Association of the *melanocortin-3(MC3R) receptor* gene with growth and reproductive traits in Mazandaran indigenous chicken

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Abstract *Melanocortin-3 receptor (MC3R)* plays an important role in the central control of energy homeostasis, and several functional polymorphisms of this gene have been detected. We have studied *MC3R* as a candidate gene responsible for variation in economically important traits in the chicken. To determine the association between *MC3R* polymorphism and phenotypic variation, a total of 190 individuals from breeding station of Mazandaran indigenous chicken was genotyped using a modified PCR-RFLP method. The association of growth and reproductive traits was studied using a generalized linear model. The association analysis suggested a positive effect of genotype AA with average egg weight at ages 28 (EW28), 30 (EW30) and 32 (EW32) weeks compared with the GG genotype ($P< 0.05$). The association results also showed a positive effect of genotype AG with average egg weight at age 30 (EW30) weeks compared with the GG genotype ($P<0.05$). In addition, the breeding values of AG genotype for average egg weight at age 32 (EW32) weeks and average egg weight at ages 28 (EW28), 30 (EW30) and 32 (EW32) weeks were higher than the GG genotype ($P< 0.05$). The findings form a basis for further analysis of the relation between genetic variations in *MC3R* gene and economically important traits, and application of molecular markers in poultry breeding.

Keywords: production traits, chicken, *MC3R*, PCR-RFLP

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Introduction

Genetic diversity in indigenous breeds is a major concern considering the necessity of preserving what may be the precious and irreplaceable richness, regarding new productive demands. Conservation should be based on a deep knowledge of the genetic resources of a specific breed. Therefore, it is important to try to characterize genetically indigenous breeds (Shojaei et al., 2011). A species without enough genetic diversity is thought to be unable to cope with the changing environment or evolving competitors and parasites, and the ability of a population to respond adaptively to environmental changes depends on the level of genetic variability or diversity it contains. Thus, studies of population genetic diversity and the structure of population within and between species may not only illustrate the evolutionary process and mechanism but also provide information useful for biological conservation of animals (Notter, 1999; Askari et al., 2011). Molecular markers are increasingly used for the study of genetic diversity of populations in recent years (Zietkiewicz et al., 1994; Zamani et al., 2013). The leptin–melanocortin system is an important regulator of energy balance through its effect on energy intake and energy expenditure (Coll et al., 2007; Seeley et al., 2004). The melanocortins, a family of peptides produced from the post-translational processing of proopiomelanocortin (POMC), regulate the ingestive behavior and energy expenditure, and elicit diverse biological effects by binding to a distinct family of G protein-coupled receptors with seven transmembrane domains (Cone, 2005). From the five cloned melanocortin receptors, two (MC3R, MC4R) have been identified as important downstream effectors regulating energy homeostasis in response to neuropeptides secreted by POMC and the agouti-related peptide (AgRP) neurons (Cone, 2005). All melanocortin receptors (MC3R) have been isolated in the chicken, and each chicken MCR subtype has a different pattern of tissue expression and function. Recently, several studies in an-

imal models suggested that MCR are essential in the regulation of feeding and energy homeostasis, respectively (Schwartz et al., 2000). Interestingly, mice with genetic disruption of MC3R gene were significantly heavier than mice lacking only MC3R, indicating a possible nonredundant participation of melanocortin receptor in obesity and adiposity-related phenotypes (Chen et al., 2000). The MC3R has been found to be associated with body weight in chickens of both sexes, and associated with intramuscular fat and abdominal fat mass in male chickens (Wang et al., 2007; Sharma et al., 2008). Some researchers reported that MC3R homozygous for knockout mutations of the MC3R gene had increased body fat with a reciprocal decrease in lean mass, not caused by increased food intake but arose from increased feed efficiency (Butler et al., 2000; Chen et al., 2000). The chicken MC3R is a protein with 325 amino acids sharing 75.3-76.8 identity with the mammalian MC3R (Takeuchi and Takahashi, 1999). Association between polymorphism in *MC3R* gene and obesity has been detected in human (Civanova et al., 2006).

