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A review on polymorphism in egg production linked genes in poultry

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Abstract
Molecular markers already provide new opportunities to speed up selection of routinely measured traits or to select for new traits that are costly and/or difficult to record in farm animals and to improve animal production. A number of literature reports suggested that the *SacI* locus in intron 4 of cGH gene associated with egg number and laying rate. Melatonin regulates various biological functions through three different receptor subtypes – MTNR1A, MTNR1B, and MTNR1CMTNR1C (Mel1C), has been identified in amphibians and birds but not in mammals. MTNR1C SNPs were statistically significantly associated with AFE and egg number at 300 days. Vasoactive intestinal peptide (VIP) gene regulates prolactin secretion in poultry, where effects of VIP on the body depend upon vasoactive intestinal peptide receptors (VIPR-1 and VIPR-2). VIPR-1 gene is considered as an indicator to reduce hatchability and improve egg quality, and have association with lower age at first egg (AFE) and higher egg production at 300 days of age. So, main objective of this review is to provide ample information related to polymorphism in egg production linked genes and their association with economic traits in chicken.

Keywords: cGH, MTNR1C, VIPR1, PCR-RFLP, polymorphism

Introduction
Growth hormone affects a wide variety of physiological parameters such as growth, egg production, body composition, appetite control, aging and reproduction (Vasilatos-Younken *et al*, 1999) [23]. SacI locus in intron 4 of cGH gene was associated with egg number and laying rate
(Markhous *et al*., 2013) [23]. Regression analysis in White leghorn Strain S revealed a significant association of hen day rate of lay and age at first egg (AFE) that was dependent on the growth hormone genotype (Feng *et al*., 1997) [4]. Melatonin (*N*-acetyl-5-methoxytryptamine) regulates various biological functions through three different receptor subtypes-MTNR1A, MTNR1B, and MTNR1C (Sundaresan *et al*., 2009; Li *et al*., 2011) [11, 22]. Melatonin regulates circadian rhythms, hibernation, feeding pattern, thermoregulation, and neuroendocrine functions of birds. An additional receptor subtype, MTNR1C (Mel1C), has been identified in amphibians and birds but not in mammals (Ebisawa *et al*., 1994) [3]. Both the MTNR1A and MTNR1C SNPs were statistically significantly associated with AFE and egg number at 300 days. Birds with AG genotype for the MTNR1C SNP had shorter AFE than those of EE and EF genotypes ($P<0.01$) (Li *et al*., 2013) [10]. Studies have been carried out to know the effect of vasoactive intestinal peptide receptors (VIPRs) genes on sexual maturity, egg productivity and reproduction performance in exotic chicken breeds and quail (Xu *et al*., 2011a, b; Ngu *et al*., 2015; Pu *et al*., 2016) [18, 74, 27]. Vasoactive intestinal peptide gene regulates prolactin secretion in poultry (Li *et al*., 2011) [11], where effects of VIP on the body depend upon vasoactive intestinal peptide receptors (VIPR-1 and VIPR-2). VIPR-1 gene is considered as an indicator to reduce hatchability and improve egg quality (Zhou *et al*., 2008b) [29], and have association with lower age at first egg and higher egg production at 300 days of age (Xu *et al*., 2011a, b) [27].

Chicken growth hormone (cGH) gene
The chicken growth hormone gene is one of the most important candidate genes that is involved in a wide variety of physiological functions, such as growth, body composition, egg production, aging, and reproduction. The growth hormone gene is located in the chromosome 27, contains 5 exons and 4 introns with a total length equal to 4.35 kbp. It was shown that

