COMPARATIVE GENOME ANALYSIS OF INTERNATIONAL TRANSBOUNDARY CATTLE BREEDS

THESIS SUBMITTED TO THE
ICAR-NATIONAL DAIRY RESEARCH INSTITUTE, KARNAL
(DEEMED UNIVERSITY)
IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE AWARD OF THE DEGREE OF

MASTER OF VETERINARY SCIENCE
IN
ANIMAL GENETICS AND BREEDING
BY
ANUKA YADAV
B.V.Sc. & A.H.

ANIMAL GENETICS AND BREEDING DIVISION
ICAR-NATIONAL DAIRY RESEARCH INSTITUTE
(DEEMED UNIVERSITY)
KARNAL -132001(HARYANA), INDIA

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This is to certify that the thesis entitled, "**COMPARATIVE GENOME ANALYSIS OF INTERNATIONAL TRANSBOUNDARY CATTLE BREEDS**" submitted by **ANUKA YADAV** in partial fulfillment of the requirements for the award of the degree of **MASTER OF VETERINARY SCIENCE IN ANIMAL GENETICS AND BREEDING DIVISION** of the **ICAR-National Dairy Research Institute (Deemed University), Karnal,** (Haryana), India is a bonafide research work carried out under my supervision and guidance and no part of the thesis has been submitted for any other degree or diploma .

Sanjeev Singh
25/8/2022

Dated:25.08.2022

Dr. Sanjeev Singh
Major Advisor

I dedicate

this work to

Dr. P. B. Nandhini

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Needless to say, errors and omissions are mine.

Date:
Place: Karnal (**Anuka Yadav)**

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LIST OF ABBREVIATIONS

S. No.	Abbreviation	Expansion
1.	QC	Quality control
2.	MAF	Minor allele frequency
3.	HWE	Hardy-Weinberg equilibrium
4.	EHH	Extended Haplotype Homozygosity
5.	LD	Linkage disequilibrium
6.	iHS	Integrated Haplotype Score
7.	SNP	Single Nucleotide Polymorphism
8.	ROH	Runs of Homozygosity
9.	BovineHD	Bovine High Density
10.	MT	Mitochondria
11.	FST	Fixation Index
12.	nROH	Total number of ROH per breed
13.	MNROH	Mean number of ROH per individual
14.	MGLROH	Mean genome coverage by ROH
15.	MGPROH	Mean genome proportion under ROH coverage
16.	ALROH	Average length of ROH
17.	FROH	Genomic inbreeding coefficient
18.	PCA	Principal component analysis
19.	DAPC	Discriminate analysis of principal component
20.	QTL	Quantitative trait loci

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ABSTRACT

Selection of the animals has resulted in differentiation of breeds exhibiting a wide range of phenotypic variation in a short amount of time. Gir and Ongole are International transboundary breeds of cattle of Indian origin, bred for dairy and meat production across different countries viz Brazil, USA, Mexico, Malaysia, Panama etc. These breeds are well adapted to Brazilian ecological niche and have undergone significant genetic differentiation in recent years. 90 cattle samples belonging to Indian Gir (n=15), Ongole (n=17), Brazilian Gyr (n=27) and Nellore (n=31) genotyped using Illumina BovineHD BeadChip were included in the current investigation. All the samples were quality checked using Plink software and after quality filtration 5.5 lakhs SNPs were retained for downstream analysis. Three complementary approaches viz., Runs of homozygosity (ROH), Integrated haplotype score (iHS) and Fixation index (F_{ST}) were implemented and these samples were analysis further, for the identification of the selection signatures. The present investigation revealed that the Pairwise F_{ST} differences between Gir versus Gyr and Ongole versus Nellore were 2.856 % and 2.354 %, respectively. Genomic regions under selection within (iHS and ROH) and among breeds (F_{ST}) were identified. A total of 4004, 3322, 3437 and 3485 genes were identified in Gir, Gyr, Ongole and Nellore, respectively under top 1% of the selected regions using the integrated haplotype score (iHS) approach. ROH method based selected regions (ROH consensus ≥20%) revealed 4285, 1768, 1663 and 1466 genes in Gir, Gyr, Ongole and Nellore cattle, respectively. F_{ST} based approach identified 1966 genes for Gir-Gyr pair and 1897 genes for Ongole-Nellore pair under top 1% selected regions. Several candidate genes were identified under top selected regions viz. IER5, MILR1, ARAP3 in Gir and PCDH9 in Ongole. These genes are responsible for immunity and body shape traits in Indian breeds of cattle. Gene related to mammary gland development, udder size and carcass (MYO16, AGAP2, MYO1B, ABCA7) in Gyr and carcass traits (PARP2, ATP10D and KCNJ11) were identified in Nellore breed of cattle. These findings suggests that selection in Indian population (Gir and Ongole) is more towards immunity and adaptation traits while Brazilian population is more selected towards carcass and milk production traits. Further studies on larger sample size using GWAS will be helpful in the validation of the present results.

सारांश

जानवरों के चयन के परिणामस्वरूप कम समय में कई प्रकार की फेनोटाइपिक भिन्नताओं को प्रदर्शित करने वाली नस्लों का विभेदीकरण हुआ है। गिर और ओंगोल भारतीय मूल के मवेशियों की अंतर्राष्ट्रीय सीमा पार नस्लें हैं, जो विभिन्न देशों जैसे ब्राजील, यूएसए, मैक्सिको, मलेशिया, पनामा आदि में डेयरी और मांस उत्पादन के लिए पाले जाते हैं। ये नस्लें ब्राजील के पारिस्थितिक क्षेत्र के लिए अच्छी तरह से अनुकूलित हैं और इनमें महत्वपूर्ण आनुवंशिक भिन्नता है। हाल के वर्ष। भारतीय गिर (एन = 15), ओंगोल (एन = 17), ब्राजीलियाई गिर (एन = 27) और नेल्लोर (एन = 31) से संबंधित 90 मवेशियों के नमूने वर्तमान जांच में शामिल किए गए थे। प्लिंक सॉफ्टवेयर का उपयोग करके सभी नमूनों की गुणवत्ता की जांच की गई और गुणवत्ता निस्पंदन के बाद 5.5 लाख एसएनपी को डाउनस्ट्रीम विश्लेषण के लिए रखा गया। तीन पूरक दृष्टिकोण अर्थात रन ऑफ होमोज़ायगोसिटी (आरओएच), इंटीग्रेटेड हैप्लोटाइप स्कोर (आईएचएस) और फिक्सेशन इंडेक्स (एफएसटी) लागू किए गए थे और इन नमूनों का आगे विश्लेषण किया गया था, चयन हस्ताक्षरों की पहचान के लिए। वर्तमान जांच से पता चला है कि गिर बनाम गिर और ओंगोल बनाम नेल्लोर के बीच जोड़ीवार एफएसटी अंतर क्रमशः 2.856% और 2.354% था। (आईएचएस और आरओएच) और नस्लों के बीच (एफएसटी) चयन के तहत जीनोमिक क्षेत्रों की पहचान की गई। एकीकृत हैप्लोटाइप स्कोर (आईएचएस) दृष्टिकोण का उपयोग करके चयनित क्षेत्रों के शीर्ष 1% के तहत क्रमशः गिर, गिर, ओंगोल और नेल्लोर में कुल 4004, 3322, 3437 और 3485 जीनों की पहचान की गई थी। आरओएच पद्धति आधारित चयनित क्षेत्रों (आरओएच सर्वसम्मति ≥20%) ने गिर, गिर, ओंगोल और नेल्लोर मवेशियों में क्रमशः 4285, 1768, 1663 और 1466 जीनों का खुलासा किया। एफएसटी आधारित दृष्टिकोण ने शीर्ष 1% चयनित क्षेत्रों के तहत गिर-गियर जोड़ी के लिए 1966 जीन और ओंगोल-नेल्लोर जोड़ी के लिए 1897 जीन की पहचान की। शीर्ष चयनित क्षेत्रों के तहत कई उम्मीदवार जीन की पहचान की गई थी। गिर में IER5, MILR1, ARAP3 और ओंगोल में PCDH9। ये जीन भारतीय नस्लों के मवेशियों में प्रतिरक्षा और शरीर के आकार के लक्षणों के लिए जिम्मेदार हैं। गाय में स्तन ग्रंथि के विकास, थन के आकार और शव (MYO16, AGAP2, MYO1B, ABCA7) से संबंधित जीन और मवेशियों की नेल्लोर नस्ल में शव लक्षणों (PARP2, ATP10D और KCNJ11) की पहचान की गई। इन निष्कर्षों से पता चलता है कि भारतीय आबादी (गिर और ओंगोल) में चयन प्रतिरक्षा और अनुकूलन लक्षणों की ओर अधिक है जबकि ब्राजील की आबादी शव और दूध उत्पादन लक्षणों के लिए अधिक चुनी गई है। GWAS का उपयोग करके बड़े नमूने के आकार पर आगे के अध्ययन वर्तमान परिणामों के सत्यापन में सहायक होंगे।

CHAPTER –1

Introduction

INTRODUCTION

For thousands of years, cattle have performed an increasingly significant role in human societies by providing milk, meat, leather, and power. More than 800 breeds of domestic cattle are conventionally categorized into the two species B. indicus (indicine or zebu) and Bos taurus (taurine). There are a number of phenotypic variations have been reported in taurine and Indian cattle, the most significant of which is a pronounced hump over the neck and shoulder in Indian cattle (Bradley and Magee 2006). Indian cattle breeds contain a diverse gene pool to adapt to a variety of agroclimatic situations. They have several physiological advantages over taurine cattle, including increased heat tolerance, resistance against gastrointestinal parasites and ticks, and less metabolic rate and food requirements, that enable them to flourish in tropical and subtropical regions such as India, Brazil, Northern Australia, the southern United States and Southern China.

According to the 20th livestock census, there are 192.49 million cattle population in India during 2019, contributing to the overall 535.78 million livestock population. Over the previous Livestock Census (2012), the total number of cattle increased by 0.8%. The significant rise in crossbred cattle and increased population of indigenous female cattle are the main causes of the increase. Our country now has 50 indigenous cattle breeds, which are categorized into milch, dual, and draught types according to their utility.

International transboundary breeds are the breeds which found in more than one country and in more than one region. According to FAO list of livestock breeds, 60 local, 8 regional transboundary and 7 international transboundary cattle breeds are present in India. Gir and Ongole are International transboundary breeds of cattle of Indian origin, selected for dairy and meat production by different countries viz., Brazil, USA, Mexico, Malaysia, Panama etc. Gyr dairy cattle were introduced to Brazil in 1912 with the majority of bulls arriving between 1914 and 1921 (Santiago, 1986). The Nellore was first recognized in Brazil in 1868, when a ship carrying two Nellore arrived in Bahia on its way to England and sold the animals. Brazilian milk and meat production relies heavily on the Indian cattle breeds Gyr, and Nellore, which were imported from India. The Gir breed of dairy cattle is renowned among milk producers for its superior milk production, exceptional fertility, ease of upkeep, heat tolerance, disease resistance, and longevity. The breed's name is derived from its origin, the Gujarati "Gir" forest. In various regions of the breeding tract, Gir is also called as Bhodali, Gujarati, Kathiawari, Desan, Surati and Sorthi. The Ongole cattle breed is a triple purpose breed, indigenous to Andhra Pradesh in the south of India. The breed's name comes from the Ongole taluk, main breeding tract of Ongole breed in the Guntur district of Andhra Pradesh. This tract was part of the Nellore District until 1904, hence the breed was named "Nellore" by outsiders. The Ongole cattle are big sized animals one of the most remarkable triple-purpose cattle of the tropics, functioning well as draught, milk and meat animals. They are advantageous due to their adaptive qualities and greater productive capability under tough tropical circumstances.

Breeds of cattle chosen for milk production and meat are important sources of nutrition for human. They are efficient ruminants, converting inferior-quality fodder into milk, energy rich fat and muscle. Because of their value, humans have made herds out of a select few founder animals that exhibit the desired trait, which causes tremendous selection pressure on these breeds. Significant losses in genetic variety are unfavorable side consequences of this process that cause issues with metabolism, reproduction, and general health, additionally, less productive breeds are sometimes overlooked, which can result in their extinction. Selective sweep studies are crucial because they provide a platform for the validation of genetic selection procedures, aid in reducing the size of the data set by a factor of ten from the SNP level to the sweep level, and act as a preliminary GWAS research to verify connection with desired traits. SNPs are currently the most popular type of marker, which are defined as the single base pair site in DNA at which various sequence alternatives exist, are the most prevalent type of genomic variation. The SNP chip is the most recent and feasible method of SNP detection.

Natural and artificial selection produce breed differentiation with a wide range of phenotypic variation within a short amount of time. The uncovering of selection imprints will aid in the discovery of genetic diversity in breeds that have evolved to a specific ecological niche and functional feature. Identification of selection footprints in these breeds suitable for various ecological niches and selected for different functional attributes will help to decipher genomic diversity in these breeds. Information derived from genomics of Gir and Ongole breeds may be helpful for identifying the genomic areas connected to polygenic traits like productivity, health, fertility, and behavior that emerged under Indian farming systems and ecological conditions.

The present study was therefore planned to detect and compare a wide spectrum recent and ancient selection signature using Illumina BovineHD BeadChip with the following objectives:

1. To identify genomic signatures in Gir versus Gyr and Ongole versus Nellore cattle.
2. To analyze the identified signatures among these international transboundary cattle breed

CHAPTER –2

Review of Literature

REVIEW OF LITERATURE

2.1. Cattle domestication and Indian cattle

Taurine (*Bos primigenius taurus*) and indicine (*Bos primigenius indicus*), the current two major domesticated cattle, are descended from the extinct wild aurochs (*Bos primigenius*) that split into two different lineages between 250,000 and 330,000 years ago. Taurine cattle are descendants of the *Bos primigenius primigenius*, which was domesticated in the Fertile Crescent around 10,000 years ago, whereas indicine cattle are descendants of the *Bos primigenius nomadicus*, which was domesticated around 8,000 years ago in the Indus Valley (Junior *et al*., 2020).

In India, according to 20th livestock census, total cattle population is 192.49 million which accounts for 35.9% of India's overall livestock population (DAHD, 2019). At present there are 50 registered indigenous cattle breeds in our country, which are categorized into milch, dual and draught type according to their utility (ICAR-NBAGR,2022).

2.1.1. Gir and Ongole cattle breed

Gir cattle

Gir cattle is a well-known Indian milch breed. The Gir hills and forests of Kathiawar, which include the Gujarat districts of Junagadh, Rajkot, Bhavnagar and Amreli are the natural habitat of the breed. In different areas of the breeding tract, this breed is also called as Bhodali, Gujarati, Desan, Kathiawari, Sorthi, and Surti. Gir cattle are primarily reared by the Rabari, Bharwad, Maldhari, Ahir, and Charan tribes of Gujarat. In pursuit of forage, they transfer their cattle from one location to another.

Coat colour of this breed ranges from reddish-brown to black and white, or all red. Like a bone shield, the forehead is large, convex, and broad. This causes the animal's eyes to seem half closed and sloppy. Ears are long, pendulous and leafy. Horns curve to form a half moon structure. Gir breed is known for their stress tolerance and resistance to a variety of tropical diseases. Bullock of this breed is used to pull huge loads across a variety of terrain. These animals have been taken to Brazil, Mexico, the United States, and Venezuela, where they are successfully bred. Gir is one of the most popular cattle breeds in tropical countries. In recent years, intense artificial selection caused by domestication has resulted in greater genetic divergence among countries.

Ongole cattle

The breed's name comes from the Ongole taluk, main breeding tract of Ongole breed in the Guntur district of Andhra Pradesh. This tract was part of the Nellore District until 1904, hence the breed was named "Nellore" by outsiders. At an average height of 600 feet above sea level, the Ongole breed can be found between 14º.27' and 16º.8' N latitude and 79º to 80.55ºE longitude. The breeding tract's average yearly rainfall varies from 40 to 100cm depending on the season. Summer temperatures reaches 45°C, while winter temperatures range from 8 to 10°C. The Ongole tract is largely plain, but as one travels west, hilly ranges emerge. The climate in the tract is dry and hot, with little abrupt fluctuations. The breeding tract of Ongole cattle has an average relative humidity of about 79 percent.

The Ongole cattle are big sized animals, having glossy white coat color called padakateeru. White coat color is the most popular for Ongole breed. On the head and neck of males, there are dark grey markings. The cows are great at milking. The breed's bullocks are often docile and well-suited to heavy work like ploughing and carting. Ongole are magnificent-looking cattle that are large, placid, and appropriate for a steady, heavy draught. They are one of the most remarkable triple-purpose cattle of the tropics, functioning well as draught, milk and meat animals. They are advantageous due to their adaptive qualities and greater productive capability under tough tropical circumstances.

2.2. International transboundary breed

According to FAO list of livestock breeds, 60 local, 8 regional transboundary and 7 international transboundary cattle breeds are present in India. International transboundary breeds are the breeds which found in more than one country and in more than one region. Gir, Ongole, Tharparkar, Sahiwal, Red Sindhi, Kangayam and Kankrej are the seven international transboundary cattle breeds of Indian origin that are found in a wide range of countries. Gir is found in 20 countries, Ongole 3, Tharparkar 5, Sahiwal 27, Red Sindhi 16, Kangayam 3, and Kankrej in 12 different countries of the world (FAO/DAD-IS)

2.3. Establishment history of Gyr and Nellore in Brazil

Gyr dairy cattle were introduced to Brazil in 1912 with the majority of bulls arriving between 1914 and 1921 (Santiago, 1986). Initially Brazilian breeders used dual purpose selection (meat and milk) in the 1960s, but some breeders discovered exceptional animals for dairy related features and shifted their breeding goals to dairy production

(Santana *et al*., 2014). Gyr animals have been widely employed in tropical and subtropical areas as a foundation for crossbreeding with European dairy breeds to create progeny that are more tolerant to harsh weather conditions. Gyr cattle are found in almost 80% of Brazilian cattle herd, either as purebred or as cross breed with Holstein cattle (Filho *et al*., 2010).

The Nellore was first recognized in Brazil in 1868, when a ship carrying two Nellore arrived in Bahia on its way to England and sold the animals. In 1960, a total of 20 Nellore was imported, and again in 1962, another 84 were imported by the Brazilian Government (http://www.nelore.org.br/). The Brazilian Nellore population is made up of less than 7,000 purebred imported animals, with the most significant imports in 1962, and became the founders of important lineages that were crucial to the herd's rapid expansion in the last 30 years (Oliveira *et al*., 2002). Indicine breeds (*Bos taurus indicus*) represent the largest portion of the of the cattle in Brazil, with the Nellore cattle having the most animals (Santiago, 1984).

2.4. SNP Bead Chip for genomic selection

Most economically significant traits of cattle are complex and quantitative in nature. It is much more challenging to identify the genes governing the desired trait since these qualities are controlled by a mix of environmental and genetic factors (Wengel *et al.,* 2015). Due to factors like poor heritability, difficulty in collecting phenotypes, or phenotypes obtained later in life, some of the traits cannot be enhanced very well using the typical breeding method (Dekker *et al.,* 2004). The characterization of variations and their relationship with quantitative trait loci (QTL) in the genome of the relevant breed is essential in order to advance genetic improvement in these traits through selection based on genetic markers. Therefore, breeding strategies that try to use the variation already present in those genes to select for superior individuals are very interested in finding the areas supporting the phenotypic variation of key traits (Kumar *et al.,* 2019). These genomic variants can be genotyped for a fair price and in an acceptable amount of time.

SNPs, which are defined as the single base pair site in DNA at which various sequence alternatives exist, are the most prevalent type of genomic variation. SNPs often exhibit low heterozygosity since they are bi-allelic, but they also benefit from low mutation rates and affordable genotyping enabling automated large-scale genotyping. The finished assembly of the bovine genome (The Bovine HapMap Consortium, 2009) provided an enormous quantity of SNP markers that could be used for genome-wide research.

The SNP chip is the most recent and feasible method of SNP detection. A SNP bead chip is a tiny piece of glass or plastic with thousands to millions of tiny spots on it that bind DNA. Each dot represents a particular SNP and a short portion of nearby DNA.

Currently, Illumina, Affymetrix Inc., and Geneseek are the three leading firms offering fixed SNP panels for bovine genome-wide SNP genotyping. All of these companies provide genotyping services with very high throughput, high genotyping precision, and low cost per SNP analysis. Fixing SNP panels provides several advantages, such as the ability to combine results from many labs and create statistical models for panels that are often used (Boison *et al.,* 2015). SNPs are currently the most popular type of marker. The most thorough genome-wide genotyping array is the BovineHD BeadChip, which has the best power for examining genetic variation in beef and dairy cattle of any breed. The BovineHD BeadChip, which has 7,77,962 SNPs and uniformly covers the complete bovine genome, allows for a wide range of applications, including genome-wide selection, identifying QTL, assessing genetic merit, cross-breed mapping, studying linkage disequilibrium, comparative genetics, and breed features for assessing biodiversity. (Illumina, FastTrack, GenomeStudio,2015)

2.5. BREED UNDER STUDY

Table 2.5.1 - Cattle breeds and their special characteristics

Breed	**Home tract**	**Climatic Condition**	**Utility**	**Special Characteristics**
Gir	India (Gujarat)	Tropical monsoon	Milk	Ability to produce more milk with even less feeding, capacity to endure stress, and resistance to a variety of tropical diseases
Ongole	India (Andhra Pradesh)	Dry and hot	Draught, Milk	Hardiness, disease resistance, capacity to thrive on scanty and dry fodder
Gyr	Brazil	Tropical and subtropical	Milk, Meat	
Nellore	Brazil	Tropical	Meat, Milk	

2.6. Selective sweep

Evolutionary along with demographic processes have shaped a varied range of animal breeds that are suited to a variety of environmental circumstances (Groeneveld *et al*., 2010).