Archaeological excavations confirmed the presence of the domestic fowl in the territory of Iran at the ancient times (Mohammadabadi et al., 2010). It is known that Persian chickens from the Gilan Province took part in the origin of the Russian Orloff breed (Mohammadabadi et al., 2010). Since 1981, twelve chicken breeding centers were established for reproducing native poultry varieties, and a total number of chickens they maintain are about 8000 birds. Currently, there are eight breeding centers in Fars, West Azarbaijan, Isfahan, Mazandaran, Khorasan, Yazd, Zanjan and Khuzestan provinces (Mohammadabadi et al., 2010). Research on native chicken populations of Iran has been initiated, and the data on the genetic variability of different loci in these populations have been published (Esmaeilkhanian et al., 2004; Mohammadabadi et al., 2010; Mohammadifar et al., 2013 ; Moazeni et al., 2016). However, data on genetic variability of *MC3R* locus in Iranian native chickens, especially in Mazandaran indigenous chicken have not been published. Therefore, the objective of this study was to identify the single nucleotide polymorphism (SNP) in *MC3R* in Mazandaran indigenous chicken, which would form a solid basis for further study on associating them with reproductive traits.

Material and methods

Experimental population and sampling

Breeding station of Mazandaran Indigenous Chicken is located at 28 km far from Sari, the provincial capital of Mazandaran state, located in the north of Iran. In 1986, around 5000 cocks and hens were purchased from rural regions across the Mazandaran province and kept in a quarantine farm for one year. From those, about 2500 birds of two sexes were kept to produce hatching eggs and the chicks produced from these eggs were transferred to the station in 1988. Since then the birds have been individually tagged and trap nest has been used for pedigree recording (Moazeni et al., 2016). Parents of each generation (about 100 cocks and 800 hens) are selected among 6000 pedigreed and performance recorded birds produced each generation. In August 2009, a total of 205 blood samples from Mazandaran indigenous chicken including 10 males and 195 females were collected. Individuals were reared in native chicken breeding station of Mazandaran and they belonged to generation 17 of the breeding station pedigreed animals. Individuals of this generation were developed by crossing 80 sires and 751 dams from generation 16. Approximate 1 mL blood per chick from the wing vein was collected and kept in a tube containing anticoagulant EDTA (ethylenediaminetetraacetic acid). All samples were transferred to the laboratory in an ice box. The genomic DNA was extracted from white blood cells using a standard salting out procedure described by Mohammadabadi et al. (2009). The DNA samples were dissolved in TE (Tris-EDTA) buffer which was made from 10 mM Tris–HCl (pH 7.5) and 1 mM EDTA (pH 8.0) and stored at 20ºC until use.

Primer synthesis and PCR–RFLP reactions

The primers were designed on the basis of DNA sequence of the *MC3R* (accession number: AB017137) using the oligonucleotide design tool Primer 5.0 software (F: 5'-CATGATTGCAATCCTGAGCACC-3' and R: 5'-GATGCAGGAGATCCGGATGAG-3'). PCR reactions were performed in a 20 µl mixture containing 10 pmol primers, 200 lM dNTP (deoxyribonucleotide triphosphate), 2 µl 10X reaction buffer which contained 1.5 mM $MgCl_2$, 1 unit of Taq-DNA polymerase (Promega, Madison, WI), and 50 ng genomic DNA as template. PCR method was used to optimize the reaction accuracy: 94ºC for 5 min, 35 cycles of 94ºC for 30 S, annealing at 60ºC for 60 S, 72ºC for 60 S, and a final extension at 72ºC for 7 min. PCR products were electrophoretically separated on 2% agarose gel (5 V/cm) and stained with ethidium bromide. PCR products were digested by 10 units of *MSPI* restriction enzymes (Fermentase, Lithuania), 6 ml of PCR product, 1.4 ml of Tango buffer and 2 ml nuclease-free water. The final volume of 10 ml was incubated in 37ºC for 12h. The fr-

agments were separated on 3.5% agarose gel stained with ethidium bromide.

