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Pit-1 gene polymorphism in bovines and its association with performance traits: A review

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Abstract

This paper aims to review the association of Pit-1 gene Polymorphism with performance traits in bovines. Many genes control quantitative economic traits like Milk production traits, each gene contributing a small effect. Recent molecular genetics leads to the identifications of the candidate genes, those having significant effects on the associated performance traits of economic importance. Being considered necessary for mammary gland development and milk yield Pit-1 gene is used as a candidate for milk production. Pit-1 gene Polymorphism and their association with performance traits in bovines could be helpful in easy animal selection and making future breeding strategies through marker-assisted selection (MAS).

Keywords: Pit-1 gene polymorphism, bovines, performance traits

Introduction

India has 192.49 million cattle and 109.85 million buffalo population (census, 2019) [6] making it 2th in world's largest cattle inventory holding country while ranks first in respect of buffaloes (FAO, 2015) [15]. Productivity importance of buffalo and crossbred cattle is towards higher side as compared to indigenous/nondescript cattle (Mavi *et al.*, 2017) [28].

Dairy animal breeders aim is focused on high milk yield per animal until now. Genetic gain per unit time along with the efficacy and accuracy of traditional selection may also be improved by incorporating current technologies like genetic markers (Markers assisted selection or MAS). Quantitative traits like Milk production traits are controlled by many genes, each one of them with small effect (Ozdemir, 2012) [39]. Recent molecular genetics leads to the identifications of genetic variation at specific loci of individual genes or candidate genes, those having significant effects on the associated performance traits of interest. The genetic variation in a gene affects the physiological pathways and phenotype. The proportion of genetic and phenotypic variation would be likely to affect the breeding strategy for the improvement of essential traits in the future. Studies conducted in recent past have successfully determined the genotypic profiles at many economically significant candidate gene loci like κ -casein, β -lactoglobulin, growth hormone, butyrophyllin, STAT-5a, prolactin and pituitary specific transcription factor etc. in several cattle breeds (Mukesh *et al.*, 2008) [32]. Quantitative trait loci (QTL) detection revealed that the region surrounding Pit-I on cattle, 1q21-q22 affected animal production (Woollard *et al.*, 2000) [57]. Pituitary transcription factor (Pit-1) has been shown to be a positive regulatory factor of Growth hormone (GH), Thyrotrophin, Prolactin (PRL) and β -subunit (TSH- β) in the mammalian pituitary (Doosti *et al.*, 2011) [12]. Bovine Pit-1, a DNA-binding POU domain 291 amino acid protein (Mattos *et al.*, 2004) [27]. Pit-1 gene is considered necessary for mammary gland development and milk yield (Oprzadek *et al.*, 2003) [36]. This gene is a candidate for milk production. Pit-1 gene Polymorphism and their association with performance traits in bovines could be useful for animal selection and breeding through marker-assisted selection (MAS).

In domestic animals, cattle, sheep and goat, Pit-1 gene was located on chromosome 1 at the centromeric region (1q21-22) (Woollard *et al.*, 2000) [57]. Identified *Hinf1* polymorphism of bovine Pit-1 gene by RFLP method in exon 6, Sequence analysis showed that the buffalo Pit-1 protein shares high homology with cattle - *Bos taurus* (100%), goat (99%), sheep (99%), human (96%) and pig (98%) (Parikh and Rank, 2013) [40].

