1 - 0.39\ e^{-0.01389age})^3$) by Von Bertalanffy, $y = 54.65\ (1 - 0.37\ e^{-0.01577age})$ and $y = 58.91\ (1 - 0.36\ e^{-0.01647age})$ by Brody were fitted well to describe body weight, wither height and hip height of Kejobong goat, respectively.

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453

454 **TABLE**

455 Table 1. Growth equations used to construct the growth model

Model	Function[A]	Inflection weight	Inflection age
Brody	$y = a (1 – b \exp^{-kt})$	-	-
Von Bertalanffy	$y = a (1 – b \exp^{-kt})^3$	$y_i = 8a/27$	$t_i = \ln(3b)/k$
Logistic	$y = a / (1 + b \exp^{-kt})$	$y_i = a/2$	$t_i = \ln(b)/k$
Gompertz	$y = a \exp (– b \exp^{-kt})$	$y_i = a/\exp$	$t_i = \ln(b)/k$

456 [A]y, observed body weight/body measurements; a, the estimated of mature body
457 weight/body measurements; b, the integration constant; k, the growth rate constant; t, the
458 animal age in day and exp, Napier's constant the base of natural logarithm.
459
460

461 Table 2. Estimated allele and genotype frequency

Variable Measured	Genotype			Allele		H	χ^2
	GG	AG	AA	G	A		
Frequencies	0.37	0.40	0.23				
Observation	13	14	8	0.57	0.43	0.49	1.18
Expectation	11.43	17.14	6.43				

462 H, Heterozygosity; χ^2, Chi square value.

463

464

465 Table 3. Significance analysis of factor affecting body weight and body measurements

Traits	Effect	Degree of freedom	f-value	p-value
BW[A]	Genotype	2	3.44	0.0335
	Age of doe	3	1.43	0.2355
	Farm	3	5.33	0.0050
	Age (linear)	1	224.97	<0.0001
	Age (quadratic)	1	17.98	<0.0001
WH[B]	Genotype	2	4.14	0.0171
	Age of doe	3	2.59	0.0537
	Farm	3	2.27	0.1021
	Age (linear)	1	238.66	<0.0001
	Age (quadratic)	1	50.99	<0.0001
CD[C]	Genotype	2	0.14	0.8677
	Age of doe	3	0.54	0.6541
	Farm	3	1.00	0.4081
	Age (linear)	1	40.44	<0.0001
	Age (quadratic)	1	10.58	0.0013
CW[D]	Genotype	2	2.41	0.0920
	Age of doe	3	2.66	0.0491
	Farm	3	5.48	0.0043
	Age (linear)	1	36.02	0.0001
	Age (quadratic)	1	9.05	0.0029
HH[E]	Genotype	2	4.25	0.0153
	Age of doe	3	2.64	0.0499

	Farm	3	1.71	0.1879
	Age (linear)	1	267.39	<0.0001
	Age (quadratic)	1	59.44	<0.0001
HW[F]	Genotype	2	1.74	0.1775
	Age of doe	3	0.71	0.5496
	Farm	3	2.27	0.1023
	Age (linear)	1	62.34	<0.0001
	Age (quadratic)	1	13.53	0.0003
HG[G]	Genotype	2	1.69	0.1873
	Age of doe	3	1.62	0.1852
	Farm	3	3.89	0.0192
	Age (linear)	1	347.92	<0.0001
	Age (quadratic)	1	70.55	<0.0001

[A]Body weight; [B]Wither height; [C]Chest depth; [D]Chest width; [E]Hip height; [F]Hip width; [G]Heart girth.

470 Table 4. Average of body weight and body measurements

Traits	Genotype		
	GG	AG	AA
Body weight (BW)			
BW0	3.75±0.76	4.26±1.02	3.51±1.06
BW2	4.91±0.75	5.39±1.20	4.87±1.20
BW4	6.12±0.89	6.57±1.38	5.84±1.95
BW6	7.39±1.01	7.91±1.63	6.74±2.15
BW8	8.24±1.14	8.87±1.89	7.85±2.62
BW10	9.07±1.21	9.72±2.26	8.64±2.89
BW12	9.87±1.33	10.52±2.56	9.19±3.08
BW14	10.64±1.49	11.36±2.78	9.80±3.10
Wither height (WH)			
WH0	33.93±3.21	35.08±2.49	31.69±4.63
WH2	37.85±2.84	37.72±4.45	36.63±2.92
WH4	40.63±2.55	40.57±4.12	39.33±4.43
WH6	42.34±2.30	43.28±2.48	40.77±5.35
WH8	44.29±2.40	45.09±3.30	42.51±4.88
WH10	45.42±1.85	45.65±3.47	42.85±5.24
WH12	46.35±2.52	47.54±3.29	44.49±4.88
WH14	47.61±2.67	49.06±3.07	45.39±4.98
Hip height (HH)			
HH0	36.57±3.19	37.60±3.40	34.23±4.73
HH2	40.09±3.30	40.78±2.55	38.34±3.55

HH4	42.89±2.85	43.56±3.67	42.00±4.72
HH6	44.84±2.68	46.39±2.52	43.92±5.37
HH8	46.63±3.01	47.67±3.12	45.39±5.02
HH10	48.01±2.00	48.33±2.91	46.03±5.62
HH12	48.99±2.41	50.56±3.08	45.96±4.76
HH14	50.55±2.57	52.15±2.99	47.82±5.75

471

472

473 Table 5. Estimated genotypic effect for body weight and body measurements for each
474 measurement

Traits	Genotypes		
	GG	AG	AA
Body weight (BW)			
BW0	3.84±0.22^{AB}	4.35±0.20^{A}	3.40±0.27^{B}
BW2	4.84±0.28	5.67±0.26	4.82±0.36
BW4	5.87±0.37	6.97±0.34	5.75±0.46
BW6	6.97±0.43^{AB}	8.40±0.40^{A}	6.59±0.55^{B}
BW8	7.80±0.52	9.43±0.47	7.71±0.66
BW10	8.57±0.59	10.35±0.54	8.54±0.75
BW12	9.29±0.65	11.17±0.60	9.17±0.84
BW14	10.03±0.69	12.03±0.63	9.71±0.88
Wither height (WH)			
WH0	34.27±0.94	35.03±0.87	32.64±1.20
WH2	37.38±1.18	38.41±1.08	36.03±1.51
WH4	39.89±1.07	41.44±0.98	39.08±1.37
WH6	41.88±0.90^{AB}	44.25±0.83^{A}	40.45±1.16^{B}
WH8	43.41±1.04	46.15±0.95	42.14±1.33
WH10	44.15±1.01^{AB}	46.83±0.93^{A}	42.33±1.29^{B}
WH12	45.59±1.03	48.53±0.95	44.34±1.32
WH14	46.69±1.04^{AB}	49.95±0.95^{A}	45.29±1.33^{B}
Hip height (HH)			
HH0	36.95±1.01	37.71±0.93	34.59±1.30
HH2	36.95±1.01	41.11±0.89	38.16±1.23

HH4	42.61±1.12	43.85±1.03	42.02±1.43
HH6	44.55±1.03	47.21±0.94	43.87±1.32
HH8	45.57±1.14	48.65±1.05	44.96±1.46
HH10	46.94±1.00	49.31±0.96	45.48±1.28
HH12	48.58±1.05^{AB}	51.28±0.97^{A}	45.82±1.35^{B}
HH14	49.59±1.09^{AB}	53.08±1.00^{A}	47.57±1.39^{B}

475 ^{A,B} In the same row, values with different superscripts are significantly different (P<0.05).

476

477

478 Table 6. Estimated parameters of growth and goodness of fit for four different growth
479 models

Parameter	Model			
	Brody	Von Bertalanffy	Logistic	Gompertz
Body weight				
a	25.29±1.01	23.01±0.47	21.65±0.30	22.48±0.39
b	0.83±0.01	0.39±0.01	2.56±0.07	1.42±0.03
k	0.006948±0.001019	0.01389±0.001097	0.0277±0.001309	0.01735±0.001143
y_i	-	6.82	10.83	8.27
t_i	-	11.75	33.93	20.10
σ^2_u	9.08±2.67	5.78±1.48	4.17±1.03	5.13±1.29
σ^2_e	0.32±0.03	0.31±0.03	0.32±0.03	0.31±0.03
GG	-3.6±0.79	-4.2±0.59	-4.64±0.49	-4.37±0.55
AG	-2.01±0.85	-3.03±0.061	-3.63±0.50	-3.26±0.56
AA	-4.53±0.95	-5.06±0.75	-5.3±0.63	-5.18±0.70
-2 Log Likehood	606.6	605.8	609.5	606.1
AIC	630.6	629.8	633.5	630.1
BIC	649.6	648.8	652.5	649.1
Wither height				
a	54.65±0.94	50.78±0.31	53.59±0.71	55.54±0.81
b	0.37±0.01	1.96±0.08	0.53±0.02	0.44±0.01
k	0.01577±0.002084	0.2606±0.01207	0.02292±0.002268	0.01934±0.002171
σ^2_u	9.93±2.56	0.0014±0.5954	9.39±2.40	9.62±2.47
σ^2_e	3.95±0.36	29.44±1.63	3.97±0.36	3.96±0.36
GG	-3.3±0.82	-6.82±0.50	-3.67±0.77	-5.02±0.79
AG	-2.76±0.81	-6.78±0.47	-3.14±0.76	-4.48±0.78
AA	-5.59±0.92	-11.91±0.64	-5.90±0.88	-7.27±0.90

-2 Log Likehood	1274.3	2217.3	1276.0	1275.1
AIC	1290.9	2233.3	1292.0	1291.1
BIC	1303.0	2246.0	1304.6	1303.8
Hip height				
a	58.91±0.72	57.73±0.73	56.26±0.56	56.61±0.62
b	0.36±0.01	0.13±0.01	0.50±0.01	0.42±0.01
k	0.01647±0.002009	0.01839±0.002112	0.02341±0.002187	0.01994±0.002092
σ^2_u	8.40±2.20	12.99±0.64	7.91±2.04	8.09±2.10
σ^2_e	3.72±0.34	3.71±0.33	3.75±0.34	3.73±0.34
GG	-2.24±0.77	-2.12±0.94	-1.56±0.73	-1.44±0.75
AG	-0.60±0.78	-0.81±0.93	0.12±0.74	0.25±0.75
AA	-4.55±0.89	-4.63±1.08	-3.60±0.86	-3.50±0.87
-2 Log Likehood	1254.6	1258.2	1256.5	1255.4
AIC	1278.6	1282.2	1280.5	1279.4
BIC	1297.6	1301.2	1299.5	1298.4

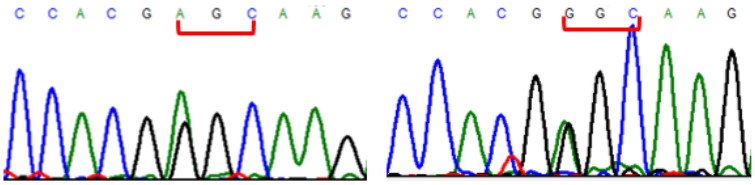
a, the estimated of mature body weight/body measurements; b, the integration constant; k, the growth rate constant; y_i, body weight (kg) at the point at inflection; t_i, age (weeks) at the point at inflection; σ^2_u; additive genetic variance; σ^2_e, error variance; AIC, akaike information criterion; BIC, bayesian information criterion.

