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SINGLE NUCLEOTIDE POLYMORPHISMS IN GROWTH HORMONE GENE ARE ASSOCIATED WITH SOME PERFORMANCE TRAITS IN RABBIT

ABDEL-KAFY E.M. [1], BASITA A. HUSSEIN[2], SARA M. ABDEL-GHANY[1], A.Y.GAMAL EL-DIN[2] AND Y.M. BADAWI[1]

1: Animal Production Research Institute, Agricultural Research Center, Dokki, Giza, Egypt

2: Department of Genetics, Faculty of Agriculture, Cairo University

***Corresponding Author: E Mail:** sayedabdkaffy@yahoo.com

ABSTRACT

The direct application of molecular techniques is the candidate genes that can represent a quite effective approach to the identified DNA markers associated with the production traits in livestock's. The aim of the present study was to evaluate effects of the growth hormone (GH) gene polymorphisms on reproduction and growth traits and to identify its allelic and genotypes frequencies in the rabbits. A total of 202 blood samples collected from APRI rabbit (118 ♀ and 84 ♂). The traits tested were: (1) body weight (W) at 5, 6, 8,10 and 12 weeks from birth, (2) daily body weight gain (DBG); (3) reproductive traits included age of puberty (AP), Kindling interval (KI), litter size and weight at birth (LS), (LW), Litter size weight at weaning(LSW) and (LWW); (4) milk production. For this purpose, DNA was extracted from rabbit blood samples and used in PCR amplification. The c.-78C>T SNP was genotyped by PCR-RFLP using the digestion by restriction enzyme *Bsh1236I (BstUI).* Association analysis between the GH C>T SNP and body weight, growth and reproductive traits was tested in rabbit populations using SAS programme. Heterozygote genotype (T/C) was associated significant ($P < 0.05$) with heavy weight of rabbits at 8 weeks and DG through 5-8 week interval. Heterozygous genotype (T/C) exhibited higher values in the DG compared to C/C and T/T genotypes. Estimated dominant genetic effect (d) was significant ($P < 0.05$) in 8 weeks. The C/C genotype showed a significant value ($P < 0.05$) associated with the early age of puberty. Estimated additive genetic effect (a) and estimated dominant genetic effect (d) in a population was insignificantly associated ($P<0.05$) within all the investigated reproductive traits in rabbits.

Polymorphism of T/C genotype was associations with milk production traits of rabbits during the first two weeks in the lactation period. Estimated additive genetic effect (a) in a population was significant (P<0.05) within the milk production at the second week of lactation period of rabbits. Estimated dominant genetic effect (d) was significant (P<0.05) within milk production at the first two weeks of lactation period of rabbits. The polymorphism of growth hormone (GH) gene in rabbits may has over dominance at the locus c.-78C>T. Positive effects of the heterozygous genotype were recorded compared to both homozygous genotypes on body weight, body gain and milk yield at the first two week. The effect of the C allele of GH gene decreased the age of puberty in rabbits. Effects of the heterozygous genotype in c.-78C>T of GH polymorphisms on the tested traits in current study and on the finishing weight in previous study could be fixed as a favorable genotype in rabbits and may be used in the Marker-assisted selection (MAS) programs to improve growth performance.

Keywords: Rabbits, GH, RLFP, Reproductive, Growth traits

INTRODUCTION

Recently, research in molecular biology has led to the generation of techniques and knowledge that assist and complement the traditional system of genetic improvement and intensifying research on the occurrence of different types of molecular markers in the livestock genome, and hence providing more information to assist studies on the quantitative characteristics of zoo technical interest (Regitano, 2005 and Garcia, 2006). At present, the state of the art of genomic tools and information available for the rabbit genome is very rare compared to the other livestock species. However, the direct application of the molecular techniques is a candidate gene that can represent a quite effective approach to identify DNA markers associated with production traits in livestock (Rothschild and Soller, 1997). A few studies have investigated candidate genes for reproduction (Peiro *et al.*, 2008; Merchan *et al.*,2009 and Garcia *et al.*,2010) for meat deposition and growth (Fontanesi *et al.*, 2011 and 2012) traits in rabbits. Specific regions of the GH genes were analyzed in order to assist breeding programs by providing additional formation in several animals. Growth hormone plays key roles in postnatal growth stage promoting and regulating many biological and metabolic functions involved or related to muscle mass deposition lipid metabolism, and bone growth, among others. The restriction fragment length polymorphism (RFLP) of the GH gene are associated with many production traits including growth rate, feed efficiency, muscle mass and fat