Natural selection is a significant driving force in altering the pattern of genetic diversity in livestock populations in such a way that it increases survival and reproductive success (Falconer and Mackay, 1996).

Breeders used purposeful or methodical selection focusing on a certain goal. These selection tactics tend to generate changes in specific genetic areas that govern breed characteristics like morphology, production performance, body conformation, reproduction, behavior, environmental adaption, and disease resistance (Saravanan *et al*., 2020). The 'Selective sweep, hitchhiking effect or genetic draft' is a phenomenon in which a new favorable mutation increases in frequency within a population and reduces diversity in the associated neutral sites. (Maynard and Haigh, 2007).

2.6.1. Types of selective sweeps

i. Hard/ classic selective sweep: A favorable mutation develops in the DNA sequence during this process and genetic diversity is observed around the favorable allele. During future generations of selection, the advantageous allele becomes more common and eventually becomes fixed in the population. Due to which, the genetic variation upstream and downstream of the advantageous allele is reduced (Saravanan *et al*., 2020).

ii. Soft selective sweep: Standing genetic variation produces soft sweeps in DNA sequences from a population with neutral mutations, where a neutral allele segregating in a population becomes advantageous as a result of environmental or genetic changes and selection leads to fixes the advantageous alleles in the population while leaving some genetic variation surrounding them (Hermisson and Pennings, 2017).

iii. Multiple origin soft sweep: It occurs as a result of recurrent independent mutations. The initial advantageous mutation in the DNA sequence causes the beneficial allele and related neutral sites to rise in frequency during selection. At the same gene, a second favorable mutation develops on a different genomic background. Both favorable mutations rise in frequency in different genetic backgrounds, but none of them can approach fixation (Pennings and Hermisson, 2006).

Selection signatures are unique genetic footprints left behind in genomic areas subjected to selection (Jensen *et al*., 2016). These are genomic areas that have significantly increased in frequency and become fixed in a population due to their functional significance in specific processes. Because of their decreased genetic variability and distinctive regional linkage disequilibrium (LD) patterns, they have a distinct selection signature (Brien *et al.*, 2014). The detection of selection footprints aids in understanding the molecular mechanisms underlying adaptation events as well as the identification of genomic areas linked to phenotypic variation (Andersson and Georges, 2004). Using a variety of statistical approaches in livestock species, researchers discovered broad selection fingerprints in the genome of cattle connected to environmental adaption and production attributes (Randhawa *et al*., 2016).

2.7. Methods of identification of selection signature

Various statistical methods have been developed to detect footprints of selection based on neutral evolutionary theory (Biswas and Akey, 2006).

Regions of the genome that were under intensive selection pressure for a long time, generate the typical genomic patterns (Illa *et al*., 2021) such as,

i. Increases or decreases the allele frequency spectrum of that selected regions

ii. Responsible for increase in number of homozygous genotypes in genome

iii. Creates long haplotypes in genome

iv. Creates intense differentiation in local population of a breed

2.7.1. Intrapopulation statistics

Intra-population statistics compare genetic data within populations to identify selection footprints. Three basic strategies based on the site frequency spectrum, LD and reduced local variability are included in this group (Weigand and Leese, 2018).

2.7.1.1. Site frequency spectrum (SFS) based

It refers to a group of tests that are based on the frequency distribution of alleles in a population. Selective sweeps enhance the quantity of high and low frequency variants while lowering the medium frequency variants number.

In this allele frequency-based neutrality tests include these three methods-

1. Tajima's D (Tajima, 1989)
2. Composite likelihood ratio test (CLR) (Lindsay, 1988)
3. Fay and Wu's H statistic (Fay and Wu, 2000)

2.7.1.2. LD based method

Selective sweeps process produces an extended linkage disequilibrium high frequency haplotype that prevents recombination during the rapid rise in frequency of a haplotype harboring a favorable mutation.

Under selection pressure selective sweeps process creates a high frequency haplotype with extended LD in genome, which inhibits recombination process of chromosome and the rapid increase in the frequency of a haplotype causes a beneficial mutation.

i. relative extended haplotype homozygosity (rEHH) method (Sabeti *et al.*, 2002)
ii. Integrated haplotype score (iHS) (Voight *et al.*, 2006)

For identification of the genome-wide footprints of positive selection Extended Haplotype Homozygosity (EHH) test is used. This test measures the decline in haplotype homozygosity within a single population in order to identify selection using the characteristics of haplotypes.

2.7.1.3. Reduced local variability-based method

Reduced local variability can be identified by different methods like-

i. By Runs of homozygosity (ROH) method (McQuillan *et al.*, 2008)

According to the hitchhiking theory the selective sweep must include sections of homozygous locus that show more homozygosity than the genome as a whole. (Almeida *et al.*, 2019). The animal that has undergone selective sweep process will show long runs of homozygosity around the target sequence (Xie *et al.*, 2019).

ii. By Pooled heterozygosity method (H_P) (Rubin *et al.*, 2010)

2.7.2. Interpopulation statistics

2.7.2.1. Single site population differentiation

i. Fixation Index (F_{ST})

This method is based on the identification of differentiation of allele frequencies across populations, or loci that are significantly fixed in various subpopulations. (Wright, 1949).

Where, F_{ST}= 0 represents no differentiation in frequency of that loci

F_{ST}= 1 show Fixed difference across populations

Significantly differentiated allele frequency across the populations higher F_{ST} values at any given locus shows positive selection, while lower F_{ST} values indicated negative selection. In fixation index method F_{ST} values are SNP-specific and can estimate the actual genetic variants which undergone selection processes (Zhao *et al*., 2015).

ii. FLK (or TFLK) method

This method is an extended version of the original LK statistic (TLK), which is based compression of observed and predicted variances of F_{ST} computed from data using a variance ratio test under neutrality (Lewontin and Krakauer, 1973).

2.7.2.2. Haplotype based differentiation methods

Various methods are

i. Cross-population extended haplotype homozygosity (XP-EHH) (Sabeti *et al*., 2007)

ii. hapFLK, a haplotype-based extension of the FLK statistic (Fariello *et al*., 2013)

In table 1 various studies related to selection signature in cattle breeds are shown.

2.8. Identification of selection signature in cattle (*Bos indicus)*

Illa *et.al.,* 2021 have identified 117 candidate genes by De-correlated composite of multiple selection signals (DCMS) method which is a combination of five different statistics in the Sahiwal genome for the identification of signatures of selection. They found some key genes related with facial pigmentation (LEF), coat color (KIT, PDGFRA, and KDR), milk fat percent (HADH, MAP3K1, CYP2U1, and SGMS2), lactation persistency (NNT, MRPS30, CCL28, NIM1K, HMGCS1, ZNF131, and CCDC152), sperm membrane integrity (OSTC), milk yield (GHR and ZNF469), susceptibility for bovine tuberculosis (PAPSS1 and RNF144B) and reproduction (NKX2-1 and DENND1A). Further they performed prioritization analysis of candidate gene and observed four important genes, viz., LEF, KIT, KDR, and MAP3K1, which has a significant role in coat color, milk fat percentage, and facial pigmentation in cattle.

According to O'Brien et al. (2014), taurine breeds (Angus and Brown Swiss) and Indian breeds differed in their levels of linkage disequilibrium (VarLD) in the autosomal genome (Nellore and Gir). The UMD3.1 Bos taurus genome assembly was used to characterize genomic regions that contained the top 0.1 and 0.01 percentile of signals, identifying genes (17 and 125) and, selection signals (26 and 165 signals) respectively. These genes included TECRL, CAST, BT.23182 or FPPS, UVRAG, MYOM1, and DNAJA1.

37 breeds of cattle have been divided into beef, dairy, and dual-purpose cattle by Gutiérrez-Gil et al. (2015), who also described the activities of many genes underlying selective sweep regions (Table 2.5.2).

Table 2.5.2 - Candidate genes by Gutiérrez-Gil et al. supporting selective sweep regions in different cattle breeds (2015)

Purpose	Candidate genes under Selection signature	Function
Dairy	ESR1, PDE3B, MAPK14, NFKB1, MAPK13, SHC3, PTEN	Metabolism
	MAPK13, TLR4, MAPK14, PELI2, IL12B, NFKB1, C1QA, C1QC, RASGRF1	Immunity
	CYP27A1, CYP2R1	Vitamin D synthesis
	ESR1, MAPK14, NFKB1	Reproduction
	COL6A2, SHC3, PTEN, LAMB3, MAPK14, LAMA5, LAMB	Cytoskeleton
Beef	RELA, IKBKB, PIP5K1A, GSK3A, CTSK	Skeletal System
	TGFB1, RELA, IKBKB, CTSK, ITGB3, NLRC4	Immunity
	TGFB1, FOSL1, RELA, NCOA2	Endocrine
	MYL4, ACTN3	Muscle contraction
	TGFB1, PTCH1, PLAT, KAT5, KAT7	Cellular metabolism
Dual purpose	RGS18, RGS2, RGS1, ATP2B2, PRKAR1B	Calcium regulation
	HTR4	Milk Yield
	MAP2K2, MAPK3	Immunity

Table 2.5.3 - Candidate genes underpinning zones of selective sweep in different breeds of cattle by iHS, ROH, F_{ST} and other common methods

Breed	Method	Candidate gene	Function	Reference
Indigenous Iraqi breeds, (Rustaqi and Jenoubi)	REHH (iHS, Rb), F_{ST}	OSGIN1, CBFA2T3, IRF8, TNFIP8, FOCAD, PRKG1, NCAM2, TMPRSS15, SLC4A4, LPCAT2 and DNMBP, PCDH15	Immune response to mammary gland inflammation, immunity, tick resistance, milk quality and production, meat quality	Alshawi *et al.*, 2019
Kenana and Butana dairy zebu cattle (Africa)	iHS, Rsb	DGAT1, GHR and ABCG2, IRAK, IL17B, HSF5, PMEL, SRD5A3, AFP	Dairy production, immune response, heat tolerance, coat color and reproductive traits	Bahbahani *et al.*, 2018
Chinese Wagyu cattle	his	ADAM12, CAPN1, IGF2R, CDK6, PLAG1, GDF5,	Meat Quality, Growth and Developmental Performance	Wang *et al.*, 2019
Vrindavani cattle	iHS, XP-EHH, F_{ST}	TNNI3K, LRP1B, APOB, FAM110B, CACNA2D1 and SPATA17	Milk Production and adaptation	Singh *et al.*, 2020
Dual purpose Gir	iHS, XP-EHH, F_{ST}	CNTN3, STK33, and TMEM117, DUSP10, NCAM1, SLC24A4, and TMEM117, BCL11A, ADAMTS3, CAPN13, CTNNA2, GC, EPHA5, SLC24A4, and SLC25A21	Reproductive trait, milk fat and protein, growth, beef, health, or body shape traits	Maiorano *et al.*, 2018

African cattle	iHS, Rsb and XP-EHH, Bayesian iHS method	ACE, ASIC3, HSPH1, GH1, MVD, HIGD2A, BCL2, CBFA2T3, AZU1, ELANE, GZMM, PRSS57, PRTN3, CFD, CD79B, MILR1, and TCAM1.	Physiological adaptations, immune response	Jemaa *et al.*, 2020
Charolais beef cattle	iHS	TFEC, MDFIC, PPP1R3A, IFRD1, MSTN, and MYOD1	Backfat thickness, double-muscle phenotype productive and growth traits	Martínez *et al.*, 2019
Shanghai Holstein cattle	iHS, ROH	IL22RA1, CALHM3, ITGA9, RGS3, NDUFB3, SOD2, SNRPA1, ALAD, ST3GAL4, EXOSC10, and MASP2	Adaptation, milk production, clinical mastitis, immune response	Liu *et al.*, 2021
6 Indicine, 5 Taurine cattle breeds	iHS, ROH, F_{ST}	NCR3, HIST1H2BN, ARID5A, DEFB4, DEFB7, HSPA1B, HSPA1L, and DNAJB4	milk production, immune response and disease resistance, thermo-tolerance, production traits	Saravanan *et al.*, 2021
Gyr (Bos indicus) dairy cattle	ROH	TRAPPC9, IRS2 and ANG, and HSF1, HSPB1, and HSPE1	milk yield and composition, heat adaptation, lactation	Peripolli *et al.*, 2018
Nellore	ROH	CTNNA1, LRRTM2, SIL1, MATR3, and PAIP2) NPBWR1, OPRK1, and MRPL1, RFX4), NAMPT and JMJD1C	function in skeletal muscle, immune response, reproduction, growth, fertility	Peripolli *et al.*, 2018
Indigenous cattle breeds (Bos indicus) Ladakhi, Siri, Kankrej, Hallikar	ROH, F_{ST}	HMOX1, H6PD, GATM, HSPH1, EGLN1, HIF1AN, HSP, PDGFRA, KIT, MC1R	Hypoxia, Adaptation, immunity, dairy traits, coat colour, heat stress	Bhardwaj *et al.*, 2021

7 Indigenous cattle breeds	F_{ST}	FAM19A2, BEST3, RAB31P, DGKA, AHCY, PIGU and PFKP	Immunity, metabolic process, glucose and sugars transportation,	Dixit *et al.*, 2021
Sahiwal, Tharparkar, Gir Vechur, Ongole Kangayam, Hariana	ROH	LYZL1, SVIL, GPX4, CCT4 PTGFR, CSN1S1, CSN2, CSN1S2, CSN3, PTGFR and HMGA2	Resistant to diseases, stress tolerant, milk production and stature	Dixit *et al.*, 2020
Nellore Gyr Angus Brown Swiss	VarLD method	TECRL, FPPS, CAST, MYOM1, UVRAG and DNAJA1	Adaptation and production trait	Brien *et al.*, 2014
Gyr	WGS, ZHp	CAMP, CATHL1, CATHL2 and CATHL3, MAPK	Pathogen- and parasite-resistance, resistant to hot temperatures and tropical diseases	Liao *et al.*, 2013

Table 2.5.4 – Summary of identified selection signature in other livestock species

Species/ Breed	**Candidate genes**	**Function**	**Reference**
Pig	GPHA2, EHD1, HNF1A, C12orf43, TRPV4, MVK, GLTP, and MMAB, PPP2R5B and MAP9, ANKRD13A, OASL and GIT2	Immune process, meat trait, lipid metabolism, reproduction and disease resistance	Yang *et al.*, 2022
Sheep (Changthangi, Deccani and Garole)	TRPM8, JADE2, PLEKHB2, SPP2, TSHR, UBE2B and PPP3CA gene	Cold adaptation, meat quality traits, and fecundity	Saravanan *et al.*, 2021
Goat	FLK, ABCG2, EFEMP1, CUX1 and PLOD3, AMPD1 and NRAS TSHB, ADAMTS20, MC1R, ASIP, SOX18 and TIMP3	Milk production, fiber production, meat production, and coat color	Bertolini *et al.*, 2018
Yak	KIT, KITLG, FGG, CDH12, FGA, FGB, PDGFRA, PEAR1, STXBP3, OR5H6 OR5K3 and OR1E1TAS2R1, TAS2R3 and TAS2R4.	Olfactory receptor, taste receptor	Kour *et al.*, 2022

CHAPTER –3

Materials & Methods

MATERIAL AND METHODS

3.1 Animal samples and genotyping

For selection signature analysis a total 90 samples of Indian Gir (n=15), Ongole (n=17), Brazilian Gyr (n=27), and Nellore (n=31) breeds of cattle were incorporated.

For Gir and Ongole breeds, the random samples were obtained from various farms across the country in accordance with the regulations and guidelines of the Institutional Animal Ethics Committee (IAEC), National Bureau of Animal Genetics Resources (ICAR-NBAGR), Karnal. The DNA samples were genotyped using an Illumina BovineHD BeadChip with 777,962 SNPs, mapped to the UMD 3.1. The genotyping platform used was the Infinium II Multi-Sample Assay (Illumina, Inc., San Diego, CA, USA). The SNP chip data were analyzed using Genome Studio software (Illumina)

For Gyr and Nellore cattle breeds Illumina BovineHD chip SNP data with 777,962 SNPs, with Chromosome position on UMD3.1 assembly obtained from Dryad data repository (Datadryad.org) and access through WIDDE (Web-Interfaced next-generation database for genetic diversity exploration) web portal.

3.2. Quality control and filtering of data

As the SNPs only present on the autosomes were considered for the present study, the unmapped SNPs, SNPs mapped on to X chromosome, and mitochondrial DNA were omitted from dataset. Quality control (QC) and filtering of raw data were performed using Plink software v1.90 (Purcell et al., 2007; Chang et al., 2015) to remove the outliers from the data and to ensure high quality of genomic data for further statistical analysis. The following quality control criteria were used to filter SNPs across the multiple samples for further analysis:

- SNP call rate < 90%
- Minor allele frequency (MAF) < 0.05
- Hardy-Weinberg equilibrium (HWE) ($P<0.001$)
- Samples with more than 10% missing genotypes were omitted.

SNPs that failed to meet these QC criteria were excluded from the analysis. SNPs remained after filtering and quality control check were used for further identification of selection signatures.

3.3. Linkage disequilibrium (LD) and pruning of the data-

The LD between each pair of adjacent SNPs was estimated using Pearson's squared correlation coefficient (r^2) statistic (Ardlie *et al.,* 2002), for each breed which depends upon the frequencies of the alleles at the loci under consideration. The r^2 values were calculated using PLINK v 1.9 keeping the window size limit of 500 kb between pair-wise SNPs. Further, to find out the number of SNPs needed for the genome-wide selection and association analysis, breed wise LD decay ($r^2 < 0.2$) analysis was performed. The LD decay with increasing distance between SNPs was analyzed using an R script and a graph was plotted. This was done by dividing the size of the cow genome (about 2.67 GB) by the average inter-marker distance with $r^2 > 0.20$.

3.4 LD pruning for identification of selective sweeps by F_{ST} method

The elimination of closely related SNPs with high LD is known as LD pruning. LD pruning was done by using PLINK software v1.90 (Purcell *et al.*, 2007; Chang *et al.*, 2015) to minimising ascertainment bias and overestimation of the diversity characteristics. This method involved estimating the level of differentiation (LD) for each SNP pair in a scanning window of 100 kb, removing one SNP from that SNP pair if its r^2 value was greater than 0.5, and repeating the process by moving the SNP window ahead by 50 SNPs, in Plink using command line (PLINK --indep-pairwise with window size: 50, SNPs shifted per step: 50 and r^2 threshold: 0.5)

3.5 Effective population size (*Ne*)

The historical and recent effective population size (*Ne*) was estimated using the SNeP v1.1 software (Barbato *et al.*, 2015). We used common PLINK input file format (.ped and .map files) for the estimation of Ne by SNeP v1.1 software. The software uses LD to estimate N_e at different t generations in the past where $t = 1/2c$ and c is the distance between SNPs in Morgans (Barbato *et al.*, 2015).

3.6 Analysis of Genetic structure of the population

Using the adegenet package for the R software, Principal Component Analysis (PCA) and Discriminant Analysis of Principal Components (DAPC) were carried out, for access to the population structure and a genetic understanding of the relationships within and across breeds. In order to display and identify trends in SNP data, principal component analysis (PCA) graphs are designed to make a low dimensional picture. The variance-standardized relationship matrix between samples is the foundation of PCA. Using PLINK v 1.9, PCA was used to evaluate the population structuring among the breeds. The top 60 principal components were selected, and PC-1 vs. PC-2, which accounted for the majority of the data variability, were shown using a R script. Out of all the output clusters using PCA, the DAPC was used to determine the ideal number of clusters (K). The lowest associated Bayesian Information Criterion (BIC) served as the foundation for the selection of K. K-means clustering of PC is used by DAPC to determine the actual number of populations. With 60 PC and 5 discriminant functions, the DAPC was run.

3.7 Selection signature identification

"Selection signatures" are the unique genetic footprints or patterns, left in the genomic regions that underwent selection. "Selective sweep" refers to the process whereby a new, beneficial mutation becomes more prevalent in a population and consequently decreases the variability of the associated neutral sites.

3.7.1. Integrated Haplotype Score (iHS)

The with in population signature of selection in four cattle breeds (n=90) were computed using the Integrated Haplotype Score (iHS) method (Voight et al.,2006). The extended haplotype homozygosity (EHH) method (Sabeti et al., 2002) is the basis for this approach and measured as the log of the ratio of the integrated extended haplotype homozygosity (EHH) score for haplotypes centering the ancestral allele to the score for haplotypes centering the derived allele. Relative Extended Haplotype Homozygosity (REHH) package of R software (Gautier et al., 2012) was used for calculation of iHS of autosomes. REHH provides a tool to identify the footprints of recent or ongoing selection using EHH-related statistics. The formula for the standardized iHS is as follows-

$$iHS = \frac{\ln\left(\frac{iHH_A}{iHH_D}\right) - E\left[\ln\left(\frac{iHH_A}{iHH_D}\right)\right]}{SD\left[\ln\left(\frac{iHH_A}{iHH_D}\right)\right]}$$

Where-

iHHA and iHHD are the integrated EHH scores for ancestral (A) and derived (D) core alleles;

E and SD are the expectation and standard deviation of iHHA/iHHD, respectively.

Standardized iHS values are transformed into piHS values by

piHS = −log10[1–2 |ΦiHS - 0.5|],

where ΦiHS is a cumulative distribution Gaussian function of iHS and piHS as a two-sided p-value (on a −log10 scale) of a test on the null hypothesis of no selection. Only SNP with putative ancestral and derived alleles defined in the data set (Rocha *et al*., 2014) were considered in the analysis.

