Identification of GH|MspI and GHR|AluI Gene Polymorphism and its Association with Calf Birth Weight of Grati-PO Cattle

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ABSTRAK

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Bobot lahir pedet (BL) merupakan salah satu kriteria seleksi yang penting untuk memprediksi bobot badan dewasa dan kemudahan melahirkan pada sapi potong. Gen GH dan GHR dianggap sebagai kandidat gen yang bertanggung jawab atas sifat pertumbuhan pada sapi. Tujuan dari penelitian ini adalah untuk mengidentifikasi polimorfisme gen GH|MspI dan GHR|AluI dan dalam hubungannya dengan BL pada sapi PO Grati. Sebanyak 186 sapi PO Grati dipelihara di kandang percobaan Loka Penelitian Sapi Potong (Lolit Sapo) dari bulan Mei hingga Desember 2017. DNA genom diisolasi dari darah seluruh sampel sapi dan digunakan dalam analisis genotipe menggunakan metode PCR-RFLP. Hasil penelitian menunjukkan bahwa rata-rata BL sapi PO Grati dalam penelitian ini adalah 25,58 ± 3,31 kg. Tidak ada perbedaan statistik untuk BL pedet antara jantan dan betina. Frekuensi genotipe CC, CT dan TT pada gen GH masing-masing adalah 1,1, 18,8 dan 80,1%, dan frekuensi alel C dan T pada gen GH masing-masing adalah 0,105 dan 0,895. Sementara frekuensi genotipe AA, AG dan GG pada gen GHR masing-masing adalah 66,1, 25,3 dan 8,6%, dan frekuensi alel A dan G pada gen GHR masing-masing adalah 0,788 dan 0,212. Dapat disimpulkan bahwa baik gen GH|MspI dan GHR|AluI bersifat polimorfik tetapi tidak secara signifikan terkait dengan BL pedet pada sapi PO Grati.

Kata Kunci: Gen growth hormone, gen growth hormone receptor, sapi PO Grati, berat lahir pedet

ABSTRACT

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Calf birth weight (CBW) is one of the important selection criteria to predict mature body weight and for calving ease in beef cattle. The GH and GHR genes are considered as candidate genes responsible for growth traits in cattle. The objectives of this study were to identify the polymorphism of GH|MspI and GHR|AluI genes and its association with CBW in Grati-PO cattle. A total of 186 Grati-PO cattle raised by Beef Cattle Research Station(BCRS) from May to December 2017. Genomic DNA were isolated from whole blood and used in genotyping analysis using the PCR-RFLP method. The result showed that the average of CBW of Grati-PO cattle in present study was 25.58±3.31 kg. There was no statistical difference for CBW between male and female. The genotype frequency of CC, CT, and TT of GH gene were 1.1, 18.8 and 80.1 %, respectively and allele frequency of C and T of the GH gene were 0.105 and 0.895, respectively. While the genotype frequency of AA, AG, and GG of GHR gene were 66.1, 25.3 and 8.6 %, respectively, and allele frequency of A and G of GHR gene were 0.788 and 0.212, respectively. It concluded that both GH|MspI and GHR|AluI gene are polymorphic but not significantly associated with CBW in Grati-PO cattle.

Key Words: Growth hormone gene, growth hormone receptor gene, Grati-PO cattle, calf birth weight

INTRODUCTION

Ongole ascendant (PO) cattle or in Indonesian called as Peranakan Ongole (PO) is one of the most popular beef cattle breeds in Indonesia. This PO breed has contributed largely in the national fulfillment of beef meat in Indonesia. Therefore, genetic improvement has been conducted by Beef Cattle Research Station (BCRS), Ministry of Agriculture of Indonesia to produce superior breeding stock of PO cattle. The breed then called as Grati-PO cattle. However, up to present the selection is still conducted by conventional method based on phenotypic data to estimate the genetic value of Grati-PO cattle. The use of marker-assisted selection in breeding program is expected to accelerate the production of superior breeding stocks at BCRS.

Growth trait is one of economically importance traits which has major concern in beef cattle production.