deposition and reproduction traits in different livestock species (Van- Laere *et al*., 2003). Polymorphisms of the GH gene were associated with milk production traits in dairy cattle (Mullen *et al*., 2010), birth weight, carcass traits in beef, cattle (Gill *et al*., 2010), growth performances in sheep, fatness, and carcass traits in pigs (de Faria *et al*., 2006). Fontanesi *et al*. (2012) identified polymorphism in the GH gene and evaluated its association with finishing weight, only. Therefore, the present study was designed to evaluate the effects of the GH gene polymorphisms on the reproduction and growth traits and to identify its allelic and genotypes frequencies in rabbits.

MATERIALS AND METHODS

Animals and traits

A total of 202 rabbit blood samples were collected from APRI rabbit line. APRI rabbits lines were reared in the experimental Rabbitry, Animal Production Research Institute, Sakha, Kafr El-Sheikh Governorate, Egypt. The association study in the body weight and growth traits was recorded for 116 APRI rabbits (84♀ and 32♂) in the growing period. Body weight and growth traits were calculated at 5, 8, and 12 weeks from birth. The daily body gain (DBG) was recorded as a growth trait at intervals 5-8, 8-12 and 5-12 weeks of age. Reproductive traits included age of puberty by day (AP) concerned as age of doe in 1st mating for pregnant, kindling interval (KI) by days; litter traits at birth were litter size (LS) and litter weight (LW). The number of individuals used to study different traits is shown in **Table 1**.

DNA extraction

DNA was extracted from rabbit blood samples using a slight modification of a protocol published by (Walsh *et al*., 1991). Briefly, 1ml of blood sample was centrifuged at 5000 rpm for 4 min. Cell pellets were suspended in TE buffer and centrifuged at 5000 rpm for 4 min. The cycle was repeated two or three times until the red color due to the erythrocytes was minimal. The pellet was treated with100 µl Chelex 100® and boiling for 20 minutes. The sample was centrifuged at 12000 rpm for 10 minutes and supernatant was separated as DNA and stored in -20˚C until use in PCR amplification.

Polymerase chain reactions (PCR)

PCR was used to amplify the GH gene through polymerase chain reaction. A couple of specific primers i.e. forward (**GTATAGTGGGATGGGGTTGG)** and reverse (5`-**TTACGCTCCCATTCAGAAGC** -3`) were used according to Fontanesi *et al*. (2012). PCR reaction was carried out in 25 µl containing 5 µl of the DNA template, 25 pmol

of each primer and 12.5µl of 2 X master mix and nuclease free water up to 25µl. The cycling protocol was 95°C for 5 min; 35 cycles at 95°C for 30 sec, 58°C for 30 sec, 72°C for 30 sec; final extension at 72°C for 10 min.

Genotyping

The c.-78C>T SNP was genotyped by PCR-RFLP using primer pairs for EMBL accession numbers: HE646284 and HE646285. The PCR product, DNA fragment of 231 bp, was digested with restriction enzyme Fast Digest *Bsh1236I (BstUI)* from Fermentas, Vilnius, Lithuania. Briefly, using 10 µl of PCR product was digested at 37°C for 60 min in a total of 30 µl of reaction volume, , including 1µl of the indicated restriction enzyme, 2 µl enzyme buffer and 17µl of dH_2O. The digestion products were electrophoresed in 3% agarose and stained with ethidium bromide. PCR-RFLP patterns **(Figure 1)** were the following: allele T resulted in an undigested fragment of 231 bp; allele C resulted in two fragments of 169+62bp.

Statistical analysis

Evaluation of the genotypes expected frequency, allele frequency, and Chi-sq Hardy-Weinberg equilibrium test for GH gene SNP were carried out on website: Online Encyclopedia for Genetic Epidemiology studies (OEGE), American Journal of Epidemiology.

Association analysis between the GH c.-78C>T SNP with body weight, growth and reproductive traits tested in APRI rabbit population was carried out using the procedure MIXED of SAS programme, version 9.2 (SAS, 1999) with a model that included the buck as a random effect and the fixed effects of sex ,year ,season, parity and genotype.

The estimates of additive and dominance effects were according to Russo *et al*., 2008. The additive and dominance effects on significant deviation from zero were tested by the t-test. Additive genetic effect (a) for the GH genotypes was estimated as half of the difference between values of the two homozygous groups as equation: a = ½(TT – CC). The dominance effect (d) at the IGF-II locus was estimated as the difference between the values of the heterozygous group and the average of the values of the two homozygous groups: d = CT − ½ (TT+ CC).