For EHH based statistics, phasing of genotyped SNPs was required. Through phasing, imputation of missing SNPs and construction of haplotypes were performed. After quality control, for finding the within breed selection signature VCF files were created individually for each breed from quality controlled ped and map files by PLINK software and phasing was performed by BEAGLE software (Browning and Browning,2010) to input the missing genotypes and to infer the haplotypes.

3.7.2. Runs of homozygosity (ROH)

Genome-wide ROH identification for each animal was done by using PLINK v1.90 software (McQuillan *et al*., 2008). Although, no LD pruning was performed in this method; however, in order to exclude short and common ROH that appeared throughout the genome as a result of LD, the minimum ROH length was fixed at 1 Mb (Purfield *et al*., 2012). These parameters and thresholds were applied to define a ROH via PLINK software (Purcell *et al*., 2007) as- i) sliding window of 50 SNPs across the genome; ii) proportion of homozygous overlapping windows was 0.05; iii) minimum number of consecutive SNPs included in a ROH was 100; iv) minimum length of a ROH was set to 1 Mb; v) maximum gap between consecutive homozygous SNPs was 1000 kb; vi) a density of one SNP per 50 kb; and vii) maximum of five SNPs with missing genotypes and up to one heterozygous genotype were allowed in a ROH.

3.7.2.1 Distribution of runs of homozygosity;

All ROH were grouped into five classes as per the nomenclature of Kirin et al. (2010) and Ferenčaković *et al*. (2013a; 2013b): 1–2, 2–4, 4–8, 8–16, and >16 Mb.

For every individual, and for each ROH length category, the mean number of ROH per individual (MNROH), the average length of ROH (ALROH) and the total number of ROH per breed (nROH) were estimated. The percentage of chromosomes covered by ROH was also calculated. First, the mean ROH length was calculated by summing all ROH (Mb) on a chromosome and dividing by the number of individuals that had ROH on that chromosome; the mean ROH length was then divided by the length of the chromosome in Mb (Dixit *et al.*,2020).

3.7.2.2 Genomic Inbreeding Coefficients

For estimation of genomic inbreeding coefficients (FROH and FHOM) PLINK v 1.9 (Purcell *et al*., 2007; Chang *et al*., 2015) was used. Inbreeding coefficient based on ROH (FROH) for each animal was calculated according to (McQuillan *et al*. 2008):

FROH = LROH/LAUTO

where LROH is the total length of all ROH in an individual genome while LAUTO refers to the autosomal genome length covered by SNPs included in the array. For each animal FROH (FROH > 1Mb and FROH > 8 Mb) was calculated according to ROH distribution within the length categories: >1 and >8 Mb.

3.7.2.3 Detection of selection signatures and the underlying genes

Overlapping ROH in four cattle breeds was analyzed using the PLINK v 1.9 software (Purcell *et al.*, 2007). The number of consensus samples was identified in each breed and ROH island frequencies were calculated by dividing the number of consensus samples with the total samples in each breed. Manhattan graph was plotted for the consensus regions in all four breeds.

The samples were analyzed using Manhattan plots of the overlapped ROH percent across the autosomes for each breed to determine the genomic areas most frequently connected to ROH. The consensus (overlapping) ROH regions with a frequency of ≥20% were considered as selection signatures and signature associated genes were identified.

3.7.3. Between breed method

Fixation Index (F_{ST})

By using genetic polymorphism data and the population genetic difference among the four breeds studied here, Fst has so far been utilized to find signs of selection.

The Pairwise Wright F_{ST} approach for single locus analysis often calculates the association between allele pairs within subpopulations and the meta-population to determine the level of differentiation software (Wright, 1949). Arlequin 3.5 software (Excoffier and Lischer, 2010) was used to determine F_{ST} for four breeds of cattle. For which PLINK software was used to perform LD pruning on quality-controlled data, following which a PED and MAP file with the pruned data was generated. The ped and map files were converted using PGD SOIDER software (Excoffier and Lischer, 2012) into an ARP format, which was then utilized as an input file for Arlequin. In order to assess the statistical significance of the genetic divergence between populations, we computed the pairwise genetic distance using 110 permutations. By computing the Slatkins linearized F_{ST} (Slaktin, 1995) implemented in Arlequin 3.5, we were able to determine the pairwise F_{ST} values (Weir and Cockerham, 1984). By calculating the molecular diversity index and identifying loci under selection, Arlequin 3.5 software generated the F_{ST} values. Since negative values have no biological meaning, the negative F_{ST} values from the SNPs marker were set to 0. (Akey *et al.*, 2002). Regions under positive selection were found by ranking F_{ST} values. By Arlequin 3.5 software the empirical P-value calculated for each SNP as a proportion of the total number of SNPs. Significant F_{ST} values are those that comes under the p value's threshold of significance of 0.01 for the population.

3.8 Bioinformatics analysis

A genomic region was considered as being under selection if it contained significant SNPs based on iHS, ROH or F_{ST} values. After identifying the significant regions under selection, gene annotation, Functional annotations like Gene Ontology (GO) terms and pathways were assigned to genes using bioinformatic tools

3.8.1. Gene Annotation:

Annotation of gene identified in selective sweep regions were performed using bovine genome assembly UMD 3.1 from the ENSEMBL (www.ensembl.org/biomart)) databases using R package Genomic Annotation in Livestock for positional candidate Loci(GALLO—https://github.com/pablobio/GALLO)software.The .gtf annotation file corresponding to the bovine gene annotation from UMD 3.1 assembly was used for gene annotation within the selective sweep region with windows size 500kb(±250kb) for iHS and FST , 2MB (±1MB) for ROH method.

3.8.2. Functional analysis:

A database for Annotation, Visualization, and Integrated Discovery (DAVID) tool(http://david.abcc.ncifcrf.gov/) was used for functional enrichment analysis terms (biological process, cellular component, and molecular function) and pathways of the genes using a list of genes with significant SNPs based on F_{ST}, ROH and iHS values and the *Bos indicus* annotation file as a reference genome.

3.8.3 Enrichment analysis-

Enrichment analysis was used to identify significant Gene Ontology (GO) of these categories: biological regulation, molecular function, cellular components, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of genes of selective sweep regions using DAVID tool.

CHAPTER –4

Results and Discussion

RESULTS AND DISCUSSION

4.1. Quality control and filtering of data

A total of 90 samples belonging to Indian Gir (n=15), Ongole (n=17), Brazilian Gyr (n=27) and Nellore (n=31) cattle breeds were investigated in the study with the objective to identify selection signature and to analyze identified signatures in these breeds.

Only the autosomal SNPs were considered for the selective sweep analysis. So, unmapped SNPs (2,591SNPs), SNPs found on the X chromosomes (39,396 SNPs), and SNPs found in mitochondrial DNA (42,669 SNPs) were omitted.

After this, for QC the following parameters were applied on remaining SNPs using Plink software-

- SNP call rate < 90%
- Minor allele frequency (MAF) < 0.05
- Hardy-Weinberg equilibrium (HWE) (P<0.001)

A total of 91 samples (Gir: 16, Gyr: 27, Ongole:17 and Nellore: 31) were genotyped by using BovineHD BeadChip (Illumina Inc., San Diego, CA) for 7,77,962 SNPs. Out of them one sample of Gir was excluded due to more than 10% missing genotypes. Hence, a total of 90 samples (Gir: 15, Gyr: 27, Ongole:17 and Nellore: 31) remained for further analysis.

2,97,831 SNPs from Gir, 2,90,510 SNPs from Gyr, 3,02,363 SNPs from Ongole, and 3,09,864 SNPs from Nellore were excluded after QC filter. Therefore, on an average, 4,37,462, SNPs 4,44,783 SNPs, 4,32,930 and 4,25,429 SNPs remained after quality control process in Gir, Gyr, Ongole and Nellore, respectively.

These QC parameters were applied on four breed merged data, and a total of 5,50,267 SNP markers and 90 samples remained of the genotype data for downstream analysis. The information on the filtered SNPs is presented in Table 4.1.1, 4.1.2 and Fig. 4.1.1, 4.1.2.

Table 4.1.1 - Filtered SNPs after quality control in four cattle breeds

Breed	Initial SNPs	Unmapped, X, MT SNPs	SNPs removed in QC	Remaining SNPs
Gir	777962	42669	297831	437462
Gyr	777962	42669	290510	444783
Ongole	777962	42669	302363	432930
Nellore	777962	42669	309864	425429

Table 4.1.2 - Chromosome wise SNPs after quality control in four cattle breeds

Chr. No.	SNPs Before QC	SNPs After QC
1	46510	34972
2	40044	29463
3	35593	26129
4	34976	25438
5	34836	25563
6	35513	28049
7	33164	26386
8	33544	25694
9	31072	24531
10	30467	21452
11	32023	22484
12	26132	19646
13	23602	17162
14	24757	20436
15	24737	18816
16	24174	18550
17	22568	16833
18	19385	14457
19	18921	12747
20	21487	16060

21	21178	15095
22	18028	12923
23	15260	12408
24	18619	13955
25	12921	9055
26	15242	11610
27	13142	10308
28	13027	9750
29	14714	10295
MT	339	0
UM	2591	0
X	39396	0
Total	777962	550267

MT: Mitochondria, UM: Unmapped

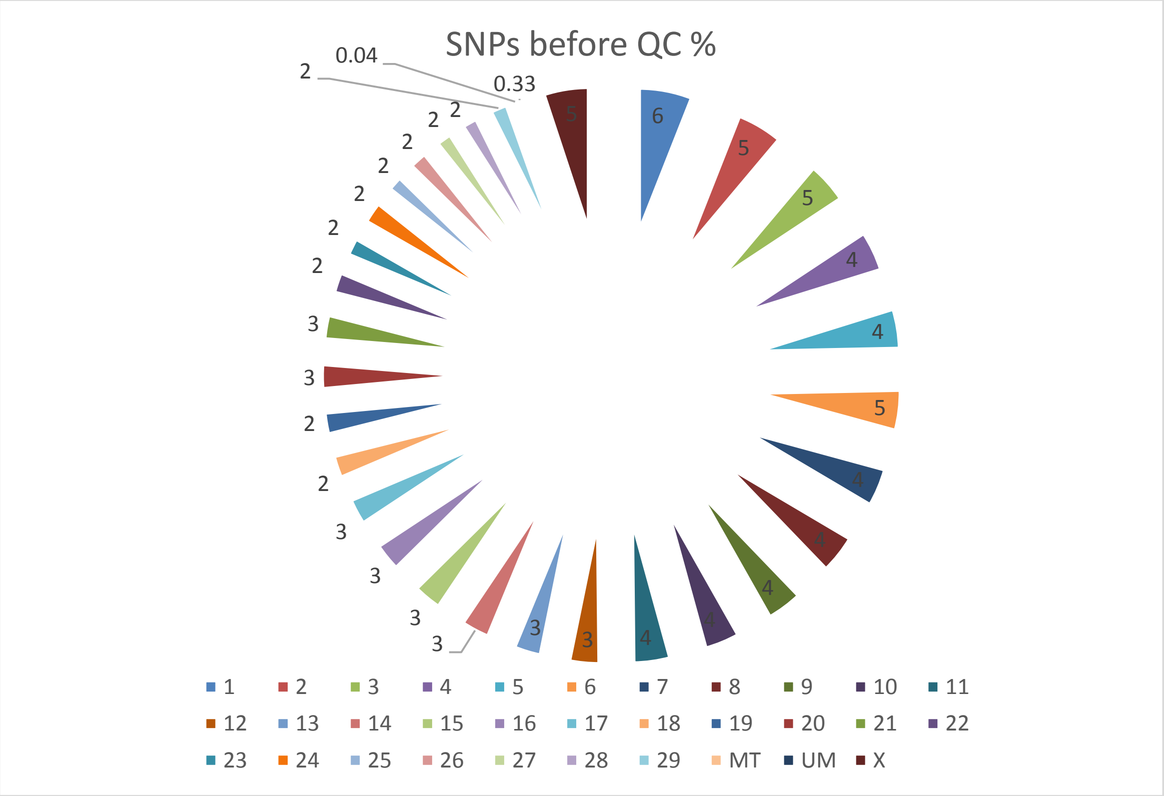

Fig-4.1.1 SNPs without filter and quality control in four cattle breeds. Number below pie chart represents chromosome and number inside represents the % contribution of SNP in each chromosome.

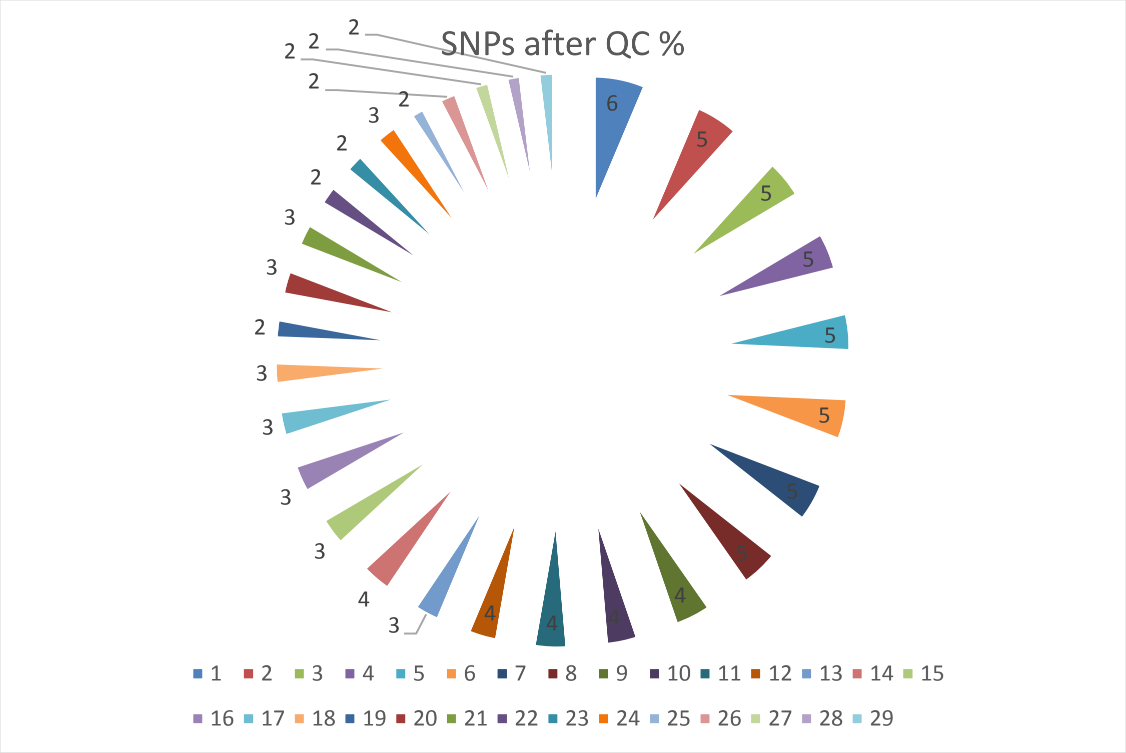

Fig-4.1.2 SNPs after filter and quality control in four cattle breeds. Number below pie chart represents chromosome and number inside represents the % contribution of SNP in each chromosome.

4.2 Linkage disequilibrium (LD) decay and pruning of the data

According to Slatkin, 2008, information of linkage disequilibrium (LD) in the genome is essential for genomic studies applied to animal breeding because it reflects the breeding system that breed and the of history of the population. As the physical distance between SNPs increased, the genome-wide average LD (r^2) decreased, which is known as LD decay.

The Fig.4.2.1, 4.2.2, 4.2.3 and 4.2.4 depicts the LD decay in Gir, Gyr, Ongole and Nellore cattle breeds respectively in 5kb interval of each bin. The LD decay (r^2 <0.2) value was estimated as 125-130kb, 65-70kb, 90-95kb, 75-80kb inter-marker distance bin in Gir, Gyr, Ongole and Nellore cattle breeds respectively.

To determine the number of markers needed to perform genomic selection in these cattle breeds, the degree and patterning of LD in four breeds was examined in the current study. The degree of LD (r^2) between the SNP marker determines the accuracy of genomic selection. For the successful utilization of genomic selection in cattle, r^2 < 0.2 was taken as the threshold for useful LD (de Roos *et al*; 2009 Goddard, 2009)

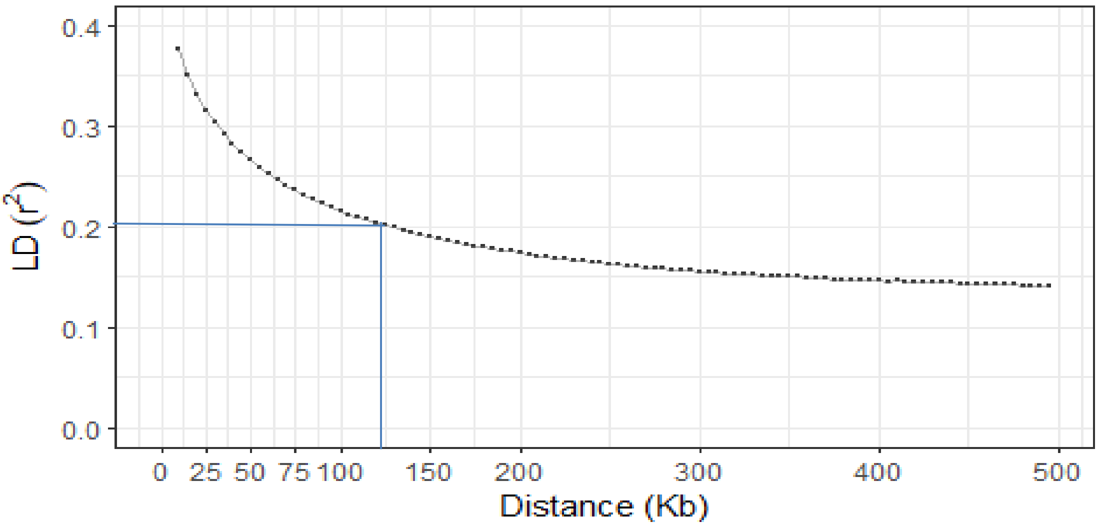

Fig-4.2.1 Decay of average LD ($r^2 < 0.2$) over distance among SNPs in Gir breed

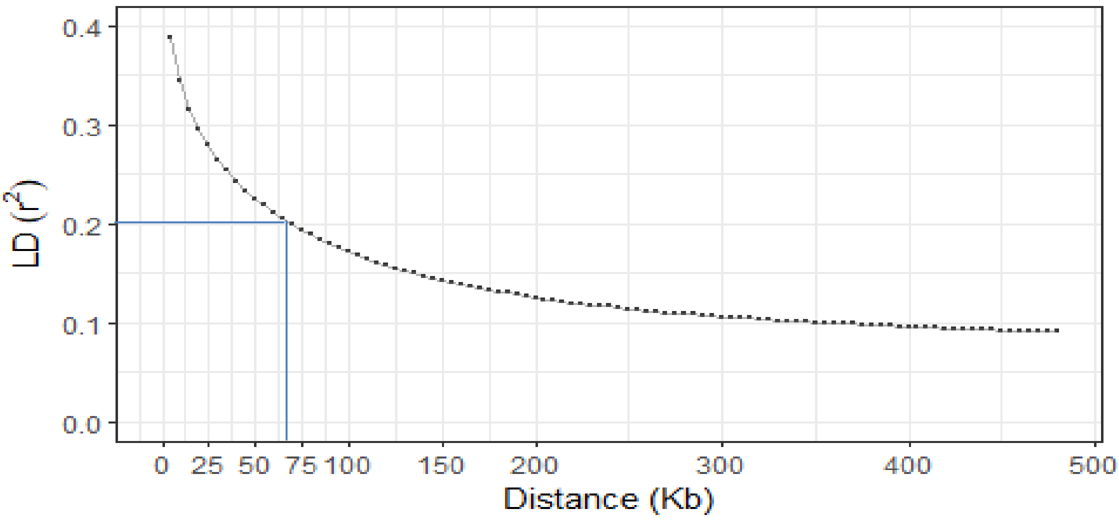

Fig- 4.2.2 Decay of average LD ($r^2 < 0.2$) over distance among SNPs in Gyr breed

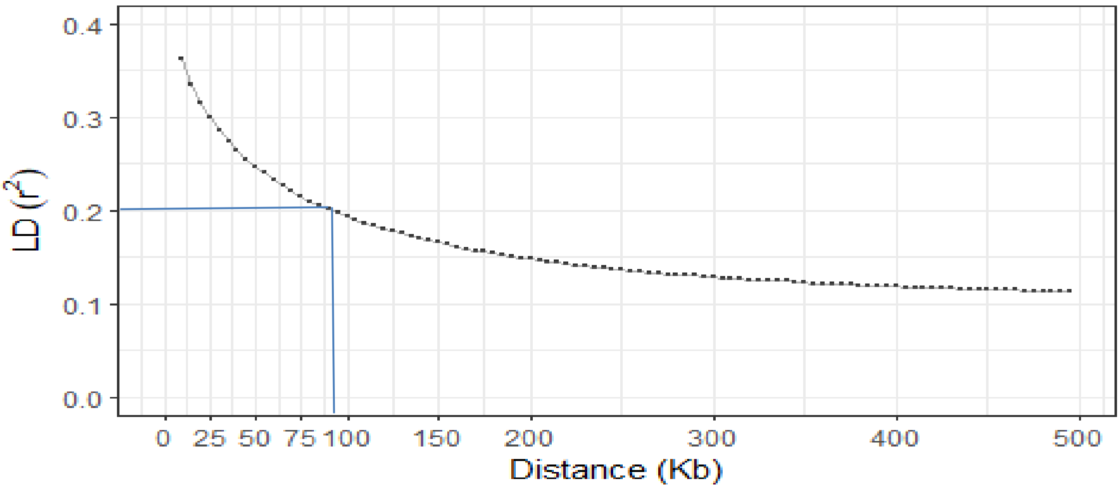

Fig-4.2.3 Decay of average LD ($r^2 < 0.2$) over distance among SNPs in Ongole breed