Birth weight can be used as indicator to predict the future body weight of cattle because of directly related to growth rate and mature live weight (Biswas et al., 2003). Furthermore, moderate genetic correlation has been found between calf birth weight (CBW) with weaning and yearling weight in PO cattle (Hartati, 2016). Conversely, CBW is commonly used as major concern for calving difficulty or dystocia in herds (Johanson & Berger 2003; Gutierrez et al. 2007). The risk of dystocia increases with increasing in CBW (Gregory, Cundiff and Koch, 1995). However, Hartati (2016) showed that response to selection of CBW in PO cattle population is still low (4.8% pergeneration) and the selection results has not caused calving difficulties. Therefore, the selection of CBW still needs to be improved to get an optimal condition in Grati-PO cattle population.

Most of economic traits are quantitative traits and controlled by many genes which each contributes a small effect to the trait (Curi et al. 2006). The Somatotrophic axis plays a key role in controlling the regulation of metabolism and physiological proccess in mammalian (Renaville, Hammadi and Portelle, 2002). It essentially consists of growth hormone (GH), insulin-like growth factors (IGF-I and IGF-II) and their associated carrier proteins and receptors (Renaville, Hammadi and Portelle, 2002). Growth hormone is a main regulator for postnatal growth in mammals (Amiri et al. 2018). Whereas, growth hormone receptor (GHR) is a mediator of GH biological activity in target cells through stimulating myogenic signal transduction (Maskur & Arman 2014). Variation in GH and GHR has been found to be associated with growth traits in several breeds of cattle. GH|*Msp*I were found to be polymorphic and significantly associated with daily weight gain in PO cattle (Sutarno at al. 2005). Whereas, GHR gene becomes the genetic marker candidate and plays important role in GH and lactation process (Fontanesi *et al.*, 2007). The GHR gene in *Bos taurus* (Simmental and Limousin cattle) and *Bos javanicus* (Bali cattle) was known to be polymorphic (Zulkharnaim, Jakaria and Noor, 2010). Furthermore, GHR gene polymorphism has been studied and has the effect on final weight and carcass traits in *Bos taurus* (Han et al. 2009).

According to previous study, the two genes (GH and GHR) could be used as strong candidate genetic marker for growth traits in cattle. These two genes could be used to support genetic selection in Grati-PO cattle. There was no report on the association of GH and GHR genes polymorphism and CBW in PO cattle. Thus, the objectives of this study were to identify the polymorphism of GH|*Msp*I and GHR|*Alu*I genes and its association with CBW in Grati-PO cattle.

MATERIALS AND METHODS

Animals and DNA

Data records of the calves birth weight were collected from 186 Grati-PO cattle raised by BCRS. Data records were collected from May to December 2017. Blood samples were collected from jugular vein into 3 mL vaccutainer tubes containing K3EDTA. DNA were isolated from whole blood samples using DNA extraction kit (Qiagen, Taiwan) and then stored -20°C for further use.

PCR amplification and PCR-RFLP

The specific fragments containing SNPs of GH and GHR gene were amplified using primer pairs designed by Sutarno et al. (2005) and Di Stasio et al. (2005), respectively. The primer information used is given in Table 1. PCR reaction was performed in a total volume of 10 µL containing of approximately 10 ng/µL of DNA, 0.2 µM of each primers, 5 µL of MyTaqTM HS Red Mix (Bioline, USA), and ddH_2O to a final volume

Table 1. The primers used to amplify specific fragments of GH and GHR gene in Grati-PO cattle

	Locus	
	GH|*Msp*I	GHR|*Alu*I
SNPs Position	+837C/T	257A/G
Region	Intron 3	Exon 10
GenBank Accession no.	JQ711182.1	AF140284.1
Primer Sequences (5' to 3')	F : CCCACGGGCAAGAATGAGGC	F : GCTAACTTCATCGTGGACAAC
	R : TGAGGAACTGCAGGGGCCCA	R : CTATGGCATGATTTTGTTCAG
Amplicon Size (bp)	329	342
Annealing temp (°C)	65.7	53.8
References	Sutarno et al. (2005)	Di Stasio et al. (2005)

of 10 µL. The PCR conditions were pre-denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 15 s, annealing for 15 s at 65.7°C (for GH|*Msp*I) and 53.8°C (for GHR|*Alu*I), extension at 72°C for 10 s, and a final extension at 72°C for 5 min. PCR products were electrophoresed on 1% agarose gels, stained with GelRed®10,000X in water (Biotium, USA) and visualized under a G-BOX Gel Documetation System (Syngene, UK). The PCR products of GH|*Msp*I and GHR|*Alu*I were digested with *Msp*I and *Alu*I restriction enzyme, respectively (New England Biolabs, USA). The digested fragments were electrophorezed on 3% agarose gels, stained with GelRed®10,000X in water (Biotium, USA) and visualized under a G-BOX Gel Documetation System (Syngene, UK).