RESULTS AND DISCUSSION

Allelic and genotypes frequencies

Three genotypes, i.e. the common homozygote (T/T), heterozygote (T/C) and uncommon homozygote (CC), groups were observed in this study **(Table 2)**. The expected genotypes under Hardy-Weinberg

equilibrium were represented in **Table 2**. The chi-square (χ^2) value indicated that the difference between the expected and the observed values for genotype counts were very close. The population was balanced and considered within the Hardy-Weinberg equilibrium. This could be due to the number of the heterozygous genotype was higher than that of both homozygous genotypes. That may maintain the balanced allele frequency in a population.

Association of the GH genotypes and body weight and growth traits

It was noticed that heterozygote genotype associated with the heavy weight in different ages during the growth period in rabbits **(Table 3)**. This increase in the weight was significant ($P < 0.05$) at 8 weeks of age **(Table 3)**. Association analysis between this SNP and the recorded trait by Fontanesi *et al*. (2012) indicated that the c.-78C>T genotypes are significantly associated with the finishing weight (P=0.0133). Least square means± standard errors of the three genotypes were as follows: genotype CC ± 2720.04 ±33.91g; CT=2778.83 ± 31.76 g and TT=2693.94±36.18g. Rabbits with the genotype CT reached a higher weight at 70 days after birth compared to those with genotype TT (P=0.0078) or genotype CC (P=0.0456). Effects of the GH on growth are observed in several tissues including bone, muscle and adipose tissue. Besides, a lot of studies carried out on ruminants confirmed the role of GH in the regulation of mammary growth (Akers, 2006; Sejrsen, *et al*., 2000 and Sejrsen *et al*., 1999). Afifi *et al.*, (2014) evaluated the relationship between the growth hormone gene (GH) polymorphisms and estimated the body weight in arabian camels. The camels with the CC genotype exhibited higher body weights than that of the CT and TT genotypes ($P \leq 0.05$).

The association of T/C and T/T genotypes with the increase in daily gain weight (DG) during different time intervals of the growth in rabbits was recorded **(Table 4)**. DG through 5-8 week interval was significantly associated ($P<0.05$) with the T/C genotype. Heterozygous genotype (T/C) exhibited higher values in the DG compared to the C/C and T/T genotypes. Fontanesi *et al*., 2012 found that rabbits with genotype CT reached a higher weight at 70 days than those of the genotype TT (P=0.0078) or genotype CC (P=0.0456). This notion supports the previous findings in other species of animals that GH gene could be promoted as a candidate gene to improve animal performance such as body weight and carcass weight in poultry (Thakur *et al*., 2006) and Angus cattle (Zhao *et al*., 2004). It is known that the growth of animals

is under hormonal control of the GH, growth hormone receptor (GHR) and insulin-like growth factor I (IGF-I). Polymorphism that occurs in the regulatory region (for example promoter region) and coding region (exons) of the genes responsible for those three hormones is influencing the expression of these genes and the function of proteins during the translation process. There is a strong indication that in all +animals the level of the blood GH reflects the GH genotype. In addition, the association between polymorphisms of the GH gene and the finishing weight in rabbits was also reported by Fontanesi *et al.,* 2012.

Estimated additive genetic effect (a) in the population was insignificant (P<0.05) within most of the body weight and growth traits investigated as shown in **Table 5**. These results indicate to the part of the genetic variances of these traits which were not affected by homozygous genotype of T and C alleles. The same results were reported by Fontanesi *et al.,* (2012) as they reported that the difference between genotypes CC and the TT and the estimated additive genetic effect (a) (13.05± 18.01 g) was in significant (P>0.470).

Estimated dominant genetic effect (d) was significant (P<0.05) for the body weight at 8 week period as shown in **Table 5**. There was an advantage to the heterozygous genotype (T/C) compared to both homozygous genotypes (T/T and C/C) within the most of the body weight and growth trait investigated as shown in Table 3. The estimated dominant genetic effect (d) was 71.84±24.42g and significant (P=0.0038) Fontanesi *et al.,* (2012). Our results could confirm the assumption of Fontanesi*et al,*. (2012) as they indicated that there may be over dominance at this locus that seemed in the genotype (T/C).