Table 7. Correlation among growth parameter within traits based on their best model

Growth Parameter	Mature weight (a)		
	BW[A]	WH[B]	HH[C]
Integration constant (b)	0.5564	0.7038	0.6652
Growth rate (k)	-0.7833	-0.8755	-0.8636

[A]Body weight; [B]Wither height; [C]Hip height

FIGURE

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[                    1 1111111112 2222222223 33333333]
[          1234567890 1234567890 1234567890 12345678]
#4B        ERTYIPEGQR YSIQNTQVAF CFSETIPAPT GKNEAQQK
#5B        .......... .......... .......... ........
#39J       .......... .......... .......... ........
#40J       .......... .......... .......... S.......
#43B       .......... .......... .......... ........
#44B       .......... .......... .......... S.......
#45B       .......... .......... .......... S.......
#49B       .......... .......... .......... S.......
#50B       .......... .......... .......... ........
#52J       .......... .......... .......... ........
#53B       .......... .......... .......... S.......
#54B       .......... .......... .......... ........
#55B       .......... .......... .......... S.......
#56J       .......... .......... .......... S.......
```

Figure 1. Amino acid alteration caused by SNP g1170A

Form#9

REVIEWER'S COMMENT

Reviewer comment to the manuscript entitled:
Appropriate Growth Models to Describe Early Growth of Kejobong Goat Based on Growth Hormone (GH) Gene Sequence Analysis

GENERAL COMMENT	
The authors have precisely explane the growth model and GH gene analysis, but it was less coherens in integrating of both analysis approaches. We suggest the atuhors to do integration of the both analysis or split this manuscript into 2 manuscripts with different topics growth model analysis or GH gene analysis.	
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Comment:	Suggestion:
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INTRODUCTION	
Comment : Please read line 53-56	Suggestion : This sentences do not support or relate directly to the topic (growth), so I suggest to delete it or If the authors still put the sentence, I suggest the author should consider with the statement in line 69-70 : animals that have a large frame size of body tend to have higher potential of growth and have a higher proportion of meat.

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Did the author design the primers or cited by an article?	Please state it.
This paper did not focus on the distribution of allele and genetic variability but focus on the comparation of growth based on two analysis with mathematical model and DNA approach. I think no relationship between allelic freq, HWE, heterozygosity (describing the genetic diversity of the population sample) with matemathical growth model?	I suggest to skip this analysis.
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Please see my comments in line 195-196 ; 121-122	
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Please add one section to discuss the integrasion between molecular analysis and growt model analysis	

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   2. no suitble among the title, hypothesis and conclusions.
   3. weak in methodology :
      .....
      .....
   4. **Miscelenaous**:
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      .....

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to me

Dr. Sutopo Sutopo:

Thank you for submitting the revision of manuscript, "Appropriate Growth Models to Describe Early Growth of Kejobong Goat Based on Growth Hormone (GH) Gene Sequence Analysis" to Journal of the Indonesian Tropical Animal Agriculture. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

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Thank you for the information.

Thank you for your response.

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REVIEWER 1

No	Line	Reviewer Comments	Author Response
1	8-10	Saya belum menemukan hubungan atau titik integrasi antara model pertumbuhan yg dianalisis dan dibahas dalam tulisan ini dengan analisis sekuen gen GH baik dalam abstrak, diskusi dan kesimpulan. Dua analisis (model matematik) dan analisis sekuen masih terilihat dibahas satu per satu blm ada analisis dan diskusi integrasi antar keduanya. Mohon diperjelas integrasinya dalam statement teori dan analisis methodologynya	Analisis sekuen gen GH digunakan untuk menentukan tipe genotype ternak, dari tipe genotype tersebut selanjutnya dianalisis menggunakan MIXED model apakah perbedaan genotype berpengaruh terhadap pertumbuhan (berat badan dan ukuran tubuh) dengan menggunakan catatan sifat kuantitatif berkala (0-14 minggu), hasil tertera pada tabel 3). selanjutnya untuk sifat kuantitatif yang significant diaplikasikan kedalam 4 model pertumbuhan non linier dengan memasukkan tipe genotype yang ditemukan untuk didapatkan persamaan model pertumbuhannya.
2	10	1.960 catatan sifat kuantitatif dari 35 individu (sampel DNA? Atau 35 sampel dna utk analisis gen GH dan 1.960 catatan sifat kuantitatif untuk analisis model pertumbuhan? Dan apakah data catatan sifat yang dipakai untuk analisis model matematik bagian dari data yang dipakai untuk analisis asosiasi (genotip dan fenotip) ➔ mohon diperjelas terutama di method dan data analysis	Total jumlah data kuantitatif 1.960 berasal dari : 35 (sample) x 7 (data kuantitatif ukuran tubuh untuk setiap ternak : BW, HW, CD, CW, HH, HW) x 8 (frekuensi pengambilan data untuk setiao ternak yaitu pada saat ternak berumur 0, 2, 4, 6, 8, 10, 12, 14 minggu)
3	11	Apa saja sifat kuantitatifnya sebutkan	Keterbatasan jumlah kata dalam abstrak sehingga untuk detail jelasnya sudah tercantum dimetode
4	13-14	Apa saja keempat model tersebut ➔ sebutkan	Keterbatasan jumlah kata dalam abstrak sehingga untuk detail jelasnya sudah tercantum dimetode
5	22-26	Bagaimana hasil evalusi dr pertumbuhan yang dibandingkan antara pertumbuhan menggunakan estimasi empat model pertumbuhan non-linier dan performan pertumbuhan dari berbagai genotype. Mengapa saya tanyakan ini karena di atas penulis menyebutkan:	Has been answered in conclusion

		"Empat model pertumbuhan non-linier diaplikasikan untuk menganalisis pertumbuhan guna membandingkan performan pertumbuhan dari berbagai genotipe" Kalimat ini sebenarnya yg menjadi core dari tulisan ini sehingga state of the art dr penelitian ini jadi terlihat jelas ada integrasi antara analisis model pertumbuhan dan analisis gen GH. Tapi seperti saya sebutkan diatas, manuskrip ini masih membahas *partially each analysis approaches* seolah-olah terspisah sehingga belum nampak *comprehensive (incoherens)*	
6	30	Comments: Same comments as above	Has been revised and clarified
7	53-56	This sentences do not support or relate directly to the topic (growth), so I suggest to delete it or If the authors still put the sentence, I suggest the author should consider with the statement in line 69-70 : animals that have a large frame size of body tend to have higher potential of growth and have a higher proportion of meat.	Actually, this sentence is a sentence that supports information about the superiority of Kejobong goat as Indonesian local goat to readers (especially foreigner readers) and as a reason why the authors used those goat as object of research
8	98	???	Has been revised
9	107	Please see my comment and suggession at line 10	Has been clarified at response comment line 10
10	118-119	Did the author design the primers or cited by an article? Please state it.	Has been revised
11	129-137	This paper did not focus on the distribution of allele and genetic variability but focus on the comparation of growth based on two analysis with mathematical model and DNA approach, so I suggest to skip this analysis. I think no relationship between allelic freq, HWE, heterozygosity (describing the genetic diversity of the population sample) with matemathical growth model?	Has been revised
12	138-141	Is the sequencing method based on SNP identified used for genotyping as well? If yes, please add the information.	Has been revised

13	178	Please add the position of the SNPs based on electrophoregram (sequencing results)	Due to 4 of 5 of SNPs identified are silent mutation (SNP 1,2,3,5), so they don't make any sense. While SNP4 as non-synonymous mutation has been showed at figure 1.
14	195-196	I think the point of view this study should concern in this results. The data for growth model analysis should be concern with animal having the gentoypes identified, so the author can determine which model appropriate to describe the genetic profile results.	Analysis steps of relationship among sequence, genotype and growth model have been explained at response comment line 8-10. The appropriate model for each quantitative traits has been clear mentioned at conclusion section
15	201-203	Comments same as above	Has been clarified
16	248-255	Did the authors compare with the sama SNP loacation? If not, then the comparation are bias	Yes, the references (Dayal et al 2016 and An et al 2011) used as comparator are in the same SNP location
17	297-298	Please add one section to discuss the integrasion between molecular analysis and growt model analysis	Has been clarified at response comment line 10
18	308	Acknowledgement???	Because it is optional (mentioned in author guideline), authors decide to not declare acknowledgement

REVIEWER 2

No	Line	Reviewer Comment	Author Respond
1	8	Mungkin dapat ditambahkan 1 kalimat sebelum pendahuluan	Has been revised
2	17 and 20	terdiri dari	Has been revised
3	31-32	Before this aims of research better to put one sentences.	Has been revised
4	39-42	This sentences make confuse with before sentences. Please rewrite and more effective sentences	Has been revised
5	44-45	We think this to early to conclude as genetic marker…???marker candidate???	Has been revised
6	53-56	Please rewrite this sentences more effective	Has been revised
7	56-57	Compare to other goats in Indonesia, Kejobong goat has high rate of growth, good reproductive performances,….conditions.	Has been revised

8	71-76	It would be better to put this paragraph combined with the last paragraph of " Introduction" to show the novelty of this research	Has been revised
9	72-74	Try to mentioned wchich breed goats?or species for each ciatation	Has been revised
10	76	combined	Has been revised
11	91	Please take the above paragraph that we suggest to state more clear novelty….novelty can be seen more clearly by providing previous research and why this reaseach are important	Has been stated in line 71-79
12	91	deleted	Has been revised
