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MOLECULAR APPLICATIONS OF CANDIDATE GENES IN GENETIC IMPROVEMENT PROGRAMS IN LIVESTOCK

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SUMMARY

*In livestock, selection programs utilizing quantitative genetics are time consuming due to long generation interval and sometimes of lowly heritable traits. Several genes to be used in selection based on their biological actions or those located in genome regions of identified Quantitative Trait Loci (QTLs) have been regarded as candidate genes affecting economic traits in livestock. Such candidate genes have successful application in identifying several DNA markers associated with production traits. Utilization of candidate genes is one of the primary methods to determine the specific genes related to the economic traits in farm animals. Using molecular techniques is a good way to achieve fast genetic improvement through identifying the genes or QTLs that affect the trait of economic importance in farm animals. This approach has enabled opportunities to enhance genetic improvement programs by direct selection on genes or genomic regions through marker-assisted selection (MAS) and gene introgression. Mapping of QTLs was ta crucial approach to identify genes related to complex traits at the genome-wide level. Recently, a genome wide association study (**GWAS**) succeeded in identifying the casual genes, using the sequence variations by single nucleotide polymorphism (SNP). GWAS is an ideal technique to discover the major genes for complex traits and is a novel way to study the genetic mechanism of such traits. Many genes affecting milk traits such as GHR and PRLR genes were identified in cattle using **GWAS** method. The objectives of the present reviewed article are: 1) Applying a fine chromosomal mapping for localizing the QTL affecting some economic traits using specific microsatellite markers or SNP's in Egyptian farm animals, 2) Selecting the molecular markers to be considered in genetic variability and genotyping, 3) Identifying the candidate genes and causative mutations associated with economic traits in these animals (e.g. cattle, buffalo, sheep, goats and rabbits), 4) Determining the genetically significant SNP markers associated with the economic traits, 5) To perform GWAS using SNP to detect potential causative mutations and genomic regions affecting some productive and reproductive traits in the Egyptian farm animals. A list of the necessary procedures and executable approach are suggested for a genetic improvement program of Egyptian farm animals using the molecular approaches, that may be outlined as: 1) Determining the main objectives, 2) Collecting and recording the phenotypic data, 3) Evaluating the animals genetically, 4) Determine the list of main equipments and chemicals required, 5) Collecting the blood samples and DNA extraction, 6) Genotyping the animals using SNPs markers, 7) Applying the bioinformatics analyses for candidate genes and detecting QTLs, 8) Preparing and editing the genotyping files, 9) Estimating the average yield deviation for each trait, 10) Applying the Genome-Wide Association Study (GWAS), 11) Applying SNP association test, 12) Applying genome-wide complex trait analysis (GCTA), 13) Estimating the genomic breeding values (GBV) to be applied in genomic selection, 14) Evaluating the prediction accuracy (EBV vs GEBV), 15) Estimating the Genomic Best Linear Unbiased Predictions (GBLUP) and SNP-GBLUP, 16) Estimating the genomic breeding values (GBV) to be applied in genomic selection (GS).*

Keywords: Livestock, Molecular applications, Candidate genes, Genetic improvement programs, GWAS, Genomic Breeding Values (GBV)

BACKGROUND

Molecular genetics can be used to identify the genes or chromosomal regions (Quantitative Trait Loci) that affect the trait of importance in livestock production (Andersson, 2001). Mapping of quantitative trait loci (QTL) was suggested as the perfect approach to identify genes related to complex traits at genome-wide study using microsatellite markers. To date in the whole genome, genome wide association study (GWAS) was used in applying the technique of single nucleotide polymorphism (SNP). GWAS has become feasible in domestic animals as a result of the development of large collections of SNPs (such as Illumine Bovine SNP50 Bead Chip that contain 50,000 SNPs) and the development of cost-effective methods for large-scale SNP analysis. Compared with traditional QTL mapping strategies, GWAS has major advantages both in the power to detect causal variants with modest effects, and in defining narrower genomic regions that harbor causal variants. Many genes for milk traits were identified in cattle using GWAS method such as ABCGDGAT1, SCD1, STATA5, ACSS2, AGPAT6,

PPARGC1A, GHR and PRLR (Zhang *et al*. 2012, Sharma *et al*. 2015).

The main challenge in any genetic improvement program is the availability of data and information about relationship between relatives. Since the markers effect can be calculated where the phenotype is available and consequently the genomic breeding value (GEBV) for a given trait can be estimated for animals which do not have a phenotype based on the markers effect that has been previously calculated in the reference population (Meuwissen *et al*. 2001). This approach can reduce the cost of breeding schemes by about 92% (Schaeffer 2006) and double the rate of genetic gain (De Roos *et al*. 2011).Genomic selection (GS) is a variant of marker-assisted selection that uses genome-wide single nucleotide polymorphisms (SNP) to predict individual breeding values for selection (Herraez *et al*., 2005). Numerous studies have shown encouraging results of applying GS in selection of purebreds (Hayes *et al*., 2009). However, except in dairy cattle, most livestocks are crossbreds with advantages of heterosis and breed complementarity. Recent studies have shown that GS is also an appealing method to select purebreds and crossbreds performance (Dekkers, 2007). As compared to alternative methods, genomic selection can give substantially greater response to selection (Piyasatian *et al*., 2007), lower the rate of inbreeding (Dekkers, 2007), and it does not require a systematic collection of pedigree that connects crossbreds to purebreds. Moreover, it is not necessary to measure the crossbred phenotypes every generation of GS, because, in theory, the estimates of SNP effects can be applied through a few generations with only a negligible loss in prediction accuracy.

Numerous strategies and statistical approaches have been developed to meet the conceptual and technical challenges and to take full advantage of the wide opportunities provided by GWAS. However, several pathway-based GWAS algorithms have been developed and implemented in different software packages (Fan *et al*. 2015). SNP2GO is one of the software used to perform pathway analysis to identify the genes and mechanisms that are involved in the expression of the trait under study (Szkiba *et al*. 2014). Finally, SNPCHiMP is a web database that can be used for genomic annotation; determine the physical position of SNPs and to determine if the SNPS are involved in intronic or intergenic region of genes (Nicolazzi *et al*. 2014).

Mapping of quantitative trait loci (QTL):

The identification and utilization of QTL provide potential for more rapid genetic improvement in selection programs, especially for traits that are difficult to improve with traditional selection (Ikeobi *et al.,* 2002).

In the last 15 years, several experimental livestock populations (F0, F1, F2 and F3) have been constructed from different breeds for use in gene and QTL mapping studies (Bulut *et al.,* 2013). Furthermore, the chromosomal scanning studies have been conducted to exemplify the chromosomal regions affecting phenotypic all traits, including economic traits in different livestock breeds. These studies are ongoing for identification of quantitative trait genes (QTGs) and quantitative trait nucleotide (QTNs) controlling these traits. Molecular data will be analyzed using the following mixed model including the fixed effects along with the additive and dominance effects of QTL as random effects (Haley *et al.,* 1994; Manly *et al.,* 2001):

yij= Xijb+ Zaa+ Zdd+ ei

Where: yij is the phenotype of animals, Xij is the designed matrix, and b is the vector of coefficients for fixed effects, *a* is the vector of additive effect of the QTL, *d* is the vector of dominance effect of the QTL, Za the probability of one homozygous type at the putative QTL locus given the marker information minus the probability of the other homozygous type at the locus given the marker information for the animal i, Zd is the probability of being heterozygous at the putative QTL locus given marker genotypes for the animal i, and ei is the random error, typically assumed to be normally distributed as N(0, $\sigma 2$) (Haley and Knott, 1992).

Molecular markers to be used:

The genetic markers can be used to enhance the genetic improvement of breeding stock through marker-assisted selection (MAS). Marker-Assisted Selection is the most widely used application of marker systems in animal breeding. Using microsatellites as direct marker that increase the accuracy of selection from 0.63 to 0.83 (Solberg *et al*., 2008).