Polymorphism in Pit-1 gene in bovines

A common belief in animal breeding is that genetic variation of quantitative traits such as

performance traits, growth rate and body composition is controlled by many genes, each with a small additive effect. A candidate gene is any DNA sequence (gene) in a chromosome considered likely to be in association with pre-specified interested phenotypes, or its protein product is suspected to be involved in supporting that interested phenotype. The genes of milk and hormones are outstanding candidate genes for linkage analysis with quantitative trait loci (QTL) because of their biological importance on the desired quantitative traits (Othman *et al.*, 2011) [38]. There are 344 QTL related to milk traits in cattle (Ogorevc *et al.*, 2009) [35]. Few of them are ABCG2, CRH, CSN3, CYP11B1, DGAT1, FGF2, GH1, GHR, KIT, LEP, LGB, ORL1, Pit-1, PRLR, SPP1, STAT1 and TG (Fontanesia *et al.*, 2015) [16]. Pit-1 (also known as POU1F1 or GHF-1) is a pituitary tissue-specific transcription factor belonging to the large family of POU domain proteins. The acronym POU derived from names of three transcription factors, the pituitary-specific Pit-1, the octamer-binding proteins Oct-1 and Oct-2, and the neural Unc-86 from *Caenorhabditis elegans* (Herr *et al.*, 1988) [17]. The POU family members have a wide variety of functions, all of which are related to the function of the neuroendocrine system and the development of an organism. Pit-1 gene is liable for pituitary development and hormone expression in mammals. The Pit-1 act as a positive regulatory factor for binding and trans-activity promoters for Growth hormone (GH) and Prolactin (PRL) and Thyrotropin subunit β (TSH β) in the mammalian anterior pituitary.

Because the PRL and the GH are crucial for mammary gland development and milk yield, the Pit-1 locus has potential as a marker for genetic variation in milk production traits. Polymorphism within the bovine Pit-1 gene RFLP detected with *Hinf*I nuclease was first described by Woolard *et al.* (1994) [56]. Moreover, different mutations in the Pit-1 gene has been described in mammals; while some of them cause GH and PRL gene-related disorders. Therefore, the gene encoding for Pit-1 was chosen as a candidate gene for genetic markers to investigate its association with different economic traits like growth, carcass traits, and lactating performance in domestic animals cattle.

Physiological effects

The role of Pit-1 in cell development and hormone secretion has been demonstrated by mutations in the Pit-1 gene of mouse and human. The Snell dwarf mouse possessed the first genetically transmitted dwarfism observed in mice. This dwarfism was characterized as a single autosomal recessive mutation on the Pit-1 gene. The mutation prevents the

development of the pituitary cells that secret growth hormone, thyrotropin and prolactin (Lin *et al.*, 1994) [24].

Another dwarf mouse, the Jackson mouse has a gross structural alteration of the Pit-1 gene and no Pit-1 expression. The Jackson mouse also has hypoplastic anterior pituitary gland and combined pituitary hormone deficiency of GH, PRL, and TSH β . Pit-1 carries out similar functions in humans as in rodents. Naturally occurring mutations in the Pit-1 gene have been found to cause combined pituitary hormone deficiency in humans (Cohen *et al.*, 1996) [9].

The dimerization interface of the two subdomains turned out to be the mutational hot spot in Pit-1 associated with combined pituitary hormone deficiency (Cohen *et al.*, 1996) [9]. Pit-1 gene inactivating mutation or deletions leads to exhibit anterior pituitary hypoplasia and dwarfism as studied in mice, it demonstrated the importance of Pit-1 in the ontogeny of the pituitary glands.

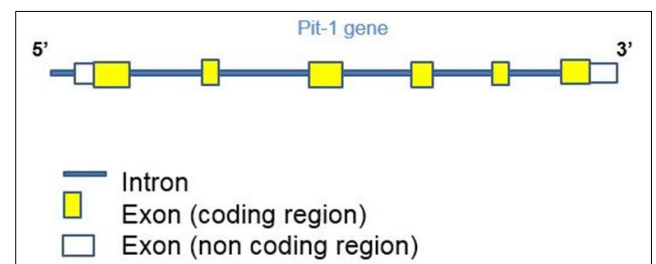


Fig 1: Organization of Pit-1 gene

In cattle, sheep and goat, Pit-1 gene is located on chromosome 1 (Moody *et al.*, 1995) [31]. Functional domains of Pit-1 protein are encoded by six separate exons (Theill *et al.*, 1992) [51]. Its sequence in cattle is known (Showalter *et al.*, 2002) [48] and available in the GenBank database at accession number AF453512. Pit-1 cDNA was cloned in bovine (Bodner *et al.*, 1988) [4].