13	91	The effect of GH…..	Has been revised
14	107	This mentioned fisrt I men quantitative record 1.960 and the 35 blood to show the power of reseach are strong	???
15	113	Is the unit of 3 cc correct?	Has been revised
16	118-120	What kind tools to design primer this primer?please mention I this paragraph	Has been revised
17	153-154	Better the year not to write..its too old…model Brody, Gompertz etc	Has been revised
18	176	For results , in general I highly recommend to put in sub title for provide each result ex; Amfilication GH Gene, Apropiate model growth using GH gene etc???	Has been revised
19	177	Delete….A total 117 bp of GH…..	Has been revised
20	177-182	To avoid lost of contact reader…it would be better to show table in subtitle	it is not in accordance with JITTA format guideline
21	233	What is SNP2?	Has been revised
22	233-234	Please start with the finding result of this research and then support with literature or previous research for discussion	Has been clear. Finding result in this research which named "SNP2" was also found in Chinese goat
23	234	How to write SNP more than one please consider to the nomenclature???	Has been revised
24	248-250	Please rewrite this sentences	Has been revised
25	284-286	Value of repeatability should be mentioned	Has been revised
26	299-300	Try to avoid use genetic marker because it still more take validation effort to reach it. Please use marker candidate…	Has been revised
27	302-303	It make confuse. Try to simplify with previous sentences	Has been revised

28	305-306	The end of this conclusion try to put the implication	Has been revised
29	335-336 and 361-363	This reference is too old..can use any update references to explain this model???the same also for other models that authors use in this analysis	Has been revised

Running Head : GH gene and growth model analysis on goat

Appropriate Growth Models to Describe Early Growth of Kejobong Goat Based on Growth Hormone (*GH*) Gene Sequence Analysis

ABSTRAK

Tujuan penelitian yaitu untuk menemukan model pertumbuhan yang tepat dalam mendeskripsikan pertumbuhan awal kambing Kejobong berdasarkan analisis sekuen gen *Growth Hormon* (GH). Materi penelitian menggunakan 35 sampel DNA dan 1.960 catatan sifat kuantitatif kambing Kejobong. Sampel DNA diamplifikasi dan disekuensing untuk mengidentifikasi SNP yang terdapat pada gen *GH* ekson 3. Pengukuran dan penimbangan bobot badan dan ukuran tubuh dilakukan pada umur 0-14 minggu. Empat model pertumbuhan non-linier diaplikasikan untuk menganalisis pertumbuhan guna membandingkan performan pertumbuhan dari berbagai genotipe dengan menggunakan Non-Linear Mixed model. Mutasi non-sinonim (g1170A→G) pada gen *GH* ekson 3 yang membentuk genotipe GG, AG dan AA secara signifikan berasosiasi dengan sifat pertumbuhan. Kambing Kejobong bergenotipe heterozigot AG menunjukkan sifat pertumbuhan yang lebih tinggi dibandingkan dengan kambing Kejobong bergenotipe homozigot AA. Meskipun demikian, kambing Kejobong bergenotipe homozigot GG memiliki sifat pertumbuhan yang sama dengan kambing Kejobong bergenotipe heterozigot AG dan homozigot AA. Model pertumbuhan yang paling tepat untuk mendeskripsikan bobot badan kambing Kejobong adalah model Von Bertalanffy,

sedangkan untuk menggambarkan tinggi badan dan tinggi pinggul adalah model Brody. SNP pada gen *GH* ekson 3 dapat digunakan sebagai penanda genetik untuk perbaikan sifat pertumbuhan kambing Kejobong.

Kata Kunci : Analisis Pertumbuhan, GH, Kambing, Model Matematika, SNP

ABSTRACT

Objectives of this study were to reveal appropriate growth models describing early growth of Kejobong goat based on Growth Hormone (*GH*) gene sequence analysis. A total of 35 DNA samples and 1.960 records of quantitative traits of Kejobong goat were collected. The exon 3 of *GH* gene was amplified and was sequenced to determine the SNP. Body weight and body measurements of the goats were taken at 0-14 weeks of age. Four non-linear growth models were applied for analysis of growth to compare growth performance of different genotypes by Non-Linear Mixed Model. A non-synonymous mutation (g1170A→G) genotyped into GG, AG and AA was significantly associated with growth traits. Animals with heterozygous genotype AG showed higher growth traits than animals with homozygous genotype AA. Nonetheless, animals with homozygous genotype GG had the same growth traits with those animals with heterozygous genotype AG and homozygous genotype AA. The most fitted model for describing body weight was Von Bertalanffy model, while for describing wither height and hip height was Brody model. SNP at exon 3 of the *GH* gene can be used as genetic marker for improvement of growth traits of Kejobong goats.

Keywords: GH, Goat, Growth analysis, Mathematical models, SNP

INTRODUCTION

Kejobong goat is one of indigenous Indonesian breeds, which only exists in Purbalingga District, Central Java Province, Indonesia, and it is conventionally raised by local farmers. This goat belongs to Southeast Asian lineage and is confirmed to be descendant from crossbred of Kacang and Etawah Grade goats (Kurnianto *et al*., 2012; Kurnianto *et al*., 2013; Lestari *et al*., 2018[A]; Lestari *et al*., 2018[B]). As the meat animals, Kejobong goat had 41.30% carcass yield that comprised 67.06% meat and 32.94% bone, while its meat is known to have less cholesterol than meat of Kacang and Etawah Grade goat (Aqsa *et al*., 2011). Kejobong goat is popular at the district because of its high rate of growth, good reproductive performance, high resistance to local diseases and parasites and ability to survive and growing ability under poor feeding conditions (Kurnianto *et al*., 2012; Febriana *et al*., 2017). However, the breeders often have difficulty to satisfy the market demand on slaughtering weight. This is probably due to limited information of appropriate breeding strategy for Kejobong goat to accomplish the breeding goal of high meat productivity.

Growth analysis can provide valuable information about mature weight, growth rate and mature time. Growth rate and body weight of animal at different ages influence productivity of meat and have deterministic effects on the profitability of meat production (Kheirabadi and Rashidi, 2019). Particularly, growth rate has large effect on meat producing efficiency up to slaughtering age which is crucial for economic success of animal production (Abbasi *et al*., 2012). According to Junior *et al*. (2013) and Ripoll *et al*. (2016), animals that have a large frame size of body tend to have higher potential of growth and have a higher proportion of meat. Therefore, besides body weight, body size is also important trait to be considered for performing animal selection. Study of growth

analysis has been done by previous researchers (Waheed *et al*., 2011; Setiaji *et al*., 2013; Zadeh *et al*., 2015; Raji *et al*., 2015; Lupi *et al*., 2016; Zadeh and Gorbani, 2018; Ghiasi *et al*., 2018; Rout *et al*., 2018; Kheirabadi and Rashidi, 2019), however they were only using phenotypic data into analysis. In this study, conventional growth analysis was modified by including genotype records to growth analysis.

Early growth of kids is an economically important trait that affecting profitability in goat production (Baranzadeh *et al*., 2012; Moghbeli *et al*., 2013; Sadeghi *et al*., 2019). Physiologically, growth of an animal is a result from a complex process of metabolism including a coordinated action of several hormones that controlled by expression of their responsible genes (Mahrous *et al*., 2018). Growth Hormone (*GH*) gene is one of numerous genes which have large effect on growth performance of an animal. *GH* gene is encoding growth hormone that produces in anterior pituitary and is necessary for postnatal growth and metabolism in vertebrates (Ge *et al*., 2003). This hormone is known to have a broad impact on biological activity in all body cells, such as controlling and coordinating the flow rate of metabolic process, enhancing glycogen, protein, DNA and RNA biosynthesis and promoting the deposition of fat and the disintegration of fatty acids and glucose in the tissue (Gorlov *et al*., 2017; Wickramaratne *et al*., 2010; Othman *et al*., 2015; Seevagan *et al*., 2015; Singh *et al*., 2015). Therefore, *GH* gene is considered to be a prime factor which affects growth performance of an animal.

Based on these backgrounds, effect of *GH* gene on growth traits, especially from a point of genetic improvement is important to build breeding plan for high meat productivity. Prospectively, result of this study is not only suggesting appropriate management practice for improving production for the breeders, but also providing information of genetic marker in Kejobong goat for breeding selection in the future

through Marker-Assisted Selection (MAS) and/or Marker-Assisted Introgression (MAI) and appropriate mathematical growth models of Kejobong goat. Therefore, objective of this study was to reveal to reveal appropriate growth models describing early growth of body weight and body measurement of Kejobong goat based on the effect of Growth Hormone (*GH*) gene sequence analysis.

MATERIALS AND METHODS

Ethical approval

All procedure involving animals were based on the standard rule of animal treating as appointed in the Republic of Indonesia's law, number 41, 2014.

Sampling and data collection

A total of 35 blood samples and 1.960 quantitative traits records of Kejobong goat were collected from Purbalingga District, Central Java Province, Indonesia. Quantitative traits records comprised body weight (BW), wither height (WH), chest depth (CD), chest width (CW), hip height (HH), hip width (HW) and heart girth (HG) at 0, 2, 4, 6, 8, 10, 12 and 14 weeks of age.

DNA extraction, Polymorphism Chain Reaction (PCR) and sequencing

Blood samples for DNA analysis were taken by 3cc spuit from *jugular venous* that previously cleaned with alcohol. The blood was then collected in vacutainer blood collection tubes with an anticoagulant (EDTA). DNA was extracted from whole blood by gSYNC DNA mini kit (Geneaid Biotech, Taiwan) according to the manufacturer's standard protocol for PCR and sequencing analysis.

Forward primer F: 5'-TAGAAATGGGGGTGTGTGGGGT-3' and reverse primer R: 5'-CATCCTCCACTGCCATCCAACA-3' (Sigma-Aldrich, Japan) were used