Statistical Analysis

Genotypic and allelic frequencies were calculated by direct counting. Deviation from Hardy–Weinberg equilibrium (HWE) were analyzed using a Chi-square test. Population genetic indexes including observed heterozygosity (Ho), expected heterozygosity (He) were calculated based on Allendorf & Luiart (2007), and value of PIC was calculated based on Botstein et al. (1980). Association between genotypes and CBW were analyzed using GLM model by SPSS IBM version 20.0 software.

RESULTS AND DISCUSSION

Calf Birth Weight of Grati-PO cattle

The descriptive statistic of CBW in Grati-PO cattle is given in Table 2. The average of CBW of Grati-PO cattle in present study was 25.58±3.31 kg. This CBW was not different from previous study using collection data from 2004 to 2013 (22.3±3.0 to 25.8±3.3 kg) (Hartati, 2016), as well as from PO cattle in Gunung Kidul district, special region of Yogyakarta (26 to 28 kg) (Baliarti, 1991), but these findings are higher than in Sumba Ongole cattle (SO) (21.20±4.60kg) (Said et al. 2016). Furthermore, CBW of Grati-PO cattle were superior than in other local Indonesian cattle such as Bali (17.73±1.72 kg) (Gunawan & Jakaria, 2011), Madura (19.78±1.22 kg) (Kutsiyah et al. 2003) or Aceh cattle (12.77±0.76) (Putra et al. 2016). However, CBW of Grati-PO cattle was much lower than in Kebumen-PO cattle (up to 31.88 ± 3.78 kg) (Maharani et al. 2018) or from the same *Bos indicus* cattle breeds in other countries such as Brahman in South Africa (32 kg) (Schoeman 1996), Brahman in Columbia (33.06±3.60kg) (Martínez et al. 2017), and Nellore in Brazil (32.30±3.80 kg) (Chud et al. 2014). This recent findings showed that breeds of cattle was associated with CBW and Ongole cattle breeds have a potential to produce higher CBW than other Indonesian local cattle. Nevertheless, CBW of Ongole cattle breed including Grati- PO cattle were much lower than in *Bos taurus* cattle breeds such as in Charolais (41 kg), Limousin (38 kg) (Schoeman, 1996), Friesian Holstein (33.8±0.6 kg) (Dhakal et al. 2013) and Belgian Blue cattle (49.2±7.1 kg) (Kolkman et al. 2010).

Based on statistical analysis, there was no differences of CBW of Grati-PO cattle between male and female (p>0.05) in present study, however CBW in male (26.08 ± 3.02 kg) tended to higher than in female (25.14±3.02 kg). In general, CBW in male and female were significantly different such observed in several previous study both in local or exotic breeds of cattle (Van Vleck & Cundiff 1998; Raphaka & Dzama 2009; Casas et al. 2012; Prasojo et al. 2010; Dillon et al. 2015; Hartati 2016; Said et al. 2016). Difference between males and females was found about 2.3 kg by Casas et al. (2012), 4.4 kg more by Herring et al. (1996). The average weight of males are being heavier than females in some stage of growth (Raphaka & Dzama 2009; Casas et al. 2012) Therefore, sex should be used as adjustment or correction factor in cattle genetic evaluation for a fair comparison of animals (Bayou et al. 2015; Raphaka & Dzama 2009). Beside sex, sire breed (Casas et al. 2012), weight of dam, season and year of calving are several factors that should be considered because affecting on CBW.

Table 2. Descriptive statistics of the birth weight calves performance of male and female of Grati-PO cattle

Sex	n	Mean±SD (kg)	Min (kg)	Max (kg)	CV (%)
Male	87	26.08±3.56	20	40	13.64
Female	99	25.14±3.02	16	35	12.03
Total	186	25.58±3.31	16	40	12.94

n = number of samples; SD= standard deviation; CV= coefficient of variation; Min = minimum value; Max = maximum value

The evidence of average of CBW in present study that was not different from previous studies (Hartati, 2016) indicates that the response to selection of CBW in Grati-PO cattle may still low. Therefore, the selection of CBW still needs to be improved. Marker-assisted selection technology could be used to accelerate genetic improvement of CBW in Grati-PO cattle. However, the optimum value of CBW should be considered because it affects calving difficulties that increases risk of death in cows and calves and additional veterinary cost (Johanson & Berger 2003; Zaborski et al. 2009).