Molecular markers can be used to detect the genetic variability, either within or among individuals, families, and populations. As stated byErhardt and Weimann (2007), the majority of molecular markers currently used are microsatellite markers, STRs (short tandem repeats) and SNPs (single nucleated polymorphism). Among all types of the molecular markers, the microsatellites are used as the most widely used markers for the analysis of genetic diversity and population structure in poultry(Maudet *et al.,* 2002). Nowadays, DNA molecular marker techniques are widely applied in the fields of germplasm identification, phylogenetic, and genetic structural analysis(Yang *et al.,* 2013). Accordingly, the microsatellite has been used to develop the markers from genes and they have been referred to as genic molecular markers (GMMs) or functional markers (FMs).

Definite number of microsatellite markers covering autosomal linkage groups and the sex Z chromosome to be considered in genotyping F0 grandparents, F1 and F2 offspring. These markers to be selected based on the degree of polymorphism and the genome coverage recommended in the molecular genetic characterization of animal genetic resources

(FAO, 2011). Detailed information about selected microsatellites are available at the FAO website (www.dad.fao.org/en/ refer/library/guideline/marker.pdf). The assessment of markers was based on their positions on the consensus map. A target for marker spacing of 10 CM was used to test markers across the genome (http://www.ncbi.nlm.nih.gov/mapview and http://www.thearkdb.org).

Genetic markers are used to provide information as bioinformatics indicators about polymorphism in allelic genotype at a given locus. The availability of molecular markers in farm animals allows the detailed analyses and evaluation of genetic diversity and furthermore the detection of genes influencing economically important traits. Molecular markers should not be considered as normal genes as they usually do not have any biological effect.

As stated by Seidel (2009), the genomic selection using the SNP markers is a powerful new tool because: 1) SNP can be detected by a number of methods such as PCR-RFLP, 2) SNP is relatively new technology using DNA chips that can be used for large scale screening of numerous samples in a minimal amount of time (Fontanesi *et al*., 2008), 3) SNP is the most recent contribution to study DNA sequence variation, and 4) SNP represents the most innovative molecular marker in genotyping studies. However, recent advances in high-throughput DNA sequencing, computer software and bioinformatics have facilitated the identification of SNP as molecular markers.

The microsatellite has been used to develop the markers from genes and they have been referred as genic molecular markers (GMMs) or functional markers (FMs).They compared the SNP results with the analysis using microsatellites and concluded that: 1) microsatellites provide high clustering success due to high polymorphic nature, 2) SNP provides broader genome coverage and reliable estimates of genetic relatedness in the genome, and 3) SNP considered to be an efficient and cost-effective genetic tool. In comparison with the highly polymorphic microsatellite markers, SNP has the following advantages: (1) It is less informative due to its balletic nature, (2) It has significant advantages over microsatellite markers as a basis for high-resolution whole genome allelotyping because of their abundance, even spacing, and stability across the genome and (3) it is used to identify the paternal and maternal alleles of a given gene based on polymorphisms. As stated by Brown (1999), SNP as a marker has the following advantages over the other types of genetic markers: 1) It has high level of polymorphism, 2) It is distributed throughout the genome, 3) It has the presence within coding regions, 4) It has introns and regions that flank genes, 5) It is simple and unambiguous assay technique, 6) It has stable Mendelian inheritance, and 7) It has low levels of spontaneous mutation, (8) SNPs are less informative due to their biallelic nature, (9) SNP has significant advantages over microsatellite markers as a basis for high-resolution whole genome allelotyping because of their abundance, even spacing, and stability across the genome, and (10) SNP technique is used to identify the paternal and maternal alleles of a given gene based on polymorphisms.(Seidel, 2009)reported that genomic selection using the SNP markers is a powerful new tool for genetic selection and this is because: 1) SNPs can be detected by a number of techniques such as PCR-RFLP, 2) SNP is relatively new technology using DNA chips that can be used for large scale screening of numerous samples in a minimal amount of time(Fontanesi *et al.,* 2008), 3) SNP is the most recent contribution to study DNA sequence variation, and 4) SNP represents the most innovative molecular marker in genotyping studies.

Identification of candidate genes in cattle:

Research on numerous candidate genes have been conducted and confirmed the fact that there are polymorphic associations between candidate genes and economic traits in cattle (Table 1).

In marker-assisted selection of dairy cattle, some genes are proposed as potential candidates associated with dairy performance traits. Among the various candidates, the prolactin gene seems to be promising, because it plays a crucial role in mammary gland development and in the initiation and maintenance of lactation and expression of milk protein genes. Prolactin (PRL) and Lactoferrin (LF) genes play important regulatory functions in mammary gland development, milk secretion, and expression of milk protein genes (Zhag *et al*, 2008). Lactoferrin gene is highly polymorphic and it has been shown that some of its variants are related to milk production traits and mastitis resistance in dairy cattle (Kaminski *et al*., 2006; Wojdak-Maksymiec *et al*., 2006). As stated by Brym *et al.* (2005), the prolactin gene is a potential quantitative trait locus and could be used as genetic marker of production traits in dairy cattle. Prolactin is known to have diverse biological functions such as water and electrolyte balance, growth and development, immune and reproductive function (Gregerson, 2006). Bovine prolactin gene is located on chromosome 23, which is composed of five exons and four introns (Dybus *et al*., 2005). Several polymorphic sites have been detected within PRL and LF genes (Deepika and Salar, 2014).

Table 1. Candidate genes associated with performance and milk traits in Cattle as cited in literature

Chr*	Candidate gene	Trait associated with gene	Breed or line	Reference
1	POU1F1 (PIT1) POUclass1	Milk production	Reggiana	Fontanesi *et al*., 2015; Woollard *et al*., 1994
	Signal transducer and activator of transcription 1, 91kDa (STAT1)	Milk production	Holstein Reggiana	Cobanoglu *et al*., 2006; Fontanesi *et al*., 2015
	Zinc finger and BTB domain containing 38 (ZBTB38)	Body measurement traits	Chinese cattle breeds	Liu *et al*., 2013
2	Myostatin (*MSTN*)	Growth and carcass traits	(Belgian Blue × British Breed)	Casas *et al*., 2004
	Prka genes*(prkay3)*	Milk, fat and protein	Holstein, Jersey and Canadienne	MacGillivary, 2009
	Glutamicacid decarboxylase 1 (GAD1)	Growth traits	Qinchuan, Jiaxian Red Nanyang	Li *et al*., 2010a
	Insulin-like growth factor binding protein-2 (IGFBP-2)	Growth, carcass and meat quality	Brahman, Hereford, Maine Anjou, Simmental, Tarentaise, Salers,Shorthorn and Black Angus	Pagan, 2002
3	Prka genes*(prkaa2)*	Milk, fat and protein	Holstein, Jersey and Canadienne	MacGillivary, 2009
	Heat shock protein family A (Hsp70) member 6 (HSPA6)	Heat tolerance	Angus	Baena *et al*., 2018
	CYP4A11 CNV gene	Growth traits	Jinnan, Qinchuan, Jiaxian Red, Nanyang and Chinese Red Steppe	Yang *et al*., 2017
4	Prka genes*(prkay2)*	Milk, fat and protein	Holstein, Jersey and Canadians	MacGillivary, 2009
	Leptin gene (LEP)	Milk production Carcass Traits	Angus, Hereford, Simmental and Reggiana	Buchanan *et al*., 2005; Fontanesi *et al*., 2015
	Calcium channel, voltage-dependent, alpha-2/ delta subunit 1 (CACNA2D1)	Mastitis incidence and milk production traits	Sahiwal and Karan Fries	Magotra *et al*., 2019
5	Prka genes*(prkayl)*	Milk, fat and protein	Holstein, Jersey and Canadienne	MacGillivary, 2009
	Oxidized low density lipoprotein (lectin-like) receptor 1 (ORL1)	Milk production	Holstein	Khatib *et al*., 2006; Fontanesi *et al*., 2015
	Apoptosis peptide activating FACTOR 1 (*APAF1)*	Fertility	Holstein	VanRaden *et al*., 2011
6	Casein kappa (CSN3)	Milk production	Reggiana	Fontanesi *et al*., 2015; Medrano and Cordova, 1990
	ATP-binding cassette, sub-family G (WHITE), member 2 (ABCG2)	Milk production	Reggiana	Russo *et al*., 2007; Fontanesi *et al*., 2015
	Secreted phosphoprotein 1 (SPP1)	Milk production	Holstein Reggiana	Khatib *et al*., 2007; Fontanesi *et al*., 2015
	V-kitHardy–Zuckerman4 feline sarcomaviraloncogenehomolog (KIT)	Milk production	Italian Holstein Reggiana	Fontanesi *et al*., 2014; Fontanesi *et al*., 2015; Fontanesi *et al*., 2010
	Lactoglobulin beta (LGB)	Milk production	Reggiana	Fontanesi *et al*., 2015; Medrano and Cordova, 1990
	peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PPARGC1A)	Meat quality traits	Holstein, Charolais, Limousin, Simmenthal, Piedmontese, Asturiana de los Valles, Pirenaica, Danish Red, Marchigiana, Asturiana de la Montaña and Avileña-NegraIbérica	Sevane *et al*., 2013

