GENETIC VARIANTS ASSOCIATED WITH TRYPANOTOLERANCE TRAIT IN CATTLE

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DECLARATION

I declare that this research thesis is entirely my work and has not been submitted for a degree in any other University

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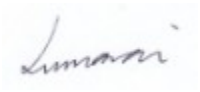
Signature:  Date: 27/07/2021

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DEDICATION

I dedicate this thesis to my parents

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First and foremost, I want to thank the Almighty God for His grace that has enabled me to successfully finish my research work.

Secondly, I want to acknowledge my study supervisors who have stood by me, provided technical support and mentored me throughout the project. Dr. Benard Kulohoma, Dr. Timothy K. K. Kamanu I am greatly indebted to you and may the good Lord bless you and give you prosperity in your future endeavors.

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LIST OF ABBREVIATIONS

AAT – African animal trypanosomiasis

GWAS – Genome wide association studies

SNP – Single nucleotide polymorphism

QTL – Quantitative trait locus

TICAM1 - Toll like receptor adaptor molecule 1

ARHGAP15 - RHO GTPase-activating protein 15

RBMS3 - RNA binding motif single stranded interacting protein 3

GRID1 - Glutamate ionotropic receptor delta type subunit 1

UTR – Untranslated region

RNA – Ribonucleic acid

DNA – Deoxyribonucleic acid

RBP – RNA binding protein

MYC - Master regulator of cell cycle entry and proliferation

MSSP - MYC gene single-strand binding protein

ARE - AU rich elements

CPE - Cytoplasmic polyadenylation element

mRNA – Messenger ribonucleic acid

ABSTRACT

Animal trypanosomiasis (Nagana), a protozoan disease, is the source of huge productivity losses to small scale farmers in sub-Saharan Africa. Nagana affects wild animals, sheep, goats, camels and cattle reducing their productivity or causing death in severe cases. Several interventions for the disease have been developed and applied including vector control using insecticides and the use of trypanocides. However, these control measures have been ineffective with the trypanosomes developing resistance to the existing trypanocides. Ineffective interventions to Nagana necessitate the need to advance a better disease control strategy. The use of the trypanotolerance trait that is expressed by some West African cattle breeds is promising because infected cattle don't develop the severe form of the disease that reduces productivity. Trypanotolerance trait can be introduced to cattle breeds that show no tolerance through breeding. This study sought to understand trypanotolerance trait by identifying the key genes involved in the trypanotolerance trait. The sample size used was n=1199 cattle from 44 cattle breeds which were organized into 4 case-control groups of African indigenous and hybrid cattle. A GWAS was performed on each of the four groups to identify the significant SNPs after quality control. A total of 36 genes were found to contain the significant SNPs in all the case-control groups. All cases groups (Sheko, N'Dama, Boran and N'DamaXBoran) were compared to the same set of controls, n=993 cattle. This control group consisted of 3 cattle breeds from Africa (n=108), 31 cattle breeds from Europe (n=693), 2 cattle breeds from South America (n=27), 2 cattle breeds from Asia (n=49), 1 cattle breed from North America (n=105) and 1 cattle breed from Australia (n=11). Separate comparison of the case groups to the same control set highlighted 6, 4, 9 and 17 genes in the Sheko, N'Dama, Boran and N'DamaXBoran comparisons respectively. The roles of some of these genes in several pathways have also been individually described in previous studies. This study suggests that the key genes responsible for the trypanotolerance trait are SUSD1, DPF3, COL19A1 and SLC19A3 among others that are found in the N'Dama and Sheko cattle breeds that are mainly involved in the molecular mechanism that may lead to reduced parasitemia.

Chapter 1

1.0 INTRODUCTION

1.1 Background

Trypanosoma congolense, the most prevalent and widespread pathogenic trypanosome species, infects cattle (*Bos taurus*/ *Bos indicus*) in most of sub-Saharan Africa resulting in life-threatening Animal African Trypanosomiasis (AAT) (Muhanguzi *et al*., 2017). Trypanosomes are transmitted by tsetse flies, and are injected into the cattle as metacyclic forms, which transform to the bloodstream forms found in circulation (Peacock *et al*., 2012). Nagana causes serious productivity losses amounting to approximately US$ 900 million per year within sub-Saharan economies (Mamoudou *et al*., 2016).

Indigenous cattle breeds like Baoule and N'Dama (*Bos taurus*) have been shown to be tolerant to the trypanosome infection (Noyes *et al*., 2011). Baoule breed in West Africa which are found in the trypanosomiasis-endemic southern part of Burkina Faso, have evolved tolerance to trypanosome infections (Albert *et al*., 2019). Pure-bred Zebu (*Bos indicus*) cattle are susceptible to trypanosomiasis but they are preferred by the farmers due to their large body sizes and more meat or milk production. Farmers often cross-bred Zebu and Baoule resulting in offsprings with improved trypanotolerance and size (Hanotte, 2002). The ancestry of the Zebu cattle breed is prominent in the large-sized admixed cattle. However, Zebu genome sections that may be associated with trypanotolerance can be expected to have higher extents of Baoule ancestry (Oleksyk *et al*., 2010).

Chromosome 22 (between 51.20 - 51.40Mb) has been suggested in previous studies to have genes that are involved in trypanotolerance (O'Gorman *et al*., 2009). The N'Dama that are trypanotolerant show a distinct and rapid transcriptional response to trypanosome infection and hence the genes involved in such immune responses can be upregulated or downregulated. Genetic variations in TICAM1 and ARHGAP15 genes are thought to confer structural and functional changes in the proteins they encode, and they have been associated with the trypanotolerance trait mechanism (Noyes *et al*., 2011).

1.2 Research question

Is there an association between mutations in the cattle genomes and trypanotolerance trait?

1.3 Objectives

1.3.1 General objective

To investigate the genetic variations associated with trypanotolerance trait in cattle.

1.4 Specific objectives

I. To identify genetic variants associated with trypanotolerance in *Bos taurus*, *Bos indicus* and hybrids.

II. To identify the genes and gene functions that may be disrupted or enhanced by variations.

1.5 Null hypotheses

There are no genetic variants associated with the trypanotolerance trait in cattle.

1.6 Justification

Both the indigenous and exotic cattle breeds produce meat, milk and manure at different efficiencies but the indigenous cattle breeds are often used for draft purposes in sub-Saharan Africa. Indicine cattle breeds are susceptible to trypanosomiasis, tick and other vector borne diseases but the trypanotolerant breeds can withstand these diseases benefiting from the trait (Noyes *et al*., 2011). It is, therefore, important to harness these trait and use it to control trypanosomiasis because trypanosomes have developed resistance to the available drugs leaving farmers with almost no options in the fight against the disease (Solomon & Workineh, 2018).

It is important to elucidate and measure the genetic variability between the trypanotolerant and susceptible cattle breeds for purposes of artificial selection in cattle. This analysis will enable the improvement of cattle productivity especially in sub-Saharan Africa, where trypanosomiasis has resulted in huge economic losses. AAT challenge is worse because of the absence of a vaccine and drug resistance that has resulted in poor cattle productivity. AAT can also be managed through improved cattle breeding for the introgression of trypanotolerance trait, which is associated with tolerance to other common diseases like tick borne diseases and helminthiasis.

Chapter 2

2.0 LITERATURE REVIEW

2.1 The cause of African animal trypanosomiasis

Trypanosoma congolense, T. brucei spp and *T. vivax* cause AAT affecting cattle mostly in sub-Saharan Africa (Berthier *et al*., 2015; von Wissmann et al., 2011). AAT also affects goats, sheep, pigs, dogs, camels, horses, buffaloes and antelopes and is caused by *T. evansi* and *T. equiperdum* (Ahmed et al., 2018; D. P. Duarte et al., 2018; Suganuma et al., 2016). These trypanosomes can also cause disease in mice models (Ghaffar *et al*., 2016; Ndungu *et al*., 2019). Trypanosome species are evolutionarily related, and phylogenetically have similar structural and functional proteins associated to their lifecycle (Carnes *et al*., 2015; Hamilton *et al*., 2009; Rodrigues *et al*., 2008).

2.2 Geographical distribution of animal trypanosome species

The tsetse fly is the primary vector of trypanosome parasite associated with regular AAT transmission mostly found in sub-Saharan Africa (Auty *et al*., 2015). *Trypanosoma congolense* is found in east, west, central and south African equatorial forests and savanna grasslands infecting cattle and small ruminants (Cecchi *et al*., 2008; Mekata *et al*., 2008; Simo *et al*., 2012). *T. vivax* are common in the eastern and western parts of Africa where tsetse flies are the exclusive vectors. In South America, biting flies mediate mechanical transfer of animal trypanosomiasis (Osório *et al*., 2008; T. W. Jones & Dávila, 2001). *T. evansi* is often found in camels of north Africa, the Middle East, south America and Asia and can cause infections in buffaloes and cattle (Dávila & Silva, 2006; Desquesnes *et al*., 2013; Reid, 2002). Poor sensitivity of diagnostic techniques makes it challenging to determine the distribution of each trypanosome species (Ngaira et al., 2005; Njiru et al., 2010; Zablotskii et al., 2003). Figure 2.1 illustrates worldwide spread of the three most common animal trypanosomes.

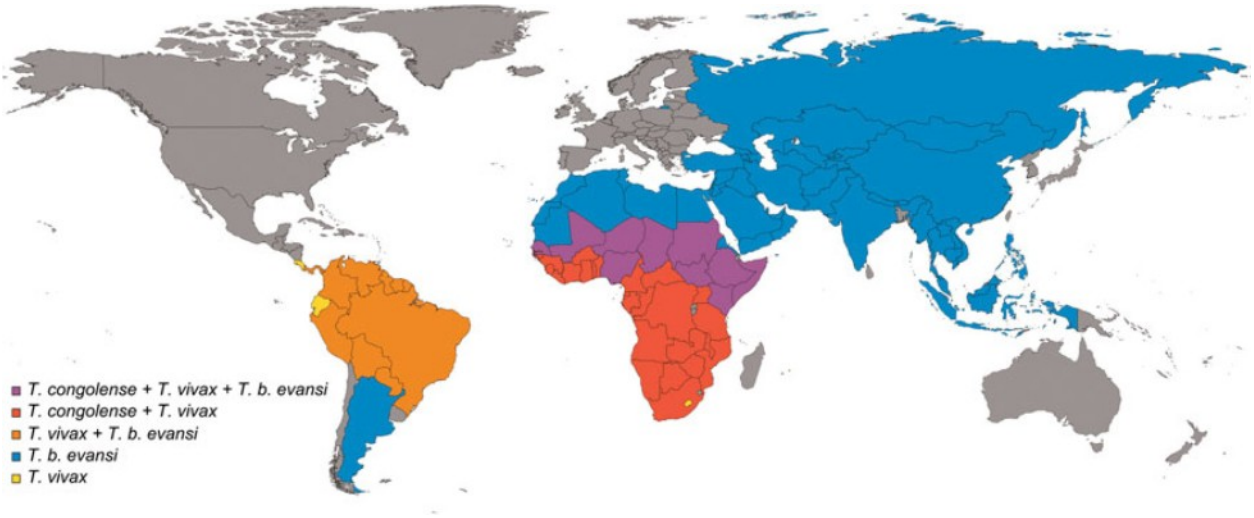

Figure 2.1: The global distribution of common livestock trypanosomes *T. congolense, T. vivax* and *T. b. evansi*

(Adapted from Auty *et al*., 2015; Giordani *et al*., 2016).