Association of the GH genotypes and reproductive traits

The C/C genotype showed a significant effect (P < 0.05) associated with the early age of puberty **(Table 6)** while, the rest of traits were insignificant as shown in **(Table 6)**. Allele C may be having a role in the GH-pituitary axes that appears in the crucial role of the GH to oogenesis and follicular development (Sirotkin *et al*., 2003 and Silva *et al*., 2009) and mammogenic action (Alsat *et al.,* 1997). Effects of the GH gene polymorphism on goat reproductions were studied. To date, more than 10 goat *GH* variants were detected, most of which involving growth traits (Gupta *et al*., 2007 and Hua *et al.,* 2008). Kölle *et al.,* (2001) reported that the *GH* gene is also involved in activating cellular functions in blastocysts, there by stimulating glucose uptake and protein synthesis. Joudrey *et al.,*

(2003) reported that during bovine embryogenesis, bovine growth hormone contributes to the proliferation, differentiation, and modulation of embryonic metabolism. Previous research studies already confirmed that these two mutations of the *GH* gene exerted a highly additive effect on growth traits in Boer bucks (Hua*et al.*, 2008). Estimated additive genetic effect (a) and estimated dominant genetic effect (d) in a population were insignificant (P<0.05) within all the investigated reproductive traits in rabbits as shown in **Table 7**.

Association of the GH genotypes and milk production:

Polymorphism of the heterozygote genotype T/C was significantly associated with the milk production traits of rabbits during the first two weeks in the lactation period **(Table 8)**. Dybusa (2002) studied the associations between polymorphism of the bovine growth hormone *(*GH*)* gene (Leu/Val) and the milk production traits of the Black-and-White cattle. Associations between the Leu/Val polymorphism and the milk production traits of cows were found only in the first lactation period. Cows with the LL genotype had the higher milk, fat and protein yield compared to the LV individuals.

Thomas *et al*., (2007) reported that heterozygous genotypes for the two GH polymorphisms appeared advantageous for traits of muscularity and adiposity in the cooperating breeding program. Two genotypes combinations of the three SNPs within the leptin gene were defined as having a good milk yield and fertility (Liefers *et al*., 2005).

Krasnopiorova *et al*. (2012) also investigated the polymorphism of the growth hormone gene in the cattle grown in Lithuania and its influence on the farming characteristics. Growth hormone gene genotype AA was found in 62.9% of the cattle, heterozygous AB genotype in 24.4% and BB genotype in 12.7%. Through investigation of the effects of genetic factors on the indicators of bovine milk yield and composition, the largest statistically significant impact of the growth hormone gene to the average percentage of fat content and milk yield was determined. It affected around 2% of the diversity of these indicators. Allele A of the growth hormone increases milk fat percentage but allele B increases milk volume during the lactation period.

Hazuchová *et al*. (2013) studied the polymorphism of the growth hormone gene (GH), and long-life milk performance traits in Slovak Spotted cows. They found that the average long-life milk, protein and fat yield in outbreed animals is significantly higher with

the genotype LL and LV than in the groups of inbreed cows. Therefore, animals with the heterozygous genotypes might have a potentially positive effect on the long-life milk performance traits. So, it appears from our results and the above mentioned reports that the effect of the growth hormone polymorphism is unequivocally clear on milk production this indicates that the allele of GH gene should be promoted for the improvement of the milk production traits.

Estimated additive genetic effect (a) in the population was significant (P<0.05) within milk production at the second week of lactation period of rabbit as shown in **Table 9**. These results indicated that this part of the genetic variances of the milk production may be affected by the allele C more than the T allele.

Estimated dominant genetic effect (d) was significant (P<0.05) within milk production at the first week of lactation period of rabbit as shown in **Table 9**. There was an advantage to the heterozygous genotype (T/C) compared to both homozygous genotypes (T/T and C/C) within the first and second week of lactation period of rabbit as shown in **Table 9.**

It is interesting to point out that both alleles (A) and (C) are closely frequent in this population. This could be due to the advantage of the heterozygous genotype compared to both homozygous genotypes that, in turn, may act in maintaining this balanced allele frequency in a population that is strongly selected towards increased fatting weight. The c.-78C>T SNP in flanking region of GH gene in rabbit was not translated to amino acids. The association analysis revealed that the dominance effect appeared to heterozygous genotype on body weight (Table 3), body gain (**Table 4**) and milk yield at first two week (**Table 8**) in rabbits. This silent mutation could have potential functional mutations in regulating post-transcriptional process, such as the transportation of mRNA from the nucleus to cytoplasm, mRNA stability (Neilson and Sandberg, 2010) also play functional roles to regulate the protein expression and influence the advanced structure (Sauna and Kimchi-Sarfaty, 2011). Conne et al., 2000 reported that non-coding SNPs harbor potentially important DNA sequence variants influencing phenotypes in mammals. These may be support our findings in present study that revealed to non-coding SNPs had associated with some performance traits in rabbits.