Cont. Table 1. Candidate genes associated with performance and milk traits in Cattle as cited in literature

Chr*	Candidate gene	Trait associated with gene	Breed or line	Reference
7	Calpastatin (CAST)	Meat quality traits	Brahman	Casas *et al*., 2006
11	Pro-opiomelanocortin (POMC)	Meat quality traits	Holstein, Charolais, Limousin, Simmenthal, Piedmontese, Asturiana de los Valles, Pirenaica, Danish Red, Marchigiana, Asturiana de la Montaña and Avileña-NegraIbérica	Thue and Buchanan, 2003; Sevane *et al*., 2013
14	Diacylglycerol O-acyltransferase 1 (DGAT1)	Milk production	Italian cattle	Scotti *et al*., 2010; Fontanesi *et al*., 2015
	Cytochrome P450, family 11, subfamily B, polypeptide 1 (CYP11B1)	Milk production	German Holstein Reggiana	Kaupe *et al*., 2007; Fontanesi *et al*., 2015
	Thyroglobulin (TG)	Fat and milk traits	Hungarian Holstein Friesian	Anton *et al*., 2008; Fontanesi *et al*., 2015
	Corticotropin releasing hormone (CRH)	Milk production	Reggiana	Buchanan *et al*., 2005; Fontanesi *et al*., 2015
	heat shock transcription factor 1 (HSF1)	Heat tolerance	Angus	Baena *et al*., 2018
	Fibroblast growth factor 2 (FGF2)	Milk production	Reggiana	Wang *et al*., 2008; Fontanesi *et al*., 2015
	Corticotropin releasing hormone (CRH)	Growth and carcass	(Saskatchewan× Manitoba)	Buchanan *et al*., 2005
15	nucleobindin 2 (NUCB2)	Growth traits	Qinchuan Jiaxian Red Nanyang	Li *et al*., 2010b
17	Prka genes*(Prkaβ1)*	Milk, fat and protein	Holstein, Jersey and Canadienne	MacGillivary, 2009
18	Melanocortin 1 receptor (*MC1R*)	Milk production	Reggiana	Russo *et al*., 2007; Fontanesi *et al*., 2015
	Melanocortin 1 receptor (*MC1R*)	Growth and carcass traits	Angus, Hereford, Simmental, and Limousine	McLean and Schmutz, 2009
19	Growth hormone (GH1)	Milk production, milk protein percentage	Canadian Holstein Reggiana	Lagziel *et al*., 1996; Fontanesi *et al*., 2015; Gollapudi, 2003
20	Growth hormone receptor (GHR)	Milk production	Canadian Holstein Reggiana	Fontanesi *et al*., 2007; Fontanesi *et al*., 2015; Gollapudi, 2003
	Prolactin receptor (PRLR)	Milk production	Reggiana	Russo *et al*., 2012; Fontanesi *et al*., 2015
22	Peroxisome proliferator activated receptor gamma (PPARG)	Meat quality traits	Holstein, Charolais, Limousin, Simmenthal, Piedmontese, Asturiana de los Valles, Pirenaica, Danish Red, Marchigiana, Asturiana de la Montaña and Avileña-NegraIbérica	Sevane *et al*., 2013
23	Prolactin gene	Growth, immune and reproductive	Different Bovine breeds	Dybus *et al*, 2005
24	Melanocortin 4 receptor (*MC4R*)	Carcass traits	crossbred Canadian steers	McLean and Schmutz, 2011
	Calpain (CAPN1)	Meat quality traits	Brahman (Piedmontese×Angus) (Jersey×Limousin)	Page *et al*., 2002; White *et al*., 2005

*Chr = chromosome number.

Identification of candidate genes in buffaloes:

Generally, the performance of buffalo cow suffering from many production and reproduction problems such as low milk yield, Short lactation periods, long dry periods, silent estrus, low conception rate, delayed maturity, long calving

intervals and a large number of days open (Aziz *et al*. 2001;Biomy 2012). These problems cause low efficiency of productive and reproductive performance. Some of the previous traits especially reproductive traits had low heritability, in addition unavailability of performance records with smallholder causing difficulty to apply traditional selection programs to improve productive and reproductive performance of buffalo cows. Therefore, it is difficult to detect the candidate genes for traits of interest. Recently, genome wide association study (GWAS) could be used to identify casual genes uses sequences variations mainly single nucleotide polymorphism (SNP).

Identification and utilization of candidate genes for economically important traits is one of the most important long-term goals to improve reproduction and productive efficiency in buffalo populations. In order to improve this efficiency, we need to understand what genes and their proteins are involved in regulation of key reproductive events; how genetic variations lead to significant physiological differences in reproductive performance, and how genes and environment interact to achieve optimum productivity. The studies in buffaloes have shown that members of the transforming growth factor beta (*TGFβ*) super family, some other genes have identified *BMP15*, *BMPR1B* and *GDF9* as major genes responsible for fertility and/or sterility in different buffalo breeds (Table 2).

Table 2. Candidate genes associated with economic traits in different breeds of buffaloes as cited in literature

Chr*	Candidate gene	Traits associated with gene	Breed used	Reference and country of work
1	Melatoninreceptor 1A (MTRN1A)	Reproduction, milk, fat and protein production	São Paulo State Bubalusbubalis	Zetouni *et al*., 2014, Brazil
			Terra Firme , Várzea (VA)	Barbosa *et al*., 2016, Brazil
2	Prolactin-like (PRL)	Milk yield and quality	Nili-Ravi	Nadeem and Maryam, 2016, Pakistan
		Milk production	Buffalo MediterraneanItaliana	Li *et al*., 2017, China
	Signaltransducer and activator of transcription1(STAT1)	Carcass	Water buffaloes	Deng *et al*., 2015, China
3	Adrenoceptor alpha 1A (ADRAIA)	Milk production	Dairy buffaloes	Araújo *et al*., 2015, Brazil
4	Insulin like growth factor 1 (IGF-I)	Milk production and Constituents	Meshing, Surti, Jaffarabadi,	Fatima *et al*., 2009, India
	Alpha-2-macroglobulin *(A2M*)	Milk yield and fat, protein percentages	Murrah buffaloes	Freitas *et al*., 2016, Brazil
5	Insulin-like growth factor 2 (IGF2)	Body weight and gains	Egyptian water buffalo	Abo-Al-Ela *et al*., 2014, Egypt
6	Casein alpha s2 (CSNS2)	Milk yield, fat, protein, casein, solids not fat and total Solids	Bhadawari , Murrah, Mehsana , Surti	Misra *et al*., 2008, India
7	Kappa-casein (CSN3)	Fat, protein, lactose, total solids	Lactating buffaloes	Otaviano *et al*., 2005, Brazil
	Secreted phosphoprotein 1 (SPP1)	Semen production	Water buffaloes	Rolim Filho *et al*., 2013, Brazil
8	Leptin (LEP)	Economic traits	Murrah buffalo	Datta *et al*., 2012, *India*
		Milk yield, fat, protein percentages	Sa˜o Paulo	Zetouni *et al*., 2013, Brazil
		Milk and fat production	Mehsana, Marathwada, Chilika, Jaffarabadi, Murrah, Nili-Ravi, Toda, Pandharpuri,	Tanpure *et al*., 2012, India
		Carcass trait	Egyptian buffaloes	Othman *et al*., 2011, Egypt

Cont. Table 2. Candidate genes associated with economic traits in different breeds of buffaloes as cited in literature