2.3 The lifecycle of Trypanosomes

The main cause of AAT is *T. congolense*, a unicellular protozoan parasite whose developmental process is divided into two stages: mammalian and vector stages *(*Awuoche *et al*., 2018; Tihon *et al*., 2017). The mammalian stage is characterized by the stumpy forms which circulate in blood, lymphatic fluid and spinal fluid and proliferate by binary fission (Silvester *et al*., 2018). In the vector stage the parasite undergoes morphological changes in the tsetse fly digestive system. The ingested stumpy forms turn to midgut procyclic trypomastigotes that proliferate and move to the mouth part as epimastigotes. The cycle takes approximately 3 weeks eventually forming metacyclics that can infect animals, as summarized in figure 2.2 (Coustou *et al*., 2010; O'Gorman *et al*., 2009; Rotureau & Van Den Abbeele, 2013).

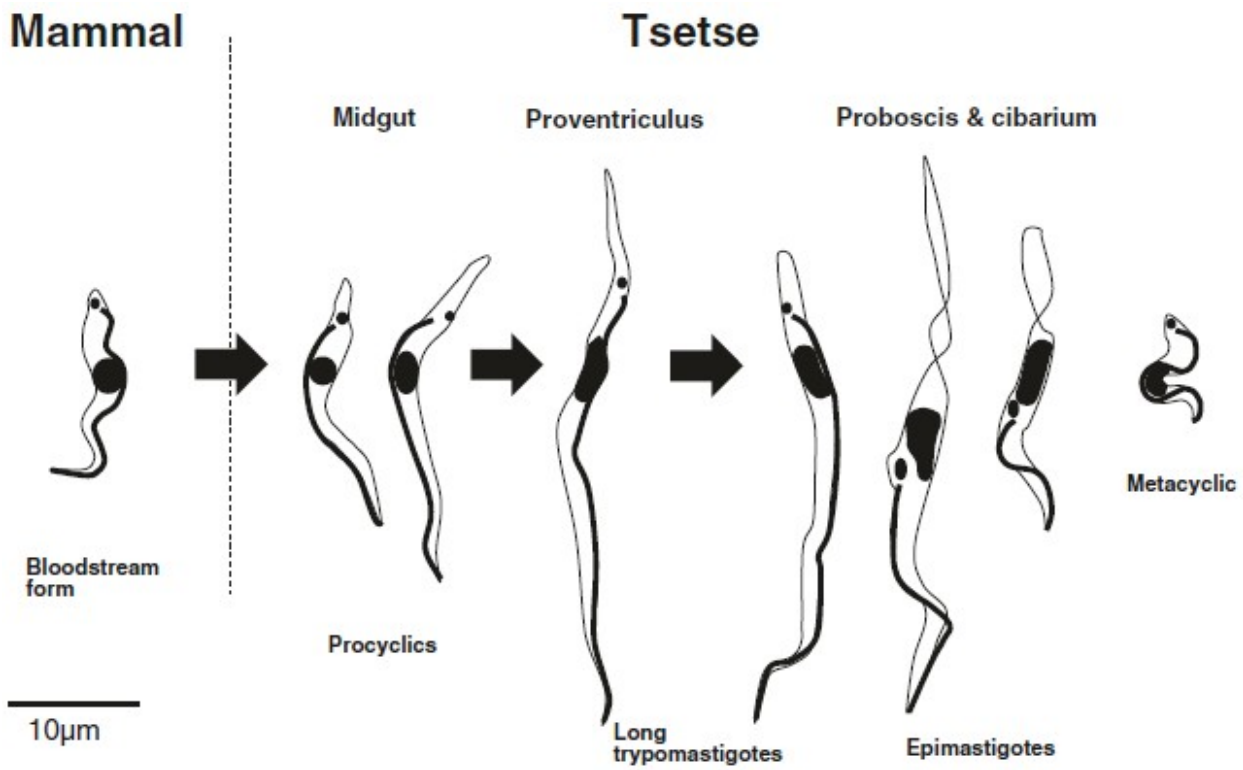

Figure 2.2: Trypanosome developmental stages in the mammalian host and the insect vector (Adapted from Peacock *et al*., 2012).

2.4 Clinical presentation of animal African trypanosomiasis in cattle

An infection is established when a trypanosome carrying tsetse fly feeds on animal blood injecting metacyclic trypomastigotes into the skin, which then enter into circulation to other body tissues (Bargul *et al*., 2016; Cayla *et al*., 2019). Successful establishment of an infection in an animal host depends on the host's immunity, virulence of the parasite and the dose of infection (Geiger *et al*., 2016; Matthews *et al*., 2015; Onyilagha & Uzonna, 2019). The disease manifests as an acute form that progresses rapidly, or chronic form that persists for long periods. Acute animal trypanosomiasis is characterized by fever, edema, adenitis, dermatitis, anemia, reproductive abnormalities and nervous disorders (Stijlemans *et al*., 2018; Suh *et al*., 2017). Chronic form of the disease has the following symptoms: swollen lymph nodes, spleenomegally, serous atrophy of fat, anemia and increased mortality especially of poor nutrition cases (Dávila & Silva, 2006). Animal trypanosomiasis is diagnosed by the microscopic observation of the parasite in blood, lymphatic fluid, milk, cerebral spinal fluid and biopsy specimen (Büscher *et al*., 2019; Pascucci *et al*., 2013; Suganuma *et al*., 2016).

Serological tests in combination with polymerase chain reaction (PCR) are applied to increase diagnostic specificity and sensitivity (Desquesnes *et al*., 2001; Ezeani *et al*., 2008; Njiru *et al*., 2005).

2.5 Cattle breeds and trypanotolerance

Domesticated cattle descended from wild aurochs and are divided into two species:

i. The *Bos indicus* whose most noticeable phenotypic characteristic is the presence of a hump at its withers and floppy ears instead of upright ones,
ii. and the *Bos taurus* that are humpless (Ababa, 2000; McTavish *et al*., 2013).

The taurine cattle, for example Nelore and Angus, are mostly found in temperate regions such as Europe while the indicine cattle, for example the Zebu and Boran, are mostly found in tropical regions such as Africa (Porto-Neto *et al*., 2013). Several cattle breeds are tolerant to trypanosomiasis, most of which are taurines found in West Africa, and they include: N'Dama, Sheko, Baoule, Orma Boran and Nuba (Mwai *et al*., 2015).

2.5.1 African indigenous cattle breeds

2.5.1.1 N'Dama cattle breed

The N'Dama cattle of West Africa are also called N'Dama petite in Senegal, Boyenca in Guinea-Bissau and Mandingo in Liberia. N'Dama are found in the following countries; Sierra Leone, Mali, Senegal, Nigeria, Ivory coast, Liberia, the Gambia and Guinea-Bissau (Mwai *et al*., 2015). These cattle are generally small in size with the mature bulls weighing 320 to 360 Kg and the mature cows 250 to 330 Kg (Ganyo *et al*., 2018). They have lyre-shaped horns, they have a fawn colour that may range from sand to black with occasional spots and they are kept for draft purposes, milk and meat (van der Waaij *et al*., 2003).

These cattle breeds are tolerant to trypanosomiasis endemic to tsetse fly infested regions of sub Saharan Africa. They are also tolerant to tick borne diseases and ticks, helminthiasis such as infections caused by *Haemonchus contortus* also referred to as stomach worms and bovine streptothricosis (Kim *et al*., 2017; Mattioli *et al*., 2000). N'Dama cattle's ability to be tolerant to parasitic diseases makes them suitable candidates for use in breed improvement programmes (Bosso *et al*., 2007). For example, N'Dama X Boran crossbreeding for increased meat productivity and improved resistance to trypanosomiasis (Orenge *et al*., 2012). These hybrid cattle have been found to express intermediate tolerance to trypanosomiasis and they

would benefit from the use of biomarkers for trypanotolerance in determining the level of expression of the trypanotolerance trait (Orenge *et al*., 2012).

2.5.1.2 Boran cattle breed

The Kenyan Boran cattle are mostly found in Eastern Africa in Ethiopia and Kenya and are part of the Zebu cattle. Kenyan Boran are generally large in size with mature males weighing 550 – 850 Kg and the females weigh 400 – 550 Kg, they mostly have a white coat that is sometimes spotted but they can also have red or brown coats. Kenyan Boran are kept mostly for meat, draft usage and are susceptible to trypanosomiasis (Rege *et al*., 2001; Rewe *et al*., 2008; Rewe *et al*., 2006). The Kenyan Boran, that is, is an improved cattle breed from the Somali Boran, Borana and the Orma Boran in terms of its beef productivity in a harsh environmental condition (Maichomo *et al*., 2005).

2.5.2 Exotic cattle breeds in Africa

2.5.2.1 Charolais beef cattle

Charolais is a taurine breed that is characterized by mature cows ~900 kg and bulls ~1,100 kg with a white colored body and pink nose. Charolais originated from France in the Charolais area and they are found in South African countries including Namibia (Capitan *et al*., 2009; Mokolobate *et al*., 2019). Charolais have been crossbred with indigenous cattle breeds to improve beef production and adaptability to the harsh tropical conditions in Africa (Wilson, 2018).

2.5.2.2 Fresian dairy cattle

Fresian are also referred to as Holstein and originated from Netherlands, Germany, Denmark and Austria. Fresian are usually black and white or red and white in color with a mature cow typically weighing 680 – 770 kg. Fresian produce 25 – 65 litres of milk per day and they are susceptible to most parasitic diseases in sub-Saharan Africa (Alqaisi *et al*., 2019; Coffey *et al*., 2016; Lembeye *et al*., 2016).