to amplify *GH* gene exon 3. PCR was carried out in total volume 50 µL comprising 1 µL KOD Plus (Toyobo, Japan), 5 µL buffer, 5 µL dNTP, 2 µL $MgSO_4$, 1.5 µL forward primer, 1.5 µL reverse primer, 32 µL PCR water and 2 µL DNA template. PCR amplification was running with an initial denaturation at 94°C for 2 min, followed by 40 cycles of denaturation at 94°C for 15 sec, primers annealing 66.8°C for 30 sec and extension at 68°C for 19 sec. PCR products were electrophoresed using 1.3% Agarose gel at 110 V for 20 min. PCR products were then visualized by UV trans-illuminator and was sequenced through Fasmac sequencing service, Japan.

Data analysis

Allelic and genotypic frequencies were directly calculated. Hardy-Weinberg Equilibrium (HWE) was tested using chi-square statistic (χ^2) as follows:

$$\chi^2 = \sum_{i=1}^{k} \frac{(o_i - e_i)^2}{e_i},$$

where χ^2 is the Chi square value; o_i the observed value of genotype frequency, e_i the expected value of genotype frequency, χ^2 the table using 5% significance level for HWE test.

Heterozygosity (H) was calculated as follows:

$$H = 1 - \sum_{i=1}^{k} p_i^2,$$

where H is the value of heterozygosity and p_i the frequency of the i^{th} of k alleles.

Sequencing result alignment was analyzed by Clustal W (Thompson *et al*., 1994) with Molecular Evolutionary Genetics Analysis (MEGA6.0) (Tamura *et al*., 2013) to find out the SNP within animals. Sequencing result then was translated into amino acids form by standard genetic code to identify amino acid alteration that caused by SNP.

Linear Mixed Model (LMM) was used to analyze association between genotype with quantitative traits by MIXED procedure in Statistical Analysis System (SAS 9.3) (SAS Institute Inc, 2011). The model was:

$$y_{ijkl} = \mu + G_i + F_j + u_k + b_1\alpha_{ijkl} + b_2\alpha^2_{ijkl} + e_{ijkl},$$

where y_{ijkl} is the observed value of a dependent variable (body weight or body measurements); μ the overall mean of the population; G_i the fixed effect of i^{th} genotype ($i = 1$ for GG, 2 for AG, 3 for AA); F_j the fixed effect of j^{th} farm group ($j = 1, 2, 3, 4$); u_k the random effect of k^{th} animal; b_1 and b_2 the linear and quadratic coefficients of partial regression, respectively; l^{th} individual measurement, α_{ijkl} age in days of a covariate and e_{ijkl} the random residual for y_{ijkl}. Difference in the least square means of the genotypes was tested by the Tukey-Kramer (Tukey, 1949).

The nonlinear growth models comprised Brody (Brody, 1945), Von Bertalanffy (Bertalanffy, 1938), Logistic (Verhulst, 1838) and Gompertz (Gompertz, 1825) and they were compared by describing animal growth (Table 1). Growth models were analyzed using Nonlinear Mixed Model (NLMM) by NLMIXED procedure of SAS 9.3 (SAS Institute Inc, 2011). Body weight or body measurements as dependent variables are influenced by genotype and age. Therefore, dummy variables were created to assess the effect of qualitative variables on dependent variables according to the method by Filho *et al.* (2014). The NLMIXED procedure was used in this study due to its flexibility in engaging the variance covariance structure which could not be identified by traditional regression approach. Also NLMIXED has ability to handle unbalance data (Aggrey, 2009; Galeano-Vasco *et al*., 2014). This procedure can reduce potential biases despite selective sampling and supply supplemental parameters that characterize variation between individual animals (Craig and Schinkel, 2001).

The models were tested for goodness of fit using -2 log likelihood, Akaike Information Criterion (AIC) (Akaike, 1974), Bayesian Information Criterion (BIC) (Schwarz, 1978) and the residual variances (σ^2_e). AIC and BIC were calculated by the following formula:

$$AIC = n\, ln\left(\frac{SSE}{n}\right) + 2k$$

$$BIC = n\, ln\left(\frac{SSE}{n}\right) + k\, ln\,(n)$$

where n is the number of observation; SSE the Sum Square Errors and *k* the number of parameters. Smaller values of AIC, BIC or σ^2_e indicate the best fit of the model to the observations.

RESULTS

Result showed that a total 117 bp of *GH* gene exon 3 encoding 38 amino acid sequence were well amplified. Sequencing result revealed 5 SNPs as transition mutation in parsimonious form, which were g1121A→G (SNP1), g1148T→C (SNP2), g1160A→G (SNP3), g1170A→G (SNP4) and g1178C→T (SNP5). Genotype frequencies of Kejobong goats were not different from HWE, and the frequency of heterozygosity was 49% (Table 2). The estimated allele of the *GH* gene exon 3 in this study was 57% and 43% for G and A, respectively. Frequencies of genotypes GG, AG and GC were 37%, 40% and 23%, respectively, so that G allele and heterozygous genotype AG were predominant in this locus.

Test of significance showed that the fixed effect of genotype together with effect of farm and linear and quadratic coefficients of age were statistically significant ($P<0.05$) in BW while the fixed effect of genotype and linear and quadratic coefficients of age were

statistically significant (P<0.05) in WH, and the fixed effect of genotype, age of doe and linear and quadratic coefficients of age were statistically significant (P<0.05) in HH. Conversely, the fixed effect of genotype was not significant in CD, CW, HW and HG (Table 3).

Animals of genotype AG demonstrated the highest BW, HW and HH then it followed with animals of genotype GG and AA (Table 4). Comparing genotypes at different periods, BW0 and BW6 in animals of genotype AG (4.35 kg and 8.40 kg) were significantly heavier (P<0.05) than animals of genotype AA (3.40 kg and 6.59 kg), while animals of genotype GG (3.84 kg and 6.97 kg) showed no significant difference with genotype AG and AA. However, there were no significant effect of genotype at BW2, BW4, BW8, BW10, BW12 and BW14.

Significant difference between genotypes for body measurements were observed in wither height (WH6, WH10, and WH14) and hip height (HH12 and HH14). Similar to body weight, animals of genotype AG had significantly (P<0.05) higher wither and hip heights than those animals of genotype AA, but there was no significant difference between animals of genotype GG with animals of genotype AG and AA (Table 5).

Estimated parameters for body weight, wither height and hip height are presented in Table 6, respectively. Growth analysis showed that Von Bertalanffy model had the lowest -2 log likelihood, and two criteria AIC and BIC compared with the other models indicating this model as the best model for describing growth of body weight in Kejobong goat. On the other hand, the highest -2 log likelihood, AIC and BIC were obtained in Logistic model. Brody model in this study showed fit to wither height and hip height well according to its value of -2 log likelihood, AIC and BIC, which was lower than Gompertz, Logistic and Von Bertalanffy model.

Von Bertalanffy model fitted best to body weight, estimated 23.01 kg mature body weight (a), 0.39 integration constant (b) and 0.01389 growth rate (k). The best estimated for wither height and hip height by Brody model were 54.65 cm and 58.91 cm for parameter a; 0.37 and 0.36 for parameter b; 0.01577 and 0.01647 for parameter k. In this study, the estimated parameter b for body weight, wither height and hip height were 0.39, 0.37 and 0.36 respectively.

Furthermore, estimated parameter k of body weight in Von Bertalanffy model was 0.01389. Negative correlation was found between parameter k and parameter a (Table 7). This result was confirmed by the fact that Brody model in this study had the slowest parameter k (0.006948) in body weight, yet it had the highest estimated parameter a (25.29 kg) among the others. Similarly, the highest parameter k in wither height (0.2606) and hip height (0.02341) had the lowest estimated parameter a (50.78 cm, 56.26 cm) in Von Bertalanffy and Logistic models respectively.

Representing variability among individual animals, estimated animal variance (σ^2_u) of the body weight in this study was 5.78. The higher the variance, the greater the difference is realized among animals. Furthermore, residual variance (σ^2_e) of the body weight in this study was 0.31 that indicated the gap between predicted value and observed value. Repeatability of body weight by intra-class correlation was 0.95 this study.

DISCUSSION

SNP2 of this study was also found in a report analyzing *GH* gene of Chinese goat (An *et al.*, 2010). Among five SNPs in this study, translation result showed SNP4 causing amino acid alteration which changes amino acid sequence in *GH* gene exon 3. SNP4 as non-synonymous mutation changed the first triplet codon of AGC encoding Serin to GGC

encoding Glycine (Figure 1) and we used it to distinguished as GG, AG and AA genotypes, whereas the other SNPs were silent mutation (SNP1 CAG>CAA(Gln); SNP2 TCT>TCC(Ser); SNP3 CCA>CCG(Pro); SNP5 AAC>AAT(Asn)). According to Nei and Kumar (2000), most of synonymous amino acid was found due to substitution of nucleotides in the third codon, while substitution of nucleotides in the first and second codon generate non-synonymous amino acid. Therefore, non-synonimous mutation that change amino acid sequence in exon region may change the peptide sequence of the encoded protein and influence the function of the protein, which was growth hormone in this study. This hormone has substantial metabolic effects on somatic growth, stimulation of protein synthesis and cellular uptake of amino acids and development of body composition (Hjortebjerg *et al*., 2017).

Result in this study agreed with a result by Dayal *et al*. (2016), in which goats with heterozygous genotype AC had the heaviest body weight among five observed genotypes in Black Bengal goat. Gorlov *et al*. (2017) reported their study in Salsk sheep that sheep with AB genotype significantly had heavier body weight, average daily gain and carcass weight than sheep with AA genotype. A contradictory result was reported by An *et al*. (2011) that goats with homozygous genotype AA significantly had higher body weight than those of heterozygous genotype AB at age of one and three months old in Chinese goat, however, wither height showed no significant difference. The different results seem to be due to genetic difference that leads to different structure of *GH* gene and limited number of observations. Therefore, further study is necessary to validate the predominant effect of heterozygote of *GH* gene with a larger number of animals and more sampled observations.