Chr*	Candidate gene	Traits associated with gene	Breed used	Reference and country of work
10	Insulin-like growth factor 2Body weights and gains receptor (IGF2R)		Egyptian buffalo	El-Magd *et al*., 2014, Egypt
	Insulin-like growth factor 1Growth traits receptor (IGF1R)		Egyptian buffalo	El-Magd *et al*., 2013, Egypt
12	Insulin-like growth factor 2Body weight and daily gains (IGF2) genes		Egyptian buffalo	El-Magd *et al*., 2014, Egypt
14	Oxytocin/neurophysin I (OXT)	Milk production traits	Dairy buffaloes	Araújo *et al*., 2015, Brazil
	Oxytocin/neurophysin I(OXT)	Milk yield	Buffalo MediterraneanItaliana	Pauciullo *et al*., 2012a, Italy
15	Diacylglycerol O-Milk production, Quality traits acyltransferase 1 (DGAT1)		The Murrah buffaloes	de Freitas *et al*., 2016, Brazil
17	Calpain 1 (CAPN1)	Carcass trait	Egyptian buffaloes	Othman *et al*., 2011, Egypt
19	Casein alpha s1 (CSNS1)	Milk yield, fat, protein,viz. Bhadawari , Murrah, casein, solids not fat and total Solids	Mehsana, Surti	Misra *et al*., 2008, India
21	Oxytocin receptor (OXTR)	Milk and fatty acids	Italian Mediterranean river buffalo	Cosenza *et al*., 2017, Italy
22	Melanocortin 4receptor(*MC4R*)	Milk production	Water buffaloes	Deng *et al*., 2016, China
23	Stearoyl-CoA desaturase(SCD)	Milk yield	Located buffaloes	Pauciullo *et al*., 2012b, Italy

*Chr = chromosome number.

Identification of candidate genes in sheep and goats:

Numerous associations' studies cited in Table 3&4 have been investigated to clarify the relationship between candidate genes and economic traits in sheep and goats.

Table 3. Candidate genes associated with economic traits in sheep as cited in literature

Chr*	Candidate gene	Traits associated with gene	Breed used	Reference and country of work
1	POU class 1 homeobox 1 gene (PIT1)	Wool weights	Makooei	Negahdary *et al*., 2014
2	Myostatin gene (MSTN)	Muscling, body weight, meat production	Norwegian White, Baluchi Karnobat Merino	Tellam *et al*., 2012; Dimitrova *et al*., 2017
3	Beta-lactoglobulin gene (β-LG)	Milk production and composition	Awassi	Jawasreh *et al*., 2019
	Insulin like growth factor I gene (IGF-I)	Wool weights	Makooei	Negahdary *et al*., 2014
	Thyrotropin releasing hormone degrading enzyme gene TRHDE	Growth traits	New Ujumqin	Zhang *et al*., 2016
	Keratin gene KRT81, 85	Wool traits	Chinese Merino (Xinjiang Type)	Sulayman *et al*., 2018
	alpha-lactalbumin gene (-LA; LALBA)	Milk traits	East Friesian Dairy Lacaune	Giambra *et al*., 2014
4	Leptin gene (LEP)	Wool weights	Makooei	Negahdary *et al*., 2014
5	Calpastatin gene	Body weights and gains, meat production	Sufflock, Traghee Karnobat Merino	Chung and Davis, 2012;Dimitrova *et al*., 2017
	Myocyte enhancer factor 2B gene MEF2B	Growth traits	New Ujumqin	Zhang *et al*., 2016

Cont. Table 3. Candidate genes associated with economic traits in sheep as cited in literature

Chr*	Candidate gene	Traits associated with gene	Breed used	Reference and country of work
	Growth and differentiation factor 9 gene GDF9	Litter size, fecundity	Barki, Ossimi, Rahmani and Mehraban	Barakat *et al*., 2017; Talebi *et al*., 2018
6	Kappa casein gene (CSN3)	Milk production and composition	Awassi	Jawasreh *et al*., 2019
	Alpha-S2-casein gene	Milk traits	Barki, Ossimi, and Rahmani	Othman *et al*., 2013
	Bone morphogenetic Protein receptor type 1b gene bmpr1b	Litter size	Mehraban	Talebi *et al*., 2018
7	Ovine Calpain 3 gene	Growth traits	Barki, Rahmani and Ossimi	Mahrous *et al*., 2016
9	Fatty acid binding protein 4 gene (FABP4)	Meat quality	Small tailed Han, Tan sheep and Inner Mongolia	Xu *et al*., 2011
	Diacylglycerol O-acyltransferase 1 gene DGAT1	Carcass weight, dressing percentage	Moghani	Noshahr and Rafat, 2014
11	Beta-1,4-N-acetylgalactosaminyl Transferase 2 (B4GALNT2)	Litter size	Mehraban	Talebi *et al*., 2018
	Keratin gene (KRT 27, 31, 36, 38)	Wool traits	Chinese Merino (Xinjiang Type)	Sulayman *et al*., 2018
	Growth hormone gene (GH)	Growth traits	Nilagiri	Cauveri *et al*., 2016
	KAP1.1 and KAP1.3 genes	Wool traits	Barki, Rahmani, Ossimi and Awassi	Farag *et al*., 2018
14	Ovine Hormone Sensitive Lipase gene (HSL)	Growth and body composition	Sufflock	Yang, 2014
16	Follistatin gene (FST)	Wool quality	Chinese Merino	Ma *et al*., 2017a
18	Callipyge gene (CLPG)	Meat production	Karnobat Merino	Dimitrova *et al*., 2017
20	Prolactin gene (PRL)	Milk production and composition	Awassi	Jawasreh *et al*., 2019
22	Dickkopf-1 gene (DKK1)	Wool production and quality	Chinese Merino	Mu *et al*., 2017
26	Ovine Uncoupling Protein 1 gene (UCP1)	Growth and carcass	Sufflock	Yang, 2014
	Ovine ADRB3	Growth and body composition	Sufflock, Dorset, and Merino	Yang, 2014;
X	Bone morphogenetic protein 15 gene (BMP15)	Litter size, fecundity	Barki, Ossimi, Rahmani and Mehraban	Barakat *et al*. 2017; Talebi *et al*., 2018

*Chr = chromosome number.

Table 4. Candidate genes associated with economic traits in different breeds of goats as cited in literature

Chr No	Candidate gene	Traits associated with gene	Breed group used	Reference and country of work
1	POU (Pit-Oct-Unc) class 1 homeobox 1 gene *(POU1F1)*	Milk yield, Litter size, Body weight	Inner Mongolia, White Cashmere , Xinongsannen dairy, Laoshan dairy, Guanzhong dairy, Guizhou Black, Matou , Banjiao, Guizhou White, Leizhou	Lan *et al*., 2007, China
	Somatostatin gene (SST)	Growth traits	Boer, Chinese Xuhuai White, Chinese Haimen	Jin *et al*., 2011,China
	POU class 1 homeobox1 gene (POU1F1)	Growth and carcass traits	Guanzhong , Hainan black	Ma *et al*., 2017b, China
		Litter size, Growth traits	Shaanbei White Cashmere	Zhang *et al*., 2019, China
2	Myostatin gene (*MSTN*)	Body weights	Mcluding Boer, Matou ,Haimen , Nubi	Zhang *et al*., 2012a, China
		Body weights and dimensions	Anhui White, Boer	Zhang *et al*., 2013, China
4	Growth hormone-releasing hormone receptor gene (GHRHR)	Body dimensions	XinongSannen, Guanzhong	Liu *et al*.,2011, China

Cont. Table 4. Candidate genes associated with economic traits in different breeds of goats as cited in literature

