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## Comprehensive review of selection signature identification: Exploring frequency-based ( $F_{ST}$ ) and Haplotype-Based (iHS) methods

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### Abstract

Genome-wide detection of selection signatures in livestock populations" makes use of high-throughput technologies to spot genetic alterations brought on by selective breeding. This knowledge can be utilized to identify potential genes that are being selected for traits that are connected with economic importance, as well as to comprehend the breeding and process of evolution that have shaped livestock populations. Identifying selection signatures is a potent approach for comprehending the underlying genetics of livestock traits and strengthening livestock breeding programs. By targeting genes under selection, breeders can improve the performance and productivity of livestock populations, which can lead to increased profits and better food security. Positive selection can fix favourable allele frequencies throughout a population and raise their frequencies, which reduces diversity at or near the selection site (Selection Sweep). Variations in allele frequency ( $F_{ST}$ ) and the deterioration of linkage disequilibrium (iHS) can be used to identify selection signatures. The goals of this review aim to give us a better understanding of how to identify selection signals in livestock, which will inform us about the genetic mechanism behind phenotypic variations within and between breeds.

**Keywords:** Comprehensive, identification,  $F_{ST}$ , iHS

### Introduction

Over the years, artificial selection has been a vital component in animal breeding by consistently improving the animal performance and productivity via the use of various selection breeding strategies. Genomic regions that control breed characteristics like morphology, body conformation, production, reproduction, behaviour, environment adaption, and illness resistance appear to be altered by the selection processes. It is anticipated that these breeding strategies will leave distinctive genomic fingerprints known as selection signatures (Nielsen, 2005; Jensen *et al.*, 2016) [44, 28]

Identification of selection signatures/footprints has become possible in recent years as a result of improvements in genotyping with high throughput technologies, accessibility of animal genomic information, and statistical methodology. Such investigations gives information on the domestication and evolutionary processes that produced a wide range of cattle breeds able to endure in various environments and production systems. Additionally, these investigations assist in the identification of potential genes associated with essential economic traits in the livestock population. After a few generations, the favorable mutation is promptly fixed, which results in a regional decrease in genetic diversity downstream as well as upstream of the favoured mutation. The process by which occurrence of new beneficial mutation increases in frequency in a population and hence reduces variability in the associated neutral sites is termed as 'Selective sweep or hitchhiking effect or genetic draft' (Braverman *et al.*, 1995; Fay and Wu, 2000; Smith and Haigh, 2007) [10, 18, 59].

Domestication has significantly altered the morphological and behavioral characteristics of modern domestic animals, in conjunction with breed formation and selection strategies aimed at increasing the production of particular goods or achieving a morphological/behavioral norm, allowed the development of a wide range of modern breeds (Diamond, 2002; Toro *et al.*, 2007; Flori *et al.*, 2009) [17, 65, 19]. These characteristics, combined with comprehensive knowledge of genomic regions that affect economically significant traits and recent developments in the field of genomics, make identifying loci subjected to selection and validating new methods

established to detect selection signatures an excellent opportunity (Hayes *et al.*, 2008; Flori *et al.*, 2009) [24, 19].

Kim and Stephan (2002) [31] reported that an expansion in the average linkage disequilibrium (LD) leading to long haplotypes is also anticipated in the area surrounding the selected site. The selection signature vanishes quickly as LD decays and high frequency neutral alleles become fixed in the population following the fixation of the beneficial selected mutation (Przeworski, 2002; Kim and Nielsen, 2004; McVean, 2007) [51, 32, 40]. Therefore, a recent selective sweep is indicated by a high frequency derived allele accompanied by a long-range LD (Sabeti *et al.*, 2002; Voight *et al.*, 2006) [57, 67]. Furthermore, in the area surrounding the selected locus, levels of within-population diversity tend to decrease whereas levels of between-population diversity tend to increase (Beaumont, 2005; Storz, 2005) [6, 65].

There are mainly two types of selection sweep; Hard sweep selective sweep in which a newly emerged allele with a powerful selective advantage rises rapidly in frequency before it reaches fixation. However, when the selected allele is part of existing genetic variation, it results in a "soft sweep," in which the selective footprint is less conspicuous and the frequency of the selected allele at the start of the selected process is the most important factor affecting the selective sweep (Przeworski *et al.*, 2005; Pritchard *et al.*, 2010) [52, 50].

#### Method of identification of selection signatures

Various statistical tools have been implemented to find the selection signatures in livestock which are based on various approaches like variation in allele frequency, decay of linkage disequilibrium, reduced local variability and population differentiation. The integrated haplotype score (iHS) and F-statistics (Fst) are the two most common method which are used identification of selection signatures (Pybus *et al.*, 2014) [53].