2.6 Control of trypanosomiasis

2.6.1 Control of the vector: use of insecticides

Vector control using insecticides has been achieved through the use of aerial spraying of deltamethrin (Kgori *et al*., 2006), mobile baits and stationary baits (Muhanguzi *et al*., 2015). Insecticides such as pyrethroids can be applied on cattle in regions that have tsetse flies feeding exclusively on cattle. In areas where tsetse flies feed on wild animals that are

trypanosome reservoirs, it is advisable not to apply insecticides on cattle because of possible re-infections (Hargrove et al., 2000, 2012). Cattle treated with insecticides have been used to eliminate tsetse fly populations and thus contributing to the reduction of the trypanosomiasis incidence (Baylis & Stevenson, 1998).

2.6.2 Control of the parasites: use of chemotherapy

The most commonly used drug compounds for the control of AAT are isometamidium chloride commonly referred to as trypamidium and diminazene aceturate commonly referred to as berenil because of their low levels of side effects (Meyer *et al*., 2016; Giordani *et al*., 2016). There is, however, an emerging trend of parasites developing resistance to the available chemotherapeutic agents thus reducing the efficacy of the drugs against the pathogens (Chitanga *et al*., 2011; Holt *et al*., 2016; Mungube *et al*., 2012). Some of the pathogens have been shown to express multiple drug resistance making disease management challenging (Mungube *et al*., 2012; Wangwe *et al*., 2019).

Other chemotherapeutic agents that have been used in the control of AAT include; homidium salts (bromide/chloride) that is used in cattle, goats and sheep (Wainwright, 2010), and quinapyramine sulphate administered in treating *T. b. evansi* in horses and camels (Ranjithkumar *et al*., 2014). Suramin sodium, the oldest trypanocide, is still being used to treat Nagana in Brazil (Faccio *et al*., 2013) and melarsomine dihydrochloride is used to treat *T. b. evansi* infections in cattle, camels, goats and horses (Desquesnes *et al*., 2011; Gutierrez et al., 2008; Tamarit et al., 2010). Resistance to the trypanocides by the trypanosomes has, however, been reported in East and West Africa (Dagnachew et al., 2015; Moti et al., 2015; Mungube *et al*., 2012; Vitouley *et al*., 2012). Trypanosomes transport the toxic drug compounds out of their cellular compartments through carrier proteins forming the basis for drug resistance (Dagnachew *et al*., 2015; Munday *et al*., 2015).

2.6.3 Host factors: use of trypanotolerance trait in cattle

A number of indigenous cattle breeds in Africa have the ability to continue being productive after an infection with the pathogenic trypanosomes and they include the N'Dama, Baoule, Sheko, Namchi, Muturu and Dahomey (Achukwi *et al*., 1997; Giordani *et al*., 2016; Noyes *et al*., 2011). Trypanotolerant breeds are used for livestock production in some endemic areas of the sub-Saharan Africa such as the west Africa (Naessens, 2006). The use of trypanotolerance trait in improved cattle breeding has therefore been suggested for the control of

trypanosomiasis as a sustainable strategy (Hanotte, 2002).

2.7 Trypanotolerance mechanism

There are two mechanisms responsible for the expression of natural tolerance to AAT in cattle;

i. The ability of the hemopoetic system to control the development of anemia in the animal
ii. The natural ability for parasitemia control (Naessens *et al*., 2002).

Trypanotolerance trait is thought to be a genetic trait but underlying mechanisms are not fully understood following studies in mice and cattle models (Abenga & Vuza, 2005). The ability of the cattle to manage anemia after primary trypanosomiasis infection depends on the initial parasitemia stage, animal's age and its genetic make-up (Andrianarivo *et al*., 1996; Authié *et al*., 1993).

A cysteine protease, known as Congopain, expressed by *T. congolense* initiates a stronger antibody response where immunoglobulin G (IgG) is expressed during primary infection (Authié *et al*., 1993). IgM is also expressed during a trypanosomiasis infection and these antibodies against trypanosome antigens are produced by activated lymphocytes (Authié *et al*., 1993; Authiée *et al*., 1993). If the trypanotolerant animal is to manage the parasitemia that is established then the severity of the anemia that develops is reduced by extension (Agur & Mehr, 1997; Andrianarivo *et al*., 1996). Blood cells that contribute to the management of anemia and parasitemia in trypanotolerant cattle include erythrocytes, monocytes, macrophages and antibody producing lymphocytes whose development can be affected by their interaction with the infecting parasite (Akinbamijo *et al*., 1998; Authié *et al*., 1993). Two genes have been found to contain SNPs that have been associated with the trypanotolerance

trait mechanism: TICAM1 and ARHGAP15 have non synonymous mutations that may be playing a critical role in the expression of this trait in the trypanotolerant cattle breeds of West Africa (Noyes *et al*., 2011).

2.8 Genome wide association studies

GWAS identifies inherited genetic variants that are associated with a particular trait or risk of a disease. The whole genome is analyzed for genetic polymorphisms such as single nucleotide polymorphisms (SNPs) that occur at greater frequency in cases (individuals with the disease or trait being assessed) than in controls (individuals without the disease or trait) (Beck et al., 2019; Genetic Investigation of ANthropometric Traits (GIANT) Consortium et al., 2015; Visscher et al., 2017). GWAS has been applied in cattle research to study beef quality and yield, milk yield and fertility (Zhou *et al*., 2019; Jiang *et al*., 2019).

Chapter 3

3.0 MATERIALS AND METHODS

3.1 Description of data

A sample size of n=1199 cattle from 44 breeds were obtained from a 1494 cattle sample. A study that investigated the ancestry of 58 cattle breeds n = 1494 from multiple independent domestication events was used and the datasets were derived from published research (McTavish *et al*., 2013). Data preprocessing was done where two cattle breeds were excluded because they had a lot of missingness, three were also excluded because they were hybrids of unknown continental origin whereas nine had less than 55k SNPs as summarized in Figures 3.1 and 3.2 and Appendix table 1. All the case groups: Sheko (n=20), N'Dama (n=59), Boran (n=44) and N'Dama X Boran (n=83) were each compared to the control group (n=993) comprising Tuli (n=16), Dexter (n=11), South Devon (n=10), Red Poll (n=11), Senepol (n=80), Jersey (n=17), Belgian Blue (n=11), White Park (n=10), Ankole-Watusi (n=12), Scottish Highland(n=15), Red Angus (n=22), Devon (n=10), Sussex (n=11), Guernsey (n=17),Galloway (n=11), Maine Anjou (n=11), Belted Galloway (n=11) , Gelbvieh (n=15), Tarentaise (n=12), Corriente (n=12), Marchigiana (n=13), Salers (n=12), Simental (n=162), Romosinuano (n=15), Romagnola (n=36), Welsh Black (n=9), Kerry (n=10), Gir (n=32), Brown swiss (n=17), Pinzgauer (n=12), English longhorn (n=10), Sahiwal (n=17), Chianina (n=14), Norwegian Red (n=28), Shorthorn (n=105), Brahman (n=105), Piedmontese (n=36), Montbeliard (n=12), Blonde d'Aquitaine (n=12) and Murray Gray (n=11) while avoiding confounding. A summary of the samples used in the study is shown on Figures 3.1 and 3.2. Being a susceptible breed, the Boran cattle was used as a case because it is exposed to the tryapanosomiasis challenge in the sub Saharan region and therefore it may be trying to adapt itself to be able to withstand the disease by expressing mutations that are yet to confer tolerance on the breed.

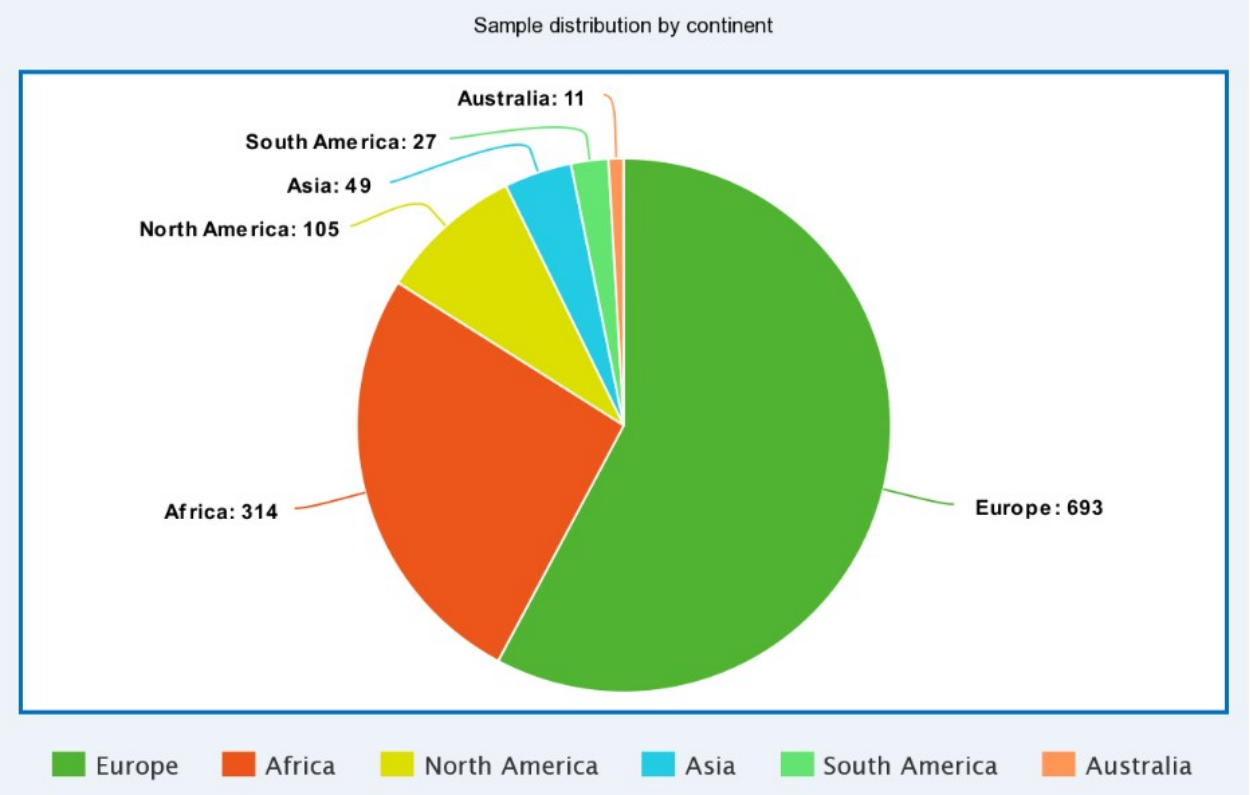

Figure 3.3: The global distribution of taurine and indicine cattle breeds used as cases and controls in the study.