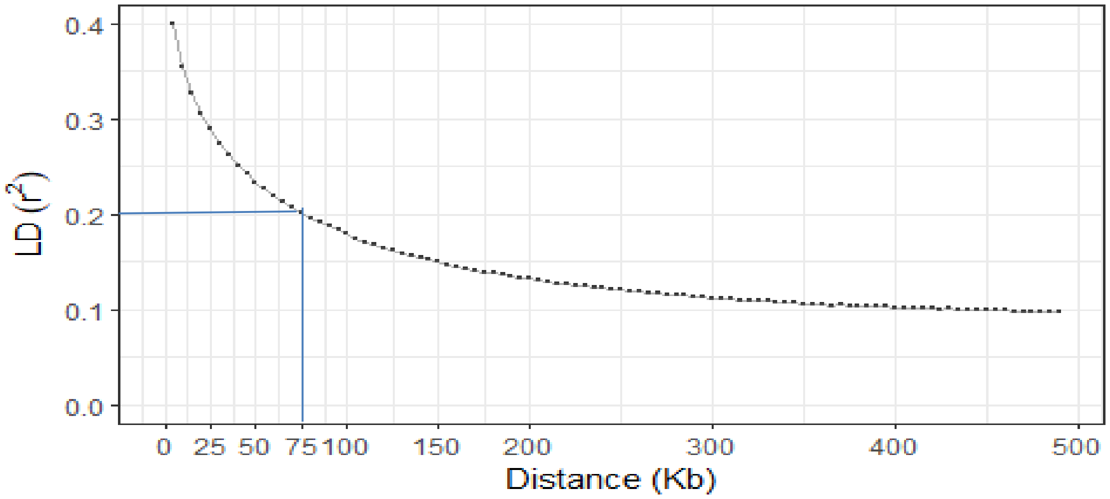

Fig-4.2.4 Decay of average LD ($r^2 < 0.2$) over distance among SNPs in Nellore breed

To prevent an overrepresentation of SNPs with the same biased information due to ascertainment bias, LD pruning was carried out (Scheper *et. al.*, 2020). SNPs with higher levels of LD (r^2 values larger than 0.5) were thus eliminated using a sliding window technique with Plink software. As a result of this pruning 4,03,532 SNPs were removed from the four-breed data set and 1,46,735 SNPs remained for further analysis. Table 4.2.1 and fig-4.2.5 show SNPs remaining after LD pruning across different autosomes in four cattle breeds

Table 4.2.1 - Chromosome wise SNPs after LD pruning

Chr. No.	SNPs removed after LD pruning	SNPs remaining After LD pruning
1	26030	8942
2	21868	7595
3	19320	6809
4	18676	6762
5	19555	6008
6	21386	6663
7	20113	6273
8	18770	6924
9	18411	6120
10	15291	6161
11	16363	6121

12	14524	5122
13	12252	4910
14	15246	5190
15	13962	4854
16	13622	4928
17	12305	4528
18	10535	3922
19	8890	3857
20	11872	4188
21	10947	4148
22	9202	3721
23	8585	3823
24	10129	3826
25	6259	2796
26	8249	3361
27	7192	3116
28	6807	2943
29	7171	3124
Total	403532	146735

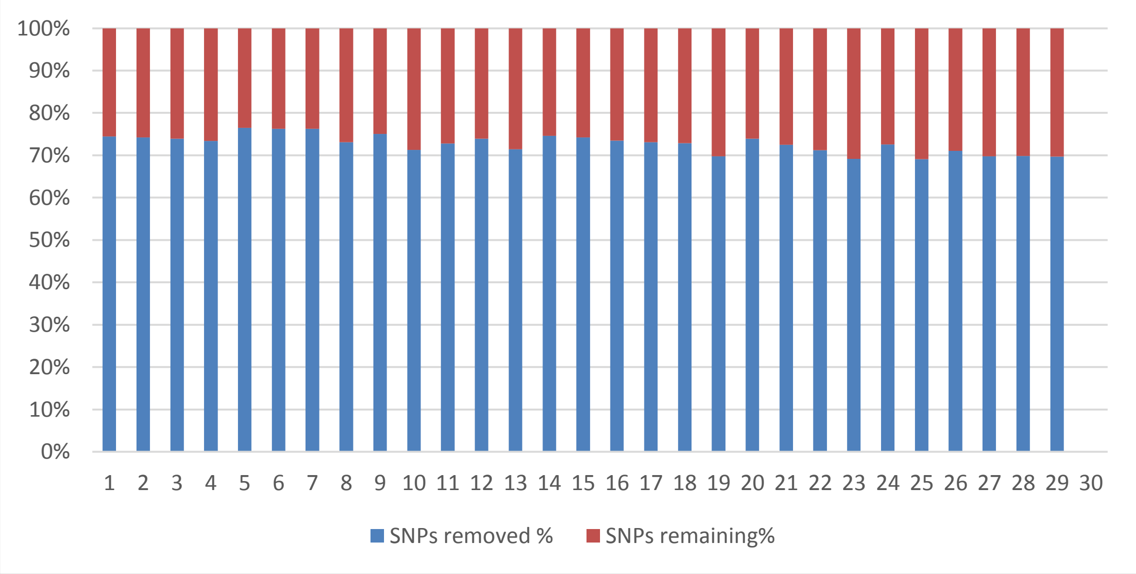

Fig-4.2.5 Chromosome wise SNPs after LD pruning

4.3 Effective population size

Ancestral and recent, effective population sizes (Ne) for four breeds of cattle were estimated using SNeP software. Estimated Ne across populations revealed a declining tendency in more recent generations. The Brazilian Gyr population showed a slow regular declining trend, whereas the Indian Gir population showed the most significant declining recent Ne. In four cattle breeds, the calculated Ne at 13 generations ago ranged from 52 to 98(Table-4.3.1). Fig-4.3.1 shows that the trajectory of the curve was linear with no dramatic changes in effective population size of four breeds.

Table 4.3.1-The estimated effective population size (Ne) in four cattle breeds over the past generations

Generation	Gir	Gyr	Ongole	Nellore
13	52	98	70	94
15	59	110	78	105
17	67	123	89	116
20	77	139	101	130
23	88	158	115	147
27	102	181	131	167
32	118	208	152	190
38	139	239	176	219
45	163	276	206	253
54	191	322	243	293
65	227	373	285	341
80	271	433	334	398
98	323	505	394	465
120	383	590	465	541
150	456	681	543	628
187	540	780	635	718
234	635	888	736	819
293	746	1005	847	929
366	870	1137	975	1047
454	1012	1276	1120	1178
553	1159	1424	1274	1313
657	1315	1582	1429	1457
759	1458	1723	1570	1591
847	1585	1852	1702	1708
914	1677	1944	1798	1798
958	1737	2010	1866	1854
983	1780	2053	1900	1876
995	1786	2073	1912	1898
999	1789	2070	1875	1924

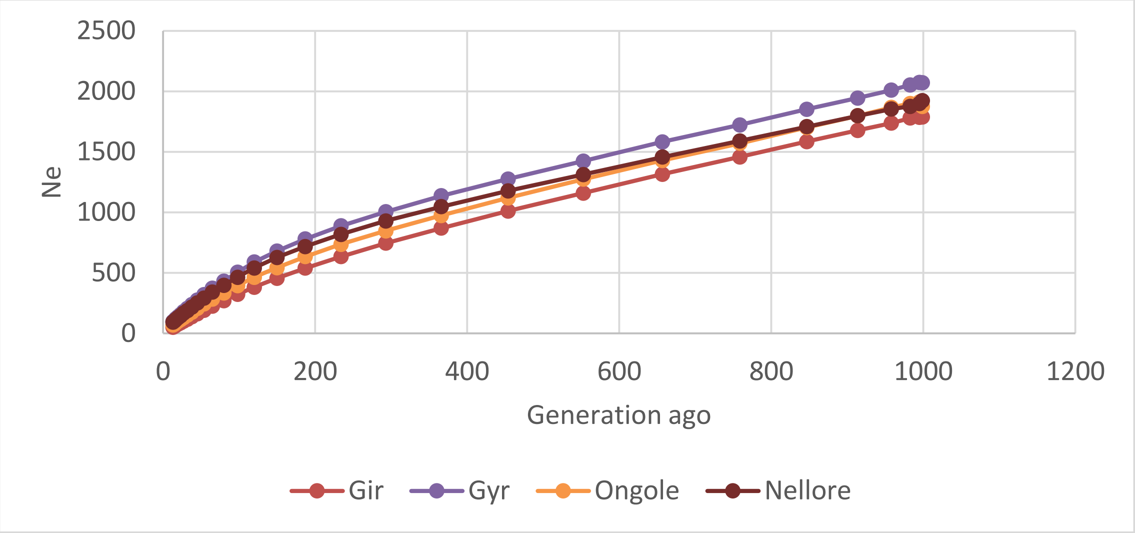

Fig-4.3.1 Effective population size (*Ne*) of four cattle breeds for 13-999 generations. X axis represents generations and Y axis represents *Ne*.

4.4 Genetic Structure of four cattle breed

Principal Component Analysis (PCA) and Discriminant Analysis of Principal Components (DAPC) were carried out using the adegenet package of the R software to access the population structure and to perceive the relationship among and across populations at a genomic level. PCA scatter plot (Fig 4.4.1), revealed that the dairy breed Gir and Gyr formed two separate clusters, whereas the nondairy breeds (Ongole and Nellore) were clustered together.Further the dairy and nondairy breeds were quite apart from each other. DAPC based on the K-means algorithm, implemented for further to test the optimum number of clusters. On the basis of minimum Bayesian information criterion (BIC) value it was clear that 2 clusters should be considered as optimum number (Fig-4.4.2 and 4.4.3).

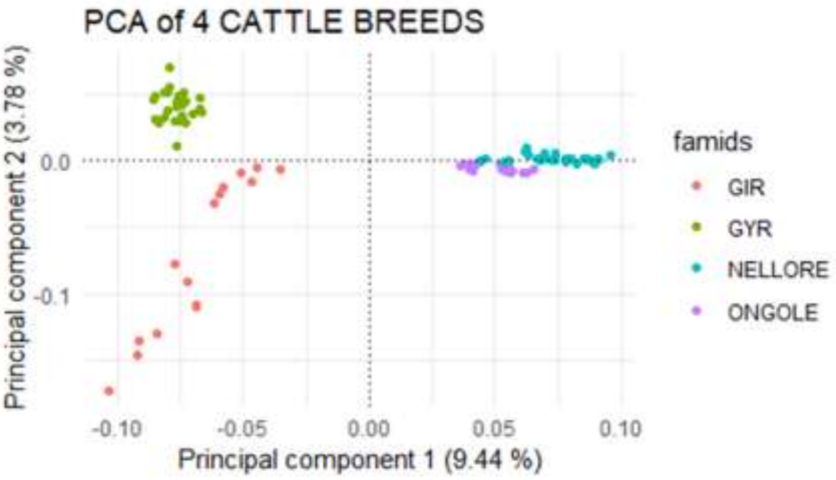

Fig-4.4.1 PCA scatter-plots of the four breeds for first two principal components

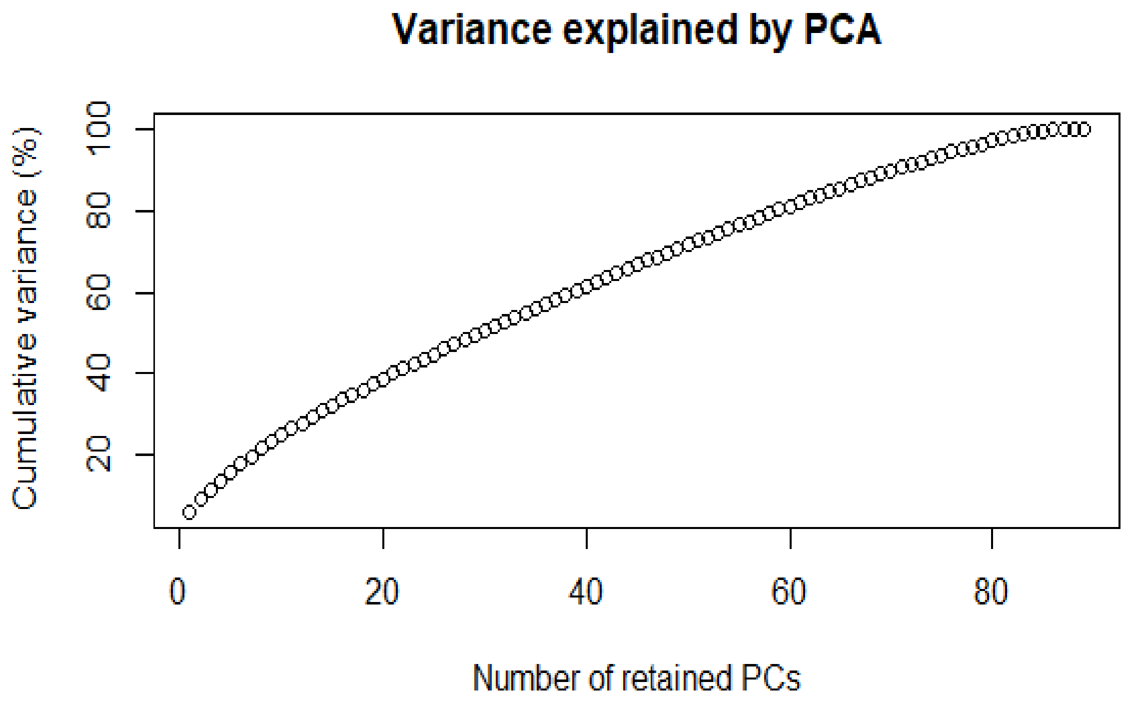

Fig-4.4.2 Cumulative variance explained by PCA

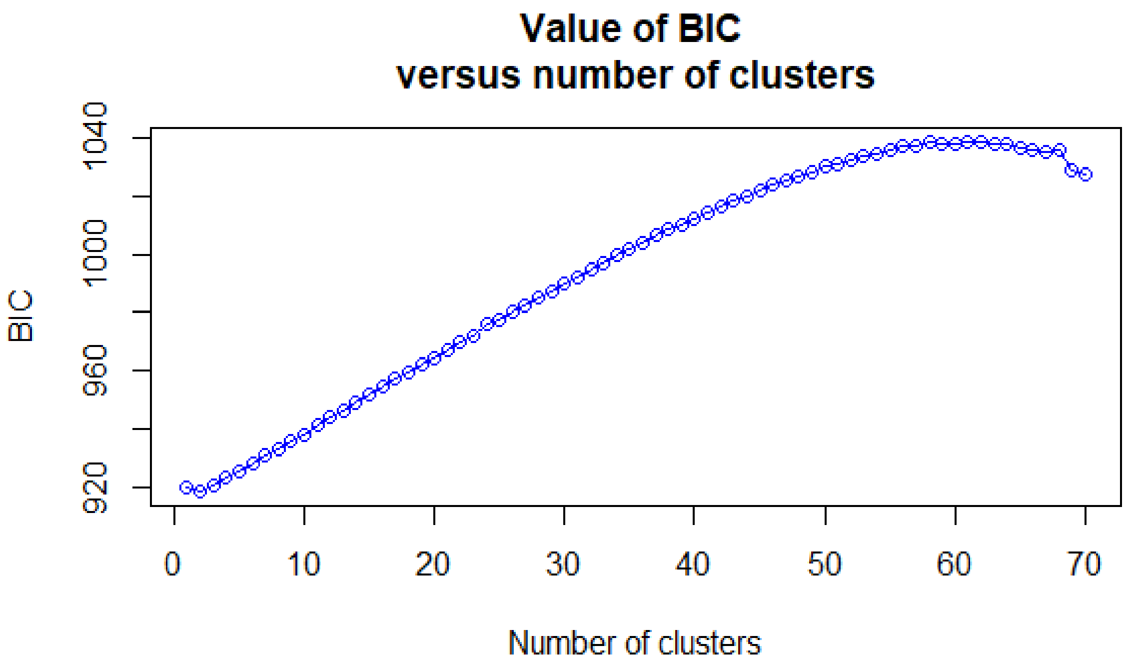

Fig-4.4.2 Plot for K-mean algorithm-based estimation of the number of clusters in four cattle breed.

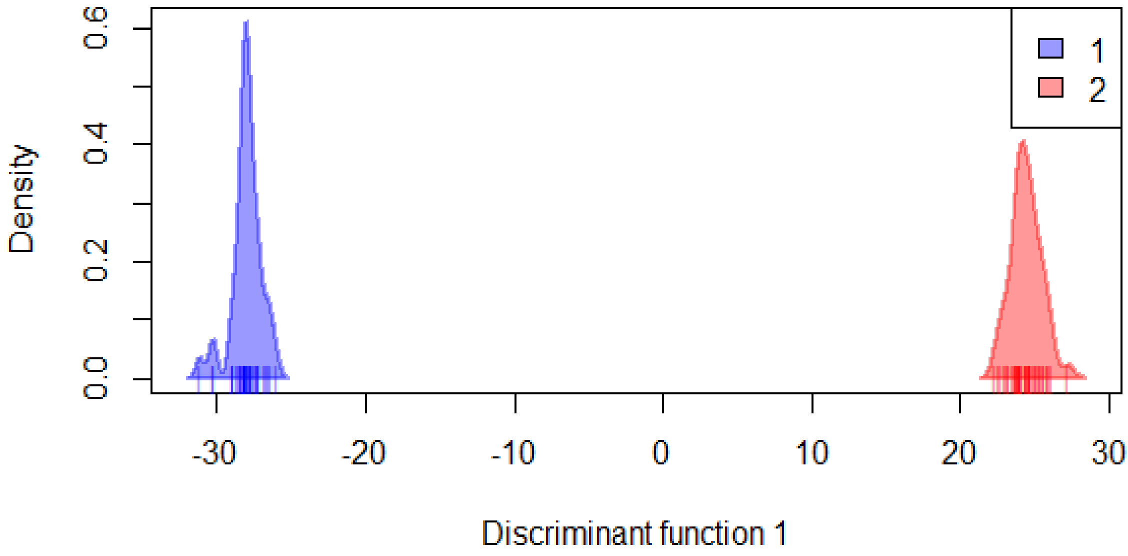

Fig-4.4.3 Plots showing first two discriminant functions of DAPC algorithm.

4.5 Within breed selective sweeps

Due to their less genetic variation and unique regional patterns of linkage disequilibrium (LD), regions pertaining signatures of selection can be identified (O'Brien, 2014).

To improve the accuracy of the identification of selection signatures, alternative methods have been suggested. In the current study we used two methods (iHS and ROH) for intra-population selection signature analyses. iHS statics is based on linkage disequilibrium while ROH method is based on reduced local variability.

4.5.1 Selection signature identification by iHS

To detect recent selection signatures within each breed we applied iHS test using the rehh R package as a set of 500 kb windows with a 250 kb overlap parameters. The false discovery rate (FDR) was determined for the p-value, to control false positives and decided the cut-off point as 1% of the FDR corrected piHS (Maiorano *et.al*., 2018). In the ranked SNP (based on piHS values) 1% of threshold was used to set the significance of iHS for the identification of genomic regions as positive signatures of selection in four breeds of cattle (Martinez *et., al.* 2019). Table 4.1 depicts the summary of identified selected regions by iHS method in four cattle breeds. Fig. 4.5.1, 4.5.2, 4.5.3, and 4.5.4 depicts the genome-wide distribution of piHS values across autosomes in Gir, Gyr, Ongole, Nellore cattle breeds, respectively.

We identified 4004 genes that were overlapping with 697 positively selected regions in Gir; 3322 genes, overlapping with 595 selected regions in Gyr; 3437genes overlapped with 595 selected regions in Ongole and 3485 genes overlapping with 603 positively selected regions in Nellore cattle. We identified 4009, 3748, 3983 and 3687 SNPs under 1% of threshold of piHS value. Table 4.5.1 contains summary of Identified selected regions by iHS method in four cattle breeds.