Measured traits

Whole information data file (18 successive generations) consisted of three fixed effects (generation, sex and hatch) and 11 recorded traits including body weight at hatch (BW1), body weight at ages 8 (BW8) and 12 (BW12) weeks, body weight at sex maturation (WSM), age at first egg (ASM), egg number (EN), first egg weight EW1), average egg weight at ages 28 (EW28), 30 (EW30) and 32 (EW32) weeks and average egg weight for the first 12 weeks of production (EW12). BW1, BW8 and BW12 have been measured in both male and female chicken. Also, three combined traits consisting of average of EW28, EW30 and EW32 (AV), intensity of egg production (EINT = (egg number/days recording) ×100) and egg mass (EM = EN×EW12) were calculated and analyzed. During 18 generations, the birds have been evaluated based on the body weight at 8 weeks, age of the hens at first egg, average egg weight and total number of eggs laid during first 12 weeks after flocks maturity (when 5% of the flock are in egg production). Economic indices were calculated for these traits and birds of two sexes were selected based on their aggregate genotypes for these traits. The goals of the breeding station on the one hand are to increase body weight, egg weight and egg number and on the other hand, to decrease age at first egg.

Statistical analyses

Pedigree and data file were prepared using Visual FoxPro 9.0 software; the relational data base management system. SAS 9.1 package was used to carry out descriptive statistics and fitting model. The significant fixed effects and their interactions were considered in an animal model. Genetic analyses were performed using ASReml software (Gilmour et al., 2006). Breeding values of growth and egg production traits were estimated using the BLUP based on model 1.

$$y = Xb + Za + e \quad (1)$$

where, y is the vector of observations; b is the vector of fixed effects of generation, sex and hatch; a is the vector of random direct genetic effects; e is the vector of random residual effects; X and Z are incidence matrices relating the observations to the respective fixed and direct genetic effects. Estimation of gene frequency was based on direct gene count method using f(A)= (2nAA+ nAa)/2n or f(G)=(2nGG+ nGg)/2n, and standard error of frequency was calculated as $(p(1-p)/2n)^{1/2}$, where n is the sample size, p is the frequency of A or G allele. Marker-trait association analyses were conducted using model 2 in GLM procedure of SAS9.1 software. The significant differences of least squares means were tested with Tukey–Kramer's multiple range tests, and a P-value of ≤0.05 was considered statistically significant.

$$Y_{ijk} = \mu + M_i + e_{ijk} \quad (2)$$

where, Y_{ijk} is the estimated breeding values of the trait, μ is the population mean, M_i is the fix effect of genotype, and e_{ijk} is the residual random error.

Results

Genotyping results

Table 1 shows the genotypic and gene frequency of *MC3R* gene and statistical description of data set is presented in Table 2. Genotypes of individuals were investigated by PCR-RFLP (Figure 1).

Table 1. Genotypic and allelic frequency of *MC3R* gene

Genotype	Number	Frequency	Allele	Frequency
GG	175	0.92	G	0.95
AG	10	0.05	A	0.05
AA	5	0.03		
Total	190	1		

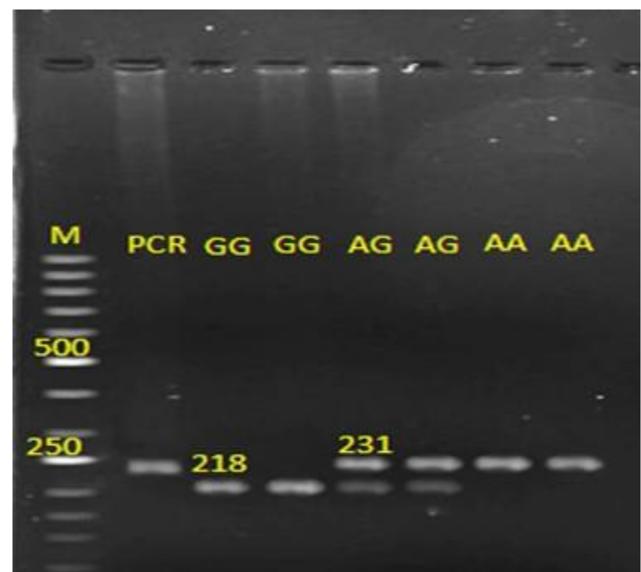

Figure 1. The electrophoretic gel patterns of the *MSPI* PCR-RFLP. Lane 1 (M) is Ladder, lane 2 (PCR) is the amplified gene fragment, lanes 3 and 4 are homozygote GG, lanes 5 and 6 are heterozygote and lanes 7 and 8 are homozygote AA.