The best model for describing growth of body weight in this study was different with previous study by Kheirabadi and Rashidi (2019), reported that Logistic model fitted worst to body weight, while Brody model fitted most accurately to body weight of Markhoz goat. In this study, estimated mature body weight (a) was 23.01 kg implying that Kejobong goat had heavier mature body weight than Raeini Cashmere goat (17.97 kg) (Ghiasi *et al*., 2018) and Nondescipt goat (6.42 to 10.55 kg) (Raji *et al*., 2015) but lighter body weight than Beetal goat (23.39 kg) (Waheed *et al*., 2011). Those values of parameter b for body weight, wither height and hip height in this study were described to represent the proportion of mature weight attained after birth, calculated by the initial weight and age value (Lupi *et al*., 2016). On the other hand, Ghiasi *et al*. (2018) stated that parameter b is a scale parameter that has no biological interpretation. Waheed *et al*. (2011) reported higher estimated values of parameter k (0.1077) in Beetal goat by Brody model. Other researchers estimated parameter k as much as 0.017 in Cashmere goat (Ghiasi *et al*. 2018) and 0.0108 in Repartida goat (Pires *et al*., 2017) by applying Gompertz model, so that Kejobong goat in this study is considered to attain mature weight later than Beetal and Cashmere goats but earlier than Repartida goat.

Negative correlation between parameter k and parameter a indicated the slower growth rate, the larger mature weight, *vice versa*. Previous studies supported this results. Kurnianto *et al*. (1998) reported that animals with slower growth rate tended to have estimated heavy body weight at maturity. Brown *et al*. (1976) stated that selection for increasing growth rate tended to decrease mature weight, yet its antagonistic association could be minimized by cross-breeding and improving feed quality. On other hand, previous study by Ghiasi *et al.* (2018) showed lower animal variance (1.29) and higher residual variance (8.01) on growth analysis of Raeni Cashmere goat using Gompertz

model than the present study. Repeatability of body weight in this study was higher than repeatability value of South African Angora goat (Snyman and Olivier, 1999) and Boerawa goat (Beyleto *et al*., 2010). The high repeatability in this study may be resulted by the fact that systematic factors affecting body weight were fitted as many as possible in NLMM and that earlier body weight was a component of latter body weight.

The NLMIXED procedure used in this study has flexibility in engaging the variance covariance structure which could not be identified by traditional regression approach. Also NLMIXED has ability to handle unbalance data (Aggrey, 2009; Galeano-Vasco *et al*., 2014). This procedure can reduce potential biases despite selective sampling and supply supplemental parameters that characterize variation between individual animals (Craig and Schinkel, 2001). Therefore, this procedure can facilitate growth analysis by including genotype information and estimates accurately the growth performance of Kejobong goats.

CONCLUSION

SNP g1170A→G in *GH* gene is associated with growth traits and can be used as genetic marker for animal selection to improve goat's growth performance. Animals with heterozygous genotype AG showed higher growth performance than homozygous genotype AA. Nonetheless, animals with homozygous genotype GG showed no difference with either heterozygous genotype AG or homozygous genotype AA. Model ($y = 23.01\ (1 - 0.39\ e^{-0.01389age})^3$) by Von Bertalanffy, $y = 54.65\ (1 - 0.37\ e^{-0.01577age})$ and $y = 58.91\ (1 - 0.36\ e^{-0.01647age})$ by Brody were fitted well to describe body weight, wither height and hip height of Kejobong goat, respectively.

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454

455 **TABLE**

456 Table 1. Growth equations used to construct the growth model

Model	Function[A]	Inflection weight	Inflection age
Brody	$y = a (1 – b \exp^{-kt})$	-	-
Von Bertalanffy	$y = a (1 – b \exp^{-kt})^3$	$y_i = 8a/27$	$t_i = \ln(3b)/k$
Logistic	$y = a / (1 + b \exp^{-kt})$	$y_i = a/2$	$t_i = \ln(b)/k$
Gompertz	$y = a \exp (– b \exp^{-kt})$	$y_i = a/\exp$	$t_i = \ln(b)/k$

457 [A]y, observed body weight/body measurements; a, the estimated of mature body
458 weight/body measurements; b, the integration constant; k, the growth rate constant; t, the
459 animal age in day and exp, Napier's constant the base of natural logarithm.
460

461

462 Table 2. Estimated allele and genotype frequency

Variable	Genotype			Allele		H	χ^2
Measured	GG	AG	AA	G	A		
Frequencies	0.37	0.40	0.23				
Observation	13	14	8	0.57	0.43	0.49	1.18
Expectation	11.43	17.14	6.43				

463 H, Heterozygosity; χ^2, Chi square value.

464

465

466 Table 3. Significance analysis of factor affecting body weight and body measurements

Traits	Effect	Degree of freedom	f-value	p-value
BW[A]	Genotype	2	3.44	0.0335
	Age of doe	3	1.43	0.2355
	Farm	3	5.33	0.0050
	Age (linear)	1	224.97	<0.0001
	Age (quadratic)	1	17.98	<0.0001
WH[B]	Genotype	2	4.14	0.0171
	Age of doe	3	2.59	0.0537
	Farm	3	2.27	0.1021
	Age (linear)	1	238.66	<0.0001
	Age (quadratic)	1	50.99	<0.0001
CD[C]	Genotype	2	0.14	0.8677
	Age of doe	3	0.54	0.6541
	Farm	3	1.00	0.4081
	Age (linear)	1	40.44	<0.0001
	Age (quadratic)	1	10.58	0.0013
CW[D]	Genotype	2	2.41	0.0920
	Age of doe	3	2.66	0.0491
	Farm	3	5.48	0.0043
	Age (linear)	1	36.02	0.0001
	Age (quadratic)	1	9.05	0.0029
HH[E]	Genotype	2	4.25	0.0153
	Age of doe	3	2.64	0.0499

	Farm	3	1.71	0.1879
	Age (linear)	1	267.39	<0.0001
	Age (quadratic)	1	59.44	<0.0001
HW[F]	Genotype	2	1.74	0.1775
	Age of doe	3	0.71	0.5496
	Farm	3	2.27	0.1023
	Age (linear)	1	62.34	<0.0001
	Age (quadratic)	1	13.53	0.0003
HG[G]	Genotype	2	1.69	0.1873
	Age of doe	3	1.62	0.1852
	Farm	3	3.89	0.0192
	Age (linear)	1	347.92	<0.0001
	Age (quadratic)	1	70.55	<0.0001

467 [A]Body weight; [B]Wither height; [C]Chest depth; [D]Chest width; [E]Hip height; [F]Hip width;
468 [G]Heart girth.
469
470

471 Table 4. Average of body weight and body measurements

Traits	Genotype		
	GG	AG	AA
Body weight (BW)			
BW0	3.75±0.76	4.26±1.02	3.51±1.06
BW2	4.91±0.75	5.39±1.20	4.87±1.20
BW4	6.12±0.89	6.57±1.38	5.84±1.95
BW6	7.39±1.01	7.91±1.63	6.74±2.15
BW8	8.24±1.14	8.87±1.89	7.85±2.62
BW10	9.07±1.21	9.72±2.26	8.64±2.89
BW12	9.87±1.33	10.52±2.56	9.19±3.08
BW14	10.64±1.49	11.36±2.78	9.80±3.10
Wither height (WH)			
WH0	33.93±3.21	35.08±2.49	31.69±4.63
WH2	37.85±2.84	37.72±4.45	36.63±2.92
WH4	40.63±2.55	40.57±4.12	39.33±4.43
WH6	42.34±2.30	43.28±2.48	40.77±5.35
WH8	44.29±2.40	45.09±3.30	42.51±4.88
WH10	45.42±1.85	45.65±3.47	42.85±5.24
WH12	46.35±2.52	47.54±3.29	44.49±4.88
WH14	47.61±2.67	49.06±3.07	45.39±4.98
Hip height (HH)			
HH0	36.57±3.19	37.60±3.40	34.23±4.73
HH2	40.09±3.30	40.78±2.55	38.34±3.55

HH4	42.89±2.85	43.56±3.67	42.00±4.72
HH6	44.84±2.68	46.39±2.52	43.92±5.37
HH8	46.63±3.01	47.67±3.12	45.39±5.02
HH10	48.01±2.00	48.33±2.91	46.03±5.62
HH12	48.99±2.41	50.56±3.08	45.96±4.76
HH14	50.55±2.57	52.15±2.99	47.82±5.75

472

473

474 Table 5. Estimated genotypic effect for body weight and body measurements for each
475 measurement

Traits	Genotypes		
	GG	AG	AA
Body weight (BW)			
BW0	3.84±0.22^{AB}	4.35±0.20^{A}	3.40±0.27^{B}
BW2	4.84±0.28	5.67±0.26	4.82±0.36
BW4	5.87±0.37	6.97±0.34	5.75±0.46
BW6	6.97±0.43^{AB}	8.40±0.40^{A}	6.59±0.55^{B}
BW8	7.80±0.52	9.43±0.47	7.71±0.66
BW10	8.57±0.59	10.35±0.54	8.54±0.75
BW12	9.29±0.65	11.17±0.60	9.17±0.84
BW14	10.03±0.69	12.03±0.63	9.71±0.88
Wither height (WH)			
WH0	34.27±0.94	35.03±0.87	32.64±1.20
WH2	37.38±1.18	38.41±1.08	36.03±1.51
WH4	39.89±1.07	41.44±0.98	39.08±1.37
WH6	41.88±0.90^{AB}	44.25±0.83^{A}	40.45±1.16^{B}
WH8	43.41±1.04	46.15±0.95	42.14±1.33
WH10	44.15±1.01^{AB}	46.83±0.93^{A}	42.33±1.29^{B}
WH12	45.59±1.03	48.53±0.95	44.34±1.32
WH14	46.69±1.04^{AB}	49.95±0.95^{A}	45.29±1.33^{B}
Hip height (HH)			
HH0	36.95±1.01	37.71±0.93	34.59±1.30
HH2	36.95±1.01	41.11±0.89	38.16±1.23

HH4	42.61±1.12	43.85±1.03	42.02±1.43
HH6	44.55±1.03	47.21±0.94	43.87±1.32
HH8	45.57±1.14	48.65±1.05	44.96±1.46
HH10	46.94±1.00	49.31±0.96	45.48±1.28
HH12	48.58±1.05^{AB}	51.28±0.97^{A}	45.82±1.35^{B}
HH14	49.59±1.09^{AB}	53.08±1.00^{A}	47.57±1.39^{B}

476 ^{A,B} In the same row, values with different superscripts are significantly different ($P<0.05$).

477

478

479 Table 6. Estimated parameters of growth and goodness of fit for four different growth
480 models

Parameter	Model			
	Brody	Von Bertalanffy	Logistic	Gompertz
Body weight				
a	25.29±1.01	23.01±0.47	21.65±0.30	22.48±0.39
b	0.83±0.01	0.39±0.01	2.56±0.07	1.42±0.03
k	0.006948±0.001019	0.01389±0.001097	0.0277±0.001309	0.01735±0.001143
y_i	-	6.82	10.83	8.27
t_i	-	11.75	33.93	20.10
σ^2_u	9.08±2.67	5.78±1.48	4.17±1.03	5.13±1.29
σ^2_e	0.32±0.03	0.31±0.03	0.32±0.03	0.31±0.03
GG	-3.6±0.79	-4.2±0.59	-4.64±0.49	-4.37±0.55
AG	-2.01±0.85	-3.03±0.061	-3.63±0.50	-3.26±0.56
AA	-4.53±0.95	-5.06±0.75	-5.3±0.63	-5.18±0.70
-2 Log Likehood	606.6	605.8	609.5	606.1
AIC	630.6	629.8	633.5	630.1
BIC	649.6	648.8	652.5	649.1
Wither height				
a	54.65±0.94	50.78±0.31	53.59±0.71	55.54±0.81
b	0.37±0.01	1.96±0.08	0.53±0.02	0.44±0.01
k	0.01577±0.002084	0.2606±0.01207	0.02292±0.002268	0.01934±0.002171
σ^2_u	9.93±2.56	0.0014±0.5954	9.39±2.40	9.62±2.47
σ^2_e	3.95±0.36	29.44±1.63	3.97±0.36	3.96±0.36
GG	-3.3±0.82	-6.82±0.50	-3.67±0.77	-5.02±0.79
AG	-2.76±0.81	-6.78±0.47	-3.14±0.76	-4.48±0.78
AA	-5.59±0.92	-11.91±0.64	-5.90±0.88	-7.27±0.90

-2 Log Likehood	1274.3	2217.3	1276.0	1275.1
AIC	1290.9	2233.3	1292.0	1291.1
BIC	1303.0	2246.0	1304.6	1303.8
Hip height				
a	58.91±0.72	57.73±0.73	56.26±0.56	56.61±0.62
b	0.36±0.01	0.13±0.01	0.50±0.01	0.42±0.01
k	0.01647±0.002009	0.01839±0.002112	0.02341±0.002187	0.01994±0.002092
σ^2_u	8.40±2.20	12.99±0.64	7.91±2.04	8.09±2.10
σ^2_e	3.72±0.34	3.71±0.33	3.75±0.34	3.73±0.34
GG	-2.24±0.77	-2.12±0.94	-1.56±0.73	-1.44±0.75
AG	-0.60±0.78	-0.81±0.93	0.12±0.74	0.25±0.75
AA	-4.55±0.89	-4.63±1.08	-3.60±0.86	-3.50±0.87
-2 Log Likehood	1254.6	1258.2	1256.5	1255.4
AIC	1278.6	1282.2	1280.5	1279.4
BIC	1297.6	1301.2	1299.5	1298.4

a, the estimated of mature body weight/body measurements; b, the integration constant; k, the growth rate constant; y_i, body weight (kg) at the point at inflection; t_i, age (weeks) at the point at inflection; σ^2_u; additive genetic variance; σ^2_e, error variance; AIC, akaike information criterion; BIC, bayesian information criterion.

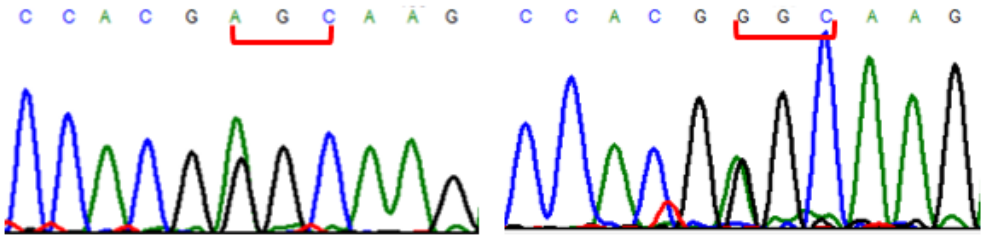
Table 7. Correlation among growth parameter within traits based on their best model

Growth Parameter	Mature weight (a)		
	BW[A]	WH[B]	HH[C]
Integration constant (b)	0.5564	0.7038	0.6652
Growth rate (k)	-0.7833	-0.8755	-0.8636

[A]Body weight; [B]Wither height; [C]Hip height

490 **FIGURE**

491

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[          1234567890 1234567890 1234567890 12345678]