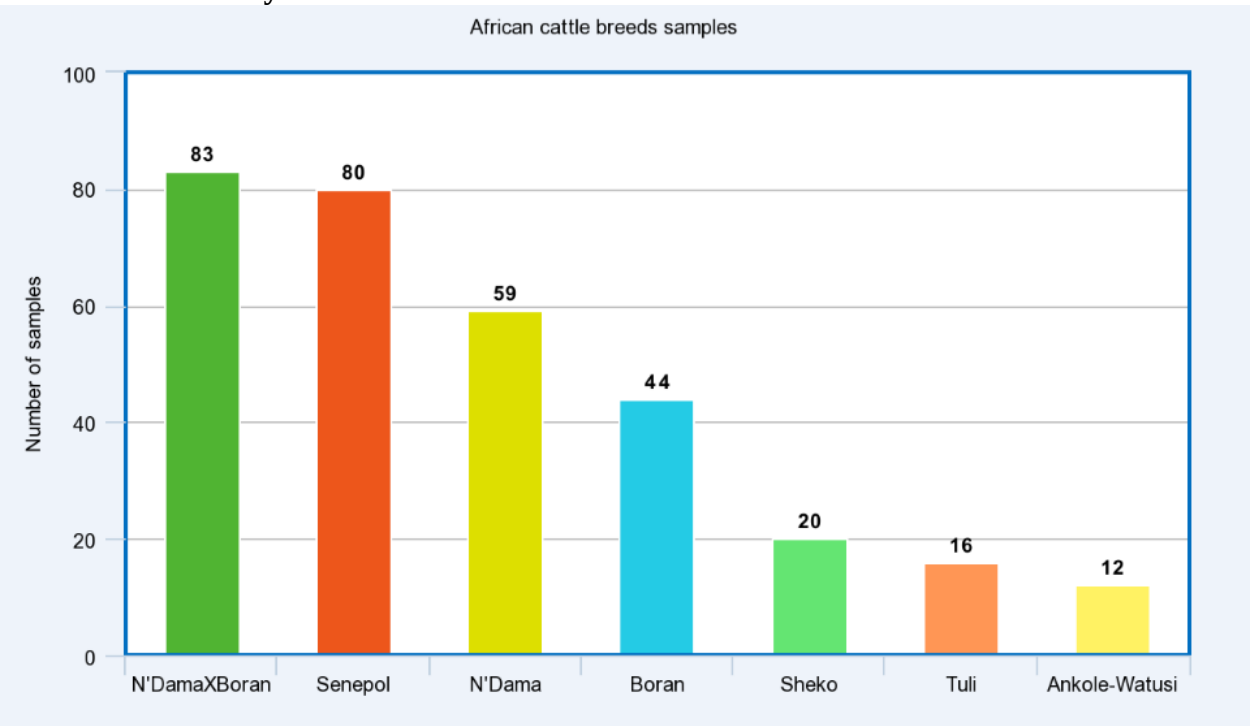

Figure 3.4: The number of samples of the African breeds.The N'Dama and Sheko are trypanotolerant, Boran is susceptible to trypanosomiasis and the N'Dama X Boran is a

hybrid with intermediate tolerance.

3.2 Performing genome wide association studies

The dataset was divided into cases and controls, four cattle breeds (Boran, N'Dama, Sheko and N'Dama X Boran) were each used as cases and the remaining 40 cattle breeds were used as controls to avoid confounding. The case-controls were used to perform genome wide association analysis on Plink (Purcell *et al*., 2007) and the data was visualized on quantile-quantile (Q-Q) plots and manhattan plots using their respective functions in the qqman package (Turner D. S. 2018) in R version 3.5.3 after performing quality control (RStudio Team 2016).

The statistical basis of GWAS involves a single SNP scan or multiple marker analysis where genotype or allele frequency is compared between cases and controls (Balding 2006; McCarthy *et al*., 2008). Additive gene models are applied mostly in the single SNP scan where adding minor allele copies increases disease or phenotype risk proportionately (Zeng *et al*., 2015). Gene models are affected by genetic dominance that makes it ineffective in association analysis (Sabourin *et al*., 2015). Multiple marker analysis uses least absolute shrinkage and selection operator (Lasso) estimation to determine the association between the genotype and phenotype (Rakitsch *et al*., 2012). Multiple testing is used to correct errors that might arise during association analysis in Plink when using linkage disequilibrium pruning and a common p-value threshold (Sobota *et al*., 2015).

3.3 Quality control

SNPs were filtered based on the following inclusion threshold parameters: missingness per individual (mind), minor allele frequency (maf), missingness per genotype (geno) and Hardy Weinberg equilibrium (hwe) based on Plink version 1.90. The SNPs that passed the filters were used to generate the qq and Manhattan plots.

Table 3.1: The inclusion threshold parameters used to filter SNPs in Plink before GWAS analysis.

Case-group	Mind	Maf	Geno	Hwe
N'Dama	0.001	0.25	0.001	1e-20
Sheko	0.01	0.25	0.001	1e-70
Boran	0.001	0.25	0.001	1e-50
N'DamaXBoran	0.001	0.25	0.001	1e-50

3.4 Overlapping SNPs

SNPs found in more than one case-control group and below a p-value threshold of 5e-08 were identified (Nazarian *et al*., 2019). The genes in which these SNPs are found and those flanking them were also identified in all the case control groups (Table 4.1- 4.4).

Chapter 4

4.0 RESULTS

4.1 Sheko significant SNPs

In the Sheko case-control group, a total of 10 SNPs were detected to be below the significance threshold with three peaks on chromosomes 2, 8 and 22, as shown in figure 3. The SNPs on chromosome 2 are on GALNT13 (base pair position: 42173258; p=3.23e-33) and SLC19A3 (base pair position: 115826791; p=5.32e-09) genes. The SNP on chromosome 16 is between RAB7B-LOC515828 (base pair position: 3762358; p=1.054e-12) and NVL (base pair position: 27466587 and p=2.084e-24) genes. Chromosome 19 SNP was on RBFOX3 (base pair position: 53332410; p=8.829e-10) gene. Other significant SNPs associated with the trypanotolerance trait were identified on chromosomes 4, 6, 9, 10, 11, 12 and 13 as summarized on Table 4.1.

Table 4.2: List of significant SNPs for the Sheko case-control group

The table shows the chromosome, position in bp (base pairs), gene and the function of the genes and lists the significant SNPs, the genes in which they are found or those flanking them and the function of the genes.

Sheko vs controls					
Chr	Pos	P-values	Gene	Definition	Function
2	42173258	3.23e-33	GALNT13	Acetylgalactosaminyltransferase 13 (GalNAc-T13)	Catalyzes the initial reaction in O-linked oligosaccharide biosynthesis
2	115826791	5.32e-09	SLC19A3	Solute carrier family 19 member 3	Thiamine transporter
3	4522681	4.44e-09	PBX1-LOC107132013		
3	79223535	2.1e-53	PDE4B	Phosphodiesterase 4B	Purine, Terpenoids and Polyketides Lipid Metabolism, Glycan Biosynthesis.
4	87004472	1.116e-15	CADPS2	Calcium Dependent Secretion Activator 2	Calcium binding proteins that regulate the exocytosis of synaptic and dense-core vesicles in neurons and neuroendocrine cells
4	98706215	3.286e-08	AGBL3	ATP/GTP binding protein-like 3	Catalyzes the deglutamylation of polyglutamate side chains generated by post-translational polyglutamylation in proteins such as tubulins.
5	25379378	8.316e-37	LOC789659-GLYCAM1		
5	42953144	1.225e-19	PTPRB	Protein Tyrosine Phosphatase Receptor Type B	PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation
5	50918096	3.783e-09	PPM1H	Protein Phosphatase, Mg2+/Mn2+ Dependent 1H	It is involved in phosphoprotein phosphatase activity

6	24398925	5.316e-09	LOC104972699		
6	74169745	5.316e-09	LOC112447016 - LOC100141023		
7	108710126	4.053e-17	LOC112447632 -MAN2A1		
8	17755514	4.17e-09	LOC785941-LOC112447965		
8	42607942	2.056e-37	LOC112447799		
8	96108670	4.058e-08	LOC112447914 -LOC783574		
9	19798784	3.631e-14	TTK-BCKDHB		
10	43229292	7.914e-31	ATP5S	ATP synthase	Mitochondrial ATP synthase catalyzes ATP synthesis, utilizing an electrochemical gradient of protons across the inner membrane during oxidative phosphorylation
10	62628026	1.834e-10	LOC101902090 -SEMA6D		
11	31105767	1.291e-12	LHCGR-FSHR		
11	84239108	3.043e-13	LOC782101-LOC100297236		
11	91328544	5.744e-19	SOX11-LOC784		
12	40456779	4.286e-10	PCDH9	Protocadherin 9	Mediates cell adhesion in neural tissues in the presence of calcium
13	12496509	1.154e-11	ECHDC3	Enoyl-CoA Hydratase Domain Containing 3	It is involved in Fatty Acid Biosynthesis
13	62991477	3.13e-08	CBFA2T2	CBFA2/RUNX1 Partner Transcriptional Co-Repressor 2	Repressor protein involved in transcription regulation.

14	81943854	2.22e-10	SNTB1	Syntrophin Beta 1	Involved in the nNOS Signaling pathway in Skeletal Muscle and Muscular Dystrophies and Dystrophin-Glycoprotein Complex.
15	33508261	3.045e-11	JHY	Junctional Cadherin Complex Regulator	Required for the normal development of cilia in brain ependymal cells lining the ventricular surfaces.
16	3762358	1.054e-12	RAB7B-LOC515828		
16	27466587	2.084e-24	NVL	Nuclear VCP Like	Catalyzes the release of specific assembly factors, such as WDR74, from pre-60S ribosomal particles through the ATPase activity.
16	58324427	2.267e-17	ASTN1	Astrotactin 1	Neuronal adhesion molecule that is required for normal migration of young post mitotic neuroblasts along glial fibers, especially in the cerebellum.
16	58757128	1.654e-12	BRINP2-TRNAG-CCC		
17	2175083	1.303e-09	NPY2R-LOC112442109		
17	73021526	5.313e-37	CCDC188-LOC112441986		
18	62017556	2.685e-29	SSC5D	Scavenger Receptor Cysteine Rich Family Member with 5 Domains	Developmental protein and receptor involved in innate immunity.
19	41204591	8.314e-12	LOC100294937-KRTAP3-1		
19	53332410	8.829e-10	RBFOX3	RNA-binding FOX protein	It is involved in the regulation of alternative splicing of pre-mRNA
20	29610780	4.489e-22	HCN1-MRPS30		
22	388140	3.729e-14	DBNL	Drebrin Like	Plays a role in the reorganization of the actin cytoskeleton, formation of cell projections,

					such as neurites, in neuron morphogenesis and synapse formation via its interaction with WASL and COBL.
22	20613110	3.631e-14	LOC100138752 - LOC112443533		
28	20821114	5.299e-21	LOC781358-LOC785503		
29	24046829	4.688e-08	NELL1	Neural EGFL Like 1	May be involved in cell growth regulation and differentiation.