Table 4.5.1 - Summary of Identified selected regions through iHS method in four cattle breeds

Breed	Positive selected region	Log piHS value for threshold 1 %	Number of SNPs in selected regions	Number of genes
Gir	697	1.84	4009	4004
Gyr	595	1.94	3747	3322
Ongole	595	1.89	3983	3437
Nellore	603	1.85	3687	3485

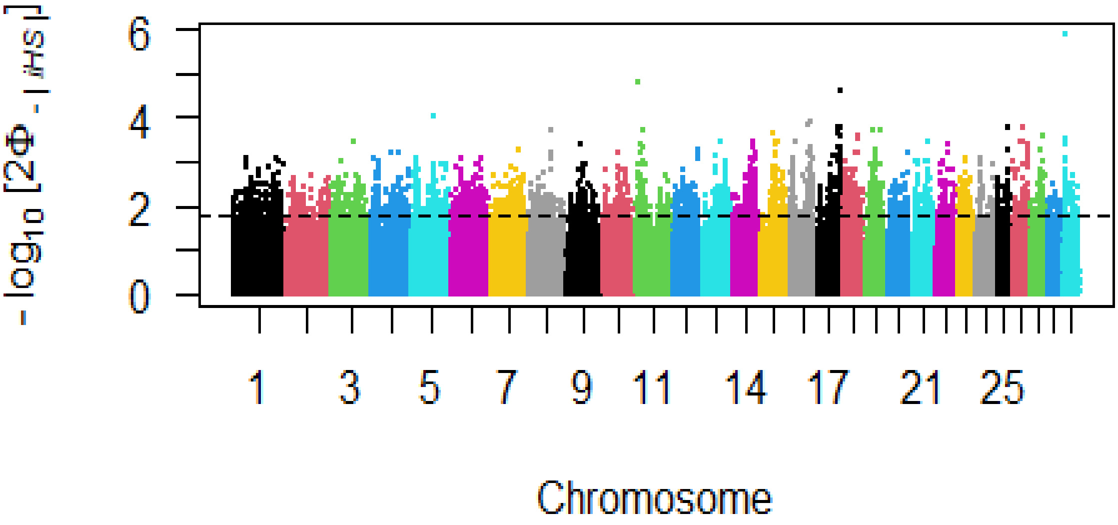

Fig-4.5.1 Manhattan plots showing genome-wide piHS analyses on Gir cattle. Horizontal dotted line marks the significance threshold (1%) applied to detect the selected region (–log10 (p iHS) =1.84)

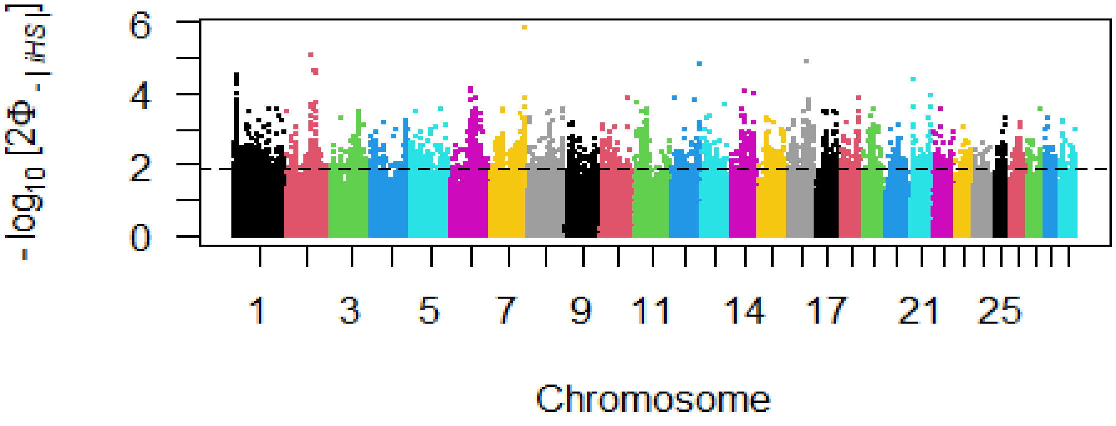

Fig-4.5.2 **Manhattan plots showing genome-wide piHS analyses on Gyr cattle. Horizontal dotted line marks the significance threshold (1%) applied to detect the selected region (–log10 (p iHS) =1.94)**

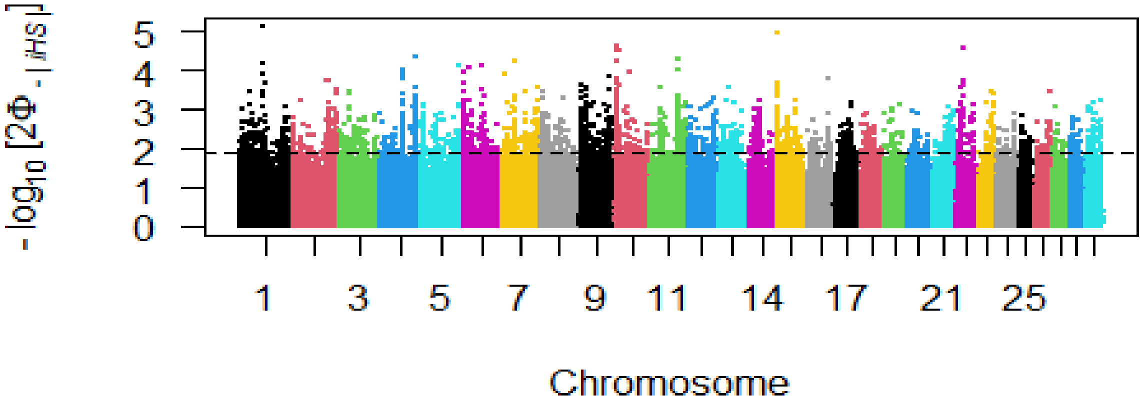

Fig-4.5.3 **Manhattan plots showing genome-wide piHS analyses on Ongole cattle. Horizontal dotted line marks the significance threshold (1%) applied to detect the selected region (–log10 (p iHS) =1.89)**

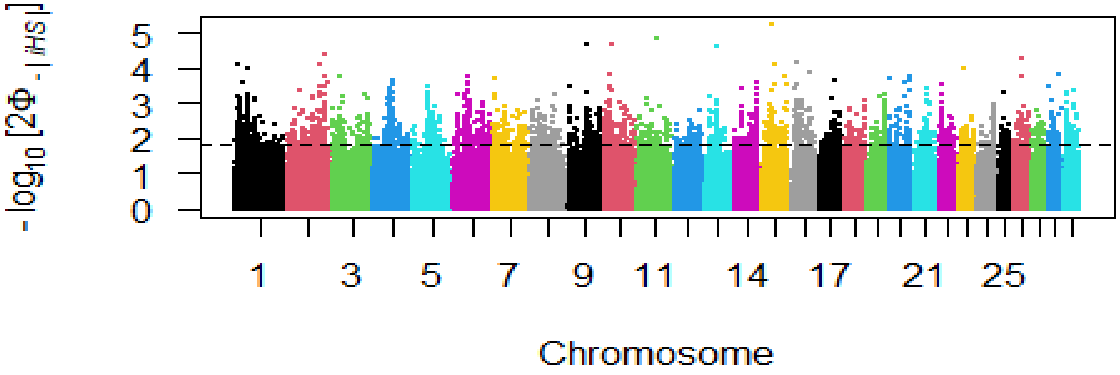

Fig-4.5.4 **Manhattan plots showing genome-wide piHS analyses on Nellore cattle. Horizontal dotted line marks the significance threshold (1%) applied to detect the selected region (–log10 (p iHS) =1.85)**

In top selected regions, we found many important traits gene for example IER5, MILR1(Gir), FER(Gyr), REG3A(Nellore) for immune response, HIKESHI, SLC18A1 (Gir) for heat tolerance, EIF5B (Gir), NRP2(Gyr), JMY, KCNF1(Ongole) for reproduction, LPL (Gir), MYO1B(Gyr), PARP2(Nellore) for carcass, RAPH1(Gyr), FGF12, SV2C (Ongole), KCNJ11, RNGTT, PCSK2, BFSP1(Nellore) for feed consumption and growth, and MYO16(Gyr), SAMM50(Ongole) for mammary structure and milk production. Top 5 selected genomic regions by iHS method with chromosome number, piHS values, genes and their functions for Gir, Gyr, Ongole and Nellore are listed in Table 4.5.2, 4.5.3, 4.5.4 and 4.5.5 respectively.

Table-4.5.2-Top 5 selected regions for Gir cattle through iHS method

Chr	**Position**	**LogpiHS**	**Gene**	**Function**	**References**
29	9043880	5.89	HIKESHI	Mediates heat stress	Bruscadin *et al.*, 2021
11	4678760	4.81	EIF5B	Reproduction	Prakapenka *et al.*, 2021
16	63633723	3.82	IER5	Immune response	Xiao *et al.*, 2019
19	49021355	3.71	MILR1	Immune response	Jemaa *et al.*, 2020
8	67507131	3.69	LPL	Fatty acid composition-Carcass traits	Oh *et al.*, 2013
			SLC18A1	Stress response	Lung *et al.*, 2018

Table-4.5.3-Top 5 selected regions for Gyr cattle through iHS method

Chr	**Position**	**LogpiHS**	**Gene**	**Function**	**References**
7	110486380	5.82	FER	Innate immune response	Flori *et al.*, 2009
2	80178900	5.03	MYO1B	Muscle development	Doyle *et al.*, 2020
12	87936404	4.82	MYO16	Mammary structure and milk production	Nazar *et al.*, 2021
2	94637868	4.62	NRP2	Reproductive trait	Shimizu *et al.*, 2006
2	92316989	4.62	RAPH1	Feed efficiency	Li *et al.*, 2019

Table-4.5.4-Top 5 selected regions for Ongole cattle through iHS method

Chr	Position	LogpiHS	Gene	Function	Reference
1	75556114	5.14	FGF12	Average daily gain	Olivieri *et al.*, 2016
10	7630434	4.54	SV2C	Body size	Raza *et al.*, 2020
10	10509736	4.5	JMY	Reproductive trait	Kiser *et al.*, 2019
11	86921219	4.29	KCNF1	Fertility trait	Tyagi *et al.*, 2021
5	1.15E+08	4.15	SAMM50	Milk protein percentage	Macciotta *et al.*, 2017

Table-4.5.5-Top 5 selected regions for Nellore cattle through iHS method

Chr	Position	LogpiHS	Gene	Function	References
15	35634639	5.24	KCNJ11	Feed consumption and growth trait	Diniz *et al.*, 2018
11	56891031	4.84	REG3A	Immune response	Carvalheiro *et al.*, 2019
9	62352959	4.67	RNGTT	Average daily feed intake	Cristobal *et a*l., 2015
10	26592994	4.67	PARP2	Carcass trait	Vignato *et al.*, 2019
13	37995690	4.6	PCSK2, BFSP1	Glucose metabolism	Weber *et al.*, 2016

We also carried out Venn analysis with genes present in top 1% selected regions by iHS method for Gir-Gyr pair and Ongole -Nellore pair of cattle. Our study based on genes present in one breed but absent in other breeds as represented by nonoverlapping segment in Venn diagram, showed breed specific selection footprints. In this comparison study we found that genes related to immunity trait (OSMR, GRK4, ARID5A) and milk production (HTR4, E2F2, LAP3 STAT1, CSN2, CSN3, CSN1S1, CSN1S2) were present in Indian Gir cattle whereas, genes related to carcass trait (*SLMAP*, *KCNA6*, MSTN, MYO6), mammary gland, udder development and milk production (UNC80, VWC2L, TRIB3, DGAT2, AGA, PTK2, MOGAT1, ART3, TRAPPC9) are present in Brazilian Gyr cattle. Similarly, in Ongole and Nellore pair comparison study, genes overlapped with 1% selected regions by iHS method we found that genes related to immune response (IL17B, IL23R, IL4R), thermotolerance (DNAJB4, FKBP4) and milk production (CSN3) were present in Indian Ongole cattle whereas, genes related to carcass trait (ERCC5, FOXA2, NPR2, ACNA2D1, MYO10, ASAP1) are present in Brazilian Nellore cattle.

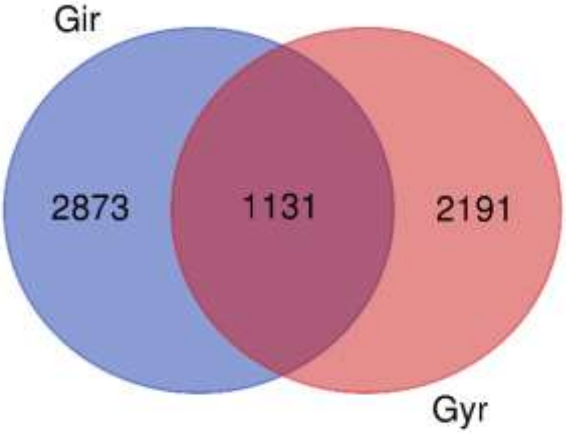

Fig-4.5.5 Venn diagram for Gir-Gyr pair with genes overlapping with selected regions by HIS method

Table-4.5.6 Some important traits related Genes present in selected regions by iHS method in Gir cattle (from nonoverlaping segment in Venn diagram)

Gene	**Function**	**References**
HTR4	Residual feed intake	Manca *et al.*, 2021
NFKB2	Adaptation	Kim and Rothschild, 2014
E2F2	Milk production	Kim *et al.*, 2015
OSMR	Immunity and mammary development	Wang *et al.*, 2018
GRK4	Immunity	Dzomba *et al.*, 2021
LAP3	Milk production	Flori *et al.*, 2009
XRN2	Reproduction trait	Saravana *et al.*, 2021
ARID5A	Immune response	Saravana *et al.*, 2021
SDR16C5, SDR16C6	Beef traits	Li & Kim, 2015
STAT1	Milk, fat and protein	Hayes *et al.*, 2009

Table-4.5.7 Some important traits related Genes present in selected regions by iHS method in Gyr cattle (from nonoverlapping segment in Venn diagram)

Gene	Function	References
AGA, PTK2, MOGAT1, ART3, TRAPPC9	Milk production traits	Saravana *et al.*, 2021
TLR4, IL2	Reducing the short term and long-term heat stress	Saravana *et al.*, 2021
UNC80, VWC2L	Rear udder height	Gonzalez, 2020
COL5A2	Collagen production	Zhao *et al.*, 2015
TRIB3	Milk protein and fat percentage	Cui *et al.*, 2014
DGAT2	Milk production trait	Shuhaib *et al.*, 2019
SLMAP	Rump fat thickness	Martins *et al.*, 2020
KCNA6	Body weight	Igoshin *et al.*, 2019
MSTN	Muscle hypertrophy	Randhawa *et al.*, 2016
MYO6	Muscle physiology	Mustafa *et al.*, 2018

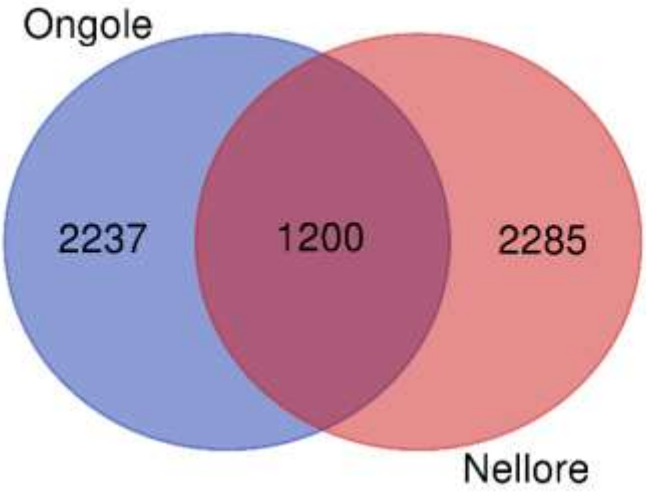

Fig-4.5.6 Venn diagram for Ongole-Nellore pair with genes overlapping with selected regions by iHS method

Table-4.5.8 Some important traits related Genes present in selected regions by iHS method in Ongole cattle (from nonoverlapping segment in Venn diagram)

Gene	**Function**	**References**
IL17B	Immune	Bahbahani *et al.*, 2018
DNAJB4	Heat tolerance	Saravanan *et al.*, 2021
CSN3	Milk production	Lee *et al.*, 2014
EBF1	Parasite tolerance	Mustafa *et al.*, 2018
LEP	Growth and fat deposition	Mustafa *et al.*, 2018
IL23R	Immunity	Huang *et al.*, 2013
FKBP4	Thermotolerance	Saravanan *et al.*, 2021
IL4R	Immune response	Flisikowski *et al.*, 2012
CLMP	Climate adaptation	Flori *et al.*, 2019
AACS	Intramuscular fat	Lee *et al.*, 2012

Table-4.5.9 Some important traits related Genes present in selected regions by iHS method in Nellore cattle (from nonoverlapping segment in Venn diagram)

Gene	**Function**	**References**
DPY19L2, XRN2	Reproduction	Saravanan *et al.*, 2021
ERCC5	Carcass traits	Ismail *et al.*, 2014
FOXA2	Carcass traits	Liu *et al.*, 2014
CCL19	Growth rate and feed efficiency	Zhang *et al.*, 2016
NPR2	Beef traits	Mustafa *et al.*, 2018
ACNA2D1	Carcass quality traits	Hou *et al.*, 2010
IL12RB1	Immunity	Kim *et al.*, 2016
LCORL	Feed intake and weight gain	Perry *et al.*, 2013
MYO10	Muscle physiology	Wang *et al.*, 2018
ASAP1	Circumference of scrotum, beef quality and production traits	Tizioto *et al.*, 2012

4.6.1 Distribution of ROH and genomic inbreeding coefficient of the breeds

We observed ROH in 90 individuals belonging to 4 different cattle breeds using Plink software applying the sliding window approach. The total number of homozygous segments (ROH) across all the breeds was 3887. The mean number of ROH per animal (MNROH) was highest in Gyr (45.04) and lowest in Ongole (41.70) (Table 5). For all length categories, the homozygous segments (ROH) were longer in Gir cattle (4.66). The mean genome length under ROH was also highest in Gir (204.03 Mb) but lowest in Gyr (161.26Mb). Most individuals are having between 100-200 Mb of ROH length (Fig 4.6.1.1, 4.6.1.3, 4.6.1.4, 4.6.1.5 and 4.6.1.6).

Compared to other cattle breeds, Gir cattle had the highest recent genomic inbreeding (FROH>8) value (0.045), whereas the Gyr breed had the lowest value (0.026). Genomic inbreeding coefficient values for FROH>1-8 was almost similar for all four breeds (Fig-4.6.1.7). Mean of sum of ROH regions (Mb), under different ROH length category for four cattle breeds were almost similar except in ROH length category >16Mb Gyr had smallest number of ROH regions (Fig-4.6.1.2).

Table-4.6.1 Genome-wide ROH distributions and it's descriptive statistics of four cattle breed.

Breed	Gir(n=15)	Gyr(n=27)	Ongole(n=17)	Nellore(n=31)
nROH	656	1216	709	1306
MNROH	43.73	45.04	41.70	42.13
Range ROH	15-96	27-79	29-63	27-62
NMROH	43.73-21.42	45.03-10.87	41.71-10.16	42.13-10.17
MGLROH(Mb)	204.03	161.26	178.73	192.35
MGPROH (%)	8.12	6.42	7.12	7.6
ALROH(Mb)	4.66	3.58	4.28	4.56
FROH>1-8Mb	0.036	0.038	0.036	0.037
FROH>8Mb	0.045	0.026	0.036	0.041

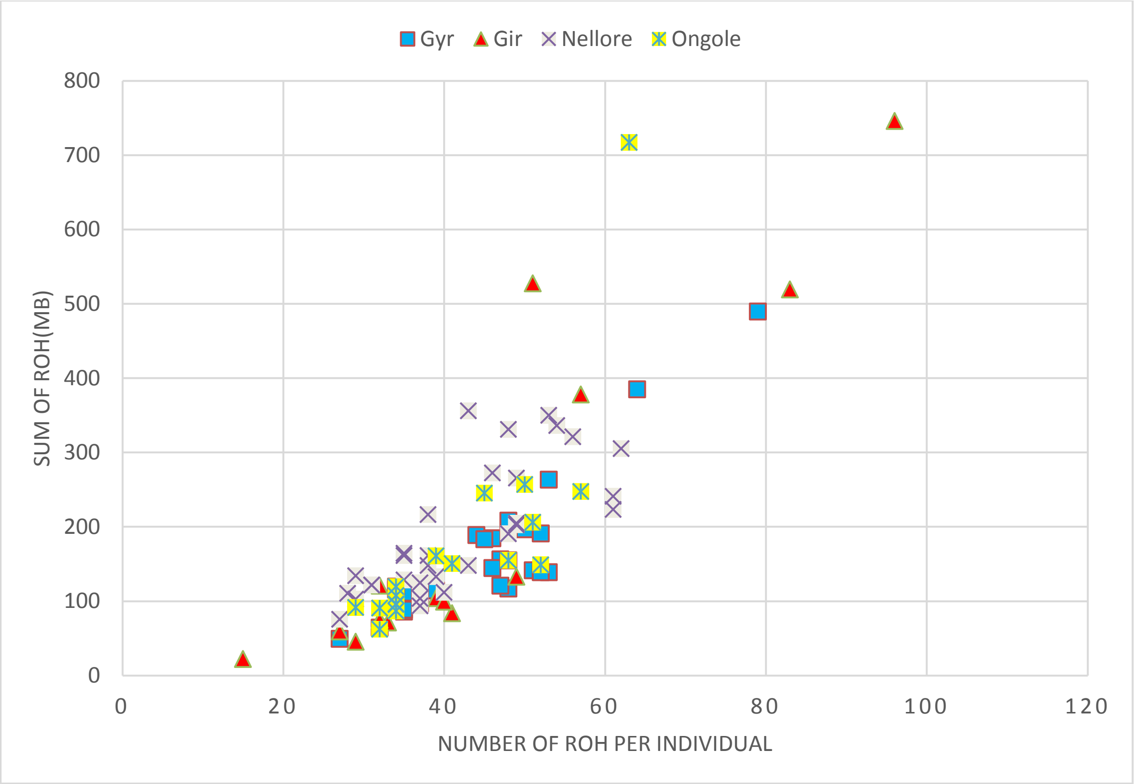

Fig-4.6.1.1 Length of the genome under ROH (Sum of ROH(Mb)) and the total number of ROH (nROH) for each individual (N=90) of four breeds of cattle