Structure of PIT-I gene

The ORF (Open Reading Frame) of PIT-I gene consisted of 876 nucleotides encoding 291 amino acids with three domains: an N-terminal transcriptional activation domain from 25-72; a POU-specific domain (POU-S) (Inter Pro: IPR000327) consisted of 75 amino acid, i.e. from 124-198 amino acids, and a POU-Homeo domain (POU-H) (Inter Pro: IPR007103) consisted of 60 amino acid, i.e. from 214-273 amino acids.

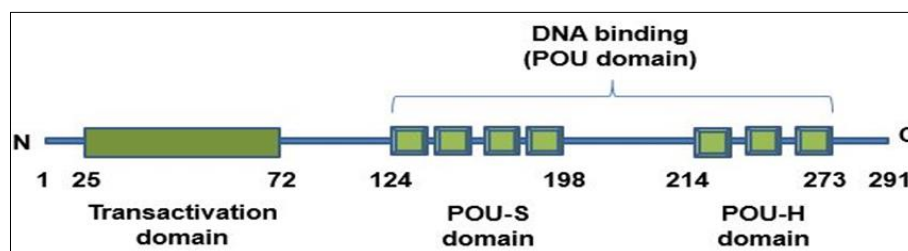


Fig 2: Structure of PIT-I gene

Less conserved N terminus domain is rich in serine and threonine residues 9 (serine/threonine activation domain, STA) mediates transcriptional activation (Theill *et al.*, 1989; Ingraham, 1993) [50, 20]. Highly Conserved regions (The POU-S and POU-H) are required for high-affinity DNA binding to

GH, PRL and TSH β genes (Cohen *et al.*, 1996) [9].

Analysis of alpha-helical domains and conserved structures in PIT-1 suggests that POU domain proteins interact with their DNA recognition sites with both the POU-H and POU-S domain contacting DNA (Ingraham, 1993) [20]. The POU-S

and the POU-H contain four α -helices and three α -helices, respectively (Klemm *et al.*, 1994)^[25].

The POU-S domain contributes to DNA-dependent Pit-1 gene interaction with itself (Theill *et al.*, 1989; Anderson and Rosenfeld, 1994; Cohen *et al.*, 1996)^[50, 2, 9].

The POU-homeo domain has considerable homology to the homeobox, which is a conserved sequence motif identified in genes that regulate developmental processes (Anderson and Rosenfeld, 1994)^[2]. The homeo domain of Pit-1 is predicted to form a helix-turn-helix motif and is required and sufficient for low-affinity DNA binding with relaxed specificity (Cohen *et al.*, 1996)^[9].

The POU-S and POU-H are separated by a non-conserved linker (Anderson and Rosenfeld 1994)^[2], necessary for high-affinity binding and accurate recognition of Pit-1 response elements (Theill *et al.*, 1989; Ingraham *et al.*, 1990)^[50, 8]. The linker can increase the local concentrations of POU-S and POU-H domains by tethering these two subdomains; it further enables the POU-S domain to have different orientations relative to the POU-H; while flexibility with POU domain recognizes DNA-binding sites (Ryan and Rosenfeld, 1997)^[45].