Table 2. Statistical description of data set for growth and egg production traits

Traits	No. of hens	Mean	Coefficient of variation
BW1 (gr)	35	35.53	8.2
BW8 (gr)	43	563.7	17.1
BW12 (gr)	38	953.9	14.5
WSM (gr)	31	1694	11.9
ASM (day)	31	165.5	9.2
EN (number)	31	36.66	3.8
EW1 (gr)	27	41.21	15.7
EW28 (gr)	17	46.91	8.5
EW30 (gr)	19	48.12	8.5
EW32 (gr)	18	49.22	8.3
EW12 (gr)	18	46.62	9.3
AV (gr)	28	46.84	13.1
EM (gr)	28	1768	3.9
EINT (%)	31	57.07	23.3

BW1, BW8, BW12= Body weight at birth, 8 and 12 weeks of age, WSM= Body weight at sexual maturity, ASM= Age at first egg, EN= Egg number, EW1= Weight of first egg, EW28, EW30 and EW32= Average egg weight at 28, 30 and 32 weeks of age, respectively, EW12= Average egg weight for first 12 weeks of production, AV= Average for EW28, 30 and 32, EM= Egg mass (= EN×EW12), EINT= Egg production intensity (= Egg Number/Days Recording)×100).

Polymorphism in chicken MC3R gene

The entire nucleotide coding regions of *MC3R*, consisting of a single exon, amplified by using direct PCR, was polymorph (3 genotypes GG, GA and AA were observed). In the *MC3R* gene, there is a silent substitution (i.e., a substitution of a base that causes no change in amino acid coding) in the coding region; Ser183Ser resulted from G > A substitution at position 1424 in the *MC3R* genomic DNA sequence.

Association results

The AG genotype had higher average egg weight at 30 weeks of age (EW30) compared with GG genotype ($P < 0.05$). The AA genotype also recorded higher average egg weight at 28 weeks of age (EW28), 30 weeks of age (EW30) and 32 weeks of age (EW32) compared with GG genotype ($P<0.05$) (Table 3). In addition, AG genotype was significantly associated with breeding value for average egg weight at 28 weeks of age (EW28), 30 weeks of age (EW30) and 32 weeks of age (EW32) and average egg weight at 30 weeks of age (EW30) compared with GG genotype (Table 4). There was no significant interaction between the gene additive effects.

Table 3. Association of the *MC3R* genotypes at the growth and egg production traits (Mean ± S.E.)

Traits	Genotype AA	Genotype AG	Genotype GG
WSM	1916.4±98.8	1758.8±69.5	1737.2±16.4
ASM	188.4±8.1	183.3±5.7	178.3±1.3
EN	43.3±3.7	40.2±2.6	40.3±0.6
EW28	52.2±2.9	48.1±1.5	47.7±0.4
EW30	51.7±2.2^{a}	52.8±1.6^{ab}	48.9±0.3^{b}
AV	53.3±1.8^{a}	51.9±1.2^{ab}	49.9±0.3^{b}
EM	2256.9±189.6	2045.5±133.3	1987.4±31.5
EINT	68.4±6.5	61.5±4.8	63.5±1.1

^{a,b} Within rows, means with commons superscripts do not differ (P>0.05).
See Table 2 for trait abbreviation.

Table 4. Association of the *MC3R* genotypes on breeding values of growth and egg production traits (Mean±S.E.)

Traits	Genotype AA	Genotype AG	Genotype GG
WSM	13.1±3.9	-32.7±2.8	-15.3±6.6
ASM	-19±2.8	-21.1±2.1	-23.4±0.5
EN	14.0±0.8	13.5±0.6	14.4±0.1
EW30	0.7±0.1	1.4±0.5	0.1±0.0
EW32	0.8±0.7^{ab}	1.3±0.5^{a}	0.1±0.0^{b}
AV	1.6±0.5^{ab}	1.9±0.3^{a}	1.2±0.1^{b}
EM	662.2±35.1	642.2±24.8	660.3±5.9
EINT	21.1±1.5	21.6±1.0	22.1±0.3

^{a,b} Within rows, means with commons superscripts do not differ (P>0.05).