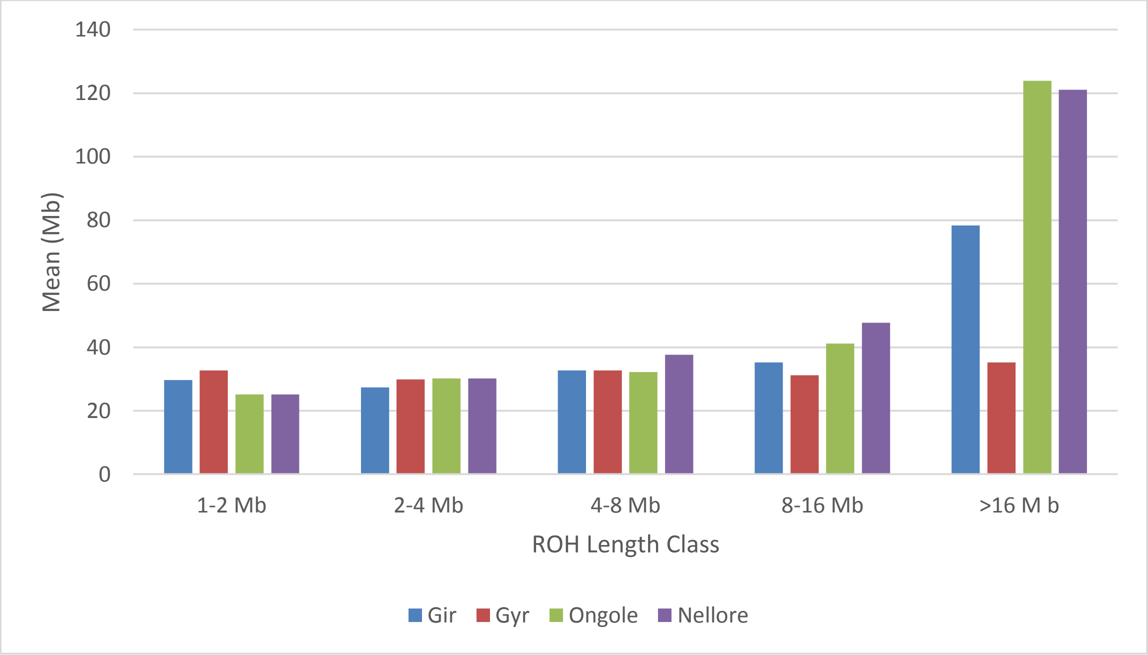

Fig-4.6.1.2 Mean of sum of ROH regions (Mb) under different ROH length category for four cattle breeds

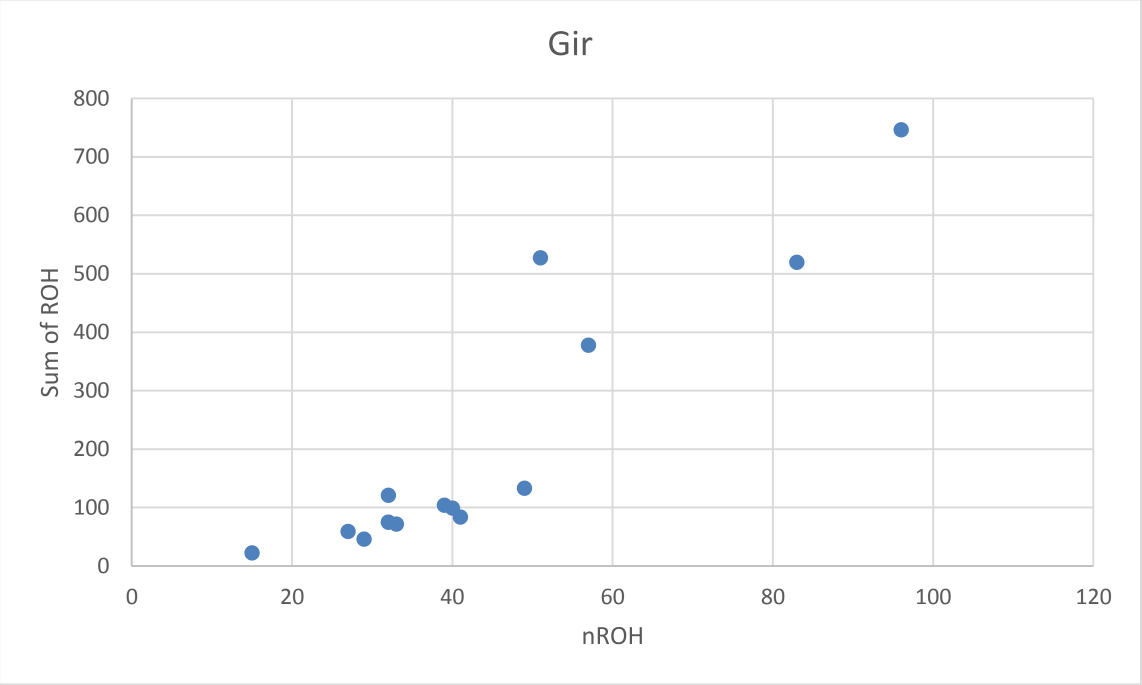

Fig-4.6.1.3 Length of ROH in genome and the total number of ROH for each animal of Gir cattle breed.

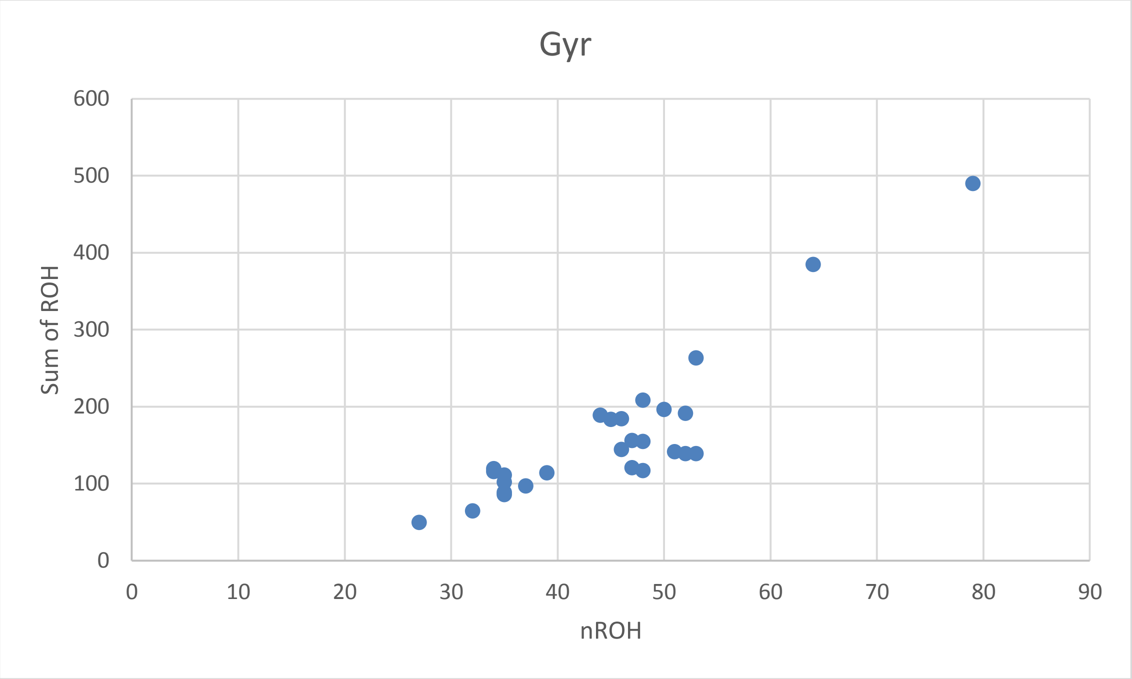

Fig-4.6.1.4 Length of ROH in genome and the total number of ROH for each animal of Gyr cattle breed.

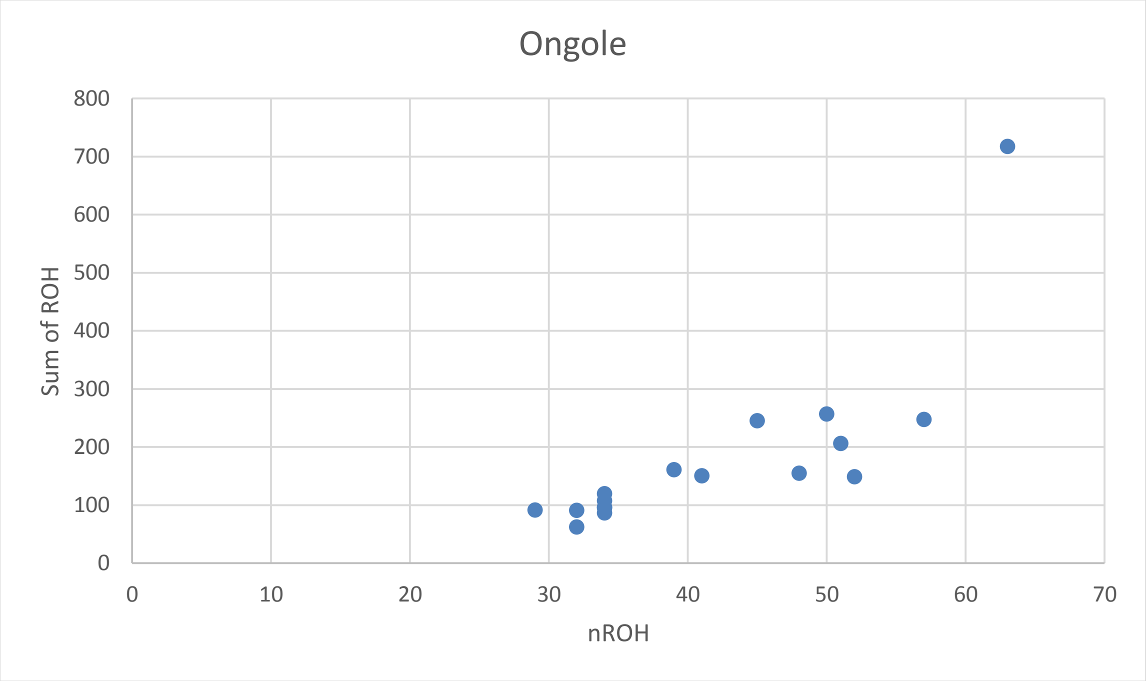

Fig-4.6.1.5 Length of ROH in genome and the total number of ROH for each animal of Ongole cattle breed

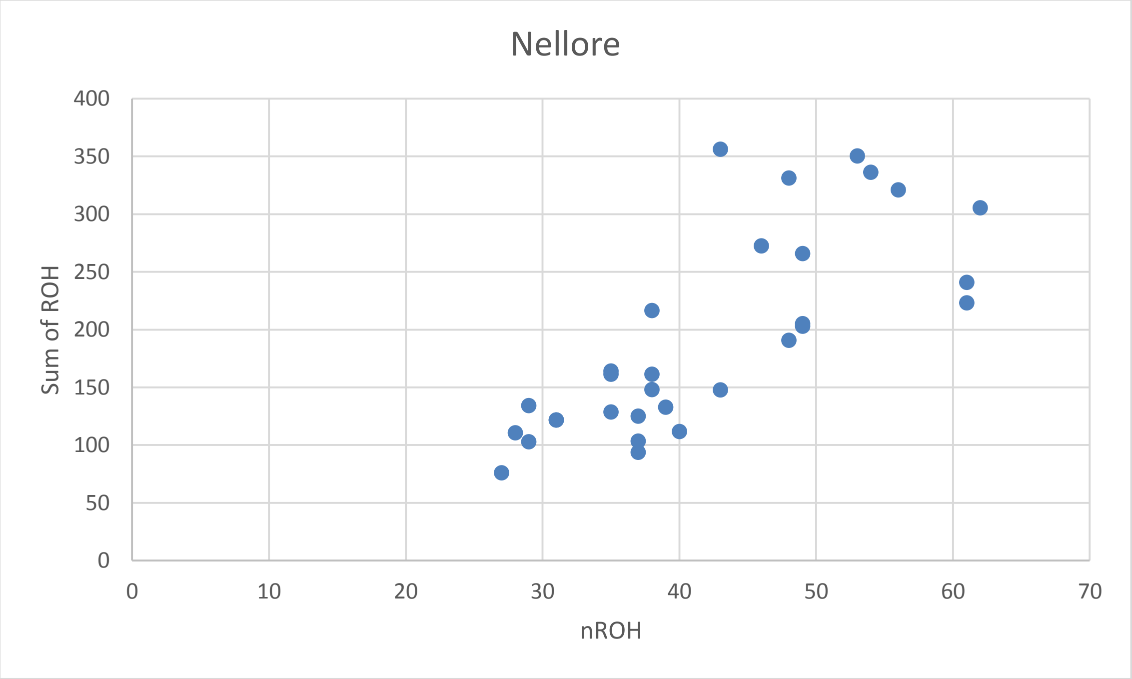

Fig-4.6.1.6 Length of ROH in genome and the total number of ROH for each animal of Nellore cattle breed

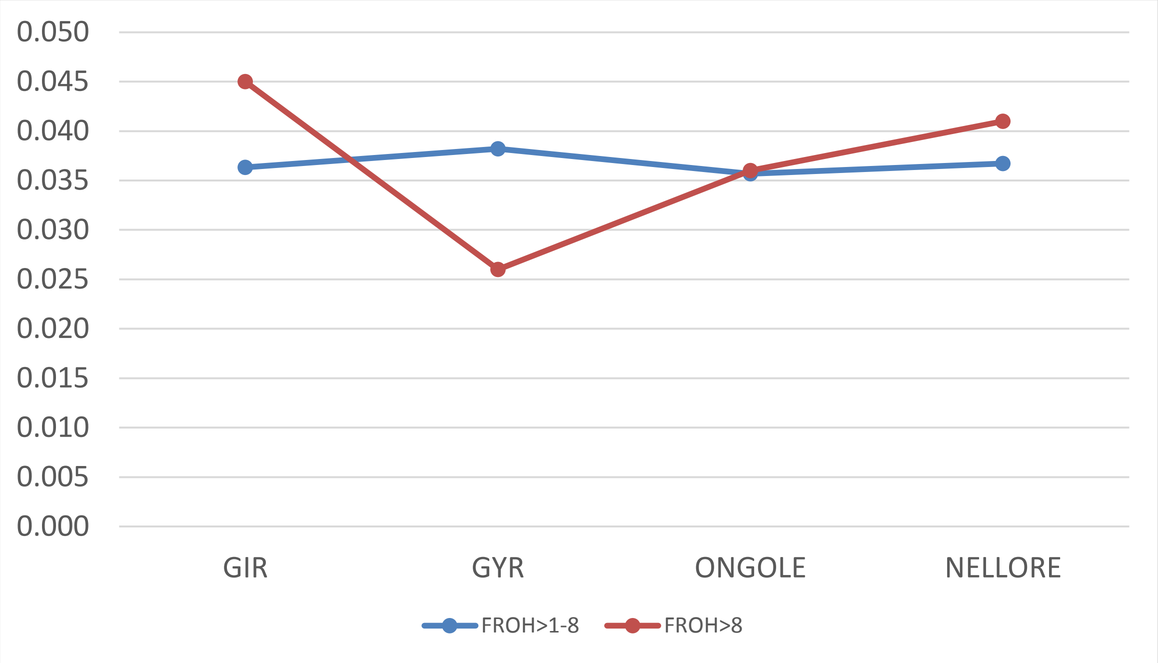

Fig-4.6.1.7 Genomic inbreeding coefficient for different ROH categories (FROH> 1-8 Mb and FROH> 8 Mb) for four cattle breeds

4.6.2 Genomic regions within overlapping ROH

Manhattan plots of the overlapping ROH percent for four breeds' (Gir, Gyr, Ongole, and Nellore) are shown in fig 4.6.2.1, 4.6.2.2, 4.6.2.3 and 4.6.2.4, respectively. To find out the gene contains, the ROHs consensus that occur in at least 20% of animals were referred to as ROH islands. For selection signature associated genes identification, the overlapping ROH regions with a frequency of ≥20% were considered as selection signature regions. In those selection signature regions, we have identified 160 ROH islands overlapping with 4285 gene in Gir, 76 ROH islands overlapping with 1768 gene in Gyr ,75 ROH islands overlapping with 1663 gene in Ongole, and 67 ROH islands overlapping with 1466 genes in Nellore cattle breed (Table 4.6.2.1).

Table-4.6.2.1 Identified selection signature regions and number of genes by ROH method

Breed	**Gir**	**Gyr**	**Ongole**	**Nellore**
Threshold (consensus region frequency %)	≥20	≥20	≥20	≥20
ROH Island	160	76	75	67
Gene	4285	1768	1663	1466

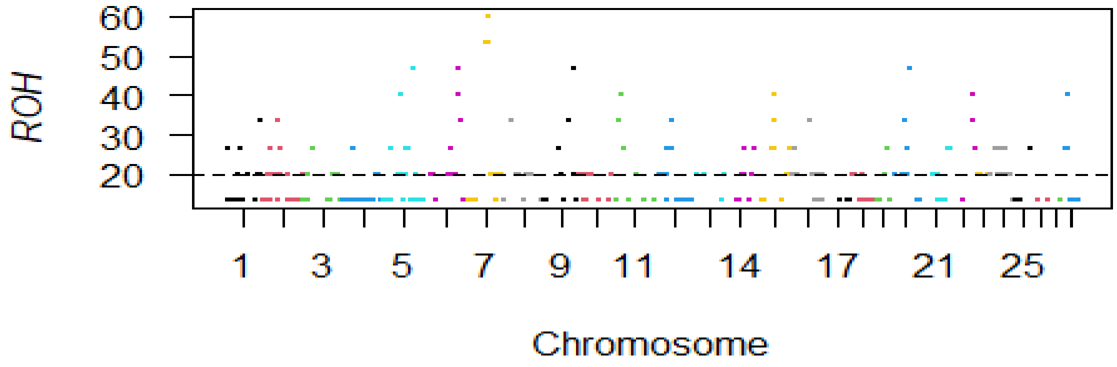

Fig-4.6.2.1 Manhattan plot of consensus (overlapping) ROH regions in Gir cattle breed. ROH regions with a frequency of ≥20% are shown above the dotted line.

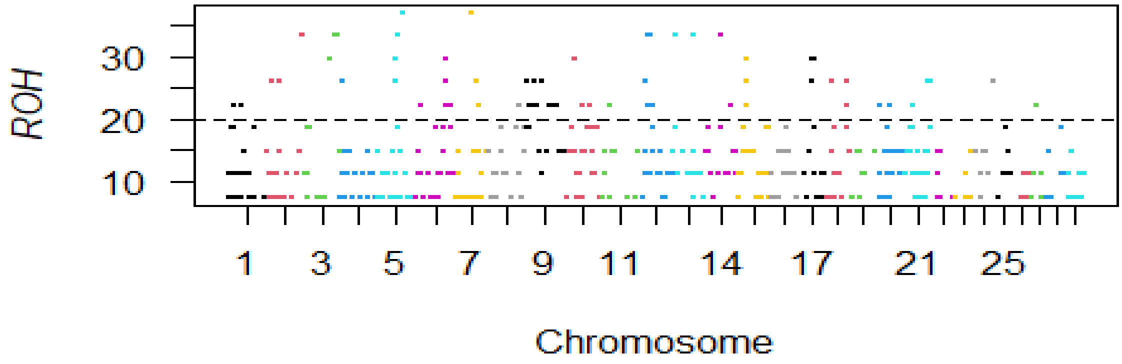

Fig-4.6.2.2 Manhattan plot of consensus (overlapping) ROH regions in Gyr cattle breed. ROH regions with a frequency of ≥20% are shown above the dotted line.

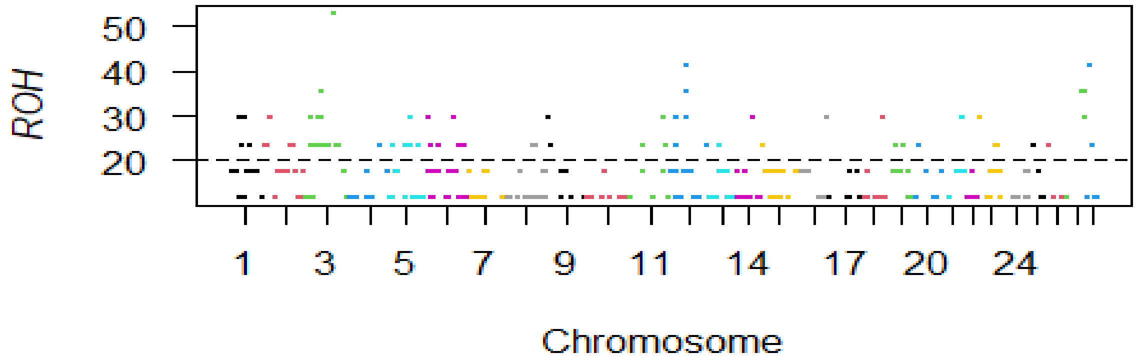

Fig-4.6.2.3 Manhattan plot of consensus (overlapping) ROH regions in Ongole cattle breed. ROH regions with a frequency of ≥20% are shown above the dotted line

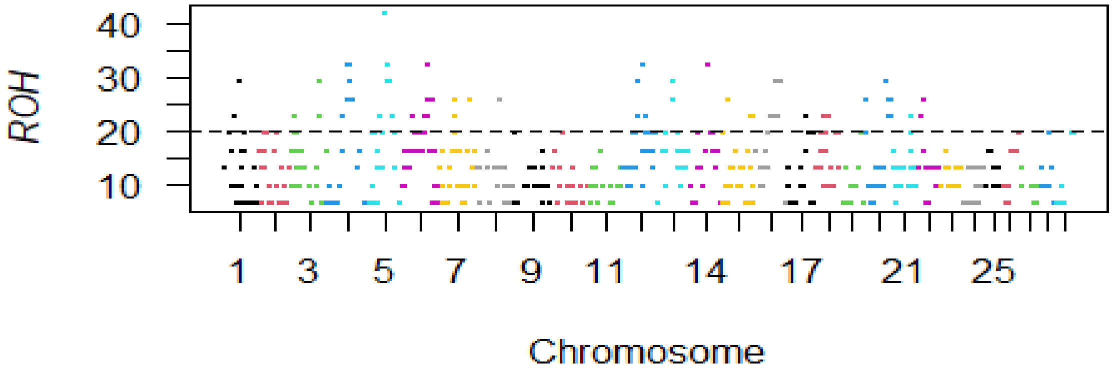

Fig-4.6.2.4 Manhattan plot of consensus (overlapping) ROH regions in Nellore cattle breed. ROH regions with a frequency of ≥20% are shown above the dotted line

In top selected regions by ROH method we found many genes related to important traits like ARAP(Gir) ALOX5AP(Gyr), FAM19A2(Nellore) for immune response, ALDH1L2, ADAMTS12(Gir), ADAM23, AGAP2(Gyr)for milk production, ABCA7(Gyr), ACADM, NKIRAS1(Ongole), ATP10D(Nellore) for carcass trait, AHI1(Gir), ADAM18, ADAM2(Ongole), ASZ1, DPY19L1, DPY19L2(Nellore) for reproduction trait PCDH9 (Ongole) for body shape traits (mainly Loin Strength).