4.2 N'Dama significant SNPs

In the N'Dama case-control group GWAS, a total of 16 SNPs were detected to be below the significance threshold with two peaks on chromosome 7, 8, 22 and 25 as shown in Figure 4. On chromosome 7 they are between LOC112447397-LOC112447627 (base pair position: 36220342; p=5. 147e-13), LOC112447561 and RPS23 (base pair position: 82051714; p=1.541e-51) and LOC107132661 and LOC112447562 (base pair position: 86005958; p=1.361e-28. On chromosome 8 the SNP is on SUSD1 gene (base pair position: 101498454; p=2.733e-30. On chromosome 22 it is between LOC100138752 and LOC112443533 gene (base pair position: 20613110; p=3.672e-30). On chromosome 25 the SNP is on LOC112444322 gene (base pair position: 3202550; p=1.661e-28). Other significant genes are on chromosome 3, 11 and 13 summarized on Table 4.2.

Table 4.3: List of significant SNPs for the N'Dama case-control group.

The table shows the chromosome, position in bp (base pairs), gene and the function of the genes and lists the significant SNPs, the genes in which they are found or those flanking them and the function of the genes.

N'Dama vs controls					
Chr	Pos	P-value	Gene	Definition	Function
3	119334975	4.318e-08	LOC615000-LOC530175		
7	36220342	5.147e-13	LOC112447397-LOC112447627		
7	82051714	1.541e-51	LOC112447561-RPS23		
7	86005958	1.361e-28	LOC107132661-LOC112447562		
8	101498454	2.733e-30	SUSD1	Sushi Domain Containing 1	May be involved in calcium ion binding.
9	9160630	2.733e-12	COL19A1	Collagen Type XIX Alpha 1	Developmental protein that is involved in Cell adhesion, Differentiation and Myogenesis
10	84150081	2.91e-23	DPF3	Double PHD Fingers 3	Activator, Chromatin regulator and Repressor that is involved in transcription regulation.
11	84239108	7.393e-17	LOC782101-LOC100297236		
12	49916383	7.274e-10	LOC112449131		
13	30634339	1.178e-10	MINDY3-PTER		
13	52889781	5.519e-13	LOC100848770-STK35		
22	20613110	3.672e-30	LOC100138752-		

			LOC112443533		
25	3202550	1.661e-28	LOC112444322		

4.3 Boran significant SNPs

In the boran case-control group GWAS, a total of 15 SNPs were detected to be below the significance threshold with three peaks on chromosomes 14 and 16. On chromosome 14 it was on PAG1 gene (base pair position: 44218065; p=1.062e-08). On chromosome 16 it was on NVL gene (base pair position: 27466587; p=7.207e-34). Other significant SNPs are on chromosome 4, 19and 24 as shown on Table 4.3.

Table 4.4: List of significant SNPs for the Boran case-control group.

The table shows the chromosome, position in bp (base pairs), gene and the function of the genes and lists the significant SNPs, the genes in which they are found or those flanking them and the function of the genes.

Boran vs controls					
Chr	Pos	P-value	Gene	Definition	Function
4	21700353	3.394e-10	LOC112446324 - LOC112446494		
8	101498454	1.318e-17	SUSD1	Sushi Domain Containing 1	May be involved in calcium ion binding.
13	30634339	1.147e-25	MINDY3-PTER		
14	44218065	1.062e-08	PAG1	Phosphoprotein Associated With Glycosphingolipid	It is involved in the regulation of T cell activation.
16	27466587	7.207e-34	NVL	Nuclear VCP Like	Catalyzes the release of specific assembly factors, such as WDR74, from pre-60S ribosomal particles through the ATPase activity.
19	46655940	4.135e-11	LOC112442751 - LOC107131395		
24	53328928	1.164e-64	DCC-MBD2		
27	1919781	5.386e-14	MYOM2-CSMD1		

4.4 N'Dama X Boran significant SNPs

In the N'Dama X Boran case-control group, a total of 47 SNPs were detected to be below the significance threshold with peaks on chromosomes 8, 9 and 11. On chromosome 8 the SNPs was on SUSD1 gene (base pair position: 101498454; p=8.734e-25), chromosome 9 it was between DSE and TRNAC-GCA (base pair position: 34362359; p= 3.65e-31) and on chromosome 11 between LOC782101 and LOC100297236 genes (base pair position: 84239108; p=2.852e-24). Other significant SNPs are on chromosomes 1, 3, 4,, 6, 10, 12, 13, 16, 17, 19, 21 and 27 as shown on Table 4.4.

Table 4.5: List of significant SNPs for the N'Dama X Boran case-control group.

The table shows the chromosome, position in bp (base pairs), gene and the function of the genes and lists the significant SNPs, the genes in which they are found or those flanking them and the function of the genes.

N'DamaXBoran vs controls					
Chr	Pos	p-value	Gene	Definition	Function
1	56421072	3.101e-09	LOC104970843		
3	67058218	2.386e-14	ZZZ3	Zinc Finger ZZ-Type Containing 3	Involved in DNA binding and transcription regulation.
4	36172960	3.101e-09	SEMA3A	Semaphorin 3A	It functions as a chemorepulsive agent, inhibiting axonal outgrowth, or as a chemoattractive agent, stimulating the growth of apical dendrites.
4	76430565	1.099e-08	ADCY1-LOC112446405		
6	116360818	3.101e-09	ZFYVE28	Zinc Finger FYVE-Type Containing 28	Negative regulator of epidermal growth factor receptor (EGFR) signaling. Acts by promoting EGFR degradation in endosomes when not monoubiquitinated.
7	19019059	3.101e-09	PTPRS	Protein Tyrosine Phosphatase Receptor Type S	Heparin-binding, Hydrolase, Protein phosphatase, Receptor that is also important in cell adhesion.
8	101498454	8.734e-25	SUSD1	Sushi Domain Containing 1	May be involved in calcium ion binding.
9	34362359	3.65e-31	DSE – TRNAC-GCA		
10	33472063	7.613e-09	LOC104973118-TMCO5A		
10	62628026	2.01e-31	LOC101902090-SEMA6D		

11	84239108	2.852e-24	LOC782101-LOC100297236		
13	12496509	7.613e-09	ECHDC3	Enoyl-CoA Hydratase Domain Containing 3	It is involved in Fatty Acid Biosynthesis
13	38402690	3.101e-09	KAT14-ZNF		
16	73955905	3.101e-09	LOC104974530 - LOC112441794		
17	19592737	3.101e-09	SLC7A11-LOC112442101		
19	46655940	1.276e-59	LOC112442751 - LOC107131395		
21	8820700	3.101e-09	LOC112443229 -LOC782362		
21	29088181	3.101e-09	PCSK6	Proprotein Convertase Subtilisin/Kexin Type 6	Implicated in the ontogenesis of bodily asymmetries by regulating the nodal cascade and it is also relevant for structural asymmetries in the human brain.
21	31068965	3.101e-09	CHRNB4-UBE2Q2		
27	1919781	2.663e-08	MYOM2-CSMD1		

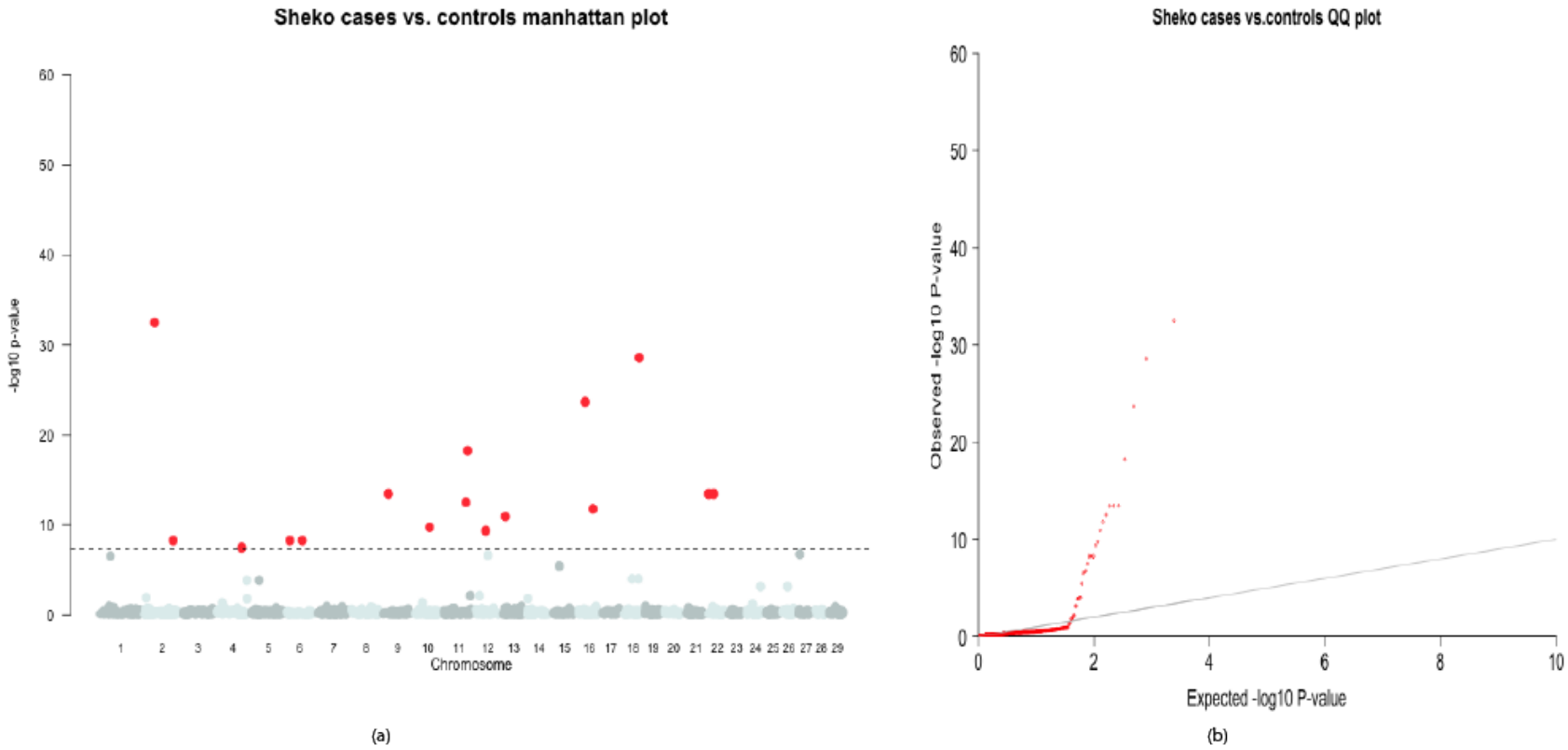

Figure 4.5: Sheko cases vs controls

(a) Manhattan plot with autosomal chromosomes 1-29 on the x axis and $-\log_{10}$p-value on the y axis. The horizontal dotted line is the significance threshold of p-value 5e-8 with the significant SNPs below it shown in red. (b) Q-Q plot with the expected $-\log_{10}$p-value on the x axis and the observed $-\log_{10}$p-value on the y axis, x=y is the grey diagonal line and the red curve are dots representing SNP p-value.