Chr No	Candidate gene	Traits associated with gene	Breed group used	Reference and country of work
	Insulin like growth factor binding protein 3 gene (IGFBP-3)	Body weights	Jamunapari	Sharma *et al*., 2013, India
5	Insulin-like growth factor I gene (IGF1)	Body weights	Nanjiang Huang	Zhang *et al*., 2008, China
		Milk yield, Body size	Guanzhong, XinongSaanen	Deng *et al*., 2010, China
		Body weight	Jamunapari	Sharma *et al*., 2013, India
7	PROP paired-like homeobox 1 gene *(PROP1*)	Growth and carcass traits	Guanzhong , Hainan Black	Ma *et al*., 2017, China
	Paired like homeodomain 1 gene (PITX1)	Growth and carcass traits	Guanzhong, Hainan Black	Ma *et al*., 2017, China
8	Lipoprotein lipase gene (LPL)	Milk yield and components	Majorera , Malaguen, Saanen, Teramana, Tinerfen, Palmera, Alpine	Badaoui *et al*., 2007b, Spain
11	SIX homeobox 3 gene *(SIX3)*	Growth and carcass traits	Guanzhong, Hainan Black	Ma *et al*., 2017, China
15	*Diacylglycerolacyltransferase*gene *(DGAT-2)*	Growth traits	Boer, Chinese Xuhuai White, Chinese Haimen	Fang *et al*., 2012, China
16	Methylenetetrahydrofolatereductase gene *(MTHFR*)	Milk production	XinongSaanen, Guanzhong dairy goats	An *et al*., 2015b, China
19	Acetyl-CoA carboxylase-a gene (ACACA)	Milk production	Saanen , Local Grey, Syrian, Maltese, Girgentana	Federica *et al*., 2008, Italy
	Acetyl-coenzyme A carboxylase *a* gene (ACACA)	Milk production	Murciano- Granadina	Badaoui *et al*., 2007a, Spain
	Growth hormone gene (*GH*)	Growth traits	Boer goat	Hua *et al*., 2009, China
		Milk production, Growth traits	Jakhrana	Gupta *et al*., 2009, India
		Growth traits	Chinese	An *et al*., 2010, China
		Litter size	Boer , Matou	Zhang *et al*., 2011, China
		Body weights and dimensions	Boer, XinongSaanen	An *et al*., 2011, China
		Milk production	primiparousSarda	Dettori *et al*., 2013, Italy
20	Growth hormone receptor gene (GHR)	Body weights and dimensions	Boer, XinongSaanen	An *et al*., 2011, China
		Body weight	Jamunapari	Sharma *et al*., 2013, India
	Prolactin receptor gene *(PRLR)*	Milk production	XinongSaanen, Guanzhong	Hou *et al*., 2013, China
		Litter size	Guanzhong , Boer	An *et al*., 2015a, China
21	Somatostatin Receptor 1 gene (SSTR1)	Growth traits	Boer goat, Chinese Xuhuai white, Chinese Haimen	Jin *et al*., 2011, China
26	Stearoyl-CoA desaturase 1 gene (*SCD1*)	Milk fatty composition	Murciano- Granadina, Malaguena breeds.	Zidi *et al*., 2010, Spain
	Paired-like homeodomain transcription factor 2 gene (*PITX2*)	Milk production	Guanzhong dairy goats	Zhao *et al*., 2013, China
	AT Motif-Binding Factor gene (*ATBF1*)	Growth traits	Hainan Black, XinongSaanen dairy goats	Zhang *et al*., 2015, China

*Chr = chromosome number.

The concept of the associations in sheep could be summarized as follows:

(1) Genes located on chromosome 1: POU class 1 Homeobox 1 gene (PIT1) (Negahdary *et al*., 2014).
(2) Genes located on chromosome 2: Myostatin gene (MSTN) (Tellam *et al*., 2012; Dimitrova *et al*, .2017).
(3) Genes located on chromosome 3: Beta-lactoglobulin gene (β-LG) (Jawasreh *et al*., 2019), Insulin like growth factor I gene (IGF-I) (Negahdary *et al*., 2014), Thyrotropin releasing hormone degrading enzyme gene TRHDE (Zhang *et al*., 2016), Keratin gene KRT81, 85 (Sulayman *et al*., 2018), alpha-lactalbumin gene (-LA; LALBA) (Giambra *et al*., 2014)
(4) Genes located on chromosome 4: Leptin gene (LEP) (Negahdary *et al*., 2014).
(5) Genes located on chromosome 5: Calpastatingene(Chung and Davis, 2012; Dimitrova *et al*. 2017), Myocyte enhancer factor 2B gene MEF2B (Zhang *et al*., 2016), Growth and differentiation factor 9 gene GDF9 (Barakat *et al*., 2017; Talebi *et al*., 2018).
(6) Genes located on chromosome 6: Kappa casein gene (CSN3) (Jawasreh *et al*., 2019), Alpha-S2-casein gene (Othman *et al*., 2013), Bone morphogenetic Protein receptor type 1b gene bmpr1b (Talebi *et al*., 2018).
(7) Genes located on chromosome 7: Ovine Calpain 3 gene (Mahrous *et al*., 2016).
(8) Genes located on chromosome 9: Fatty acid binding protein 4 gene (FABP4) (Xu *et al*., 2011), Diacylglycerol O-acyltransferase 1 gene DGAT1(Noshahr and Rafat, 2014).
(9) Genes located on chromosome 11: Beta-1,4-N-acetylgalactosaminyl Transferase 2 B4GALNT2 (Talebi *et al*., 2018), Keratin gene (KRT 27, 31, 36, 38) (Sulayman *et al*., 2018), Growth hormone gene GH (Cauveri *et al*., 2016), KAP1.1 and KAP1.3 genes (Farag *et al*., 2018).
(10) Genes located on chromosome 14: Ovine Hormone Sensitive Lipase gene (HSL) (Yang, 2014), Genes located on chromosome 16; Follistatin gene (FST) (Ma *et al*., 2017a).
(11) Genes located on chromosome 18: Callipyge gene CLPG (Dimitrova *et al*.2017).
(12) Genes located on chromosome 20: Prolactin gene (PRL) (Jawasreh *et al*., 2019).
(13) Genes located on chromosome 22: Dickkopf-1 gene (DKK1) (Mu *et al*., 2017).
(14) Genes located on chromosome 22: Ovine Uncoupling Protein 1 gene (UCP1), Ovine ADRB3 (Yang, 2014).
(15) Genes located on chromosome x: Bone morphogenetic protein 15 gene (BMP15) (Barakat *et al*. 2017; Talebi *et al*., 2018).

Also, the concept of the associations in goats could be summarized as follows:

(1) Genes located on chromosome 1: POU (Pit-Oct-Unc) class 1 homeobox 1 gene (POU1F1) (Lan *et al*., 2007), Somatostatin gene (SST) (Jin *et al*., 2011), POU class 1 homeobox 1 gene (POU1F1) (Ma *et al*., 2017b; Zhang *et al*., 2019).
(2) Genes located on chromosome 2: Myostatin gene (MSTN) (Zhang *et al*., 2012a, Zhang *et al*., 2013).
(3) Genes located on chromosome 4: Growth hormone-releasing hormone receptor gene (GHRHR) Liu *et al*. (2011), Insulin like growth factor binding protein 3 gene (IGFBP-3) (Sharma *et al*., 2013).
(4) Genes located on chromosome 5: Insulin-like growth factor I gene (IGF1) (Zhang *et al*., 2008; Deng *et al*., 2010; Sharma *et al*., 2013).
(5) Genes located on chromosome 7: PROP paired-like homeobox 1 gene PROP1 gene, Paired like homeodomain 1 (PITX1) gene (Ma *et al*., 2017b).
(6) Genes located on chromosome 8: Lipoprotein lipase gene (LPL) (Badaoui *et al*., 2007b).
(7) Genes located on chromosome 11: SIX homeobox 3 gene (SIX3) (Ma *et al*., 2017b).
(8) Genes located on chromosome 16: Diacylglycerolacyltransferase gene (DGAT-2) (Federica *et al*., 2008), Genes located on chromosome 19: Acetyl-coenzyme A carboxylase α gene (ACACA) (Badaoui *et al*., 2007a), Growth hormone gene (GH) (Hua *et al*., 2009, Gupta *et al*., 2009, An *et al*., 2010, Dettori *et al*., 2013).
(9) Genes located on chromosome 20: Growth hormone receptor gene (GHR) (An *et al*., 2011), Prolactin receptor gene (PRLR) (Hou *et al*., 2013; An *et al*., 2015a).
(10) Genes located on chromosome 21: Somatostatin Receptor 1 gene (SSTR1) (Jin *et al*., 2011).
(11) Genes located on chromosome 26: Stearoyl-CoA desaturase 1 gene (SCD1) (Zidi *et al*., 2010), Paired-like homeodomain transcription factor 2 gene (PITX2) (Zhao *et al*., 2013), AT Motif-Binding Factor gene (ATBF1) (Zhang *et al*., 2015).