Table1: Number of rabbits used to study different traits

Growth traits		Reproductive traits		Milk yield traits	
202		No	Litters	No	Litters
118♀	84♂	118♀	307	73	182

Table 2: Genotyping data, Hardy-Weinberg equilibrium (P≤0·05) and allele frequencies of the GH in rabbit.

Items	Genotyping frequency				Allele frequency	
	T/T	C/C	T/C	TOT	Allele T	Allele C
Obs.	53	38	111	202	0.54	0.46
Exp.	58.28	43.28	100.44			
χ^2= 2.23Chi Square value χ^2 table (1 D.F.) at P < 0.05=3.84						

Table 3: Association analysis between the GH genotypes and individual body weight in different age of the growing periods

Genotypes	Traits	W5	W6	W8	W10	W12
Pro.		ns	ns	**	ns	ns
T/T n= 53	LSM	547.5	704.2	837.8[ab]	1164.9	1540.1
	±SE	25.4	25.4	34.3	61.7	82.0
C/C n=38	LSM	559.8	675.1	772.7[b]	1071.3	1429.1
	±SE	34.1	31.7	40.1	75.1	97.4
T/C n=111	LSM	595.8	701.1	868.6[a]	1139.2	1465.0
	±SE	15.4	14.9	17.7	33.0	42.4
P- Value		0.1929	0.7137	0.0727	0.5996	0.6379

** Significant effect of genotype (P≤ 0.05), ns=non Significant, LSM=least squares means, W=week.
[a,b] Values having different superscripts in the column are significantly different(P≤ 0.05).

Table 4: Association analysis between the GH genotypes and daily gain (DG) weight intervals of the growing period

Traits		DG5-6	DG5-8	DG5-10	DG5-12
	Pro.	ns	**	ns	ns
T/T	LSM	10.8	11.8[ab]	16.5	19.4
	±SE	1.36	1.11	1.44	1.45
C/C	LSM	8.9	8.3[b]	13.7	17.7
	±SE	1.58	1.32	1.76	1.81
T/C	LSM	11.6	12.20[a]	15.3	17.4
	±SE	0.2606	0.0254	0.77	0.75
	P-Value	0.2606	0.0254	0.5682	0.4979

Significant effect of genotype (P< 0.05), ns=non Significant, LSM=least squares means; [a,b] Values having different superscripts in the column are significantly different(P < 0.05)

Table 5: Additive and dominance effects (±SE) for the genotypes of the GH (c.-78 C>T) body weight and growth trait in rabbits.

Traits	Additive effect ± SE	P	Dominance effect ± SE	P
W5	-4.59±22.40	0.8384	43.9953±24.2507	0.0718
W6	10.15±25.07	0.6877	18.6771±24.4213	0.4460
W8	9.9314±27.8018	0.7234	82.6162±31.2110*	0.0094

W10	**-13.2268±61.4591**	**0.8312**	**89.2965±58.2205**	**0.1286**
W12	**-34.1545 ±84.6294**	**0.6898**	**95.7795±79.9666**	**0.2343**
DG5-6	**0.8370±0.8903**	**0.3549**	**1.2902±1.1793**	**0.2766**
DG5-8	**0.8821±0.7022**	**0.2187**	**1.5806±1.0076**	**0.1199**
DG5-10	**-0.05438±1.4117**	**0.9696**	**1.1266±1.3746**	**0.4147**
DG5-12	**-0.6484±1.5519**	**0.6798**	**-0.6525±1.4867**	**0.6619**

Table 6: Association analysis between the GH genotypes (c.-78C>T) and reproductive traits of rabbits

.	Traits	AP	KI	LSB	LWB	LSW	LWW
Pro.		**	ns	ns	ns	Ns	Ns
T/T n=31	LSM	189.6 [a]	59.84	6.23	337.93	4.22	2244.9
	±SE	5.13	4.10	0.22	17.64	0.27	144.6
C/C n=22	LSM	161.62 [b]	58.44	6.56	346.02	4.71	2476.6
	±SE	6.02	4.93	0.19	15.2	0.23	123.4
T/C n=65	LSM	192.3[a]	65.23	6.36	344.9	4.67	2496.6
	±SE	4.01	3.82	0.18	14.9	0.23	126.5
P- Value		0.0005	0.4778	0.3566	0.9090	0.2214	0.2497