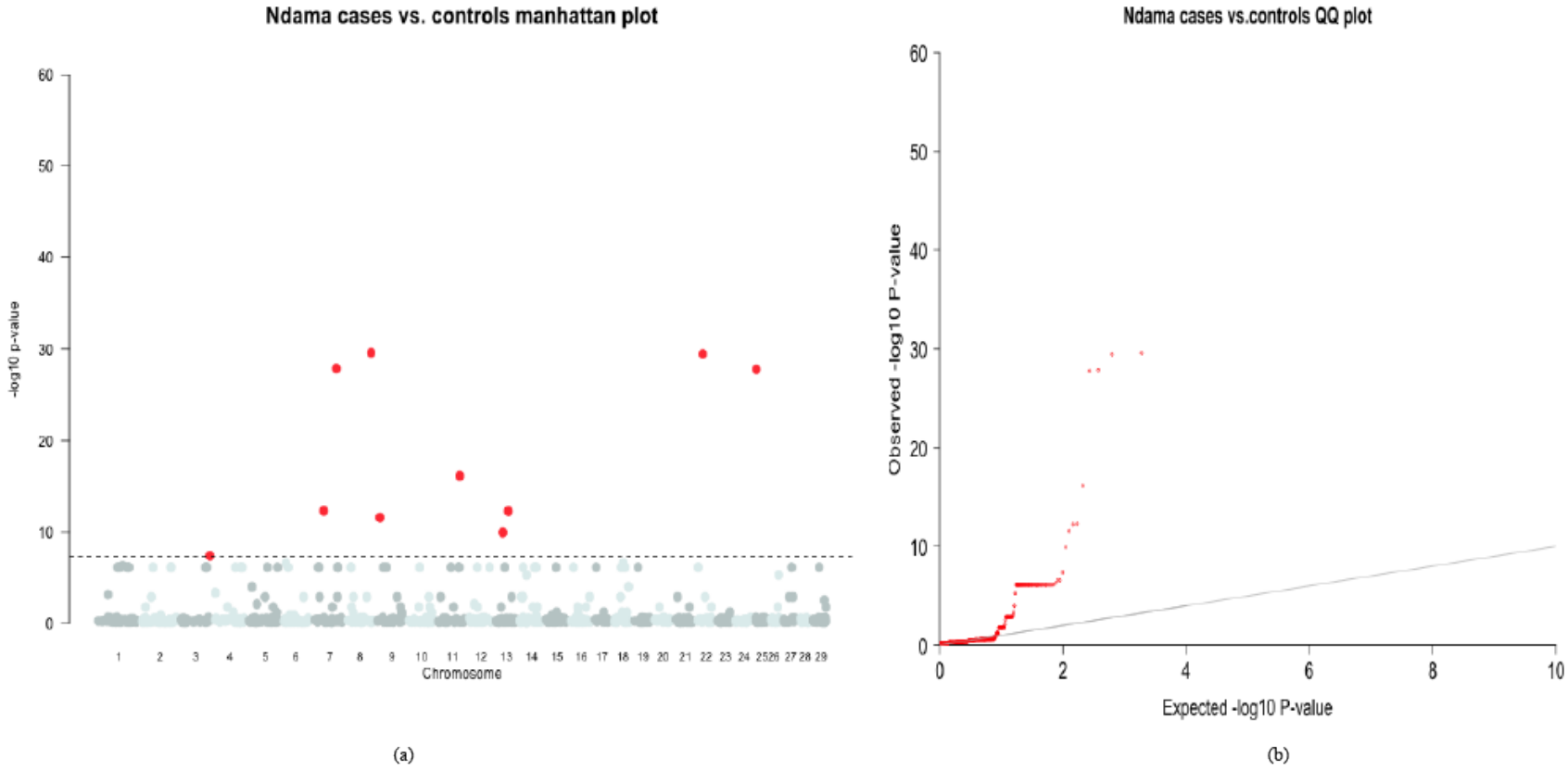

Figure 4.6: Ndama cases vs controls.

(a) Manhattan plot with autosomal chromosomes 1-29 on the x axis and $-\log_{10}$p-value on the y axis. The horizontal dotted line is the significance threshold of p-value 5e-8 with the significant SNPs below it shown in red. (b) Q-Q plot with the expected $-\log_{10}$p-value on the x axis and the observed $-\log_{10}$p-value on the y axis, x=y is the grey diagonal line and the red curve are dots representing SNP p-value.

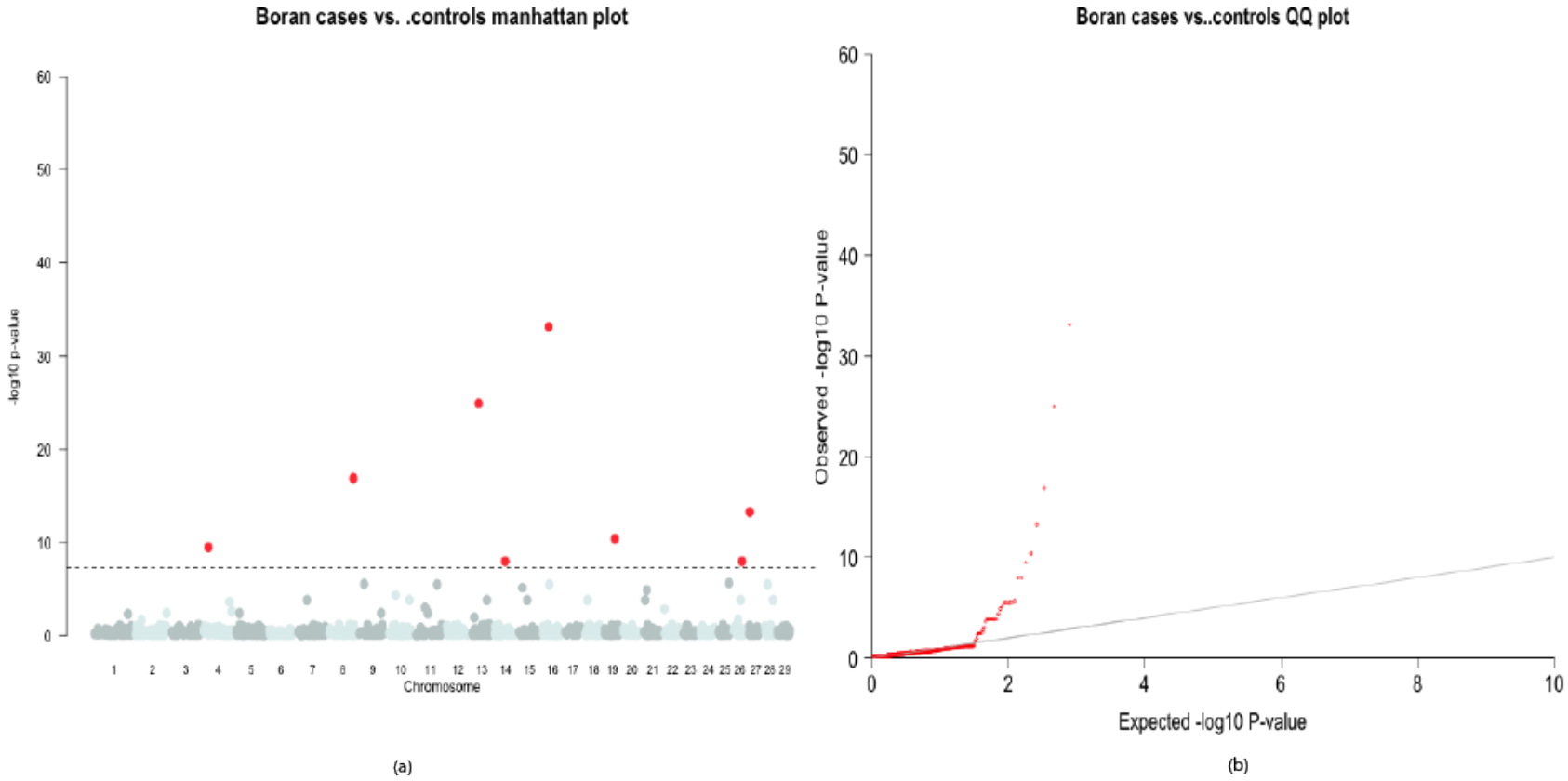

Figure 4.7: Boran cases vs controls.

(a) Manhattan plot with autosomal chromosomes 1-29 on the x axis and $-\log_{10}$p-value on the y axis. The horizontal dotted line is the significance threshold of p-value 5e-8 with the significant SNPs below it shown in red. (b) Q-Q plot with the expected $-\log_{10}$p-value on the x axis and the observed $-\log_{10}$p-value on the y axis, x=y line is the grey diagonal line and the red curve are dots representing SNP p-value.