The Pit-1-POU-S domain makes similar DNA contacts to those of Oct-1-POU-S and conserved with many made by the prokaryotic repressors. The Oct-1-POU-S domain recognizes a GCAT half-site while the corresponding sequence recognized by the Pit-1-POU-S domain, GTAT, is on the opposing strand. As a result, the orientation of the Pit-1-POU-S domain relative to the Pit-1-POU-H domain is flipped as compared to the Oct-1-POU-S structure indicating the remarkable flexibility of the Pit-1-POU-S domain in adapting to variations in sequence within site. The C-terminus of helix 3 has an extended structure. The POU-S and POU-H domain of each Pit-1 molecule make major groove contacts on the same face of the DNA as the constraints imposed by its linker. As a result, the Pit-1 POU domain homodimer substantially surrounds its DNA binding site. In the PIT-1, POU domain the homodimer dimerization interface is formed between the POU-H domain (the C-terminal end of helix 3) of one Pit-1 molecule and the POU-S domain (N-terminus of helix I and the loop between helices 3 and 4) of the other Pit-1 molecule (Schonemann *et al.*, 1995)^[47].

Pit-1 Gene expression

Pit-1 might be configured differently on different sites as it binds to a complex pattern site in enhancers and promoters of genes regulated by it. These binding sites' sequence vary widely around a weak consensus sequence (A/T) (A/T) TATNCAT (Jacobson *et al.*, 1997)^[23].



Fig 3: Pit-1 Binding sites of target gene

GH gene expression is controlled by a pituitary specific promoter site with two essential binding sites for Pit-1, i.e.

GH-1 (-96 to -70) and GH-II (-134 to -106) for GH promoter activity in both *in vitro* as well as *in vivo* (Bodner *et al.*, 1988)^[4]. Prolactin transcription depends upon a distal enhancer segment (-1830 to -1530) and proximal promoter region (-422 to -36), each containing four Pit-1 binding sites (Nelson *et al.*, 1988)^[34]. Pit-1 shows a unique promoter spacing for prolactin gene transcriptional activation requirement. The transcriptional regulation is sensitive to the placement of the most proximal Pit-1 binding site and also the spacing between the TATA box and the proximal binding site on the prolactin gene (Smith *et al.*, 1995)^[49]. The prolactin gene also has a composite Ets/Pit-1 binding site and Ets protein, while Pit-1 functionally cooperate to permit transcriptional regulation (Howard and Maurer, 1995).

The 5' flanking region of the TSH- beta gene (-128 to -92) has a Pit-1 binding site. Three more upstream regions within the 5' flanking region of the TSH promoter at -274 to -258 (TSH A), -336 to -326 (TSH B) and at -402 to -385 (TSH C) contain sequences similar to the Pit-1 consensus binding sites and can bind Pit-1 (Mason *et al.*, 1993)^[26].

Pit-1 transcription is maintained by auto-regulation after the amount of protein has reached a critical level via two Pit-1 response elements and additional transcriptional regulation. Auto-regulation is carried out via Pit-1(binding site), is located at position -60 to -15 and has a positive effect on transcription and Pit-B2 (recognition element) is located just downstream of the start site of transcription has an inhibitory effect. These two elements work together to precisely control the basal level of Pit-1 expression (Chen *et al.*, 1990; McCormick *et al.*, 1990)^[8, 29].

Pit-1 promoter region around positions -200 and -155 has two binding sites for cAMP regulatory element binding protein (CREB) which regulates Pit-1 by cAMP (Chen *et al.*, 1990)^[8]. The intracellular level of cAMP also regulated by environmental causes which affect Pit-1 gene transcription, which is mediated by the CREB or related family members (Theill and Karin, 1993)^[52]. Restricting the expression of Pit-1 is mediated in part by Activin and inhibin; those are involved in somatotroph activities (Theill and Karin, 1993)^[52]. A regulated balance between co-repressor complex that contains N-15CoR/SMRT, mSin3A/B, histone deacetylases and a co-activator complex that includes the CREB-binding protein (CBP) and p/CAF determines the activity of Pit-1 (Xu *et al.*, 1998)^[58].