#4B        ERTYIPEGQR YSIQNTQVAF CFSETIPAPT GKNEAQQK
#5B        .......... .......... .......... ........
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#43B       .......... .......... .......... ........
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#49B       .......... .......... .......... S.......
#50B       .......... .......... .......... ........
#52J       .......... .......... .......... ........
#53B       .......... .......... .......... S.......
#54B       .......... .......... .......... ........
#55B       .......... .......... .......... S.......
#56J       .......... .......... .......... S.......
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492

493 Figure 1. Amino acid alteration caused by SNP g1170A

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#35852 Review

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We have reached a decision regarding your submission to Journal of the Indonesian Tropical Animal Agriculture, "Appropriate Growth Models to Describe Early Growth of Kejobong Goat Based on Growth Hormone (GH) Gene Sequence Analysis".

Our decision is to: Accept Submission

Thank you for your contribution.

Mr. JITAA UNDIP
Faculty of Animal and Agricultural Sciences, Diponegoro University
jitaa.undip@gmail.com

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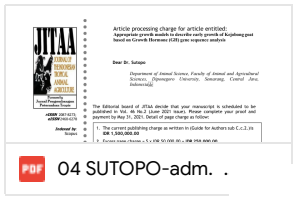

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Appropriate growth models to describe early growth of Kejobong goat based on Growth Hormone (GH) gene sequence analysis

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ABSTRAK

Tujuan penelitian yaitu untuk menemukan model pertumbuhan yang tepat dalam mendeskripsikan pertumbuhan awal kambing Kejobong berdasarkan analisis sekuen gen *Growth Hormon* (GH). Materi penelitian menggunakan 35 sampel DNA dan 1.960 catatan sifat kuantitatif kambing Kejobong. Sampel DNA diamplifikasi dan disekuensing untuk mengidentifikasi SNP yang terdapat pada gen *GH* ekson 3. Pengukuran dan penimbangan bobot badan dan ukuran tubuh dilakukan pada umur 0-14 minggu. Empat model pertumbuhan non-linier diaplikasikan untuk menganalisis pertumbuhan guna membandingkan performan pertumbuhan dari berbagai genotipe dengan menggunakan Non-Linear Mixed model. Mutasi non-sinonim (g1170A→G) pada gen *GH* ekson 3 yang membentuk genotipe GG, AG dan AA secara signifikan berasosiasi dengan sifat pertumbuhan. Kambing Kejobong bergenotipe heterozigot AG menunjukkan sifat pertumbuhan yang lebih tinggi dibandingkan dengan kambing Kejobong bergenotipe homozigot AA. Meskipun demikian, kambing Kejobong bergenotipe homozigot GG memiliki sifat pertumbuhan yang sama dengan kambing Kejobong bergenotipe heterozigot AG dan homozigot AA. Model pertumbuhan yang paling tepat untuk mendeskripsikan bobot badan kambing Kejobong adalah model Von Bertalanffy, sedangkan untuk menggambarkan tinggi badan dan tinggi pinggul adalah model Brody. SNP pada gen *GH* ekson 3 dapat digunakan sebagai penanda genetik untuk perbaikan sifat pertumbuhan kambing Kejobong.

Kata Kunci : Analisis Pertumbuhan, GH, Kambing, Model Matematika, SNP

ABSTRACT

Objectives of this study were to reveal appropriate growth models describing early growth of Kejobong goat based on Growth Hormone (*GH*) gene sequence analysis. A total of 35 DNA samples and 1.960 records of quantitative traits of Kejobong goat were collected. The exon 3 of *GH* gene was amplified and was sequenced to determine the SNP. Body weight and body measurements of the goats were taken at 0-14 weeks of age. Four non-linear growth models were applied for analysis of growth to compare growth performance of different genotypes by Non-Linear Mixed Model. A non-synonymous mutation (g1170A→G) genotyped into GG, AG and AA was significantly associated with growth traits. Animals with heterozygous genotype AG showed higher growth traits than animals with homozygous genotype AA. Nonetheless, animals with homozygous genotype GG had the same growth traits with those animals with heterozygous genotype AG and homozygous genotype AA. The most fitted model for describing body weight was Von Bertalanffy model, while for describing wither height and hip height

was Brody model. SNP at exon 3 of the *GH* gene can be used as genetic marker for improvement of growth traits of Kejobong goats.

Keywords: GH, Goat, Growth analysis, Mathematical models, SNP

INTRODUCTION

Kejobong goat is one of indigenous Indonesian breeds, which only exists in Purbalingga District, Central Java Province, Indonesia, and it is conventionally raised by local farmers. This goat belongs to Southeast Asian lineage and is confirmed to be descendant from crossbred of Kacang and Etawah Grade goats (Kurnianto *et al*., 2012; Kurnianto *et al*., 2013; Lestari *et al*., 2018[A]; Lestari *et al*., 2018[B]). As the meat animals, Kejobong goat had 41.30% carcass yield that comprised 67.06% meat and 32.94% bone, while its meat is known to have less cholesterol than meat of Kacang and Etawah Grade goat (Aqsa *et al*., 2011). Kejobong goat is popular at the district because of its high rate of growth, good reproductive performance, high resistance to local diseases and parasites and ability to survive and growing ability under poor feeding conditions (Kurnianto *et al*., 2012; Febriana *et al*., 2017). However, the breeders often have difficulty to satisfy the market demand on slaughtering weight. This is probably due to limited information of appropriate breeding strategy for Kejobong goat to accomplish the breeding goal of high meat productivity.

Growth analysis can provide valuable information about mature weight, growth rate and mature time. Growth rate and body weight of animal at different ages influence productivity of meat and have deterministic effects on the profitability of meat production (Kheirabadi and Rashidi, 2019). Particularly, growth rate has large effect on meat producing efficiency up to slaughtering age which is crucial for economic success of animal production (Abbasi *et al*., 2012). According to Junior *et al*. (2013) and Ripoll *et al*. (2016), animals that have a large frame size of body tend to have higher potential of growth and have a higher proportion of meat. Therefore, besides body weight, body size is also important trait to be considered for performing animal selection. Study of growth analysis has been done by previous researchers (Waheed *et al*., 2011; Setiaji *et al*., 2013; Zadeh *et al*., 2015; Raji *et al*., 2015; Lupi *et al*., 2016; Zadeh and Gorbani, 2018; Ghiasi *et al*., 2018; Rout *et al*., 2018; Kheirabadi and Rashidi, 2019), however they were only using phenotypic data into analysis. In this study, conventional growth analysis was modified by including genotype records to growth analysis.

Early growth of kids is an economically important trait that affecting profitability in goat production (Baranzadeh *et al*., 2012; Moghbeli *et al*., 2013; Sadeghi *et al*., 2019). Physiologically, growth of an animal is a result from a complex process of metabolism including a coordinated action of several hormones that controlled by expression of their responsible genes (Mahrous *et al*., 2018). Growth Hormone (*GH*) gene is one of numerous genes which have large effect on growth performance of an animal. *GH* gene is encoding growth hormone that produces in anterior pituitary and is necessary for postnatal growth and metabolism in vertebrates (Ge *et al*., 2003). This hormone is known to have a broad impact on biological activity in all body cells, such as controlling and coordinating the flow rate of metabolic process, enhancing glycogen, protein, DNA and RNA biosynthesis and promoting the deposition of fat and the disintegration of fatty acids and glucose in the tissue (Gorlov *et al*., 2017; Wickramaratne *et al*., 2010; Othman *et al*., 2015; Seevagan *et al*., 2015; Singh *et al*., 2015). Therefore, *GH* gene is considered to be a prime factor which affects growth performance of an animal.

Based on these backgrounds, effect of *GH* gene on growth traits, especially from a point of genetic improvement is important to build breeding plan for high meat productivity. Prospectively, result of this study is not only suggesting appropriate management practice for improving production for the breeders, but also providing information of genetic marker in Kejobong goat for breeding selection in the future through Marker-Assisted Selection (MAS) and/or Marker-Assisted Introgression (MAI) and appropriate mathematical growth models of Kejobong goat. Therefore, objective of this study was to reveal to reveal appropriate growth models describing early growth of body weight and body measurement of Kejobong goat based on the effect of Growth Hormone (*GH*) gene sequence analysis.

MATERIALS AND METHODS

Ethical approval

All procedure involving animals were based on the standard rule of animal treating as appointed in the Republic of Indonesia's law, number 41, 2014.

Sampling and data collection

A total of 35 blood samples and 1.960 quantitative traits records of Kejobong goat were collected from Purbalingga District, Central Java Province, Indonesia. Quantitative traits records comprised body weight (BW), wither height (WH), chest depth (CD), chest width (CW), hip height (HH), hip width (HW) and heart girth (HG) at 0, 2, 4, 6, 8, 10, 12 and 14 weeks of age.

DNA extraction, Polymorphism Chain Reaction (PCR) and sequencing

Blood samples for DNA analysis were taken by 3cc spuit from *jugular venous* that previously cleaned with alcohol. The blood was then collected in vacutainer blood collection tubes with an anticoagulant (EDTA). DNA was extracted from whole blood by gSYNC DNA mini kit (Geneaid Biotech, Taiwan) according to the manufacturer's standard protocol for PCR and sequencing analysis.

Forward primer F: 5'-TAGAAATGGGGGTGTGTGGGGT-3' and reverse primer R: 5'-CATCCTCCACTGCCATCCAACA-3' (Sigma-Aldrich, Japan) were used to amplify *GH* gene exon 3. PCR was carried out in total volume 50 µL comprising 1 µL KOD Plus (Toyobo, Japan), 5 µL buffer, 5 µL dNTP, 2 µL $MgSO_4$, 1.5 µL forward primer, 1.5 µL reverse primer, 32 µL PCR water and 2 µL DNA template. PCR amplification was running with an initial denaturation at 94°C for 2 min, followed by 40 cycles of denaturation at 94°C for 15 sec, primers annealing 66.8°C for 30 sec and extension at 68°C for 19 sec. PCR products were electrophoresed using 1.3% Agarose gel at 110 V for 20 min. PCR products were then visualized by UV trans-illuminator and was sequenced through Fasmac sequencing service, Japan.