different SNP's (G662A, T3094C, C3199T, etc.) are present in various gene regions (introns, exons, etc.) (Nie *et al*., 2005) [15]. Mou *et al*. (1995) [13] reported the presence of 2 *Msp*I sites in chicken intron 1, with 1 *Msp*I RFLP being established. Kuhnlein *et al*. (1997) analyzed 12 non-inbred strains of White Leghorn chicken by PCR-RFLP at three *Msp*I sites (PM1, PM2 and PM3) and one *Sac*I site (PS1). These sites were located at intron 1 (PM3), intron 3 (PM2), and intron 4 (PM1, PS1), respectively. Msp1 polymorphism in the intron 1 was associated with egg productivity of poultry (Feng *et al*., 1997) [4]. Compared to other animals, the intron regions of the cGH gene are highly polymorphic. Furthermore, studies using RFLP have shown that these polymorphisms are associated with egg production, abdominal fat, resistance to Marek's disease or avian leucosis, and meat yield traits (Fotouhi *et al*., 1993; Kuhnlein *et al*., 1997) [8]. Genotyping using PCR-RFLPs method was performed in various populations of Chinese native chickens and it was recommended that an allele present in intron 1 of cGH gene might be linked to laying performance (Mou *et al*. 1995) [13]. Kulibaba (2015) [9] studied growth hormone polymorphism in Poltavskaya Glinistaya chicken breed and reported the results of assessment of *MspI* polymorphism in the intron1 of the growth hormone gene, there were individuals of three of six possible genotypes AA, AB and AC, in the studied chicken population. No individuals with genotype BC was found in the studied population. With regards to SacI polymorphism in the intron 4 of the growth hormone gene, individuals of two genotypes were found, i.e. AB (SacI+/ SacI-) and BB (SacI+/ SacI+) in the studied population.

PCR-RFLPs of the cGH gene were studied in various populations of Chinese native chickens and it was suggested that an allele present in intron 1 might be linked to laying performance (Ip *et al*., 2001) [6]. Kansaku *et al*. (2003) studied Nagoya, Gifujidori and Geline chickens wherein the PCR product digested with *MspI* for PM1, PM2 and PM3 or *SacI*for PSI. In the Nagoya chicken, no genetic variation was detected, whereas, in the Gifujidori, PM1 and PM3 were polymorphic. Both Gifujidori and Geline chickens showed no association between RFLP at *Msp I* loci and number of eggs produced. In contrast, the PSI allele was closely associated with the production level of eggs in the Geline chicken. Genotype ´+/-´ showed a significantly higher number of eggs produced than genotype ´-/-´. Research results from cGH /*SacI*polymorphism study in indigenous chicken flock (Fars province) showed chicken with ´+/+´ produced more eggs than those with other genotypes (P<0.05). Chickens with ´+/+´ and´ - /-´ also had a greater laying rate than those with´+/-´ (P<0.05). The frequencies of´+´ (SacI-RFLP) and A (MspI- RFLP) were 0.898 and 0.599, respectively; therefore it may be assumed that the GH gene affected egg production by regulating reproduction in the chickens (Makhous *et al*., 2013). Su *et al*. (2014) [21] studied 4 SNPs of cGH affecting egg production traits in recessive white chicken and Qingyuanpatridge chickens by PCR- Ligase detection reaction, found that haplotypes of the 4 single nucleotide polymorphisms were significantly associated with egg production traits of chicken age at first egg laying, BW, EW, and EN 300. H1H6 was the most advantageous diplotype for egg production. Kulibaba (2015) [9] demonstrated, the differences in egg production between individuals with different genotypes due to Sac I polymorphism of GH gene in Poltavskaya Glinistaya chicken, individuals with heterozygous genotype AB (SacI + / SacI -) were characterized by greater egg productivity than chickens with genotype BB (SacI-/ SacI-). Research by Vu and Ngu (2016) [25] also found that desired alleles of GH gene were associated with egg production in Noi Chickens.