#### Integrated Haplotype Score (iHS)

The iHS is a within-population method and has primarily been used to reveal selection signatures within a single population. It is based on differential levels of linkage disequilibrium (LD) and hence enhances LD on chromosomes that contain the derived (selected) allele but not the unselected allele, which acts as a "control" allele. Therefore, iHS used for detection of recent positive selection at a locus having a rapidly increased frequency at selected sites (Voight *et al.*, 2006) [67]. This method is an extension of the EHH method of selection signatures and based on comparing EHH between derived and ancestral alleles within a population.

The iHS value is simply a measure of how unusual the haplotypes surrounding an SNP with comparison to the rest of the genome (Voight *et al.*, 2006) [67]. In this statistics, each SNP is treated as a core SNP and the test begins with computation of the EHH for each core SNP. Each core SNP can be ancestral or derived because SNPs are biallelic loci. The integral of the observed decay of EHH from a core SNP until EHH hits 0.05 (the area under the curve in an EHH vs. distance plot) is computed for the test. On the basis of whether it was computed from the ancestral or the derived allele of the core SNP, this value is called as the integrated EHH (iHH) and is designated as iHHA or iHHD. This value is then standardized so that direct comparisons between various SNPs can be made independently of allele frequencies (Voight *et al.*, 2006) [67].

The main advantage of using iHS over EHH is that it helps in overcoming the effect of heterogeneous recombination rates across the genome. iHS is the most extensively used haplotype-based statistic and has the greatest power to detect selection when the selected allele has swept to intermediate frequencies but the derived allele must have only been on a separate background (Haplotype) prior to selection and must not have reached fixation. The main drawback of *iHS* tests is that rely on allele frequencies at core SNPs, hence their power for detecting selection when the selected allele has reached fixation is limited.

#### Fixation Index (Fst)

The most commonly used statistics of single site genetic differentiation has been Wright Fixation Index (Wright, 1943) [71], which used several sets of parameters for differentiation of natural population in terms of genetic variations. Wright (1951) [72] coined the term "fixation index" (Fst) to describe the degree of genetic differentiation between populations based on variations in allele frequencies. Fst compares the genomic variation at a locus between populations to the variation within populations. Therefore, Fst is a statistical test which measures the evidence of selection because high Fst values are the proof of positive selection and low values are indicator of negative or neutral selection (Kullo and Ding, 2007) [33]. Because, whenever divergent selection operates on one or more loci, and markers found within or near such genes will have high  $F_{ST}$  values. These loci could be used to identify genomic areas that have been subjected to selection (Gianola *et al.*, 2010) [52].

The main advantage of  $F_{ST}$  over multi-locus testing approaches such as SFS or LD in that it is SNP-specific and can theoretically show the real genetic variants under selection. Because single locus  $F_{ST}$  values are highly variable and selective sweeps will cause a full series of SNPs to have an elevated  $F_{ST}$  profile, it is more efficient to look for a number of consecutive SNPs with higher  $F_{ST}$  score rather than studying each SNP separately.

$F_{ST}$  has been widely employed to detect the selection signatures in domesticated species. For e.g Boyko *et al.*, (2010) [9] found that a large number of SNPs with high Fst values between dog breeds are related with phenotypic traits such as size, ear morphology and coat color. Akey *et al.*, (2002) [1] used 1Mb sliding windows on ~21,000 SNPs in 10 breeds of dogs for the identification of pattern of variation in particular breeds on larger areas with high Fst values. A highly distinct region on chromosome 13 in Shar-Pei contains the HAS2 gene, which was later linked to the wrinkled skin phenotype of this breed (Olsson *et al.*, 2011) [46].

A comparable study used a newly constructed high-density genotyping array with 170K uniformly spaced SNPs to examine 46 breeds and discovered 44 genomic locations with extreme differentiation across the dog genome.

#### Selection Signatures in Livestock

Domestication causes dramatically changes in the behavior and morphology of livestock species. In the early phases of domestication, selection was not done on the basis of some selection criteria i.e., unconscious selection was performed for the traits. This early phase of selection was then followed by rigorous selection which has objectives on the basis on them traits were selected for the selection (Diamond, 2002; Gregory, 2009) [17, 23].

The development of specialized breeds, which were produced to improve a particular products or to meet a morphological standard, increased the variations between domesticated animals and their wild relatives, as well as resulting in an enormous variety of different populations, each with specific traits related to their specialization. It has been found that some of these traits were influenced by several interacting genes but with smaller impact. Hence, these results showed a unique opportunity to learn more about the molecular basis of these traits, especially since the majority of economically important livestock traits are quantitative in nature (Andersson and Georges, 2004) [2]. These studies helps to identify the genes or the gene combination which were targeted by selection procedure and were related with the same traits but selected differentially between breeds and hence revealed the genes important for genetic correlations and the domestication process (Schlötterer, 2003; Hayes *et al.*, 2008; Ojeda *et al.*, 2008; Flori *et al.*, 2009; MacEachern *et al.*, 2009) [58, 24, 45, 19, 38].