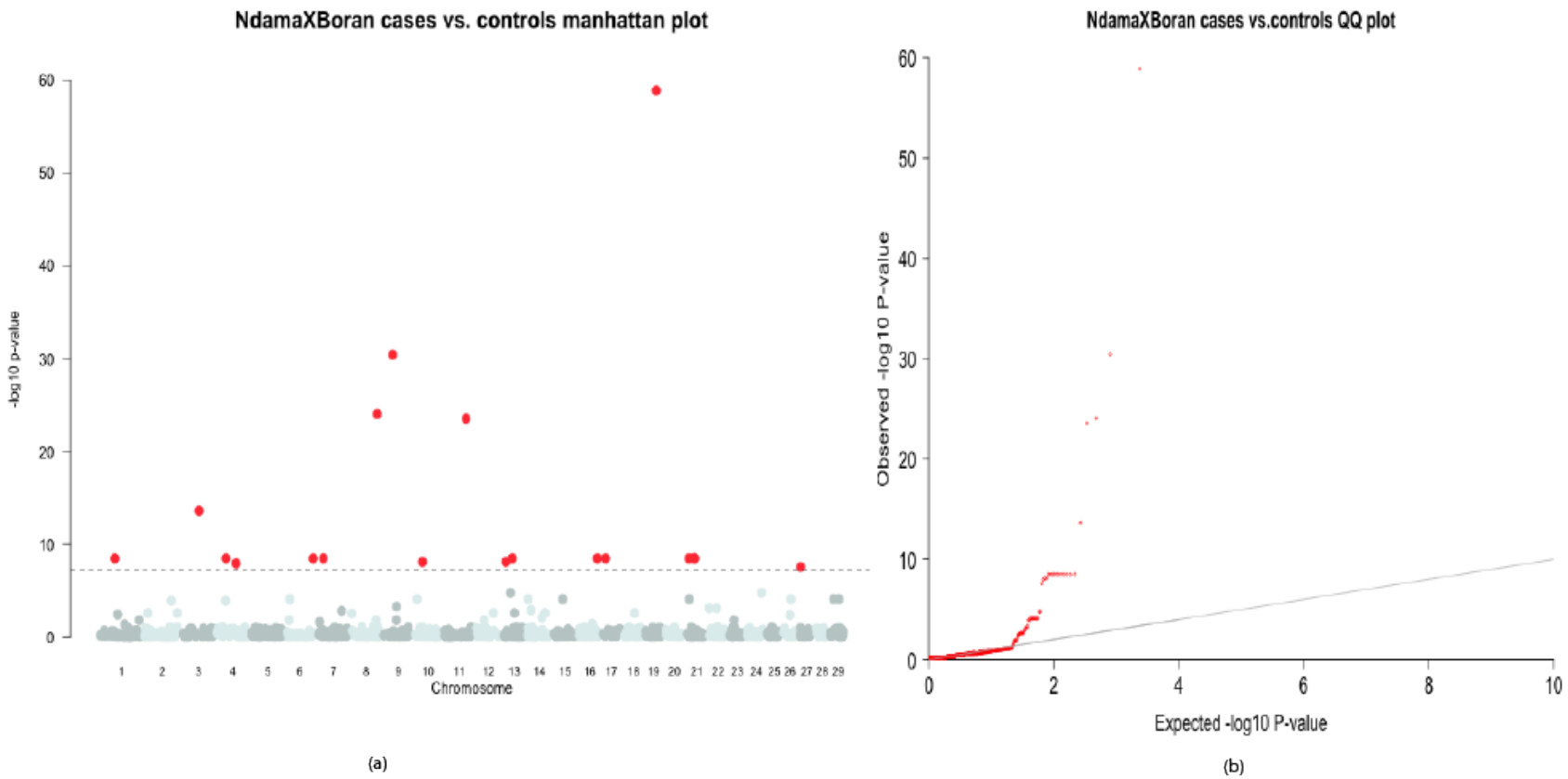

Figure 4.8: NdamaXboran cases vs controls

(a) Manhattan plot with autosomal chromosomes 1-29 on the x axis and $-\log_{10}$p-value on the y axis. The horizontal dotted line is the significance threshold of p-value 5e-8 with the significant SNPs below it shown in red. (b) Q-Q plot with the expected $-\log_{10}$p-value on the x axis and the observed $-\log_{10}$p-value on the y axis, x=y is the grey diagonal line and the red curve are dots representing SNP p-value.

Chapter 5

5.0 DISCUSSION

5.1 Genes identified in trypanotolerant cattle breeds

The significant SNPs identified from GWAS analysis were used to determine the genes that might be important in trypanotolerance trait expression for three cattle groups in the study; the trypanotolerant (Sheko and N'Dama), susceptible (Boran) and the hybrid (N'Dama X Boran). The functions and the potential role of these key genes in the trypanotolerance trait are described.

In the Sheko case-control group, see Table 4.1 and Figure 4.1, acetylgalactosaminyl transferase 13 (GALNT13) gene encodes a protein enzyme that is involved in the o-glycosylation process that affects inflammation, cell migration and proliferation (Gill *et al*., 2013; Hennet *et al*., 1995). This post translational modification process entails the attachment of a sugar molecule to the oxygen atom of serine (Ser) or threonine (Thr) residues in a synthesised protein and in eukaryotes, it occurs in the endoplasmic reticulum, Golgi apparatus and occasionally in the cytoplasm (Steen *et al*., 1998). O-glycans are involved in the movement of immune cells (Hounsell *et al*., 1996). Glycosaminoglycans (GAGs) are formed when long chains of repeating sugar units are linked to a protein by another one or more sugar side chains creating proteoglycans such as heparan sulphate and keratan sulphate (Pomin & Mulloy, 2018; Spiro, 2002). The synthesised O- linked oligosaccharide is a mucin type O- glycan that is important in the synthesis of keratosulfate (KS) found in cornea, brain, epithelial, neural and skeletal tissues with several molecular functions that include cell motility, adherence and communication (Funderburgh, 2002; Leiphrakpam et al., 2019; Weyers et al., 2013). Lumican is a proteoglycan that contains many KS chains associating with the cluster of differentiation 14 (CD14) that triggers toll-like receptor 4 (TLR4) to enable pathogen endocytosis (Caterson & Melrose, 2018; Funderburgh, 2000, 2002; Shao et al., 2013). KS chains constitute other proteoglycans, that mostly play structural roles, namely: thyroglobulin, transferrin, mammallin, SV2 (synaptic vescicle 2), fibromodulin, osteoglycin/mimecan, osteoadherin and keratocan (S. Chen & Birk, 2013; Sommarin *et al*., 1998). Lumican is involved in the clearing of trypanosome parasites from the cattle's blood by phagocytosis in macrophages and monocytes, therefore, causing a reduction in the observed parasitaemia (Wu *et al*., 2007).

Solute carrier family 19 member 3 (SLC19A3) gene encodes a thiamine transporter 1 or 2 (THTR1/2) protein on the small intestinal epithelial cell membrane that moves vitamin B1 (Thiamine) obtained from the diet from the intestinal lumen into epithelia (Jungtrakoon *et al*., 2019; Vernau *et al*., 2013). Thiamine is a cofactor of oxoglutarate dehydrogenase and pyruvate dehydrogenase that are essential enzymes in the tricarboxylic acid cycle for the generation of adenosine triphosphate (Frank *et al*., 2007). Apart from its metabolic functions, thiamine plays other roles such as the activation of immune system, tissue maintenance processes, cell signaling, and dynamics of the cell membrane and neuron communication (Hosomi & Kunisawa, 2017; Manzetti *et al*., 2014). Vitamin B1 helps mount an immune response that curbs the viability of mycobacterium tuberculosis, a bacterial pathogen, in macrophages and neutrophils during endocytosis and this might also be the case with the infecting trypanosomes in cattle (de Andrade *et al*., 2014; Weiss & Schaible, 2015). Thiamine has an effect on inflammation in the brain, immunoglobulin expression and immune cells activity (Ottinger *et al*., 2012; Zimitat & Nixon, 2001). In tissue maintenance, thiamine is involved in cerebral metabolism and its deficiency in humans is associated with various disease conditions such as cardiomyopathy and beriberi (Thornalley, 2005). Vitamin B1 has cytotoxic effect on the trypanosome cells causing death and subsequently reducing parasitemia in trypanotolerant Sheko (Bâ, 2008).

Phosphodiesterase 4B protein is encoded by PDE4B gene and it is essential for mucin up regulation through an ERK dependent fashion by affecting the cAMP pathway and it has been clinically associated with schizophrenia which is a disorder of the nervous system (Gurney, 2019; McGirr et al., 2016). This protein has been shown to stimulate natural immunity that is important during infections like those of the trypanosome protozoan parasites (Komatsu et al., 2013; Koo et al., 2011; Reyes-Irisarri et al., 2007). This protein plays its role by modulating the functions of immune cells like the T helper cells that are important in mounting an immune response during infections (Blackman et al., 2011; Jin & Conti, 2002). Apart from playing a role on natural immunity, this gene also helps in maintaining the integrity of epithelial cell walls found on blood vessels and this may help reduce the spread of trypanosomes to other parts of the body (Blackman et al., 2011).

CADPS2 is a Calcium Dependent Secretion Activator 2 gene that encodes a protein that is involved in the development of the cerebellar where it is a regulator of neurotrophin release and it has been associated with autism (Carter, 2019; Sadakata et al., 2007) This gene plays an important role during synaptic transmission on the neurons and mutations that are found in it contribute to an increase in susceptibility to autism (Matsuzaki et al., 2012). This gene has been shown to play a role in the immune system during an infection in the host eukaryotic organism (Chen & Birk, 2013; Shoja-Taheri et al., 2019; Wang et al., 2014). This gene affect the development of immune cells via the cytoskeleton pathway and this affects the immune responses during infections by viruses, protozoa and other pathogens (Chen & Birk, 2013).

AGBL3 is an (ATP/GTP binding protein-like 3) Carboxypeptidase 3 gene that encodes a protein that is involved in the deglutamylation of proteins such as tubulins and it has been associated with cataracts and internal hemorrhoids alongside immune disorders (Retamozo et al., 2018). This gene plays an important role in the development and normal functioning of the nervous system where it is implicated in the development of dementia condition in some humans (Retamozo et al., 2018). By belonging to the class of metallocarboxypeptidases, this protein is important in the normal function of the immune system especially by maintaining the normal functioning of phagocytic cells such as macrophages (Garcia-Pardo et al., 2017; Sanglas et al., 2009; Turner et al., 2002). AGBL3 is a metallocarboxypeptidase that plays a role at the point of entry of pathogens such as helminths in the host organisms. A mutation in AGBL3 may lead to modifications in the structure and functioning of the tubulins found in the cytoskeleton and hence impairs immune activity. Deglutamylation helps to reduce neurodegeneration in the nervous system and it is carried out by the carboxypeptidases (Burke et al., 2018; Rogowski et al., 2010).

PTPRB is a Protein Tyrosine Phosphatase Receptor Type B gene that encodes a protein that is involved in the regulation of TIE2 important in the development of endothelial cells in blood vessels and it has been implicated in the enhancement of the development of a number of cancers (Hale et al., 2017; Kim et al., 2019; Soady et al., 2017; Weng et al., 2019). The TIE pathway has been used as a therapeutic target in the treatment of cardiovascular disorders in human beings (Saharinen et al., 2017). The TIE pathway interacts with the Angiopoietin 2 pathway to contribute towards the mounting of an effective immune response against cancer and infections

in mammals (Fujimoto et al., 2020; Gál et al., 2020; Hendriks & Pulido, 2013; Ruddraraju et al., 2020).