Review for Polymorphism in Pit-1 gene

Polymorphism at various sites of pit-1 genes has been studied by various researchers; however, exon 6 is most commonly studied. Various primers used for exon 6 are given in table 1. Commonly used Enzyme used for exon 6 restriction was *Hinf*I. Gene frequency varies from one herd to another (Table 2). Analysis of literature leads us to variation in gene frequency from A:0.95/B:0.05 (in grey bulls) to A:0.088/B:0.912 (in Jordan native cattle). Average gene frequency for allele A was 0.391, and that of allele B is 0.609 (average of gene frequency of allele A given by all the researchers in table 2). Further evaluation of Table 2, the difference between average observed (0.338) and average expected heterozygosity (0.344) was negligible.

In Murrah buffalo (Mavi *et al.*, 2017)^[28] Egyptian buffaloes (Othman *et al.*, 2011)^[38] Indonesia buffaloes (Misrianti *et al.*, 2010)^[30] reports of Pit-1 allele fixation were found; however, study in Mehsana Buffalo (Parik and Rank, 2013)^[40] showed polymorphism.

Association of Pit-1 polymorphism with performance traits

Association studies of Pit-1 Gene with performance traits conducted by various researchers is given in Table 3. Pit-1 was found to be having significantly associated with milk production (Moody, 1995; Zwierzchowski *et al.*, 2002; Parmentier *et al.*, 1999; Reza *et al.*, 2010; Doosti *et al.*, 2011 and Chauhan *et al.*, 2015) [31, 65, 41, 44, 12, 7], protein yield (Renaville *et al.*, 1997; Parmentier *et al.*, 1999; and Reza *et al.*, 2010) [42, 41, 44], fat yield (Mattoss *et al.*, 2004; Chauhan *et al.*, 2015) [27, 7], body conformation traits. (Renaville *et al.*, 1997^b; Oprzadek, 2003; Reza *et al.*, 2010) [42, 36, 44] remarkable growth performance, (Renaville *et al.*, 1997^b; Doosti *et al.*, 2011) [42, 12] and fertility traits (Doosti *et al.*, 2011) [12]. While studies showing no associations between Pit-1 (*Hinf1*) polymorphism and milk production traits were also found in the literature (Dybus *et al.*, 2004; Zakizadeh *et al.*, 2007; Aytekin and Boztepe, 2013) [13, 62, 3]. Ozdemir (2012) [39] while working with Holstein and Native Ear cattle in turkey and Trakovicka *et al.* (2015) [53] while working with Holstein cattle in Slovak republic found polymorphism with Pit-1 gene having a PCR product of 260bp digested by *Hinf1* restriction enzyme. Chauhan *et al.* (2015) [7] in Sahiwal cattle using PCR-RFLP revealed 600 bp product and restriction digestion

with *Hinf1* showed three types of genotypes. Further, they discovered a significant difference among the three genotypes for total milk yield and milk yield at 300 days with AA genotype showing higher value than AB and BB genotypes in the first lactation. Zabeel *et al.* (2018) [61] in native cattle in Kerbala city found significant associations between Pit-1 gene polymorphism and milk yield traits.

Summary & Conclusion

Most of studies by various scientists have shown in different breeds that Pit-1 gene, have significant association with economic traits in bovines, might be used as potential molecular genetic markers in breeding programs. But due to less number of animals involved in earlier studies, further researches are needed to properly examine the associations of polymorphisms of Pit-1 with growth and efficiency traits in large populations of distinct bovine species and breeds. In addition, the functional mechanisms of identified SNPs or haplotypes affecting growth and efficiency traits should be further investigated. Along with the Pit -1 gene other genes of economic importance should be simultaneously studied in same population so that relative weightage may be more precisely decided in index selection of marker assisted selection.