Melatonin Receptor 1C (MTNR1C) gene

The melatonin receptors are G protein-coupled receptors (GPCR) that bind melatonin. Three types of melatonin receptors have been cloned. The *MTNR1A* (or *Mel1A* or *MT1*) and *MTNR1B* (or *Mel1B* or *MT2*) receptor subtypes are present in humans and other mammals, while an additional melatonin receptor subtype *MTNR1C* (or *Mel1C* or *MT3*) has been identified in amphibians and birds. Research has shown that the three common melatonin receptors regulate physiological processes, including seasonal reproduction and ovarian physiology. In birds, melatonin regulates circadian rhythm, hibernation, feeding pattern, thermoregulation, and neuroendocrine functions (Courtillot *et al*., 2010) [2]. Melatonin is found in ovarian follicular fluid (Rönnberg *et al*., 1990) [19], suggesting a direct effect of this hormone on ovarian function. The effects of melatonin on ovarian function vary with tissue structure, cell type, and with the fact whether the species is a seasonal or non-seasonal breeder (Soares *et al*., 2003) [20].Two high-affinity melatonin receptor types, *MTNR1A* and *MTNR1B*, have been cloned in humans, sheep, Siberian hamsters, mice, and rats (Nishiyama *et al*., 2009) [16] and found to exhibit different molecular structures and chromosomal locations among these species. An additional receptor subtype, *MTNR1C* (*Mel1C*), has been identified in amphibians and birds but not in mammals (Ebisawa *et al*., 1994) [3]. Melatonin binding sites were identified in the ovaries of birds, suggesting a possible role of melatonin in various ovarian functions (Poon and Pang, 1994) [17]. The ovarian *MTNR1A*, *MTNR1B,* and*MTNR1C* transcripts are equivalent to the brain receptors recently characterized in chickens and their expression suggests a direct influence of melatonin on female reproductive processes of domestic chickens (Sundaresan *et al*., 2009) [22]. *MTNR1A* and *MTNR1C* genes are significantly associated with both AFE and EN in chickens (Li *et al*., 2013) [10].

Li *et al*. (2013) [10] studied association of three melatonin receptor genes with reproductive traits in Erlang Mountain chicken and reported that the birds with AA genotype for the *MTNR1C* SNP, lacking the *MTNR1C*M*bo*I restriction site, exhibited statistically significantly higher weight at first egg (WFE) (P<0.05), they exhibited statistically significantly lower EN values (P<0.01) than those with both the GG and AG genotypes. Chickens with the AG genotype at *MTNR1C* and at *MTNR1A* produced their first eggs earlier (but, perhaps consequentially, eggs of lower weight) and produced more eggs at 300 days of age than chickens with other genotypes. The apparent production advantage to the AG genotype at *MTNR1C* having lower AFE and higher EN is consistent with the excess of heterozygous genotype at this locus compared equilibrium expectations, suggesting strong balancing selection (over dominance). Research by Vu and Ngu (2016) [25] also found that desired alleles of MTNR1C gene were associated with egg production in Noi Chickens.

Vasoactive intestinal peptide receptor- 1 (VIPR1) gene

Vasoactive intestinal peptide *(VIP)* gene regulates prolactin secretion in poultry (Li *et al*., 2009) where effects of *VIP* on the body depend upon vasoactive intestinal peptide receptors (*VIPR*-1 and *VIPR*-2). VIPR-1 gene is considered as an

indicator to reduce hatchability and improve egg quality (Zhou *et al*., 2008b) [29]. Although there are evidences that *VIPR*-1 gene may play a role in the regulation of hormone secretion mechanism mentioned above, the association between polymorphism in this gene and egg production is less evident and depends heavily on each different population. Zhou *et al*. (2008b) [28] identified the 128 variation sites in *VIPR*-1 gene, every 102 bp generated 1 SNP on an average by partial cloning and sequencing from six chicken populations *viz*., Red Jungle Fowls, TaiheSilkie, Xinghua chickens, Gushi chickens, White Recessive Rock broilers, and Leghorn Layers. Compared SNP density of each region, 5′ flanking region had highest variation rate as every 83 bp generated 1 SNP on an average; and then the intron, every 93 bp generated 1 SNP. Three SNPs in exon 2, exon 3, and exon 6 were found in CDS of the *VIPR*-1 gene; one in exon 2 (A+457G) altered translated mature protein (Ser18Gly). They genotyped D+19820I directly with 3% agarose gel electrophoresis for PCR product amplified by primers (F: GCC ATC TTG CTC CCC CCT AC and R: GCA GCA AAG CCC TAA AAG CAT T) and for other polymorphisms, the PCR products were digested at 37°Cover night with *Csp*6I, *FspB*I, *Mbo* I, *Tai*I, *Hpa*II, *Mbi*I, *Hha*I, *Msp*I, *Taq*I, *Xap*I, and *Mva*I, respectively. They found that the mutations at loci A+284G, A+457G, C+598T, D+19820I, C+37454T, C+42913T, and C+53327T might be associated with broodiness. There were significant associations (p<0.05) between C+598T in intron 2 and broody frequency (%), and C+53327T and duration of broodiness, in which allele C was positive for duration of broodiness.