*GH|Msp*I and *GHR|Alu*I gene polymorphism

The allele and genotype frequencies of *GH|Msp*I and *GHR|Alu*I in Grati-PO cattle are shown in the Table 3 and Table 4. In *GH|Msp*I gene, the TT genotype (or *Msp*I$^{-/-}$ genotype) was the most frequent genotype (80.1%) observed in Grati-PO cattle, while the CC genotype (or *Msp*I$^{+/+}$ genotype) found to be rare (1.1%). In previous study, the *Msp*I$^{-/-}$ genotype was also the most frequent genotype (79%) in Indian Ongole (Sodhi et al. 2007). Although the frequency is lower than the present study, Musa et al. (2013) also reported the same results that the *Msp*I$^{-/-}$ genotype was the highest genotype found in Kenana (67%) and Butana cattle (47%). In *Bos taurus* cattle, the *Msp*I$^{+/+}$ genotype relatively high such in Holstein heifers (77%) (Arango, et al. 2014), Limousin (40.9%) and Simmental (77.3%) (Jakaria et al. 2009). The *Msp*I^{-} allele was the common allele found Grati-PO cattle (0.895). This pattern is also found in other Indonesian breeds of cattle such in Pesisir cattle (0.800) (Jakaria et al. 2007), Bali cattle (1.000) (Jakaria et al. 2009) and Sumba Ongole cattle (0.820) (Agung et al. 2018). Interestingly, this is contrary to the result on PO cattle from Grobogan district (Grobogan-PO cattle), where the frequency of *Msp*I^{-} allele was lower (0.26) than *Msp*I^{+} allele (0.76) and the *Msp*I$^{-/-}$ was the lowest genotype (Sutarno et al. 2005). Meanwhile, the frequency of C allele was found to be high in *Bos taurus* cattle such in Limousin (0.636) and Simmental cattle (0.889) (Jakaria et al. 2009). This result indicates that the *Msp*I$^{-/-}$ genotype and *Msp*I^{-} allele may be high in *Bos indicus* since it was also found to be highest genotype and allele in 17 Indian cattle breeds (Bos indicus) (Sodhi et al. 2007) and as explained by Lagziel et al. (2000). The difference genotype and allele frequency in Grobogan-PO cattle from other *Bos indicus* cattle may be due to the different of selection and breeding history. However, it needs further investigation

In *GHR|Alu*I, the AA genotype was observed to be the most frequent (66.1%), while the GG genotype found in lowest proportion (8.6%) in Grati-PO cattle. The A allele was the common allele found in Grati-PO cattle (0.788). In other Indonesian local cattle, AA genotype was also as the common allele such in Bali cattle (99.8%) and Pesisir cattle (60.4%) as well as for

Table 3. Allele and genotype frequencies of GH|*Msp*I in Grati-PO cattle

Gene	Sex	n	Genotype Frequency (%)			Allele Frequency		χ2test
			*Msp*I$^{+/+}$	*Msp*I$^{+/-}$	*Msp*I$^{-/-}$	*Msp*I^{+}	*Msp*I^{-}	
GH|*Msp*I	Male	87	1.1 (1)	23.0 (20)	75.9 (66)	0.126	0.874	0.144
	Female	99	1.0 (1)	15.2 (15)	83.8 (83)	0.086	0.914	0.120
	Total	186	1.1 (2)	18.8 (35)	80.1 (149)	0.105	0.895	0.001

n = number of samples; χ2tab = 3.841, χ2test <χ2tab means the genotype frequency is in HWE