Table 1: Different Forward and reverse Primers Pairs for amplification of Pit-1 gene found in literature

Sr. No.	Name of Gene		Primer Sequence 5' ---> 3'	Number of Base Pairs (in primers)	References
1	Pit-1	Forward	ACT CGC TAT TAC ACA ATA GGA GAG CCT	27	Ozdemir (2012) [39] Trakovicka <i>et al.</i> (2015) [53]
		Reverse	TCC TGC CAA CTC CTC ACC TCC C	22	
2	Pit-1	Forward	GAG CCT ACA TGA GAC AAG CAT C	22	Javanmard <i>et al.</i> (2005) [21] Misrianti <i>et al.</i> (2010) [30] Ahmadi <i>et al.</i> (2015) [11] Chauhan <i>et al.</i> (2015) [7]
		Reverse	AAA TGT ACA ATG TGC CTT CTG A	22	
3	Pit-1	Forward	AGC ATG CGC TCT CTT GGT GC	20	Parik and Rank (2013) [40]
		Reverse	AAG GCG CAG CCG CAT GTA GA	20	
4	Pit-1	Forward	CAA TGA GAA AGT TGG TGC	18	Moody (1995) [31] Mattoss <i>et al.</i> (2004) [27]
		Reverse	TCT GCA TTC GAG ATG CTC	18	
5	Pit-1	Forward	AAA CCA TCA TCT CCC TTC TT	20	Doosti <i>et al.</i> (2011) [12] Othman <i>et al.</i> (2011) [38] Aytekin and Boztepe (2013) [3] Mavi <i>et al.</i> (2017) [28]
		Reverse	AAT GTA CAA TGT GCC TTC TGA G	22	

Table 2: Different studies found in the literature on various breeds for genotype and allele frequency of Pit-1 polymorphism

Breed	Number of animals understudy	Genotype frequency			Allele frequency		Expected heterozygosity	Length of PCR Fragment	Reference
		AA	AB	BB	A	B			
Italian H-F Bulls	89	0.022	0.315	0.553	0.188	0.812	0.305	451 bp	Renaville <i>et al.</i> (1997) [43]
Belgian Blue	350	0.200	0.445	0.355	0.423	0.577	0.488		
Holstein	196	0.026	0.257	0.717	0.155	0.845	0.262	451 bp	Oshima and Serrano (2003) [37]
Black and White Bulls	144	0.063	0.368	0.569	0.247	0.753	0.372	451 bp	Oprzadek <i>et al.</i> (2003) [36]
Angus beef cattle	416	0.111	0.440	0.450	0.331	0.669	0.443	451 bp	Zhao <i>et al.</i> (2004) [64]
Gry bulls	40	0.900	0.100	0.000	0.95	0.05	0.095	1355 bp	Mattos <i>et al.</i> (2004) [27]
Poland Black-and-White cows	900	0.052	0.382	0.566	0.243	0.757	0.368	451 bp	Dybus <i>et al.</i> (2004) [13]
Holstein-Friesian	46	0.10	0.35	0.55	0.283	0.717	0.405	451 bp	Vargas <i>et al.</i> (2004) [54]
Sarabi	82	0.451	0.341	0.207	0.622	0.378	0.470	600 bp	Javanmard <i>et al.</i> (2005) [21]
Golpayegani	57	0.614	0.263	0.123	0.746	0.254	0.379		
Sistani	38	0.842	0.158	0.000	0.921	0.079	0.145		
Taleshi	70	0.614	0.314	0.071	0.771	0.229	0.353		
Manzadrani	26	0.692	0.269	0.038	0.827	0.173	0.286		
Dashtiyari	8	0.625	0.000	0.375	0.625	0.375	0.469		
Golpayegani x Brown Swiss F ₁	13	0.000	0.769	0.231	0.385	0.615	0.473		
Nellore	79	0.795	0.205	0.000	0.897	0.103	0.185	1301 bp	Curi <i>et al.</i> (2006) [11]
Canchim	30	0.800	0.167	0.033	0.883	0.117	0.207		
1/2 Simmental	30	0.733	0.267	0.000	0.867	0.133	0.231		