Top 5 selected genomic regions with chromosome number, ROH consensus frequency %, genes and their functions for Gir, Gyr, Ongole and Nellore are listed in Table 4.6.2.2, 4.6.2.3, 4.6.2.4 and 4.6.2.5, respectively.

Table-4.6.2.2-Top 5 selected regions for Gir cattle by ROH method

Chr	**Position**	**ROH consensus %**	**Gene**	**Function**	**References**
7	52275709-52929978	60	ARAP3	Immune response	Kukuckova *et al.*, 2016
5	70086279-71021432	46.67	ALDH1L2	Milk fat traits	Awemu *et al.*, 2016
6	80607709-81621853	46.67	EPHA5	Associated to feed conversion ratio	Santana *et al.*, 2016
9	71471003-72352223	46.67	AHI1	Fertility-related traits	Fonseca *et al.*, 2021
20	39868670-40659335	46.67	ADAMTS12	Milk production and carcass weight	Gao *et al.*, 2017

Table-4.6.2.3-Top 5 selected regions for Gyr cattle by ROH method

Chr	Position	ROH consensus %	Gene	Function	References
7	44606792-45098558	37.04	ABCA7	Beef tenderness	Zhao *et al.*, 2020
2	96082524-96406227	33.33	ADAM23	Milk protein production	Devani *et al.*, 2020
3	81712792-83644705	33.33	AK4	Maintenance and growth	Takeda *et al.*, 2019
5	57785345-57889506	33.33	AGAP2	Mammary gland development and lactation	Chao *et al.*, 2019
12	28112252-29508940	33.33	ALOX5AP	Immunity	Crookenden *et al.*, 2017

Table-4.6.2.4-Top 5 selected regions for Ongole cattle by ROH method

Chr	Position	ROH consensus %	Gene	Function	References
3	67358567-67444935	52.94	ACADM	Fat depot and meat quality	Shuang Ji *et al.*, 2014
12	38569321-39089985	41.17	PCDH9	Body shape traits-Loin Strength	Xubin Lu *et al.*, 2021
28	8320150-8954672	41.17	ACTN2	Feed efficiency	Vaughn *et al.*, 2022
27	35616336-36884022	35.29	ADAM1, ADAM2	Fertility trait	Meslin *et al.*, 2012
27	39259827-40378667	35.29	NKIRAS1	Intramuscular fat deposition	Albrecht *et al.*, 2016

Table-4.6.2.5-Top 5 selected regions for Nellore cattle by ROH method

Chr	Position	ROH consensus %	Gene	Function	References
5	49187829-49842685	41.94	AVPR1A	Response to heat stress	Cordero *et al*, 2017
5	51113065-51662116	41.94	FAM19A2	Immune response	Dixit *et al.*, 2021
4	49494267-50563384	32.26	ASZ1	Spermatogenesis	Bickhart *et al.*, 2016
4	59133075-60707778	32.26	DPY19L1, DPY19L2	Reproduction	Saravanan *et al.*, 2021
6	67218464-67952179	32.26	ATP10D	Influences beef color traits in Nellore	Garzon *et al.*, 2021

Similar to iHS method, for ROH method also we plotted Venn diagram with genes present in ROH consensus frequency ≥20% selected regions for Gir-Gyr and Ongole - Nellore pair of cattle.

Genes which were present in one breed but absent in other breed, were related to their characteristic features. In ROH method, the study based on the non-overlapping parts of Venn diagram, we found genes related to immune response (CLEC10A, HSPA9), adaptation (RNASEK, CREB3L1), parasite tolerance (EBF1) and milk production (HAL, AGTRAP, CSN1S1, CSN1S2, CSN2, CSN3) present in Indian Gir breed whereas, genes related to carcass trait (MYO6, FAM219A, BBS12, LTBP4, OGFRL1, CHMP5) and milk production (NCAM2, ART3) were present in Brazilian Gyr cattle (Fig 4.6.2.5 and table 4.6.2.6 and 4.6.2.7). Non-overlapping section in Venn diagram of Ongole breed harbors genes related to Immune response (CDC6, MFSD6), Thermal resistance (DNAJA1, HSPB9), production trait (PTEN, PPP1R12A, ERCC5) (Fig 4.6.2.6 and Table 4.6.2.8). In case of Nellore cattle genes related to adaptation (MTOR), disease resistance (PRDM2), parasite tolerance (PDPN) and carcass trait (BAMBI, ABHD5, EFHD2) were present. (Fig 4.6.2.6 Table 4.6.2.9)

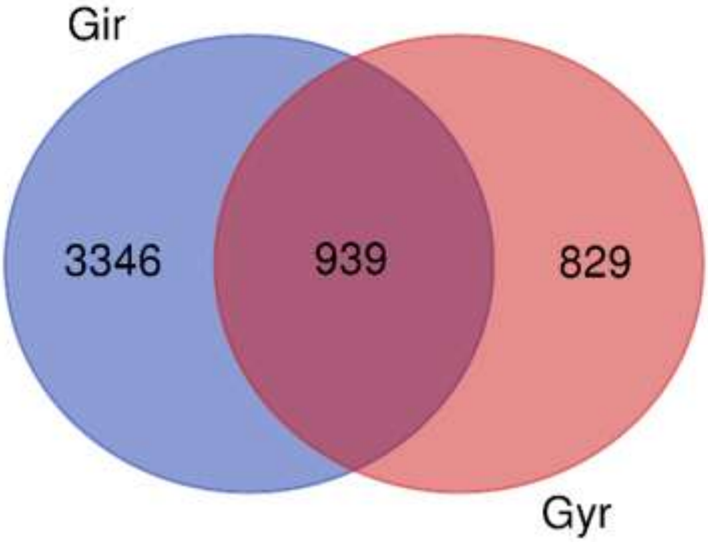

Fig-4.6.2.5 Venn diagram for Gir-Gyr pair with genes overlapping with selected regions by ROH method

Table-4.6.2.6 Some important traits related Genes present in selected regions through ROH method in Gir cattle (from nonoverlapping segment in Venn diagram)

Gene	**Function**	**References**
HAL	Milk protein yield and milk yield	Lu *et al.*, 2021
CREB3L1	Response to heat stress	Sigdel *et al.*, 2019
AGTRAP	Milk production	Randhawa *et al.*, 2016
CLEC10A	Immunity	Bahbahani *et al.*, 2015
CSN1S1, CSN1S2, CSN2, CSN3	Milk production	Huang *et al.*, 2012
EBF1	Parasite tolerance	Mustafa *et al.*, 2018
ERAL1	Meat quality in beef	Gutierrez *et al.*, 2019
TLR10, TLR6	Mastitis resistance	Flori *et al.*, 2014
RNASEK	Adaptation	Bahbahani *et al.*, 2015
HSPA9	Immune response	Randhawa *et al.*, 2016

Table-4.6.2.7 Some important traits related Genes present in selected regions by ROH method in Gyr cattle (from nonoverlapping segment in Venn diagram)

Gene	Function	References
DNAJA1	Thermal resistance	O'Brien *et al.*, 2014
NCAM2	Milk quality and production	Alshawi *et al.*, 2019
MYO6	Muscle physiology	Mustafa *et al.*, 2018
FAM219A	Beef tenderness	Carvalho *et al.*, 2017
BBS12	Meat weight, foreshank weight, and silverside weight	Chang *et al.*, 2019
LTBP4	Skeletal muscle development and growth (feed efficiency)	Mota *et al.*, 2022
OGFRL1	Intramuscular and subcutaneous adipocyte proliferation	Gutierrez *et al.*, 2018
ART3	Milk fat rate	Gao *et al.*, 2017
CHMP5	Growth and meat production trait	Zhang *et al.*, 2013
PHKB	Feed efficiency related traits	Oliveira *et al.*, 2014

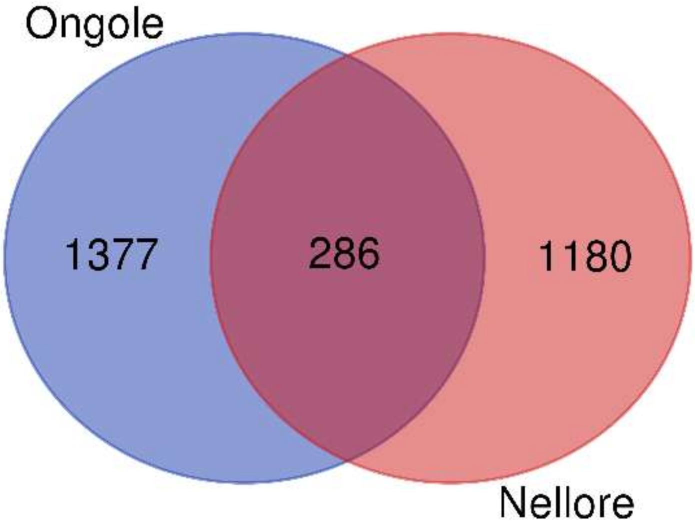

Fig-4.6.2.6 Venn diagram for Ongole-Nellore pair with genes overlapping with selected regions by ROH method

Table-4.6.2.8 Some important traits related Genes present in selected regions by ROH method in Ongole cattle (from nonoverlapping segment in Venn diagram)

Gene	**Function**	**References**
CDC6	Immune response	Makina *et al.*, 2015
COL11A1	Growth	Wang *et al.*, 2018
DNAJA1	Thermal resistance	O'Brien *et al.*, 2014
HSPB9	Thermal resistance	Mustafa *et al.*, 2018
PTEN	Lactation	Wang *et al.*, 2014
IGFBP4	Growth and muscle development	Makina *et al.*, 2015
MSTN	Muscle hypertrophy	Randhawa *et al*., 2016
PPP1R12A	Beef traits	Choi *et al.*, 2015
MFSD6	Immunity	Zhao *et al.*, 2015
ERCC5	Carcass traits	Ismali *et al*., 2014

Table-4.6.2.9 Some important traits related Genes present in selected regions by iHS method in Nellore cattle (from nonoverlapping segment in Venn diagram)

Gene	**Function**	**References**
SSTR1	Growth trait	Jin *et al.*, 2011
ISG15	Immune response	Haq *et al.*, 2016
MTOR	Adaptation	Kim and Rothschild, 2014
PDPN	Parasite tolerance	Mustafa *et al*., 2018
BAMBI	Beef quality trait	Yang *et al.*, 2020
PDE1C	Body weight	Lili Du *et al.*, 2021
PRDM2	Disease resistance	Ghoreishifar *et al*., 2020
HK3	Glucose metabolism pathways (Growth)	Naserkheil *et al*., 2021
ABHD5	Improve carcass quality traits	Raza *et al.*, 2019
EFHD2	Growth and muscle development	Makina *et al*., 2015

4.7.1 Cross population Genomic variability and Selection signature by Fixation index (F_{ST}) method

Arlequin software based on FDIST technique(Beaumont, 1966), was used to calculate the fixation index (F_{ST}) at various significance levels to measure genetic divergence for each locus between two populations. SNPs remained after LD pruning of merged data of four cattle breed (146735 SNPs) were utilized to calculate genetic diversity. The genomic distance study of these cattle breeds using Arlequin software showed varying levels of genetic differentiation. Reynold's genetic distances and pairwise F_{ST} values showed that Gir and Nellore breeds had the highest levels of divergence, while Ongole and Nellore had the lowest divergence (Table-4.7.1). Pairwise F_{ST} differences between Gir versus Gyr and Ongole versus Nellore were 2.856 % and 2.354 %, respectively.

Table-4.7.1 Reynold's genetic distance (above the diagonal) and Pairwise F_{ST} differences (below the diagonal) for four cattle breeds.

Breed	Gir	Gyr	Ongole	Nellore
Gir	0.00000	0.02898	0.06652	0.07015
Gyr	0.02856	0.00000	0.06222	0.06558
Ongole	0.06435	0.06033	0.00000	0.02383
Nellore	0.06774	0.06348	0.02354	0.00000

4.7.2 Selection signature identification by pairwise F_{ST} method

We also applied pairwise F_{ST} approach to identify genetic differentiation among Indian and Brazilian cattle breeds that may result from various selection pressures**.** The measurement of population differentiation based on variations in the allelic frequencies is known as fixation index (F_{ST}). Fixation index analysis is used to detect allele frequency differences in a segment of genome between breeds or populations. When the nearby SNP loci exhibit high F_{ST} as a result of the hitch-hiking effect caused by divergent selection between populations, the genomic region can be considered under selective sweep (Qanbari *et al.*, 2011).

In the current study, there were two breed pairs (Gir-Gyr and Ongole-Nellore) for which we estimated F_{ST} values. Under top 1% threshold (− log P value = 2) we found 621 SNPs for Gir versus Gyr and 599 SNPs for Ongole versus Nellore cattle breed. We plotted

Manhattan plot for Genome wide F_{ST} values with a threshold line at − log P value = 2 for Gir-Gyr and Ongole-Nellore pair (Fig-4.7.2.1 and Fig-4.7.2.2 respectively) which clearly demonstrated the presence of selection signature in various genomic areas.

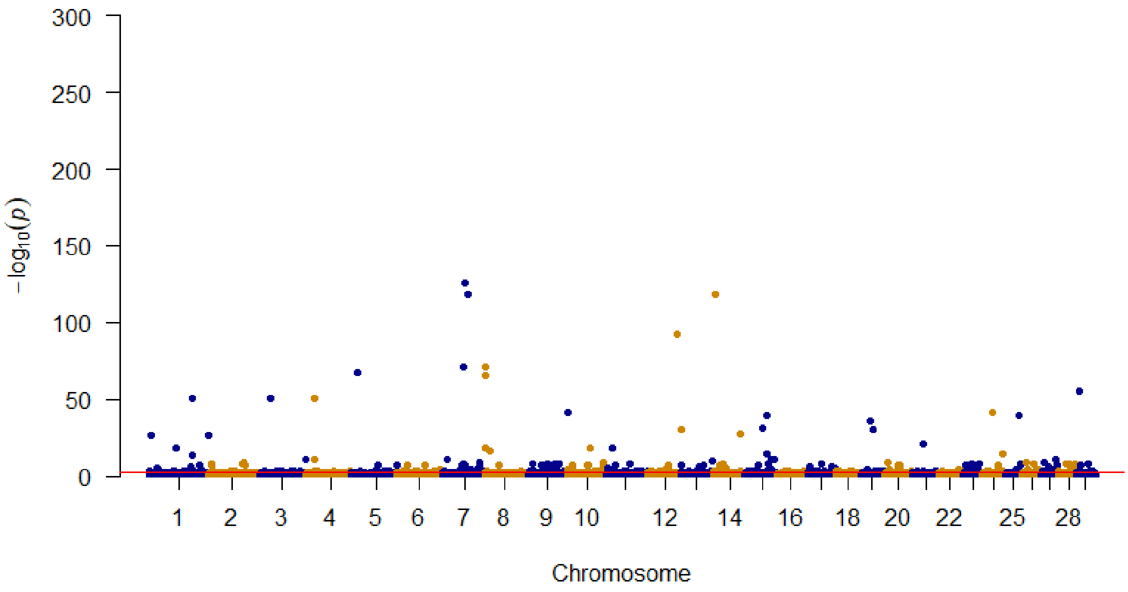

Fig-4.7.2.1 Manhattan plot of F_{ST} values Gir-Gyr cattle breed pair.

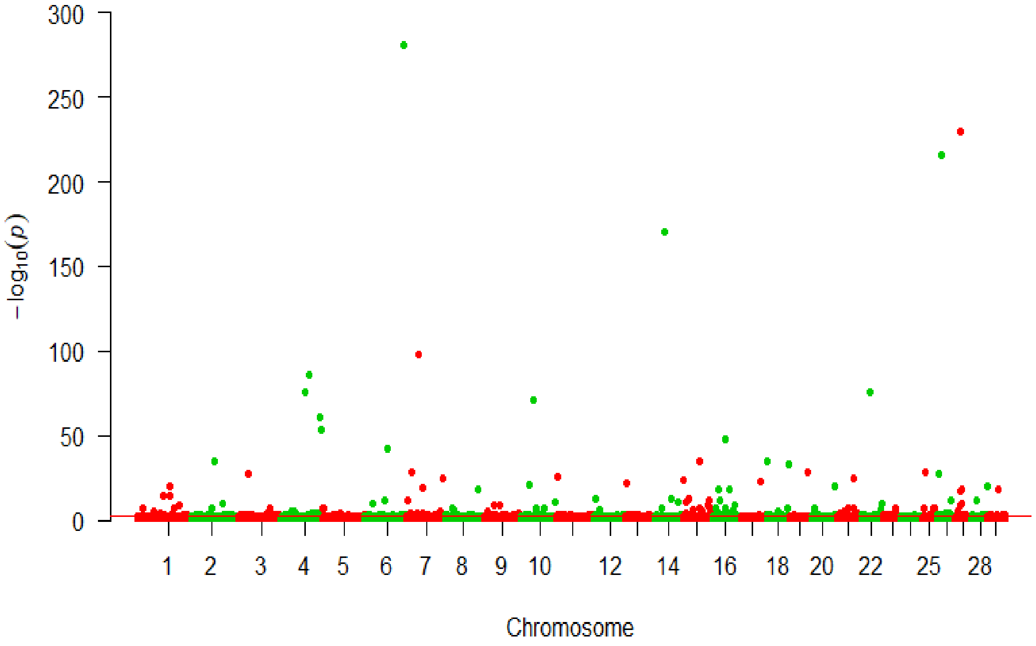

Fig-4.7.2.2 Manhattan plot of F_{ST} values Ongole-Nellore cattle breed pair.

The corresponding candidate genes were annotated using the bovine genome assembly data source for top 1% selected region (P <0.01). Selected regions of Gir-Gyr pair corresponds to 1966 genes, whereas Ongole-Nellore pair it corresponds to1897 genes.

Tables 4.7.2.1 and 4.7.2.2 give summary of top selected regions gene related to adaptation, feed efficiency trait, milk production, reproduction, and carcass traits, for Gir-Gyr and Ongole-Nellore pair respectively.

Table-4.7.2.1 Top ten selected regions by F_{ST} method (Gir-Gyr)

Chr	Position	-Log F_{ST}	Gene	Function	References
7	59058936	126	PRELID2	FE related traits and body weight	Lu Fu *et al.*, 2020
7	66859967	118	GRIA1,	Weaning weight	Yi Li *et al.*, 2015
14	5707136	118	FAM135B	Milk production	Liu *et al.*, 2021
12	79585832	92	SLC15A1	Protein digestion and absorption	Gaowa *et al.*, 2021
7	54519397	71	ARAP3	Immune response	Kukuckova *et al.*, 2016
8	1208626	71	CLCN3	Backfat thickness	Martins *et al.*, 2020
8	696574	65	ANXA10	Residual feed intake (RFI)	Santana *et al.*, 2014
1	1.17E+08	50	MBNL1	Growth, carcass and fertility traits	Bolormaa *et al.*, 2015
3	26133854	50	TRIM45	Beef tenderness	Bongiorni *et al.*, 2016
4	22948181	50	DGKB	Insulin secretion	Gan *et al.*, 2019

Table-4.7.2.2 Top ten selected regions by F_{ST} method (Ongole-Nellore)

Chr	Position	-Log F_{ST}	Gene	Function	References
27	12605598	230	TENM3	Carcass yield traits	Zhang *et al.*, 2019
14	29050593	169	ASPH	Growth and development	Duan *et al.*, 2021
4	82431663	85	POU6F2	DNA-binding functions that regulate transcription	Freua *et al.*, 2016
4	67462808	75	CPVL	Immunity	Wang *et al.*, 2022
10	35459226	71	THBS1	Thermal adaptations	Igoshin *et al.*, 2021
15	45633733	35	PPFIBP2	Milk lactose percentage	LiYuan *et al.*, 2017
18	965484	34	UQCRFS1	Reproductive trait	Mezera *et al.*, 2020
2	65133093	34	NCKAP5	Flight speed: temperament trait	Valente *et al.*, 2016
18	61226177	33	NLRP12	Immune response	Silveira *et al.*, 2016
19	51750775	28	PYCR1	Milk fatty acid composition	Palombo *et al.*, 2018

4.8 Overlapping genes by iHS and ROH method

Fig 4.8.1 and Tables 4.8.1 and 4.8.2 give summary of gene under top selected regions which were overlapping with iHS and ROH methods for Gir, and Gyr respectively.