Table 4. Allele and genotype frequencies of GHR|*Alu*I in Grati-PO cattle

Gene	Sex	n	Genotype Frequency (%)			Allele Frequency		χ2test
			AA	AG	GG	A	G	
GHR|*Alu*I	Male	87	65.5 (57)	26.4 (23)	8.0 (7)	0.787	0.213	3.855
	Female	99	66.7 (66)	24.2 (24)	9.1 (9)	0.788	0.212	7.472
	Total	186	66.1 (123)	25.3 (47)	8.6 (16)	0.788	0.212	11.133

n = number of samples; χ2test <χ2tab means the genotype frequency is in HWE a allele in Bali cattle (0.991) and Pesisir cattle (0.615) (Zulkharnaim et al. 2010). Same as in Simmental cattle, the most frequent genotype was AA genotype (64.19%) and the A allele was the common allele (0.720) (Ardicli et al. 2017) However, it differs from Simmental and Limousin raised in Malang Artificial Insemination Center (BBIB Singosari), Malang which the G allele was the common allele (0.714 and 0.735, respectively (Zulkharnaim et al. 2010). While, Di Stasio et al. (2005) have identified the A and G allele were almost equally distributed in Piemontese cattle.

Gene association

Analysis results for the association between genotype of *GH|Msp*I and *GHR|Alu*I with CBW in Grati-PO cattle is shown in Table 5. In the present study, genotype of *GH|Msp*I gene was not significantly associated with CBW in Grati-PO cattle either using separated analysis between males and females or combined from two sexes. No significant differences between genotype and mature body weight (MBW) was also observed in Pesisir cattle (Jakaria et al. 2007). However, GH|*Msp*I gene was found to be associated with MBW in Grati dairy cows, in which CC genotype were found to be higher than CT and TT (Maylinda 2011). Different results were found by Arango, et al. (2014), in which the TT genotype was the highest for parameters of weight at first estrus and weight at first calving ($p<0.05$) in Holstein heifers. These indicate that the *GH|Msp*I gene has a different effect on body weight at different stage of the physiological status and cattle breeds. However, Arango et al. (2014) stated that the T allele is favorable in cattle specialized for meat production while the C allele is favourable in cattle specialized for milk production. Grati-PO cattle is meat-type breed of cattle, and in the present study gave indication that TT genotype tend to be higher in CBW than CT genotype, although it is not statistically different.

In *GHR|Alu*I gene, the genotype was also not significantly associated with CBW in Grati-PO cattle. This result is similar to those reported by Di Stasio et al. (2005) and Ardicli et al. (2017), for association between *GHR|Alu*I gene and growth traits in Piemontese, Angus and Simmental cattle. However, Di Stasio et al. (2005) showed that the A allele is significatly higher in drip loss than the G allele in Piemontese and Angus cattle. In other study, (Komisarek et al. 2011) reported that *GHR|Alu*I gene affected milk fat and protein content on 209 individuals of Jersey cattle. It gave some indication that the *GHR|Alu*I gene might do not associated with growth and production traits, but associated with meat and milk quality traits.

Table 5. Association between genotype and CBW in Grati-PO cattle

Sex	GH|*Msp*I[a]				GHR|*Alu*I			
	Genotype	n	CBW (kg)	Sig.	Genotype	n	CBW (kg)	Sig.
Male	+/+	1	30.5	-	AA	57	25.8±3.4	ns
	+/-	20	25.7±2.9	ns	GA	23	26.1±3.1	ns
	-/-	66	26.1±3.7	ns	GG	7	28.1±5.5	ns
Female	+/+	1	30.0	-	AA	66	25.3±3.3	ns
	+/-	15	24.4±2.8	ns	GA	24	24.7±2.7	ns
	-/-	83	25.2±3.0	ns	GG	9	25.3±1.3	ns
Male and Female	+/+	2	30.3±0.4	-	AA	123	25.5±3.4	ns
	+/-	35	25.1±2.9	ns	GA	47	25.4±2.9	ns
	-/-	149	25.6±3.4	ns	GG	16	26.6±3.9	ns

n = number of samples
CBW = calf birth weight
[a]both in male, female and its combination, the frequency of *Msp*I$^{+/+}$ genotype is very small, so this record was not included in analysis
sig. = significance level of 0.05
ns = not significant

CONCLUSION

It could be concluded that both *GH|Msp*I and *GHR|Alu*I gene are polymorphic but not significantly associated with CBW in Grati-PO cattle. Further investigation in larger samples and other cattle breeds will needed to study the effect of the *GH|Msp*I and *GHR|Alu*I on CBW.

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