Identification of candidate genes in rabbits:

Hull and Harvey (2000) recorded that growth hormone gene (GH) is not classically considered as a reproductive hormone gene; although it has function, like: (1) it has great roles in reproductive function and secretion and action of LH and FSH, (2) it is required for sexual differentiation and pubertal maturation, (3) it participates in gonadal steroid genesis, gametogenesis and ovulation, and (4) it required for fetal nutrition and growth during pregnancy and for mammary development and lactation. Several studies have shown significant associations with body weighs in rabbits (Fontanesi *et al*., 2008; Zhang *et al*., 2012b; Fontanesi *et al*., 2012; Peng *et al*., 2013; Sahwan *et al*., 2014; Wu *et al*., 2015; Othman *et al*., 2015; El-Aksher *et al*.,

2016; El-Sabrout and Aggag, 2017; Migdal *et al*., 2018).

In this concept, the following candidate genes in rabbits are considered:

1) Progesterone receptor gene (PGR) located on chromosome 1 (Peiró *et al*., 2008).
2) Fibroblast growth factor gene (FGF) located on chromosome 3 (El-Sabrout and Aggag, 2017).
3) Insulin-like growth factor 1 and 2 genes (IGF1and IGF2) located on chromosome 4 ((Fontanesi *et al*., 2012; El-Sabrout and Aggag, 2017).
4) Myostatin gene (MSTN) located on chromosome 7 (Fontanesi *et al*., 2012;; Peng *et al*., 2013).
5) Melanocortin 4 receptor gene (MC4R) located on chromosome 9 (El-Sabrout and Aggag, 2017).
6) Growth hormone receptor gene (GHR) located on chromosome 11.(Zhang *et al*., 2012b).
7) Growth hormone gene (GH) located on chromosome 19 (Abdel-Kafy *et al*., 2016; El-Sabrout and Aggag, 2017).

Table 5. Candidate genes associated with economic traits in rabbits as cited in literature

Chr*	Candidate gene	Traits associated with gene	Breed , line	Reference and country of work
1	Progesterone receptor gene (*PGR)*	Litter size	H and L lines	Peiró *et al*. 2008, Spain.
		Body weight	V-line, Sinai Gabali	El-Aksher *et al*. 2016,Egypt
3	Fibroblast growth factor gene *(FGF)*	Body weight	V-line, Alexandria	El-Sabrout and Aggag 2017,Egypt
4	Insulin-like Growth Factor 1 gene *(IGF-1)*	Body weight	V-line, Alexandria	El-Sabrout and Aggag 2017, Egypt
	Insulin-like growth factor 2 gene *(IGF2)*	Body weight	Different genetic groups	Fontanesi *et al*. 2012,Italy
7	Myostatingene (*MSTN*)	Meat production	Belgian Hare, Burgundy Fawn, Checkered Giant, Giant Grey	Fontanesi *et al*. 2008,Italy
		Growth and Carcass	Z2 line, Z4 line, Z2×Z4 cross line	Lu *et al*. 2011, China
		Body weight	Ira, Champagne, Tianfu black	Peng *et al*. 2013,China
		Body weight	V-line, Alexandria	El-Sabrout and Aggag 2017,Egypt
	Leptingene (*LEP*)	Carcass and meat quality	Zealand White,Belgian Giant, Giant Grey	Migdal *et al*. 2018, Poland
9	Melanocortin 4 receptor gene *(MC4R)*	Body weight	V-line, Alexandria	El-Sabrout and Aggag 2017, Egypt
10	Phosphorglyceratemutasegene *(PGAM2*)	Body weight	Tianfublack,Ira, Champagne	Wu *et al*. 2015, China
11	Growth hormone receptor gene *(GHR)*	Body weight	Tianfu black, Ira, Champagne	Zhang *et al*. 2012, China
		Growth traits	New Zealand White, V-line, Californian, Alexandria	Sahwan *et al*. 2014, Egypt
		Body weights	V-line, Alexandria	El-Sabrout and Aggag 2017 ,Egypt
	Calpastatingene *(CAST)*	Meat quality	Champagne, Tianfu Black	Wang *et al*. 2016,China
12	Basic fibroblast growth factor gene *(BFGF)*	Body wrights	Japanese rabbits	Inoue *et al*. 2006, Japan.
14	*POU1F1* gene	Meat quality	Hyla, Champagne, Tianfu Black	Wang *et al*. 2015, China
15	Fibroblast growth factor 5 gene *(FGF-5)*	Body weights	Local Egyptian	Othman *et al*. 2015, Egypt
18	Phosphorglyceratemutasegene *(PGAM)*	Body weights	V-line, Alexandria	El-Sabrout and Aggag 2017,Egypt

Cont. Table 5. Candidate genes associated with economic traits in rabbits as cited in literature

Chr*	Candidate gene	Traits associated with gene	Breed , line	Reference and country of work
19	Growth hormone gene *(GH)*	Meat production	Belgian Hare, Burgundy Fawn, Checkered Giant, Giant Grey	Fontanesi *et al.* 2008,Italy
		Body weights	APRI Line	Abdel-Kafy *et al.* 2016, Egypt
		Body weights	V-line, Alexandria	El-Sabrout and Aggag 2017, Egypt

*Chr = chromosome number.

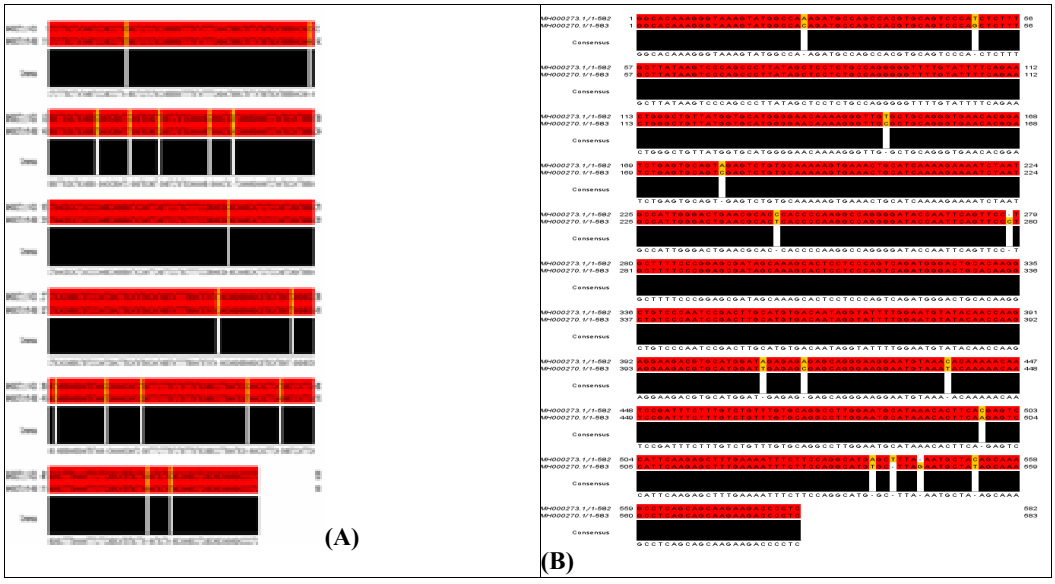
Molecular characterization of candidate genes in livestock breeds:

The candidate genes in local livestock breeds must be characterized for the following genetic parameters:

1) Allelic and genotypic frequencies and the genetic diversity of candidate genes to be assessed by calculating the effective number of alleles *(Ne)*, the observed (*Ho*) and the expected (*He*) heterozygosity using GENALEX software, version 6.5 (Peakall and Smouse, 2012):
2) Hardy-Weinberg equilibrium (HWE) within each population was estimated using GENEPOP program (Raymond, 1995); http://genepop.curtin.edu.au/) performing the Chi-square test for each genetic group studied.
3) The polymorphism information content (PIC) was calculated using CERVUS software, version 3 (Kalinowski *et al.,* 2007):
4) The F-statistic of the reduction in heterozygosity due to inbreeding within each population (FIS) were calculated using GENEPOP software, version 3.4 (Raymond, 1995); http://genepop.curtin.edu.au/).