VIPR-1/*Taq*I polymorphism was closely associated with incubation time and the first laying age and individuals carrying CC genotype had a longer incubation period and earlier first laying age (Zhou *et al*., 2008 a, b) [29].VIPR-1 gene is considered selective support indicator to reduce hatchability and improve egg quality (Zhou *et al*., 2008a) [28]. Comparison of allele frequency on VIPR-1/*Taq*I polymorphism pointed out that most of the experimental chickens in the population had a higher proportion of C allele (Abbasi and Kazemi, 2011) [1]. Xu *et al*. (2011a) [26] observed the polymorphisms at loci A1661691G, C1704887T and C1715301T of VIPR-1 gene by *Tai*I, *Hha*I and *Taq*I restriction enzymes and associated significant effect (P<0.05) of SNP A1661691G with AFE; whereas other two SNPs did not have any significant association. Xu *et al*. (2011b) [27] reported polymorphisms at loci A1661691G, C1704887T and C1715301T of *VIPR*-1 gene by *Tai*I, *Hha*I and *Taq*I restriction enzymes, respectively. They found the highly significant association of C1704887T (P<0.001) and significant effect of C1715301T with EN300, also found the influence of this polymorphism on total egg production of NingduSanhuang laying chicken of 300 days, in which C allele benefited more in the selection process. Xu *et al*. (2011b) [27] reported that chickens with CC genotype had lower total egg production after 300 days as compared with chickens carrying TT genotype. This also implied that egg production had a negative correlation with hatching time and therefore the two polymorphisms on VIPR-1 gene could be potential molecular markers for the improvement of egg production in Noi chickens. Ngu *et al*. (2015) identified the variations by PCR-RFLP (C>T) transition mutations at locus C1715301T by *VIPR*-1/ *Taq*I for 486 bp and at locus C1704887T by *VIPR*-1/*Hha*I 434 bp), and reported significant associations between genotypes and egg numbers (P<0.05) in 20 weeks of laying (28-47 weeks of age) in the Noi chicken (n =111 for *VIPR*-1/*Taq*I and n = 125 for *VIPR*-1/*Hha*I) of Vietnam. The highest egg yield was reported in chickens with CC genotype at VIPR-1/*Taq*I or VIPR-1/*Hha*I position (49.8 to 50.9 eggs) (Ngu *et al*., 2015). Pu *et al*. (2016) [18] studied VIPR1 as candidate gene to analyze SNPs and association with egg production traits on three quail population, showed that two mutations at loci G373T (*BsrD*I) and A313G (*HpyCH4*IV) were significantly associated with egg weight.Vu and Ngu (2016) also found that desired alleles of *VIPR1* gene were associated with egg production in Noi Chickens.

Conclusion

DNA based molecular markers have been developed and identified for economic traits in several species including poultry. The identification of genetic/ DNA markers and the development of marker assisted selection (MAS) provides an effective approach for genetic improvement programs. The growth hormone gene is located in the chromosome 27, contains 5 exons and 4 introns with a total length equal to 4.35 kbp, the intron regions of the cGH gene are highly polymorphic.Melatonin receptors regulate physiological processes, including seasonal reproduction and ovarian physiology. AA genotype for the *MTNR1C* SNP, lacking the *MTNR1CMboI* restriction site, exhibited statistically significantly higher weight at first egg (P<0.05), they exhibited statistically significantly lower EN values (P<0.01) than those with both the GG and AG genotypes. Chickens with the AG genotype at *MTNR1C* and FF at *MTNR1A* produced their first eggs earlier and produced more eggs at 300 days of age than chickens with other genotypes. VIPR-1/*Taq*I polymorphism was closely associated with incubation time and the first laying age and individuals carrying CC genotype had a longer incubation period and earlier first laying age.VIPR-1 gene is considered selective support indicator to reduce hatchability and improve egg quality.

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