### Selection Signatures in Cattle

Bovine breeds are mainly divided into two major categories indicine and taurus. Several breeds have emerged within each group, with significant intra and inter-group variability in terms of productivity (milk yield and quality, meat production), morphological (coat color, presence/absence of horns), and adaption (disease resistance, heat tolerance) traits (The Bovine HapMap Consortium, 2009) [8]. Several genome-wide studies have been conducted, each concentrating on a different approach and using a different group of breeds for finding the selection signatures in bovines (Prasad *et al.*, 2008; Barendse *et al.*, 2009; Flori *et al.*, 2009; Gautier *et al.*, 2009; Hayes *et al.*, 2009; MacEachern *et al.*, 2009; The Bovine HapMap Consortium, 2009; Li *et al.*, 2010a; Qanbari *et al.*, 2010, 2011; Stella *et al.*, 2010; Wiener and Wilkinson, 2011; Hosokawa *et al.*, 2012) [49, 4, 19, 20, 25, 38, 8, 35, 54, 55, 61, 70, 26].

Various experiments in beef cattle have been discovered selection signatures in the centromeric region of BTA14 by using methods such as variations in allele frequencies, iHS, and FST (Hayes *et al.*, 2009; The Bovine HapMap Consortium, 2009) [25, 8], an area involved in the regulation of marbling and fatness traits (Barendse, 1999; Moore *et al.*, 2003; Thaller *et al.*, 2003; Casas *et al.*, 2005; Pannier *et al.*, 2010). In recent years, an increase in intramuscular fat percentage in Australian Angus, as well as asignificant impact of this area on fat traits, may corroborate the selection signature found in these studies (Hayes *et al.*, 2009) [25].

Bellinge *et al.*, (2005) [7] reported the presence of double-muscle phenotype and growth differentiation factor 8 (GDF-

8) in some beef breeds of cattle. Wiener *et al.*, (2003); Wiener and Gutierrez-Gil, (2009) [69] reported the decrease in heterozygosity surrounding these genes in double-muscle breeds and there is increase in LD has been demonstrated by using iHS approach (The Bovine HapMap Consortium, 2009) [8].

Barendse *et al.*, (2009) [4]; The Bovine HapMap Consortium. (2009) [8]; Qanbari *et al.*, (2011) [55] used the Fst method to find the selection signatures in median region of BTA2 gene in beef breed of cattle. It has been revealed that the region surrounding to this gene contains many other gene which are related with feed efficiency like R3H Domain Containing 1 (R3HDM1), Zinc finger, RAN Binding Containing 3 (ZRANB3) genes and intramuscular fat in beef breeds (Barendse *et al.*, 2007, 2009). Cobanoglu *et al.*, (2006) found the existence of QTLs affecting milk fat and protein traits in the region surrounding the Signal Transducer and Activator of Transcription 1(STAT1) gene in Holstein breed of cattle. Cole *et al.*, (2009) [16] found the area surrounding the Sialic Acid Binding Ig-Like Lectin 5 (SIGLEC-5) and Zinc Finger Protein 577 (ZNF577) genes has been linked to Net Merit and several related traits in Holstein cattle, including conformation, longevity, and calving ease.

### Selection Signatures in Pigs

About 9000 years ago, pig domestication occurred independently in numerous locations across Eurasia (Larson *et al.*, 2005) [34]. Domestic pig species are present in vast range of environment and exhibit wide variations in behavioral, morphological and ecological characteristics (Larson *et al.*, 2005; Chen *et al.*, 2007) [34, 12]. Ma *et al.*, (2014) [37] used three between-population and two within-population methods to detect the selection signatures on the X chromosome in three pig breeds by using Illumina Porcine 60k SNP chip. They employed Fst and Integrated Haplotype Score (iHS) for the detection of selection sweeps. In the detection of selection footprints by using inter-population approaches, 4, 2 and 4 potential selection regions by Fst were identified in Landrace, Chinese Songliao and Yorkshire. For within-population approaches, 7, 10 and 9 potential selection regions were identified in Landrace, Chinese Songliao and Yorkshire by iHS.

Bioinformatics analyses on X chromosome of pigs by various studies identified that the genes associated with meat quality, reproduction and immune were found in potential selection regions. Following are the example of candidate gene enrichment under selection regions and their functions identified in pigs.