1/2 Angus	245	0.295	0.693	0.012	0.641	0.389	0.438		
Nayang	100	0.210	0.510	0.280	0.465	0.535	0.497	451 bp	Xue <i>et al.</i> (2006) ^[59]
Qinchuan	218				0.232	0.768	0.356	451 bp	Yan <i>et al.</i> (2006) ^[60]
China HF					0.13	0.87	0.23		
Manzadrani	96	0.167	0.406	0.427	0.370	0.630	0.466	451 bp	Zakizadeh <i>et al.</i> (2007) ^[62]
Sarabi	84	0.083	0.381	0.536	0.274	0.726	0.398		
Golpayegani	110	0.109	0.455	0.436	0.336	0.664	0.446		
Holstein	111	0.059	0.297	0.644	0.208	0.792	0.329		
Simmental	76	0.118	0.197	0.685	0.217	0.783	0.340	1350 bp	Viorica <i>et al.</i> (2007) ^[55]
16 distinct Indian native cattl	723	0.002	0.119	0.881	0.063	0.937	0.118	1350 bp	Mukesh <i>et al.</i> (2008) ^[32]
Holstein cows	262	0.031	0.450	0.519	0.256	0.744	0.381	451 bp	Edriss <i>et al.</i> (2008) ^[14]
5/8 Charolais 3/8 Zebu					0.13	0.87	0.23	1301 bp	Carrijo <i>et al.</i> (2008) ^[5]
21/32 Charolais 11/32 Nelore					0.27	0.73	0.39		
Jordan native cattle	36	0.000	0.176	0.8235	0.088	0.912	0.160	422 bp	Jawasreh <i>et al.</i> (2009) ^[22]
Holstein-Friesian	45	0.046	0.255	0.697	0.174	0.826	0.288		
Qinchuan	67	0.030	0.403	0.537	0.232	0.768	0.356	451 bp	Zhang <i>et al.</i> (2009) ^[63]
Limousin x Qinchuan	47	0.043	0.277	0.681	0.181	0.819	0.296		
Angus x Qinchuan	36	0.111	0.444	0.444	0.333	0.667	0.444		
Germany Yellow x Qinchuan	42	0.071	0.214	0.714	0.178	0.822	0.293		
Najdi	84	0.357	0.298	0.667	0.185	0.816	0.301	451 bp	Nassiri <i>et al.</i> (2010) ^[33]
Holstein-Friesian	45	0.022	0.445	0.533	0.244	0.756	0.369	611 bp	Misrianti <i>et al.</i> (2010) ^[30]
East Anatolian Red	71	0.14	0.54	0.32	0.41	0.59	0.483	260 bp	Ozdemir (2012) ^[39]
Holstein	181	0.04	0.31	0.65	0.20	0.80	0.319		
Brown Swiss cattle		0.12	0.51	0.37	0.37	0.63	0.47	451 bp	Aytekin and Boztepe (2013) ^[3]

Table 3: Different studies found in the literature on various breeds for Pit-1 polymorphism and performance association