Bioinformatics sequencing and pairwise alignment of candidate genes:

PCR products of candidate genes must be partially sequenced and registered Assessment of the genetic variability in the studied populations must be performed via identifying SNPs and gaps in F1 sequences and the parental sequences for all studied genes and SNPs. For example in an Egyptian poultry study (Saleh, 2019), the pairwise sequence alignment of gallinacin genes of the parents compared with F1 generation is illustrated in Figure 1 and Table 6.The high genetic variation considered was located in the regions associated with the innate immune response to bacteria (Sugiarto and Yu, 2004;Higgs *et al.*, 2005;Morammazi and Habibi, 2017)and having the role in increasing the resistance to diseases (Bar-Shira and Friedman, 2006). For gallinacin-2 gene, a 583 bp product amplified from gallinacin 2 genomic DNA sequence had many substitution SNPs (Figure 1; Saleh, 2019): Seventeen SNPs were identified between Fayoumi and ½ Fayoumi ½Rhode Island with identity ratio of 97% and eleven SNP and three gaps with ½R½F with high identity percent of 98%. Also, 12 SNPs were identified in Rhode Island with ½F½R cross with identity ratio of 98% and 21 SNPs and one gap in R with ½R½F cross with high identity percent of 96%.



(A) **(B)**

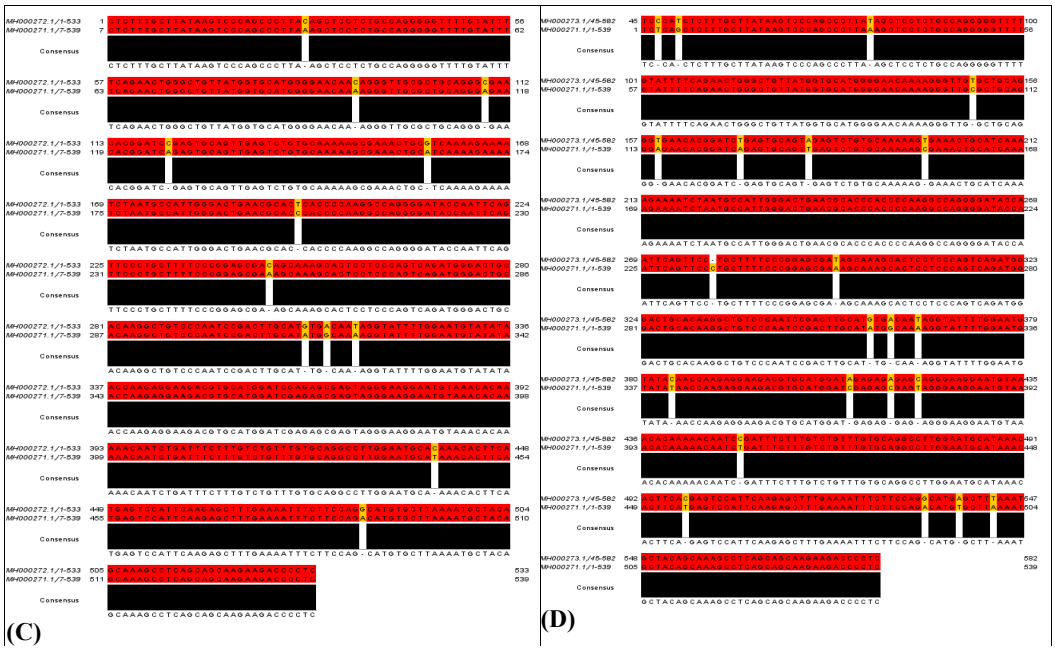


Figure 1: Pairwise sequence alignment of *Gal 2* gene of the parents compared with F1 generation in chickens as cited by Saleh, 2019 (set A: for F with ½F½R), (set B: for F with ½R½F), (set C: for R with ½F½R) and (set D: for R with ½R½F).

Table 6. Sequence of Gal 2 gene of the parents compared with F1 generation

Pairwise genetic groups	No. of SNPs	No. of gaps	Identity ratio (%)
Fayoumi with ½ Fayoumi ½Rhode Island	17	-	97
Fayoumi with ½R½F	11	3	98
Rhode Island with ½F½R	12	-	98
Rhode Island with ½R½F	21	1	96

Polymorphism detection techniques (RAPD, AFLP and PCR-RFLP):

For animal genotyping, DNA polymorphisms are detected by varieties of techniques, the most common being randomly amplified polymorphic DNA (RAPD)(e.g. Nagy *et al*., 2010; Jawasreh *et al*., 2011; Qasim *et al*., 2011), single stranded conformation polymorphisms (SSCP) (e.g.Bastos *et al*., 2001), amplified fragment length polymorphisms (AFLP) by restriction fragment length polymorphisms (RFLP) (e.g.Abdel-rahman *et al*., 2010). These polymorphic procedures have been used for several purposes like genetic analysis of inbred strains, quantitative traits loci, variable number of tandem repeats (VNTR), microsatellites as short tandem repeats (STR), diversity analysis and single nucleotide polymorphisms SNP(e.g. Pariset *et al*., 2006).The Random Amplified Polymorphism DNA technique (RAPD) was invented as a genetic marker in 1990(Williams *et al.,* 1990). The Amplified Fragment Length Polymorphism technique (AFLP) was originally described by Zabeau and Vos (1993). DNA polymorphisms may be detected in different ways, the most common being Restriction Fragment Length Polymorphism (RFLP). PCR-Restriction Fragment Length Polymorphism (PCR-RFLP) is a popular technique for genotyping which associated with the creation of a restriction enzyme recognition site (Narayanan, 1991). The more recently developed PCR-RFLP is an alternative method which takes the advantage of PCR techniques to enable more samples to be analyzed in a shorter time with very small amounts of DNA. However, Zaglol (2019) concluded that The PCR-RFLP technique is an appropriate tool for screening the genotypes of *GH*gene and for evaluating the genetic polymorphism in rabbit's breeds.

The PCR-RFLP consists of two main steps: first, amplifying DNA using the standard PCR (i.e. amplification), second, digesting PCR product using restriction enzymes (i.e. Digestion). Hailu and Getu (2015) stated that the most important advantages of the PCR-RFLP technique include: 1) it was widely applied for the analysis of genetically determined diseases, 2) inexpensiveness and lack of requirements for advanced instruments, 3) it has easy design and can be accomplished using public available programs, 4) RFLP is labor-intensive and time-consuming, 5) it can be used to check out only specific mutations at enzyme cut sites, 6) detecting the polymorphism is relatively low, 7) it has high reliability, because it is generated from specific sites via known restriction enzymes and the results are constant over time and location, and 8) it can be used to detect the oncogenes in gene mapping and phylogenetic analysis and for the study of association

relations of candidate genes with performance traits. The disadvantages of the PCR-RFLP method as stated by Rasmussen (2012) include: 1) it requires specific endonucleases in identifying the exact variation, and 2) it requires several SNP in affecting the same restriction enzyme recognition site.

Model for detecting the molecular associations between genotypes of candidate gene and economic traits:

To detect the molecular associations between the genotypes of *GH* candidate gene and economic traits, the effects of SNP genotype on different traits to be estimated using PEST software(Groeneveld, 2006) and applying the following multi-trait animal model (defined in matrix notation):

y= Xb + Zaua + e

Where y = vector of observed trait the animal; b= vector of fixed effects, the i^{th} genotype of GH gene (three genotypes); X and Za = incidence matrices corresponding to the fixed and additive random effects of the animal (ua), respectively; e = vector of random residual effects.

Molecular associations between candidate genes and economic traits in livestock:

In molecular study in Egypt, Mohamed (2019) concluded that: 1) the lactoferrin and prolactin genes could be considered as the essential major genes for milk yield and components in dairy cattle, 2) The strong associations among genotypes of prolactin and lactoferrin genes and milk yield traits could be used as a powerful tool in selection, 3), In Elkarada Friesian herd, we can select towards AA and AB genotypes for lactoferrin gene in Friesian cattle in Egypt, 4) For prolactin gene in Friesian Sakha and Elkarada herds, the CD genotype was the highest genotype in milk and protein yields taking into account NaeI as restriction enzyme so this genotype must be the main target in selection, 5) in other local Baladi herds, the generalized least square means for GGGT, and TT genotypes groups were 724, 294 and 584 kilogram of milk yield, respectively and the differences among the three genotypes in milk, fat and protein yields were not significant.