**Table 1:** Shows the Details of candidate gene.

Candidate gene	Gene function	References
ZDHH9	Associated with congenital splay leg	(Maak <i>et al.</i> , 2010) [36]
ACE2	Associated with the inhibition of the differentiation of adipocytes	(Van-Laere <i>et al.</i> , 2003) [66]
S100G	Associated with the establishment and maintenance of pregnancy	(Choi <i>et al.</i> , 2009) [14]
STS	Associated with estrogen actions	(Suzuki <i>et al.</i> , 2011) [63]
RS1	Associated with the X-linked juvenile retinoschisis	(Steiner-Champlaud <i>et al.</i> , 2006) [60]
AGTR2	Associated with the preeclampsia	(Zhou <i>et al.</i> , 2013) [75]
OBP	Odorant-binding proteins	(Mamone and DAuria, 2008) [39]
ATP1B4	Plays essential role in perinatal development	(Pestov <i>et al.</i> , 2011) [48]
ACSL4	Associated with the pork quality	(Rusc <i>et al.</i> , 2011) [56]
TRPC5	Associated with the fight against cardiovascular disease	(Hu <i>et al.</i> , 2009) [27]

### Selection signatures in sheep and goat

Around 9000 years ago, sheep and goats were the first domesticated livestock species. The vast distribution of these species is reflected by their adaptation to varied environments which resulted in tremendous morphological variation among populations (Diamond, 2002; Gentry *et al.*, 2004; Naderi *et al.*, 2008; Chessa *et al.*, 2009; Kijas *et al.*, 2009) [17, 21, 43, 13, 29]. Since their domestication, sheep have been used and selected for meat, wool and milk production (Chessa *et al.*, 2009; Kijas *et al.*, 2009) [13, 29]. Kijas *et al.*, (2012) [30] used the  $F_{ST}$  method by performing a genome wide scan on a panel of 2819 individuals from 74 sheep breeds. They identified the thirty-one selection sweeps which contained the genes associated with coat color, bone morphology, growth and reproduction traits. Another genome wide scan was conducted by Moradi *et al.*, (2012) [12] by using approximately 50K SNPs to find the selection signatures on a group of fat and thin tailed sheep breeds. They postulated that at least three regions in all of the three breeds (OAR5, OAR7 and OARX chromosomes) have undergone selection.

Zhu *et al.*, (2019) [74] employed the  $F_{ST}$  methods in their proposed study for the detection of selection signatures on X chromosome in three sheep breeds with different tail types. They identified 49, 34 and 55 candidate selection regions in large-tailed Han, Altay and Tibetan sheep, respectively. Moreover, the bioinformatics analysis of the genes present in these areas were associated with fat metabolism like *DHRSX*, *CACNA1F* and *PNPLA4*, energy metabolism like *FAM58A* gene was linked, skeletal muscle development like *SRPK3* gene and with immune system like the *IL2RG* gene. They also identified the selection signatures on the X chromosome in several sheep genes which are associated with reproduction.

Zhu *et al.*, (2015) [73] performed another genome-wide scan by using an OvineSNP50 Bead Chip and implemented two methods of selection signatures integrated haplotype score and fixation index analyses to detect selection signatures on the X chromosome in three sheep breeds. They detected 49, 34, and 55 candidate selection regions respectively.

Bioinformatics analysis of some of the genes in these regions is associated with the reproduction. They identified some selection regions which contain the genes that had human orthologs, including *BKT*, *CENPI*, *GUCY2F*, *MSN*, *PCDH11X*, *PLP1*, *VSIG4*, *PCDH19*, *PDHA1* and *SRPX2*. The *VSIG4* and *PCDH11X* genes are involved in function related with immune system and disease, *PDHA1* is related with biosynthetic related pathways, and *PCDH19* is related with the nervous system and skin.

### Conclusion

The detection of selection signatures plays a crucial role in understanding the genetic basis of adaptation in livestock populations. In this paper, we discussed two widely used methods,  $F_{ST}$  and  $iHS$ , to identify these selection signatures. Through  $F_{ST}$  analysis, we assessed the genetic differentiation between populations, allowing us to pinpoint regions that have undergone positive selection. This method provides insights into the genes and genetic variants that contribute to traits important for local adaptation and production performance. Furthermore, the  $iHS$  method enabled us to identify recent positive selection events, focusing on selective sweeps around advantageous alleles. By examining extended haplotypes, we were able to unravel the genomic regions

associated with important traits and uncover potential candidate genes involved in livestock adaptation.

The combination of  $F_{ST}$  and  $iHS$  methods provides a comprehensive approach to detect selection signatures, offering a deeper understanding of the evolutionary forces shaping livestock populations. These findings contribute to the knowledge of breed-specific adaptations, facilitate genetic improvement programs, and aid in the development of more resilient and productive livestock breeds.

### Future Prospects

Moving forward, further advancements in genomic technologies and analytical approaches will continue to enhance our ability to detect selection signatures with greater precision and accuracy. This will ultimately pave the way for targeted breeding strategies and the conservation of genetic diversity in livestock populations, ensuring their long-term sustainability and resilience in the face of changing environments and evolving production challenges.

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