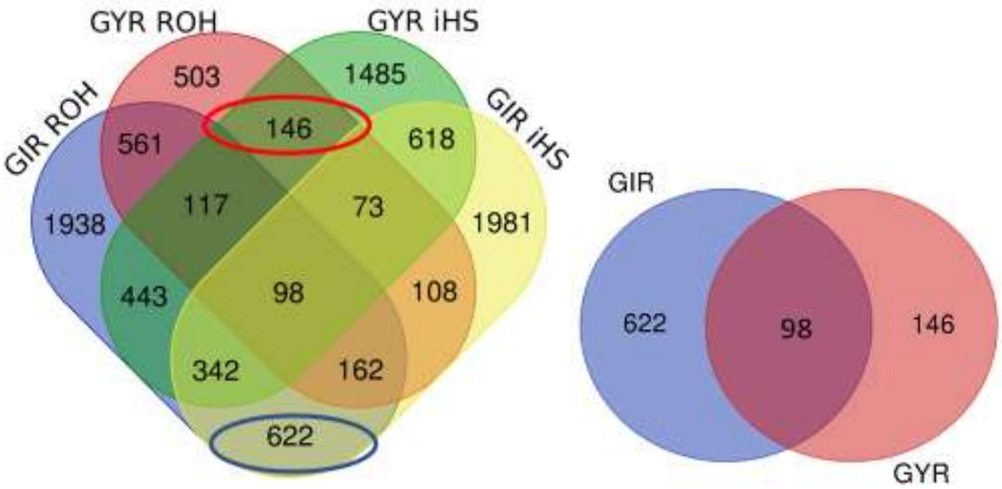

Fig-4.8.1 **Venn diagram showing overlapping genes with iHS and ROH method in Gir and Gyr pair**

Table-4.8.1 Top overlapping regions genes (iHS and ROH method) for Gir

Chr	BP1	BP2	Gene	Function	References
29	9075490	10411282	RAB38	Coat color and ocular hypopigmentation	Hollmann *et al.*, 2017
7	51638010	52167178	MYOT, WNT8A	Carcass trait	Huang *et al.*, 2017
6	83229855	86053293	JCHAIN	Bovine immunoglobulin	Kulseth *et al.*, 1994
8	16379607	17517971	TUSC1	Tumor suppressor gene	Shan *et al.*, 2013
11	13040867	15778397	ANKRD53	Reproductive trait	Mota *et al.*, 2022
12	35655948	36202823	CRYL1	Feed efficiency trait	Lam *et al.*, 2018
15	46838495	47057360	TRIM34	Immune response	Zhihai Si *et al.*, 2006
20	30557633	31702537	PRKAA1	Reproductive trait	Foroughinia *et al.*, 2016
1	4597540	5429503	KRTAP11-1, KRTAP8-1, KRTAP7-1	Horn formation, hair keratin-associated protein	Stafuzza *et al.*, 2018

Table-4.8.2 Top overlapping regions genes (iHS and ROH method) for Gyr

Chr	BP1	BP2	Gene	Function	References
2	96082524	96406227	MAP2	Immune response	Mwangi *et al.*, 2002
13	50412956	50976614	FERMT1	Body weight	Sanchez *et al.*, 2020
3	67077293	67433085	MIGA1	Reproductive trait	Liu *et al.*, 2017
9	17347695	17641710	SH3BGRL2	Growth trait	Zhao *et al.*, 2020
17	34520340	36438437	ANKRD50	Intra muscular fat	Roberts *et al.*, 2018
18	50789851	50789851	AKT2	Feed efficiency traits	Olivieri *et al.*, 2016
21	22970484	23214925	CRTC3	Carcass trait	Wu *et al.*, 2019
6	93750680	95226862	ART3	Milk protein and fat traits	Gao *et al.*, 2017
7	65203867	65807602	GLRA1	Feed conversion ratio	Saravanan *et al.*, 2021
8	76086513	77219793	BNIP3L	Reproductive traits	Meszarosova *et al.*, 2022

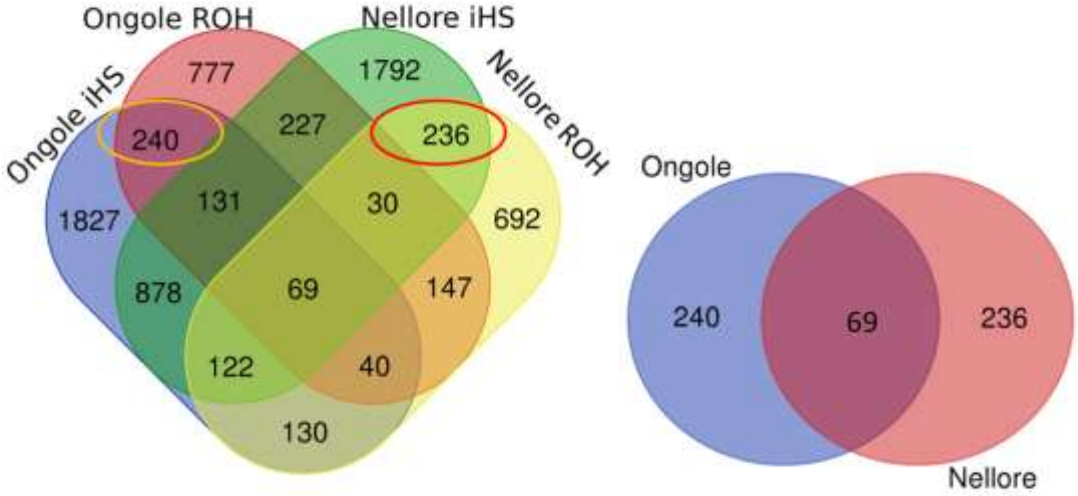

Fig-4.8.2 Venn diagram showing overlapping genes with iHS and ROH method in Ongole and Nellore pair

Table-4.8.3Top overlapping regions genes (iHS and ROH method) for Ongole

Chr	BP1	BP2	Gene	Function	References
3	67358567	67444935	ADGRL4	Immune response	Singh *et al.*, 2020
28	8320150	8954672	ACTN2	Feed efficiency	Vaughn *et al.*, 2022
12	35911635	36222679	TNFRSF19	Adaptation	Gautier *et al.*, 2017
27	35616336	36884022	DKK4	Body measurement trait	Gao *et al.*, 2013
2	12949930	13540896	PPP1R1C	Muscularity in beef cattle	Doyle *et al.*, 2020
6	6510612	6510612	FABP2	Feed efficiency	Bickhart *et al.*, 2012
11	79381085	79776541	KCNS3	Growth and development	Duan *et al.*, 2021
14	38236401	38249263	EYA1	Beef quality traits	Caldas *et al.*, 2014
23	175972	1129479	BAG2	heat stress response	Taiwo *et al.*, 2022
1	55650814	55772311	TRAT1	Immune response	Trovato *et al.*, 2015
2	5215631	5265036	HS6ST1	Lipid metabolism in muscles	Jiang *et al.*, 2011

Table-4.8.4 Top overlapping regions genes (iHS and ROH method) for Nellore

Chr	**BP1**	**BP2**	**Gene**	**Function**	**References**
4	59133075	59295152	EEPD1	Beef quality traits	Yan li, 2020
4	49494267	50563384	CHN2	Muscle growth	Sorbolini *et al.*, 2015
14	52624059	53907852	TRPS1	Carcass	Lee *et al.*, 2011
5	55881766	56000054	APOF	Meat production	Mei *et al.*, 2021
7	84405258	85143005	CKMT2	Tenderness of beef	Muniz *et al.*, 2021
13	40545108	40756118	FOXA2	Growth trait	Liu *et al.*, 2014
16	56475433	57517349	TNR	Reproductive trait	Melo *et al.*, 2017
17	50019621	50062343	SLC15A4	Meat quality	Page *et al.*, 2016
18	17985297	19664337	CYLD	Carcass trait and hump development	Mei *et al.*, 2019
20	58362806	59405551	OTULIN	Immunity-colostrum albumin concentration	Lin *et al.*, 2020

4.9 Gene Ontology Analysis

Table-4.9.1 Summary of significantly enriched GO_BP term and KEGG pathway related to important traits in Gir

GO TERM	GENE	P-VALUE
GO BP TERM		
GO:0007204~positive regulation of cytosolic calcium ion concentration	33	0.000188
GO:0071356~cellular response to tumor necrosis factor	33	0.000317
GO:0043524~negative regulation of neuron apoptotic process	37	0.000418
GO:0043065~positive regulation of apoptotic process	63	0.000544
GO:0043547~positive regulation of GTPase activity	43	0.000852
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	185	0.001602
GO:0001580~detection of chemical stimulus involved in sensory perception of bitter taste	16	0.001868
KEGG Pathway		
bta04670: Leukocyte transendothelial migration	40	0.000206
bta04514: Cell adhesion molecules	53	0.000458
bta05223: Non-small cell lung cancer	27	0.000999
bta04666: Fc gamma R-mediated phagocytosis	33	0.001036
bta04360: Axon guidance	53	0.00146
bta00565: Ether lipid metabolism	21	0.002165
bta00270: Cysteine and methionine metabolism	20	0.00256
bta04530: Tight junction	50	0.00634
bta04070: Phosphatidylinositol signaling system	29	0.018109

Table-4.9.2 Summary of significantly enriched GO_BP term and KEGG pathway related to important traits in Gyr

GO TERM	GENE	P-VALUE
GO BP TERM		
GO:0070328~triglyceride homeostasis	10	0.000063
GO:0050801~ion homeostasis	9	0.000065
GO:1903489~positive regulation of lactation	9	0.000112
GO:0030879~mammary gland development	11	0.000181
GO:0031667~response to nutrient levels	9	0.000184
GO:0030335~positive regulation of cell migration	32	0.000199
GO:0046427~positive regulation of JAK-STAT cascade	11	0.000355
GO:2001238~positive regulation of extrinsic apoptotic signaling pathway	9	0.00093
GO:0007160~cell-matrix adhesion	15	0.002574
KEGG Pathway		
bta04010: MAPK signaling pathway	47	0.000503
bta04151: PI3K-Akt signaling pathway	54	0.003119
bta04917: Prolactin signaling pathway	17	0.005719
bta04064: NF-kappa B signaling pathway	20	0.009975
bta04724: Glutamatergic synapse	20	0.010947
bta04060: Cytokine-cytokine receptor interaction	46	0.011502
bta04141: Protein processing in endoplasmic reticulum	27	0.013213
bta05022: Pathways of neurodegeneration - multiple diseases	63	0.014119
bta04080: Neuroactive ligand-receptor interaction	49	0.041194

Table-4.9.3 Summary of significantly enriched GO_BP term and KEGG pathway related to important traits in Ongole

GO TERM	GENE	P-VALUE
GO BP TERM		
GO:0046427~positive regulation of JAK-STAT cascade	17	0.000123
GO:0030879~mammary gland development	14	0.000139
GO:1903489~positive regulation of lactation	11	0.000145
GO:0031667~response to nutrient levels	11	0.000287
GO:0045931~positive regulation of mitotic cell cycle	12	0.000403
GO:0008284~positive regulation of cell proliferation	63	0.000997
GO:0034765~regulation of ion transmembrane transport	25	0.001161
GO:0072659~protein localization to plasma membrane	30	0.00149
GO:0000122~negative regulation of transcription from RNA polymerase II promoter	97	0.002294
GO:0030217~T cell differentiation	11	0.002413
KEGG PATHWAY		
bta05017: Spinocerebellar ataxia	34	0.00065
bta04080: Neuroactive ligand-receptor interaction	72	0.000982
bta04720: Long-term potentiation	19	0.002039
bta05200: Pathways in cancer	92	0.003244
bta04917: Prolactin signaling pathway	21	0.003809
bta03250: Viral life cycle - HIV-1	18	0.004331
bta04142: Lysosome	27	0.027965

Table-4.9.4 Summary of significantly enriched GO_BP term and KEGG pathway related to important traits in Nellore

GO TERM	GENE	P-VALUE
GO BP TERM		
GO:0051044~positive regulation of membrane protein ectodomain proteolysis	8	0.000232
GO:0032088~negative regulation of NF-kappaB transcription factor activity	18	0.002492
GO:0001570~vasculogenesis	15	0.002956
GO:0090090~negative regulation of canonical Wnt signaling pathway	27	0.003626
GO:0009952~anterior/posterior pattern specification	21	0.005541
GO:0010909~positive regulation of heparan sulfate proteoglycan biosynthetic process	4	0.007395
GO:0045893~positive regulation of transcription, DNA-templated	53	0.007434
GO:0016310~phosphorylation	13	0.035613
KEGG PATHWAY		
bta00190: Oxidative phosphorylation	31	0.001129
bta05020: Prion disease	51	0.001965
bta00380: Tryptophan metabolism	14	0.002965
bta05010: Alzheimer disease	67	0.003114
bta04714: Thermogenesis	44	0.003223
01200: Carbon metabolism	24	0.005364
bta00620: Pyruvate metabolism	12	0.011453
bta04929: GnRH secretion	15	0.01779

Discussion

In the present study, our objective was to detect selection of signatures in Indian (Gir and Ongole) versus Brazilian (Gyr and Nellore) cattle breeds and analyze identified signatures using bovine 777K SNP chip data. In various studies Bovine HD chip has been successfully used to detect selection signatures in many cattle breeds (Alshawi et al., 2019; Bahbahani et al., 2018). In the current study we employed three complementary approaches (iHS, ROH, and F_{ST}) to determine selection signatures in genomic regions among four population of cattle breed (Gir, Gyr, Ongole and Nellore).

Low F_{ST} values in this study show that, though the breeds were selected for distinct purpose (milk/meat), some levels of similarity still exist. Low levels of genetic difference between breeds are expected in regions of the genome that are neutral or subject to balanced selection, while divergent levels are expected in regions that are the target of directional selection. Due to the fact that the two populations of these two breeds in the current study belonged to the same breed and descended from the same recent ancestral population, it is possible that low F_{ST} values were found. As a result, many alleles were anticipated to be fixed often in both populations. Gyr, being a dual-purpose breed, was first artificially selected for both meat and milk, which may account for the expected levels of closeness and low F_{ST} values between the two populations. Allele frequencies may gradually move toward desirable phenotypes under artificial selection, leaving behind signature of selection. Originally, the Ongole breed of cattle is a triple-purpose breed. Brazilian breeders started artificial selection of Nellore cattle for meat purposes in the last few decades, and the population are now displaying signs of selection for meat trait.

In Indian Gir cattle, by iHS and ROH methods we found various genes related to immune response, disease resistance, adaptation, thermotolerance and milk production in selected regions. In top 5 selected region of Gir by iHS method we found genes related to immune response like IER5(immediate early response 5) gene present on chromosome 16 involved in regulation of the cellular response for mitogenic signals (Xiao et al., 2019) and MILR1 (Mast Cell Immunoglobulin Like Receptor 1) (chr:19) gene that has role in mast cell degranulation and transmembrane signaling receptor activity. Gene ARAP3 (ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3) (chr:7) found in Gir cattle in top selected region by ROH approach play an important role in immune response and has been previously reported by Kukuckova *et al.*, 2016) in cattle.

Thermotolerance related gene HIKESHI (heat shock protein nuclear import factor hikeshi) was identified in selected region with highest iHS value in Gir (chr:29). This gene codes a nuclear transport receptor that interacts with FG-nucleoporins to facilitate the nuclear import of 70 kDa heat-shock proteins (Hsp70s) in response to heat shock (Bruscadin et al., 2021). Gene CREB3L1(cAMP responsive element binding protein 3 like 1) also found in selected region in Gir cattle involved in endoplasmic reticulum stress response which is caused by accumulation of misfolded proteins and enhances cell survival during thermal stress (Greenwood et al., 2015)

We found enriched GO terms and KEGG pathways in Gir cattle which has direct or indirect relation with immune response. GO_BP terms GO:0007204 (regulation of cytosolic calcium ion concentration is associated with Ion Transport and Immunity), GO:0043524 (negative regulation of neuron apoptotic process) is associated to neuron apoptosis processes and inflammatory responses, and GO:0001938 (positive regulation of endothelial cell proliferation), and KEGG pathway bta04670 (Leukocyte trans endothelial migration) were found to be significantly enriched and have a role in immune response.

We observed that the top selected regions in Brazilian Gyr comprise genes involved in milk production, mammary, udder development, and carcass characteristics. AGAP2 (ArfGAP with GTPase domain, ankyrin repeat and PH domain 2) (chr:5) gene recognized by ROH method has crucial role in mammary gland development and milk production (Chao *et al.,* 2019). MYO16 gene (myosin XVI) (chr:12) significantly associated with teat length traits had effect on milk production in dairy cows. ABCA7 gene (ATP binding cassette subfamily A member 7) (chr:7) identified in Gyr has role in beef tenderness. MYO1B gene (myosin IB) (chr:2) identified in top selected region has role in muscle development. ANKRD50 and CRTC3 genes commonly detected by iHS and ROH based selection regions in Gyr breed had significant role in carcass trait. We observed that enriched GO term and KEGG pathways in Gyr cattle were related to milk production and carcass trait. Enriched GO_BP term GO:0030879 (mammary gland development), and KEGG pathway bta04917 (Prolactin signaling pathway) were directly associated with milk production trait and GO_BP term GO:0046427 (positive regulation of JAK-STAT cascade) and KEGG bta04010 (MAPK signaling pathway) was associated to carcass trait. According to Wang et al. (2009), the enriched mitogen-activated protein kinase (MAPK) signaling pathway is known to play a significant role in the inhibition of adipogenesis and is also involved in the regulation of a wide range of cellular processes, such as proliferation, differentiation, migration, and apoptosis (Schaeffer and Weber, 1999; Wada and Penninger, 2004)

In Ongole breed we observed PCDH9 (protocadherin 9) gene (chr:12) in top selective sweep region related to body shape trait responsible for loin strength in drought cattle breeds. The enriched terms related to immunity and milk production GO:0030879 (mammary gland development), GO:1903489 (positive regulation of lactation), GO:0030217 (T cell differentiation and KEGG pathway bta04917 (Prolactin signaling pathway), bta03250 (Viral life cycle - HIV-1), bta04142 (Lysosome).

PARP2, ATP10D, KCNJ11 genes known to be associated with growth and carcass trait were found in top five selected regions of Nellore cattle. PARP2 (poly (ADP-ribose) polymerase) gene found on chr;10 and KCNJ11 (potassium inwardly rectifying channel subfamily J member 11) gene have association with carcass trait in beef cattle. The ATP10D gene, which is located in genomic regions on BTA6, produces the ATPase Phospholipid Transporting 10D protein, a member of the P-type ATPases family's subfamily IV, which is essential for the translocation of phospholipids from the surface to the interior of biological membranes (Tumaini Kengia et al., 2013). This gene has role in affecting meat color traits in Nellore cattle. We observed enriched GO term and KEGG pathways related to carcass trait in Nellore cattle like- GO_BP GO:0010909 (positive regulation of heparan sulfate proteoglycan biosynthetic process), GO:0016310 (phosphorylation) and KEGG pathway bta00190 (Oxidative phosphorylation), bta00380 (Tryptophan metabolism), bta00620 (Pyruvate metabolism).

Our findings revealed major genes involved in production and adaptability traits in Indian and Brazilian breeds of cattle. In Gir and Ongole breeds, the genes responsible for disease resistance, thermotolerance underwent extensive selection. However, due to artificial intensive selection, the genes for production qualities were more prevalent in Gyr and Nellore breeds.

CHAPTER –5

Summary and Conclusions

SUMMARY AND CONCLUSIONS

5.1 Summary

1. The purpose of current study was to find out genomic regions under the influence of selective forces and to analyse those footprints of decades of intensive artificial and natural selection for economically significant traits among Gir versus Gyr and Ongole versus Nellore, international transboundary cattle breeds based on Illumina BovineHD BeadChip data.
2. For tracing ongoing sweeps, the three integrated methods (iHS, ROH and F_{ST}) were used.
3. The results of current investigation showed 2.856% Pairwise F_{ST} differences between Gir versus Gyr and 2.354% between Ongole versus Nellore.
4. Regions of the genome that may include targets of positive selection as windows in the extreme of empirical distribution after estimating |iHS| for each locus.
5. We identified a total of 4004, 3322, 3437 and 3485 genes in Gir, Gyr, Ongole and Nellore respectively, under top 1% of the selected regions using the integrated haplotype score (iHS) approach.
6. We observed 160, 76, 75 and 67 selected regions (ROH consensus $\geq$20%) on the basis of ROH method overlapping with 4285, 1768, 1663 and 1466 genes in Gir, Gyr, Ongole and Nellore cattle, respectively.
7. Under top 1% selected regions, based on F_{ST} approach identified 1966 genes for Gir-Gyr pair and 1897 genes for Ongole-Nellore pair.
8. Important candidate genes were identified under top selected regions viz. IER5, MILR1, ARAP3 in Gir and PCDH9 in Ongole. These genes are responsible for immunity and body shape traits in Indian breeds of cattle.
9. We found gene related to mammary gland development, udder size and carcass (MYO16, AGAP2, MYO1B, ABCA7) in Gyr as well as carcass traits (PARP2, ATP10D and KCNJ11) in Nellore breed of cattle.

5.2 Conclusion

- Analysis based on PCA, Reynold's genetic distance and pairwise FST explains that there are lower genetic differences present in these international transboundary breeds.
- Transboundary breeds though subjected to selection for different utilities, have retained their breed selection footprints.
- Highly selected regions show that Indian Gir and Ongole have been selected for immunity traits and hardiness while the Brazilian Gyr for has highly selected regions for milk and meat production and Nellore for meat production.
- Our findings, which are based on selected footprints, add to the body of knowledge on the genomics of adaptability and production traits in livestock. It also offers important insights for upcoming research on the relationship between genotype and phenotype and the advancement of cattle breeding.

5.3 Recommendations

- We can further extend the above developments to gain deeper insights into the selection footprints of economically significant traits present in the genome of these cattle breeds in the future by conducting a study similar to this one with higher coverage data.
- From current study identified SNPs under the influence of selection can be verified in larger herd by GWAS for future application in functional genomic studies, developing breed-specific SNP panels and can be helpful in breeding schemes and conservation programmes.

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