**** Significant effect of genotype (P < 0.05), ns=non Significant, LSM= least squares means.**
[a,b] values having different superscripts in the column are significantly different(P< 0.05)
AP=Age of puberty by day, KI= Kindling interval, LS=Litter size, LW=Litter weight

Table 7: Additive and dominance effects (±SE) for genotypes of the GH (c.-78C>T) in reproductive traits of rabbits

Traits	Additive effect ± SE	P	Dominance effect ± SE	P
Age of Puberty	**10.8±5.79**	**0.0899**	**-20.6± 11.7**	**0.0978**
Kindling Interval	**2.0691±2.9607**	**0.4878**	**7.8296±4.4270**	**0.0797**
Litter size at birth (LSB)	**-0.00639±0.3057**	**0.9834**	**0.2246±0.4387**	**0.6096**
Litter Weight at birth(LWB)	**-16.9161±19.8833**	**0.3988**	**-31.2313±27.4848**	**0.2583**
Litter size at weaning (LSW)	**-0.5145±0.3919**	**0.1980**	**-0.8539±0.22**	**0.6410**
Litter weight at weaning (LWW)	**-397.54±225.77**	**0.0873**	**319.32±321.43**	**0.3239**

Table 8: Association analysis between the GH genotypes with milk production (MP)

	Traits	Milk1	Milk2	Milk3	Milk4	Milk5
TT n=19	LSM	72.5[b]	80.0 [b]	127.5	115.0	97.50
	SE	5.02	9.65	9.61	15.2	18.61
CC n=14	LSM	78.75[b]	112.7 [a]	143.54	102.35	85.50
	SE	2.89	5.04	5.54	11.50	13.16
TC n=40	LSM	96.42[a]	121.8 [a]	138.57	85.0	51.25
	SE	3.79	5.91	7.26	13.61	15.19
P-Value		0.0012	0.0056	0.3683	0.3580	0.1397

Table 9: Additive and dominance effects (±SE) obtained for the GH in milk production of rabbits

Traits	Additive effect ± SE	P	Dominance effect ± SE	P
Milk W1	**-3.1250±2.1695**	**0.1717**	**19.3661±4.5785 ***	**0.0004**
Milk W2	**-16.3636±4.2234 ***	**0.0022**	**16.1607±8.7748**	**0.0804**
Milk W3	**-8.0208±5.5398**	**0.1697**	**-0.9598±8.9347**	**0.9155**
Milk W4	**6.3214±10.3958**	**0.5582**	**-21.9545±16.0908**	**0.1940**
Milk W5	**6.0000±10.5252**	**0.5812**	**-32.2500±16.8293**	**0.0734**

***Significant at P≤ 0.05.**

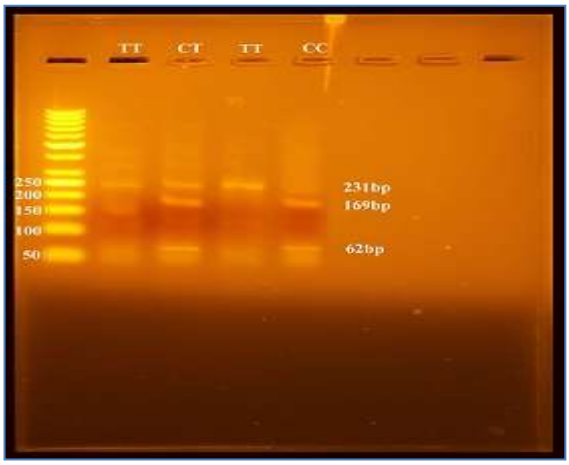

Figure 1: Gel electrophoresis showing PCR-RFLP product identifying the genotypes of the GH gene in rabbits. Allele with genotype T resulted in an undigested fragment of 231 bps .Allele with genotype C resulted in two fragments of 169 +62bps

CONCLUSION

The polymorphism of the growth hormone (GH) gene in rabbits may has a dominance effect over at locus c.-78C>T. Positive effects of the heterozygous genotype compared to both homozygous genotypes on body weight, body gain and milk yield at first two week can be observed. The C allele of the GH gene caused a decreased in the age of puberty in rabbits. Moreover, effects of the heterozygous genotype in c.-78C>T of GH polymorphisms on the tested traits in the current study and on the finishing weight in the previous study could be fixed as a favorable genotype in rabbits**.**

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