Data analysis

Allelic and genotypic frequencies were directly calculated. Hardy-Weinberg Equilibrium (HWE) was tested using chi-square statistic (χ^2) as follows:

$$\chi^2 = \sum_{i=1}^{k} \frac{(o_i - e_i)^2}{e_i},$$

where χ^2 is the Chi square value; o_i the observed value of genotype frequency, e_i the expected value of genotype frequency, χ^2 the table using 5% significance level for HWE test.

Heterozygosity (H) was calculated as follows:

$$H = 1 - \sum_{i=1}^{k} p_i^2,$$

where H is the value of heterozygosity and p_i the frequency of the i^{th} of k alleles.

Sequencing result alignment was analyzed by Clustal W (Thompson *et al*., 1994) with Molecular Evolutionary Genetics Analysis (MEGA6.0) (Tamura *et al*., 2013) to find out the SNP within animals. Sequencing result then was translated into amino acids form by standard genetic code to identify amino acid alteration that caused by SNP.

Linear Mixed Model (LMM) was used to analyze association between genotype with quantitative traits by MIXED procedure in Statistical Analysis System (SAS 9.3) (SAS Institute Inc, 2011). The model was:

$$y_{ijkl} = \mu + G_i + F_j + u_k + b_1\alpha_{ijkl} + b_2\alpha^2_{ijkl} + e_{ijkl},$$

where y_{ijkl} is the observed value of a dependent variable (body weight or body measurements); µ the overall mean of the population; G_i the fixed effect of i^{th} genotype (i = 1 for GG, 2 for AG, 3 for AA); F_j the fixed effect of j^{th} farm group (j = 1, 2, 3, 4); u_k the random effect of k^{th} animal; b_1 and b_2 the linear and quadratic coefficients of partial regression, respectively; l^{th} individual measurement, α_{ijkl} age in days of a covariate and e_{ijkl} the random residual for y_{ijkl}. Difference in the least square means of the genotypes was tested by the Tukey-Kramer (Tukey, 1949).

The nonlinear growth models comprised Brody (Brody, 1945), Von Bertalanffy (Bertalanffy, 1938), Logistic (Verhulst, 1838) and Gompertz (Gompertz, 1825) and they were compared by describing animal growth (Table 1). Growth models were analyzed using Nonlinear Mixed Model (NLMM) by NLMIXED procedure of SAS 9.3 (SAS Institute Inc, 2011). Body weight or body measurements as dependent variables are influenced by genotype and age. Therefore, dummy variables were created to assess the effect of qualitative variables on dependent variables according to the method by Filho *et al.* (2014). The NLMIXED procedure

Table 1. Growth equations used to construct the growth model

Model	Function[A]	Inflection weight	Inflection age
Brody	$y = a (1 – b \exp^{-kt})$	-	-
Von Bertalanffy	$y = a (1 – b \exp^{-kt})^3$	$y_i = 8a/27$	$t_i = \ln(3b)/k$
Logistic	$y = a / (1 + b \exp^{-kt})$	$y_i = a/2$	$t_i = \ln(b)/k$
Gompertz	$y = a \exp (– b \exp^{-kt})$	$y_i = a/\exp$	$t_i = \ln(b)/k$

[A]y, observed body weight/body measurements; a, the estimated of mature body weight/body measurements; b, the integration constant; k, the growth rate constant; t, the animal age in day and exp, Napier's constant the base of natural logarithm.

was used in this study due to its flexibility in engaging the variance covariance structure which could not be identified by traditional regression approach. Also NLMIXED has ability to handle unbalance data (Aggrey, 2009; Galeano-Vasco *et al*., 2014). This procedure can reduce potential biases despite selective sampling and supply supplemental parameters that characterize variation between individual animals (Craig and Schinkel, 2001).

The models were tested for goodness of fit using -2 log likelihood, Akaike Information Criterion (AIC) (Akaike, 1974), Bayesian Information Criterion (BIC) (Schwarz, 1978) and the residual variances (σ^2_e). AIC and BIC were calculated by the following formula:

$$AIC = n\, ln \left(\frac{SSE}{n}\right) + 2k$$

$$BIC = n\, ln \left(\frac{SSE}{n}\right) + k\, ln\, (n)$$

where n is the number of observation; SSE the Sum Square Errors and *k* the number of parameters. Smaller values of AIC, BIC or σ^2_e indicate the best fit of the model to the observations.

RESULTS

Result showed that a total 117 bp of *GH* gene exon 3 encoding 38 amino acid sequence were well amplified. Sequencing result revealed 5 SNPs as transition mutation in parsimonious form, which were g1121A→G (SNP1), g1148T→C (SNP2), g1160A→G (SNP3), g1170A→G (SNP4) and g1178C→T (SNP5). Genotype frequencies of Kejobong goats were not different from HWE, and the frequency of heterozygosity was 49% (Table 2). The estimated allele of the *GH* gene exon 3 in this study was 57% and 43% for G and A, respectively. Frequencies of genotypes GG, AG and GC were

Table 2. Estimated allele and genotype frequency

Variable	Genotype			Allele		H	χ^2
Measured	GG	AG	AA	G	A		
Frequencies	0.37	0.40	0.23				
Observation	13	14	8	0.57	0.43	0.49	1.18
Expectation	11.43	17.14	6.43				

H, Heterozygosity; χ^2, Chi square value.

37%, 40% and 23%, respectively, so that G allele and heterozygous genotype AG were predominant in this locus.

Test of significance showed that the fixed effect of genotype together with effect of farm and linear and quadratic coefficients of age were statistically significant (P<0.05) in BW while the fixed effect of genotype and linear and quadratic coefficients of age were statistically significant (P<0.05) in WH, and the fixed effect of genotype, age of doe and linear and quadratic coefficients of age were statistically significant (P<0.05) in HH. Conversely, the fixed effect of genotype was not significant in CD, CW, HW and HG (Table 3).

Animals of genotype AG demonstrated the highest BW, HW and HH then it followed with animals of genotype GG and AA (Table 4). Comparing genotypes at different periods, BW0 and BW6 in animals of genotype AG (4.35 kg and 8.40 kg) were significantly heavier (P<0.05) than animals of genotype AA (3.40 kg and 6.59 kg), while animals of genotype GG (3.84 kg and 6.97 kg) showed no significant difference with genotype AG and AA. However, there were no

Table 3. Significance analysis of factor affecting body weight and body measurements

Traits	Effect	Degree of freedom	f-value	p-value
BW[A]	Genotype	2	3.44	0.0335
	Age of doe	3	1.43	0.2355
	Farm	3	5.33	0.0050
	Age (linear)	1	224.97	<0.0001
	Age (quadratic)	1	17.98	<0.0001
WH[B]	Genotype	2	4.14	0.0171
	Age of doe	3	2.59	0.0537
	Farm	3	2.27	0.1021
	Age (linear)	1	238.66	<0.0001
	Age (quadratic)	1	50.99	<0.0001
CD[C]	Genotype	2	0.14	0.8677
	Age of doe	3	0.54	0.6541
	Farm	3	1.00	0.4081
	Age (linear)	1	40.44	<0.0001
	Age (quadratic)	1	10.58	0.0013
CW[D]	Genotype	2	2.41	0.0920
	Age of doe	3	2.66	0.0491
	Farm	3	5.48	0.0043
	Age (linear)	1	36.02	0.0001
	Age (quadratic)	1	9.05	0.0029
HH[E]	Genotype	2	4.25	0.0153
	Age of doe	3	2.64	0.0499
	Farm	3	1.71	0.1879
	Age (linear)	1	267.39	<0.0001
	Age (quadratic)	1	59.44	<0.0001
HW[F]	Genotype	2	1.74	0.1775
	Age of doe	3	0.71	0.5496
	Farm	3	2.27	0.1023
	Age (linear)	1	62.34	<0.0001
	Age (quadratic)	1	13.53	0.0003
HG[G]	Genotype	2	1.69	0.1873
	Age of doe	3	1.62	0.1852
	Farm	3	3.89	0.0192
	Age (linear)	1	347.92	<0.0001
	Age (quadratic)	1	70.55	<0.0001

[A]Body weight; [B]Wither height; [C]Chest depth; [D]Chest width; [E]Hip height; [F]Hip width; [G]Heart girth.

Table 4. Average of body weight and body measurements

Traits	Genotype		
	GG	AG	AA
Body weight (BW)			
BW0	3.75±0.76	4.26±1.02	3.51±1.06
BW2	4.91±0.75	5.39±1.20	4.87±1.20
BW4	6.12±0.89	6.57±1.38	5.84±1.95
BW6	7.39±1.01	7.91±1.63	6.74±2.15
BW8	8.24±1.14	8.87±1.89	7.85±2.62
BW10	9.07±1.21	9.72±2.26	8.64±2.89
BW12	9.87±1.33	10.52±2.56	9.19±3.08
BW14	10.64±1.49	11.36±2.78	9.80±3.10
Wither height (WH)			
WH0	33.93±3.21	35.08±2.49	31.69±4.63
WH2	37.85±2.84	37.72±4.45	36.63±2.92
WH4	40.63±2.55	40.57±4.12	39.33±4.43
WH6	42.34±2.30	43.28±2.48	40.77±5.35
WH8	44.29±2.40	45.09±3.30	42.51±4.88
WH10	45.42±1.85	45.65±3.47	42.85±5.24
WH12	46.35±2.52	47.54±3.29	44.49±4.88
WH14	47.61±2.67	49.06±3.07	45.39±4.98
Hip height (HH)			
HH0	36.57±3.19	37.60±3.40	34.23±4.73
HH2	40.09±3.30	40.78±2.55	38.34±3.55
HH4	42.89±2.85	43.56±3.67	42.00±4.72
HH6	44.84±2.68	46.39±2.52	43.92±5.37
HH8	46.63±3.01	47.67±3.12	45.39±5.02
HH10	48.01±2.00	48.33±2.91	46.03±5.62
HH12	48.99±2.41	50.56±3.08	45.96±4.76
HH14	50.55±2.57	52.15±2.99	47.82±5.75

significant effect of genotype at BW2, BW4, BW8, BW10, BW12 and BW14.

Significant difference between genotypes for body measurements were observed in wither height (WH6, WH10, and WH14) and hip height (HH12 and HH14). Similar to body weight, animals of genotype AG had significantly ($P<0.05$) higher wither and hip heights than those animals of genotype AA, but there was no significant difference between animals of genotype GG with animals of genotype AG and AA (Table 5).

Estimated parameters for body weight, wither height and hip height are presented in Table 6, respectively. Growth analysis showed that Von Bertalanffy model had the lowest -2 log likelihood, and two criteria AIC and BIC compared with the other models indicating this model as the best model for describing growth of body weight in Kejobong goat. On the other hand, the highest -2 log likelihood, AIC and BIC were obtained in Logistic model. Brody model in this study showed fit to wither height and hip height well according to its value of -2 log likelihood, AIC and BIC, which was lower than Gompertz, Logistic and Von Bertalanffy model.

Von Bertalanffy model fitted best to body weight, estimated 23.01 kg mature body weight (a), 0.39 integration constant (b) and 0.01389 growth rate (k). The best estimated for wither height and hip height by Brody model were 54.65 cm and 58.91 cm for parameter a; 0.37 and 0.36 for parameter b; 0.01577 and 0.01647 for parameter k. In this study, the estimated parameter b for body weight, wither height and hip height were 0.39, 0.37 and 0.36 respectively.

Furthermore, estimated parameter k of body weight in Von Bertalanffy model was 0.01389.

Table 5. Estimated genotypic effect for body weight and body measurements for each measurement

Traits	Genotypes		
	GG	AG	AA
Body weight (BW)			
BW0	3.84±0.22^{AB}	4.35±0.20^{A}	3.40±0.27^{B}
BW2	4.84±0.28	5.67±0.26	4.82±0.36
BW4	5.87±0.37	6.97±0.34	5.75±0.46
BW6	6.97±0.43^{AB}	8.40±0.40^{A}	6.59±0.55^{B}
BW8	7.80±0.52	9.43±0.47	7.71±0.66
BW10	8.57±0.59	10.35±0.54	8.54±0.75
BW12	9.29±0.65	11.17±0.60	9.17±0.84
BW14	10.03±0.69	12.03±0.63	9.71±0.88
Wither height (WH)			
WH0	34.27±0.94	35.03±0.87	32.64±1.20
WH2	37.38±1.18	38.41±1.08	36.03±1.51
WH4	39.89±1.07	41.44±0.98	39.08±1.37