Abdel-Kafy *et al.* (2016) estimated the association between the *GH* C>T SNP with body weight, growth and reproductive traits in rabbit populations and reported that: (1) heterozygote genotype (T/C) was significantly associated with heavy weight of rabbits at 8 weeks and daily gain through 5-8 week interval compared to TT and CC genotypes ($P<0.05$), (2) The polymorphism of growth hormone gene (*GH*) in rabbits may has over-dominance at the locus c.-78C>T, and (3) Positive effects of the heterozygous genotype were recorded compared to both homozygous genotypes on body weights and body gains, i.e. the heterozygous genotype in c.-78C>T of *GH* polymorphisms could be used as a favorable genotype in rabbits and may be used in the Marker-assisted selection (MAS) programs to improve growth performance. Zaghloul (2019) stated that there were significant associations between *GH* gene and growth traits and this confirmed the fact that this gene could be used as a candidate gene as Marker-assisted selection in genetic improvement programs (MAS) to improve growth performance in rabbits and enhance the semen traits in the Egyptian rabbits.

Suggested genetic improvement program in the Egyptian cattle using molecular approaches:

Using traditional selection for genetic improvement of farm animals will cause slow and low genetic progress and using biotechnology techniques are the best way to achieve fast genetic improvement. The list of the necessary steps to perform a genetic improvement program in the Egyptian farm animals using the molecular applications could be summarized as follows:

Step No	Procedure and Executable Approach
1	**Determining the main objectives:** 1) To use the molecular information using genome-wide association approach to detect quantitative trait loci associated with some economic traits and use the significant QTLs in marker assisted selection. 2) To estimate the genomic breeding values (GBV) and their reliabilities for the genotyped animals and select the best cows and bulls in cattle based on their GBV to be parents for the next generation (genomic selection). 3) To use the semen of the best evaluated sires with the highest GBVs (proven sires) in the artificial insemination of the best evaluated cows and recording the same productive and reproductive traits on the resulted progeny.
2	**Collecting and recording the phenotypic data to get the full pedigree file for all animals (cows and bulls).:** Not adequate records must be discarded to ensure a homogenous data set. Adequate number of animals (e.g. 445 cows and 55 bulls) will be used. Pedigreed animals will be used to estimate the breeding value of the animals for the studied traits.
3	**Evaluating the animals genetically:** The genetic evaluation of animals will be carried out using a univariate animal model using the BLUPF90 software (Misztal *et al*., 2002). The breeding value will be estimated by an animal model using BLUPF90 software (Misztal *et al*., 2014) fitting univariate approach. The assumed model was: **y = Xb + Za + e** where, y= vector of observations, b= vector of fixed effects with an incidence matrix X, a= vector of random animal effects with incidence matrix Z, and e= vector of random residual effects
4	**Determine the list of main equipments required and the main list of chemicals for DNA extraction:** The necessary equipments chemicals are: PCR machine, Real-time PCR, Gel electrophoresis, Gel Documentation

System, Vortex, Centrifuge 30000 rpm under cooling, Biosafety cabinet,EDTA, Ethidium Bromide, Magnesium chloride, dNTPs, PCR Master Mix (2X), Sybr green master mix kits, PFU Taq DNA Polymerase, Agarose, Phenol (nucleic acid grade), DNA isolation Kit from animal tissues, Micropipettes set, Eppendorf.

5 **Collecting the blood samples and DNA extraction:**
The blood samples will be collected under sterile conditions by jugular vein puncture using 5-ml vacuum tubes of polypropylene containing EDTA. The samples will transfer to the laboratory in iceboxes containing ice packs and stored at -20° C until extract the genomic DNA. Genomic DNA extraction: genomic DNA will extract using a standard phenol-chloroform extraction protocol and ethanol precipitation methods (Sambrook, 1989).

6 **Genotyping the animals:**
The animals will be genotyped using SNPs markers.

7 **Applying the bioinformatics analyses for candidate genes and detecting QTLs:**
For bovine genome, a list of previously reported QTL for the traits was obtained from animal QTL db, release 30 (Hu *et al*., 2016) (http://www.animalgenome.org/QTLdb).

8 **Preparing and editing the genotyping files (Nicolazzi *et al*., 2014):**
Significantly markers ($P < 0.001$) not deviated from Hardy-Weinberg proportion were used.

9 **Estimating the average yield deviation for each trait:**
The yield deviation for each animal will be estimated using a mixed model procedure implemented in SAS software, version 9.4 (SAS 2014, SAS Institute Inc., Cary, NC, USA).

10 **Applying the Genome-Wide Association Study (GWAS):**
This step will be performed using the linear regression model as implemented in PLINK software (Purcell *et al*., 2007), where the average daily deviations will be regressed on the number of copies of the alleles using the PLINK software.
The animals with more than 20% missing marker genotype will excluded from the analysis. An SNP will be removed from the analysis if it had minor allele frequency less than 2%, call rate less than 90% and exhibiting deviation from Hardy-Weinberg equilibrium (HWE) with $P < 10\text{-}6$. Filtration of the marker data was performed with Plink software (Purcell *et al*. 2007). A genome wide association analysis will performed using linear regression model in the way of SNP-by-SNP, though, regressing the average daily deviations on SNP alleles and will be implemented by Plink software. The PLINK software that will be used for analyzing the GWAS using the following model:
$$\mathbf{y = xb+e}$$
Where, y is a vector of each GBVs of the genotyped individuals, x is each SNP information and b is coefficient value for x vector.

11 **Applying SNP association test:**
We will use genomic control p-value instead of normal p-value to search for the genes closely associated with economic traits, the National Center for Biotechnology Information (NCBI) database will be used.

12 **Applying genome-wide complex trait analysis (GCTA):**
The software v1.25.3 will be used to estimate the heritability of the average yield deviation (Yang *et al*., 2011).

13 **Estimating the genomic breeding values (GBV) to be applied in genomic selection:**
The genomic breeding values (GBV) will be estimated as the sum of the effects of dense genetic markers, or haplotypes of these markers, across the entire genome capturing all the quantitative trait loci (QTL) that contribute to variation in a trait. The QTL effects, inferred from individual single nucleotide polymorphism (SNP) markers, are first estimated in a large reference population with phenotypic information. In subsequent generations or in related populations, only marker information is required to calculate GEBV.

14 **Evaluating the prediction accuracy (EBV vs GEBV) :**
The correlation between the estimated traditional breeding values (EBV; using phenotypic data and pedigree) and the genomic breeding values (GBV)must be estimated, as well as the reliability of the two breeding values. Both the reliability of GEBV and the correlation between EBV and GEBV were used to evaluate the prediction accuracy (Moser *et al*., 2009).

15 **Estimating the Genomic Best Linear Unbiased Predictions (GBLUP) and SNP-GBLUP:**
The mixed model will be used to estimate the breeding values include BLUP and best linear unbiased estimation. These models estimate the fixed effects such as sex and predict the random effects such as SNPs for a given quantitative phenotype. The proposed mixed model and its solution are presented as follows:
$$\mathbf{y = Xb+Zu+e}$$
Where y is the vector of phenotypic values, X and Z are the design matrices; b and u are vectors of fixed and random effects, respectively. To compare the estimated breeding values (EBV) of the total SNPs with trimmed SNPs (unadjusted cutoff p-value 0.01), we will use the G-BLUP which adopts the genomic relationship matrix (GRM) with total pruned SNPs and SNP-GBLUP which utilizes the SNP-SNP relationship matrix with trimmed SNPs (Lee *et al*., 2014).

16 **Estimating the genomic breeding values (GBV) to be applied in genomic selection (GS):**
The genomic breeding values (GBV) and their reliabilities for the genotyped animals will be used to select the best cows and bulls based on their GBV to be parents for the next generation (genomic selection).
The genomic selection (GS) is a form of marker assisted selection in which genetic markers covering the whole genome are used so that all quantitative trait loci (QTL) are in linkage disequilibrium with at least one marker. This approach has become feasible due to revolution in SNP discovery method like deep sequencing and throughput SNP genotyping on DNA chip.

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