Discussion

Using a candidate gene approach, we identified polymorphism in the exon of the *MC3R* gene in Mazandaran chickens. The SNP in the exon included synonymous and non-synonymous polymorphisms. At any given position in a DNA sequence, a nucleotide can be substituted by any of the 4 nucleotide bases and may result in biallelic SNP. This occurs due to the low substitution rate of single nucleotides, estimated to be between 1×10^{-9} and 5×10^{-9} per nucleotide per year at neutral positions in mammals (Vignal et al., 2002). Based on these values, the probability of two independent base changes occurring at a single position is very low (Vignal et al., 2002). In vitro studies conducted by Feng et al. (2005) showed that double homozygosity for *MC3R* sequence variants of *C17A* and *G214A* affected melanocortin receptor function. In addition, Santoro et al. (2007) found that the *MC3R C17A* and *G214A* variants affected the childhood obesity. Moreover, Lee et al. (2002) reported that the *T548A* mutation of *MC3R* gene was associated with obesity in human. In the study herein, we found an *A/G* mutation at base position 1424. Even though this mutation in the chicken *MC3R* do not lead to amino acid change, but was interestingly associated with growth and reproductive traits. Although the nucleotide substitution or the frame-shift mutation of the genetic mutati-

on might be able to change the amino acid sequence, or terminate producing peptide synthesis of complete peptide chains, because of the genetic code with degeneracy, some alkali gene replacement may not cause amino acid sequence change. Our results showed synonymous variations, that is code base sequence change with no amino acid sequence change. The reason why the mutation with same amino acid sequence affected the traits in other studies is still unclear. Hence, the aim of this study was to analyze the association of the SNP genotypes of *MC3R* gene with chicken growth and reproductive traits. The results of association analysis between single SNP of chicken *MC3R* gene and growth and reproductive traits substantiated our conjecture that the genotypes of this SNP were significantly associated with the economically important traits in chicken. In summary, commercial breeding programs of chickens have become more and more complex, thus it would be important for the breeders to use molecular methods such as marker assisted selection (MAS) method to improve the economically important traits, while maintaining the overall fitness. The results of this study indicated that SNP markers were associated with growth and reproductive traits, thus it could be concluded that *MC3R* gene plays an important role in the regulation of reproductive traits in chickens. In the other words, the *MC3R* gene shows great potential for use in molecular MAS programs to control growth and reproductive traits.

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همبستگی ژن گیرنده ملانوکورتین-۳ (*MC3R*) با صفات رشد و تولید مثل در ماکیان بومی مازندران

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چکیده گیرنده ملانوکورتین-۳ (*MC3R*) نقش مهمی در کنترل مرکزی هموستازی انرژی بازی می‌کند و چندین چند شکلی عملکردی از این ژن شناسایی شده‌اند. در این پژوهش، ژن کاندیدا *MC3R*، که مسئول تغییر در صفت‌های اقتصادی مهم ماکیان است بررسی شد. برای تعیین همبستگی بین چند شکلی ژن *MC3R* و تغییر فنوتیپی، شمار ۱۹۰ پرنده از ایستگاه اصلاح نژاد طیور بومی مازندران با روش PCR-RFLP اصلاح شده تعیین ژنوتیپ شدند. همبستگی رشد و تولید مثل با مدل خطی تعمیم یافته بررسی شد. آنالیز همبستگی، اثر مثبت ژنوتیپ AA با میانگین وزن تخم مرغ در سنین ۲۸، ۳۰ و ۳۲ هفتگی را در مقایسه با ژنوتیپ GG پیشنهاد داد ($P < 0.05$). نتایج همبستگی هم‌چنین اثر مثبت ژنوتیپ AG با میانگین وزن تخم مرغ در سن ۳۰ هفتگیرا در مقایسه با ژنوتیپ GG نشان داد ($P < 0.05$). ارزش‌های اصلاحی ژنوتیپ AG برای میانگین وزن تخم مرغ در سنین ۲۸، ۳۰ و ۳۲ هفتگی بالاتر از ژنوتیپ GG بود ($P < 0.05$). یافته‌های این پژوهش پایه و اساسی را برای آنالیز بیشتر همبستگی بین تغییرهای ژنتیکی در ژن *MC3R* و صفت‌های مهم اقتصادی و کاربرد نشانگرهای ژنتیکی در بهنژادی ماکیان را تشکیل می‌دهند.