Breed/ Hard understudy	Findings regarding the association between Pit-1 gene and Performance traits	Reference
Bos taurus (cattle)	The A allele of the Pit-1 gene has a significant role in milk production as cattle with genotype AA and AB contain high levels of milk production than BB genotype.	Moody (1995) ^[31]
Friesian cattle	Allele A in Pit-1 locus emphatically affected milk production traits.	Sabour <i>et al.</i> (1996) ^[46]
Italian Holstein-Friesian bulls	Allele A showed a significant advantage over the B allele for milk yield (P<0.10) protein yield (P<0.05) some conformation traits like body depth (P<0.10) angularity (P<0.10) rear leg set (P<0.10) and also less fat percentage (P<0.10) Pit-1 polymorphism was found to be associated with milk yield and conformation traits in cattle. Within Italian Holstein-Friesian cattle the allele A of Pit-1 (frequency 0.18) showed a significant superiority over the allele B for milk and milk protein yields and body conformation traits.	Renaville <i>et al.</i> (1997) ^[43]
Italian HF	Cows with genotype BB had remarkable growth performance that could be used for breeding new lines of beef cattle.	Renaville <i>et al.</i> (1997) ^[43]
Friesian cattle	it was shown that allele A in the Pit-1 locus positively affected milk production traits	Zwierchowski <i>et al.</i> (2002) ^[65]
	The significant advantage of the <i>Hinf1</i> B allele for milk (+222.4) and protein (+9.17) yields while inferiority for fat yield (-2.29%).	Parmentier <i>et al.</i> (1999) ^[41]
Holstein Friesian cows	AA genotype of Pit-1 had a significant effect on the total milk yield	Oshima and Serrano (2003) ^[37]
Black-and-White bulls	The effect of Pit-1 genotype was observed on carcass dimensions only. The AA homozygotes had higher chest circumference chest depth and circumference of round but BB homozygotes had a higher round width.	Oprządek <i>et al.</i> (2003) ^[36]
Black-and-White cattle	Found no significant associations between Pit-1 <i>Hinf1</i> polymorphism and milk production (P>0.05).	Dybus <i>et al.</i> (2004) ^[13]
Gyr Bulls	<i>Hinf1</i> variants are associated with the fat yield. AB genotype bulls (16.6 kg) were superior than AA genotype (6.5 kg) for fat yield (P<0.05).	Mattos <i>et al.</i> (2004) ^[27]
Dairy cows from Central Chile.	AA genotype was advantageous for milk yield and not favourable for the reproductive traits taking into account the breeding values of animals	Vargas <i>et al.</i> (2004) ^[54]
Golpayegani breed and Holstein cattle of Iran	No significant association observed between Pit-1 <i>Hinf1</i> polymorphism and milk production in (P>0.05) found the transition from A to G in nucleotide 1256 responsible for <i>Hinf1</i> allele.	Zakizadeh <i>et al.</i> (2007) ^[62]
Najdi cattle	No significant association was obtained for Pit-1 genotypes on milk traits.	Nassiri <i>et al.</i> (2010) ^[33]
Italian Holstein Friesian cattle.	Allele A was significantly superior over allele B for milk and milk protein yields and body conformation traits	Reza <i>et al.</i> (2010) ^[44]
Holstein cattle	AA genotypes of the Pit-1/ <i>Hinf1</i> genotype could be useful in fertility traits and create the next generation for an increase in milk production and growth	Doosti <i>et al.</i> (2011) ^[12]
Romanian Simmental cattle	Polymorphism in relation to milk yield fat and protein percent and confirmed this locus as the candidate genes that may produce differences in milk characteristics and can be used in marker assisted selection.	Cosier <i>et al.</i> (2012) ^[10]
Brown Swiss Cattle	Non-Significant (0.05%) associations between the Pit-1 polymorphism and production traits	Aytekin and Boztepe (2013) ^[3]
Mehsana buffalo	SNP c.160 T>A was significantly associated with the milk fat percentage (P=0.0358).	Parik and Rank

		(2013) ^[40]
Slovak Simmental cattle	Pit-1/ <i>Hinf1</i> genotypes and milk production parameters – milk protein and fat yield (kg) in standard length of lactation were not significant.	Trakovicka <i>et al.</i> (2015) ^[53]
Holstein dairy cows	Milk production were significantly higher in cows with genotype lacking the allele A (BB) than those with the genotype having the allele A (AB AA)	Ahmadi <i>et al.</i> (2015) ^[11]
Sahiwal cattle	Significant difference was found among the 3 genotypes for total milk yield and milk yield at 300 days with AA genotype showing higher value than AB and BB genotypes in the first lactation.	Chauhan <i>et al.</i> (2015) ^[7]
Holstein Cattle	Cattle with AB genotype have milk with significantly higher fat percentage in comparison with AA and BB genotypes.	Hoseinzadeh <i>et al.</i> (2015) ^[18]

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