WH6	41.88±0.90^{AB}	44.25±0.83^{A}	40.45±1.16^{B}
WH8	43.41±1.04	46.15±0.95	42.14±1.33
WH10	44.15±1.01^{AB}	46.83±0.93^{A}	42.33±1.29^{B}
WH12	45.59±1.03	48.53±0.95	44.34±1.32
WH14	46.69±1.04^{AB}	49.95±0.95^{A}	45.29±1.33^{B}
Hip height (HH)			
HH0	36.95±1.01	37.71±0.93	34.59±1.30
HH2	36.95±1.01	41.11±0.89	38.16±1.23
HH4	42.61±1.12	43.85±1.03	42.02±1.43
HH6	44.55±1.03	47.21±0.94	43.87±1.32
HH8	45.57±1.14	48.65±1.05	44.96±1.46
HH10	46.94±1.00	49.31±0.96	45.48±1.28
HH12	48.58±1.05^{AB}	51.28±0.97^{A}	45.82±1.35^{B}
HH14	49.59±1.09^{AB}	53.08±1.00^{A}	47.57±1.39^{B}

^{A,B} In the same row, values with different superscripts are significantly different (P<0.05).

Negative correlation was found between parameter k and parameter a (Table 7). This result was confirmed by the fact that Brody model in this study had the slowest parameter k (0.006948) in body weight, yet it had the highest estimated parameter a (25.29 kg) among the others. Similarly, the highest parameter k in wither height (0.2606) and hip height (0.02341) had the lowest estimated parameter a (50.78 cm, 56.26 cm) in Von Bertalanffy and Logistic models respectively.

Representing variability among individual animals, estimated animal variance (σ^2_u) of the body weight in this study was 5.78. The higher the variance, the greater the difference is realized among animals. Furthermore, residual variance (σ^2_e) of the body weight in this study was 0.31 that indicated the gap between predicted value and observed value. Repeatability of body weight by intra-class correlation was 0.95 this study.

DISCUSSION

SNP2 of this study was also found in a report analyzing *GH* gene of Chinese goat (An *et al*., 2010). Among five SNPs in this study, translation result showed SNP4 causing amino acid alteration which changes amino acid sequence in *GH* gene exon 3. SNP4 as non-synonymous mutation changed the first triplet codon of AGC encoding Serin to GGC encoding Glycine (Figure 1) and we used it to distinguished as GG, AG and AA genotypes, whereas the other SNPs were silent mutation (SNP1 CAG>CAA(Gln); SNP2 TCT>TCC(Ser); SNP3 CCA>CCG(Pro); SNP5 AAC>AAT(Asn)). According to Nei and Kumar (2000), most of synonymous amino acid was found due to substitution of nucleotides in the third codon, while substitution of nucleotides in the first and second codon generate non-

Table 6. Estimated parameters of growth and goodness of fit for four different growth models

Parameter	Model			
	Brody	Von Bertalanffy	Logistic	Gompertz
Body weight				
a	25.29±1.01	23.01±0.47	21.65±0.30	22.48±0.39
b	0.83±0.01	0.39±0.01	2.56±0.07	1.42±0.03
k	0.006948±0.001019	0.01389±0.001097	0.0277±0.001309	0.01735±0.001143
y_i	-	6.82	10.83	8.27
t_i	-	11.75	33.93	20.10
σ^2_u	9.08±2.67	5.78±1.48	4.17±1.03	5.13±1.29
σ^2_e	0.32±0.03	0.31±0.03	0.32±0.03	0.31±0.03
GG	-3.6±0.79	-4.2±0.59	-4.64±0.49	-4.37±0.55
AG	-2.01±0.85	-3.03±0.061	-3.63±0.50	-3.26±0.56
AA	-4.53±0.95	-5.06±0.75	-5.3±0.63	-5.18±0.70
-2 Log Likehood	606.6	605.8	609.5	606.1
AIC	630.6	629.8	633.5	630.1
BIC	649.6	648.8	652.5	649.1
Wither height				
a	54.65±0.94	50.78±0.31	53.59±0.71	55.54±0.81
b	0.37±0.01	1.96±0.08	0.53±0.02	0.44±0.01
k	0.01577±0.002084	0.2606±0.01207	0.02292±0.002268	0.01934±0.002171
σ^2_u	9.93±2.56	0.0014±0.5954	9.39±2.40	9.62±2.47
σ^2_e	3.95±0.36	29.44±1.63	3.97±0.36	3.96±0.36
GG	-3.3±0.82	-6.82±0.50	-3.67±0.77	-5.02±0.79
AG	-2.76±0.81	-6.78±0.47	-3.14±0.76	-4.48±0.78
AA	-5.59±0.92	-11.91±0.64	-5.90±0.88	-7.27±0.90
-2 Log Likehood	1274.3	2217.3	1276.0	1275.1
AIC	1290.9	2233.3	1292.0	1291.1
BIC	1303.0	2246.0	1304.6	1303.8
Hip height				
a	58.91±0.72	57.73±0.73	56.26±0.56	56.61±0.62
b	0.36±0.01	0.13±0.01	0.50±0.01	0.42±0.01
k	0.01647±0.002009	0.01839±0.002112	0.02341±0.002187	0.01994±0.002092
σ^2_u	8.40±2.20	12.99±0.64	7.91±2.04	8.09±2.10
σ^2_e	3.72±0.34	3.71±0.33	3.75±0.34	3.73±0.34
GG	-2.24±0.77	-2.12±0.94	-1.56±0.73	-1.44±0.75
AG	-0.60±0.78	-0.81±0.93	0.12±0.74	0.25±0.75
AA	-4.55±0.89	-4.63±1.08	-3.60±0.86	-3.50±0.87
-2 Log Likehood	1254.6	1258.2	1256.5	1255.4
AIC	1278.6	1282.2	1280.5	1279.4
BIC	1297.6	1301.2	1299.5	1298.4

a, the estimated of mature body weight/body measurements; b, the integration constant; k, the growth rate constant; y_i, body weight (kg) at the point at inflection; t_i, age (weeks) at the point at inflection; σ^2_u; additive genetic variance; σ^2_e, error variance; AIC, akaike information criterion; BIC, bayesian information criterion.

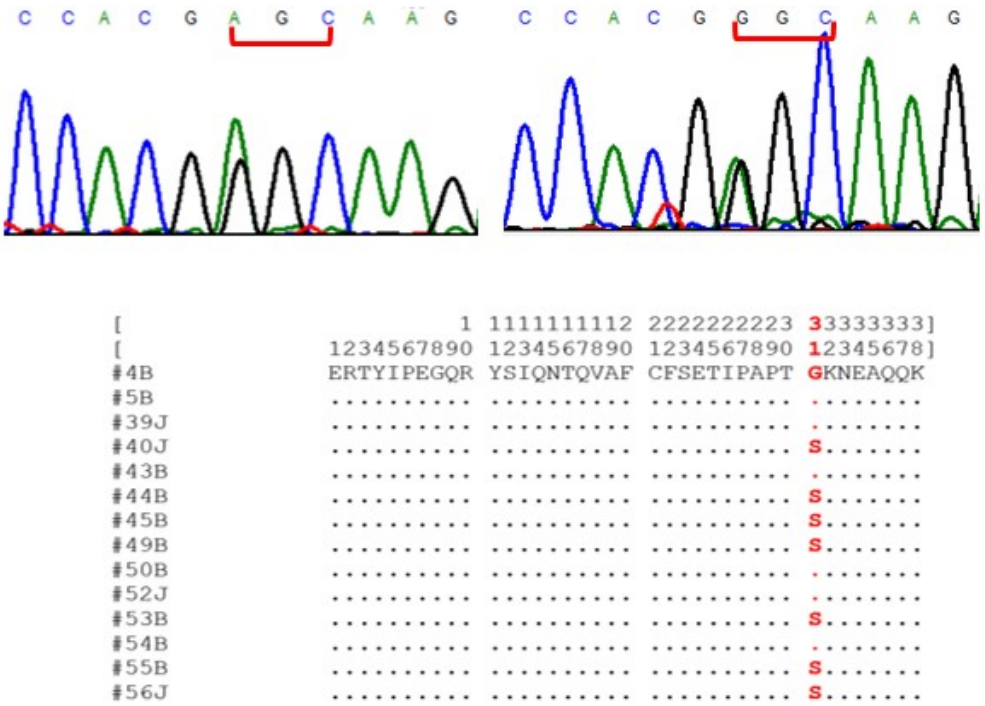

Figure 1. Amino acid alteration caused by SNP g1170A

Table 7. Correlation among growth parameter within traits based on their best model

Growth Parameter	Mature weight (a)		
	BW[A]	WH[B]	HH[C]
Integration constant (b)	0.5564	0.7038	0.6652
Growth rate (k)	-0.7833	-0.8755	-0.8636

[A]Body weight; [B]Wither height; [C]Hip height

synonymous amino acid. Therefore, non-synonimous mutation that change amino acid sequence in exon region may change the peptide sequence of the encoded protein and influence the function of the protein, which was growth hormone in this study. This hormone has substantial metabolic effects on somatic growth, stimulation of protein synthesis and cellular uptake of amino acids and development of body composition (Hjortebjerg *et al*., 2017).

Result in this study agreed with a result by Dayal *et al*. (2016), in which goats with heterozygous genotype AC had the heaviest body weight among five observed genotypes in Black Bengal goat. Gorlov *et al*. (2017) reported their study in Salsk sheep that sheep with AB genotype significantly had heavier body weight, average daily gain and carcass weight than sheep with AA genotype. A contradictory result was reported by An *et al*. (2011) that goats with homozygous genotype AA significantly had higher body weight than those of heterozygous genotype AB at age of one and three months old in Chinese goat, however, wither height showed no significant difference. The different results seem to be due to genetic difference that leads to different structure of *GH* gene and limited number of observations. Therefore, further study is necessary to validate the predominant effect of heterozygote of *GH* gene with a larger number of animals and more sampled observations.

The best model for describing growth of body weight in this study was different with previous study by Kheirabadi and Rashidi (2019), reported that Logistic model fitted worst to body weight, while Brody model fitted most accurately to body

weight of Markhoz goat. In this study, estimated mature body weight (a) was 23.01 kg implying that Kejobong goat had heavier mature body weight than Raeini Cashmere goat (17.97 kg) (Ghiasi *et al*., 2018) and Nondescipt goat (6.42 to 10.55 kg) (Raji *et al*., 2015) but lighter body weight than Beetal goat (23.39 kg) (Waheed *et al*., 2011). Those values of parameter b for body weight, wither height and hip height in this study were described to represent the proportion of mature weight attained after birth, calculated by the initial weight and age value (Lupi *et al*., 2016). On the other hand, Ghiasi *et al*. (2018) stated that parameter b is a scale parameter that has no biological interpretation. Waheed *et al*. (2011) reported higher estimated values of parameter k (0.1077) in Beetal goat by Brody model. Other researchers estimated parameter k as much as 0.017 in Cashmere goat (Ghiasi *et al*. 2018) and 0.0108 in Repartida goat (Pires *et al*., 2017) by applying Gompertz model, so that Kejobong goat in this study is considered to attain mature weight later than Beetal and Cashmere goats but earlier than Repartida goat.

Negative correlation between parameter k and parameter a indicated the slower growth rate, the larger mature weight, *vice versa*. Previous studies supported this results. Kurnianto *et al*. (1998) reported that animals with slower growth rate tended to have estimated heavy body weight at maturity. Brown *et al*. (1976) stated that selection for increasing growth rate tended to decrease mature weight, yet its antagonistic association could be minimized by cross-breeding and improving feed quality. On other hand, previous study by Ghiasi *et al.* (2018) showed lower animal variance (1.29) and higher residual variance (8.01) on growth analysis of Raeni Cashmere goat using Gompertz model than the present study. Repeatability of body weight in this study was higher than repeatability value of South African Angora goat (Snyman and Olivier, 1999) and Boerawa goat (Beyleto *et al*., 2010). The high repeatability in this study may be resulted by the fact that systematic factors affecting body weight were fitted as many as possible in NLMM and that earlier body weight was a component of latter body weight.

The NLMIXED procedure used in this study has flexibility in engaging the variance covariance structure which could not be identified by traditional regression approach. Also NLMIXED has ability to handle unbalance data (Aggrey, 2009; Galeano-Vasco *et al*., 2014). This procedure can reduce potential biases despite selective sampling and supply supplemental parameters that characterize variation between individual animals (Craig and Schinkel, 2001). Therefore, this procedure can facilitate growth analysis by including genotype information and estimates accurately the growth performance of Kejobong goats.

CONCLUSION

SNP g1170A→G in *GH* gene is associated with growth traits and can be used as genetic marker for animal selection to improve goat's growth performance. Animals with heterozygous genotype AG showed higher growth performance than homozygous genotype AA. Nonetheless, animals with homozygous genotype GG showed no difference with either heterozygous genotype AG or homozygous genotype AA. Model ($y = 23.01 (1 – 0.39 e^{-0.01389age})^3$) by Von Bertalanffy, ($y = 54.65 (1 – 0.37 e^{-0.01577age})$) and ($y = 58.91 (1 – 0.36 e^{-0.01647age})$) by Brody were fitted well to describe body weight, wither height and hip height of Kejobong goat, respectively.

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APPROPRIATE GROWTH MODELS TO DESCRIBE EARLY GROWTH OF KEJOBONG GOAT BASED ON GROWTH HORMONE (GH) GENE SEQUENCE ANALYSIS by **SUTOPO ET AL 2021**

No	Page	Section	Column	Paragraph	Written	Correction
1	125	Introduction	2	2	Therefore, objective of this study was to reveal to reveal appropriate growth models...	Therefore, objective of this study was to reveal appropriate growth models…
2	127	Results	-	-	Table in Table 1 using 2 space	Change into 1 space
3	127	Result	-	-	Table in Table 2 using 2 space	Change into 1 space