PPM1H is a Protein Phosphatase, Mg2+/Mn2+ Dependent 1H gene that codes for a protein that has been associated with multiple endocrine neoplasia (Berndsen et al., 2019; Shreeram & Bulavin, 2008; Taylor & Mossman, 2015). This gene also plays a significant role in cilia formation, it controls Rab protein dephosphorylation and it plays a significant role in cancer development (J. Fu et al., 2020; H. Zhu et al., 2016). Protein dephosphorylation negatively regulates the Leucine-rich repeat kinase 2 (LRRK2) pathway in immune cells and this pathway is associated with inflammatory ailments and it may modulate inflammation during infections (Dzamko & Halliday, 2012; Herbst & Gutierrez, 2019).

ATP5S also known as DMAC2L is a gene that encodes a subunit of mitochondrial ATP synthase subunit s that is important in the energy transduction activity of the ATP synthase complex (Brüggemann et al., 2017; Lee et al., 2011). ATP5S has been associated with alternative splicing in cells therefore it modulates the process of protein formation and it is important in the development of the cardiac system (Grahn et al., 2020; Monlong et al., 2014). This gene is also important in the regulation of the macrophage energy status that controls the levels of cholesterol in the body (Karunakaran et al., 2015). ATP5S is important the generation of energy in immune cells in the form of ATP that is a signaling molecule necessary for the inflammatory process and T cell immunity during infections (Bours et al., 2006). ATP promotes immune responses and it has been used for therapeutic purposes in various cancers (Silva-Vilches et al., 2018).

PCDH9 is a Protocadherin 9 gene that encodes a protein that is potentially involved in the suppression of tumors and it is a cell migration inhibitor of some cancerous cells (Wang et al., 2012, 2014; Xiao et al., 2018). This protein is involved in cell-cell adhesion that is calcium dependent and it affects immune cells contributing to the development of neurological disorders such Parkinson disease (Aue et al., 2018; Kedmi et al., 2011; Yu et al., 2019). PCDH9 also affects the miRNA biogenesis pathway that is important in the normal functioning of the immune system in animals by decreasing infection severity, controlling the progression of infections and they are it is (Angerer et al., 2018; Boueiz et al., 2017; H. Liu et al., 2018).

ECHDC3 is an Enoyl-CoA Hydratase Domain Containing 3 gene encoding a protein that plays a role in fatty acid metabolism and it has been associated with various cardiovascular diseases, Alzeimer's disease and diabetes (Duarte et al., 2016; Patel et al., 2021; Sharma et al., 2019; Yin et al., 2019). Sensitivity to insulin and the biosynthesis of fatty acids in immune cells is important during the activation of immune components by mediating inflammation and receptor activation during an infection in animals (Howie et al., 2018; G. Kumar et al., 2019). The biosynthesis of lipids is implicated in multiple cancers and it is essential in controlling the progression of a number of infections via the CD4+ cells (J. Fu et al., 2020).

CBFA2T2 is also known as CBFA2/RUNX1 and it is a Partner Transcriptional Co-Repressor 2 gene that is involved in transcription regulation blocking differentiation of hematopoietic cells and it promotes leukemogenesis (Chen et al., 2017; Kumar et al., 2008). Additionally, this gene regulates the pluripotency of stem cells (Burton & Torres-Padilla, 2016; Guastadisegni et al., 2010; Tu et al., 2016). Hematopoiesis blocking may result in conditions such as neutropenia that reduces the population of immune cells that are required for fighting infections that the animal is exposed to which also have a negative impact on the process (Man et al., 2021; Meng et al., 2020; Pascutti et al., 2016).This gene has also been identified as a biomarker for severe asthma in humans (Bigler et al., 2017).

SNTB1 is a Syntrophin Beta 1 gene that encodes a protein that is involved in the autophagy process and it is implicated in myopia and deafness (Liu et al., 2021; van Duyvenvoorde et al., 2014; Ye et al., 2019). This gene has also been associated with lung cancer in humans and diseases of the cardiac system (Galvan et al., 2013; Joehanes et al., 2013; Zhang et al., 2017). This gene plays an important role in innate immunity of animals through the macrophages that are essential for phagocytosis (Eslamloo et al., 2017).

JHY is a Junctional Cadherin Complex Regulator gene that regulates the differentiation of ependymal cells and it is involved in ciliogenesis (Appelbe et al., 2013; Muniz-Talavera & Schmidt, 2017). Cadherin complexes are important in maintaining the integrity of cell-cell junctions that are found on endothelial cells that line the blood vessels that the trypanosomes can penetrate to colonize other tissues during infection (Bhat et al., 2019; Brückner & Janshoff, 2018; Dorland & Huveneers, 2017; Van den Bossche et al., 2012). The tight junctions' integrity

is altered by the onset of cancer and as a result of inflammatory responses that develop during infections to allow immune cells to permeate the blood vessel wall (Daulagala et al., 2019; Gloushankova et al., 2017; Mehta et al., 2015; Reglero-Real et al., 2016).

NVL is a Nuclear (Valosin-containing-protein) VCP Like gene also called CDC48 that codes for a protein that catalyzes the release of specific assembly factors in the ribosome through the ATPase activity. This gene has been implicated in nervous disorders such as Schizophrenia (Fujiwara et al., 2011; Lingaraju et al., 2019; Sehrawat et al., 2021; M. Wang et al., 2015) . NVL plays a role in the immunity of cattle towards *Mycobacterium bovis* and it is important in protozoan infections as well by contributing to the inflammatory process that is initiated (Xu et al., 2019). Valosin-containing protein is essential for the degradation of proteins in cells apart from causing cell death (Jia et al., 2018; Yeo et al., 2016; Yeo & Yu, 2016; W. Zhu et al., 2018).

ASTN1 is an astrotactin 1 gene that acts as a receptor on nerve cells regulating glial-guided cellular movements through interactions between astrotactin 1 and neuronal cadherin (Chang, 2017; Horn et al., 2018; Lara et al., 2018). ASTN1 helps repair neurons and it might be implicated in the expression of symptoms when the nervous system is affected during a trypanosomiasis infection, either on the adult animal or foetus (Lionel et al., 2014; Ni et al., 2016; Yi et al., 2016). ASTN2 controls ASTN1 expression on cell membranes (P. M. Wilson et al., 2010). These two proteins belong to the membrane attack complex or perforin (MACPF) family that are mostly involved in performing cellular lysis (Adams, 2002; Kondos et al., 2010; Ni et al., 2016). In humans, trypanosomes invade cerebral spinal fluid causing nervous system complications while in animals they also live in extravascular tissues including the brain of wild animals (Anderson et al., 2011; Steverding, 2008; Stijlemans et al., 2018). In cattle, ASTN1 protein affects the activation of B cells in the immune system and consequently antibody production that is required in mounting an immune response against invading trypanosomes (Chen et al., 2020).

SSC5D is a Scavenger Receptor Cysteine Rich Family Member with 5 Domains gene that encodes a protein that is involved in innate immunity being found in macrophages and T-lymphocytes (Bessa Pereira *et al*., 2016; Gonçalves *et al*., 2009). This gene also plays a

significant role in immunity at the interface of innate and adaptive immunity (Carvalho-Santos *et al*., 2011; Lozano & Martínez-Florensa, 2017; Oliveira & Carmo, 2017).

RBFOX3 is a Ribonucleic acid (RNA) binding Fox (forkhead box)-3 homolog 1 gene that is important in red blood cell formation where it modulates alternative splicing in tissues (Conboy, 2017; Kucherenko & Shcherbata, 2018; G. H. Lee & D'Arcangelo, 2016; Lee et al., 2016; Pedrotti et al., 2015). RBFOX1 is also involved in immune reactions during bacterial infections and blood vessel growth and development (Cieply & Carstens, 2015; Gallego-Paez et al., 2017; Gehman et al., 2012; Nazario-Toole et al., 2018; Pistoni et al., 2013).

DBNL is a Drebrin Like gene that encodes a protein that is involved in endocytosis in synapses in the nervous system and also in immunity through their action on the cytoskeleton (Herrera et al., 2021; Inoue et al., 2019). DBNL has been shown to play a significant role in cancer progression and it is key during cortical development ((Fish et al., 2016; Hakanen et al., 2019; Lozano & Martínez-Florensa, 2017). DBNL is involved in apoptosis and in enhancing the survival of cancerous cells through the immune system and this may have an impact on the immune cells that are required to mount a response against the invading trypanosomes in infected cattle (Hakanen et al., 2019).

NELL1 is a Neural Epidermal growth factor-like (EGFL) 1 gene that encodes a protein that is involved in the regulation of cell growth and differentiation of various tissues such as bones (Aghaloo et al., 2007; Fulterer et al., 2018; James et al., 2015; Lai et al., 2020; Li et al., 2019; J. Wang et al., 2017; X. Zhang et al., 2010). NELL 1 gene also important in the immune system where it interacts with Immuniglobulin G, contributes to the inflammatory process necessary for fighting infections and it is implicated in cancers (Caza et al., 2021; Franke et al., 2007; Kundu et al., 2018).

These significant genes in the Sheko cattle breed are associated with the following metabolic pathways:

hsa00230 Purine metabolism - Homo sapiens (human) (1)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa00230.args

hsa00512 Mucin type O-glycan biosynthesis - Homo sapiens (human) (1)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa00512.args

hsa00514 Other types of O-glycan biosynthesis - Homo sapiens (human) (1)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa00514.args

hsa03008 Ribosome biogenesis in eukaryotes - Homo sapiens (human) (1)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa03008.args

hsa04024 cAMP signaling pathway - Homo sapiens (human) (1)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa04024.args

hsa04520 Adherens junction - Homo sapiens (human) (1)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa04520.args

hsa04928 Parathyroid hormone synthesis, secretion and action - Homo sapiens (human) (1)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa04928.args

hsa04977 Vitamin digestion and absorption - Homo sapiens (human) (1)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa04977.args

hsa05032 Morphine addiction - Homo sapiens (human)

https://www.genome.jp/kegg-bin/show_pathway?162097970492803/hsa05032.args

In the N'Dama case-control group, see Table 4.2 and Figure 4.2, SUSD1 is a Sushi Domain containing 1 gene that is important in the formation of adhesion and complement proteins that is important in the functioning of the complement system that is involved in immunity. This protein has been shown to play a role in the diseases of the nervous system such as amyotrophic lateral sclerosis and in blood such as chronic myeloid leukemia (Dervishi et al., 2018; Halbach et al.,

2016). SUSD1 is also associated with neurocognitive disorders (Nilsson et al., 2017). The complement system is important in the enhancement of phagocytosis, the production of antibodies that are necessary in the fight against infections such as trypanosomes and it is part of both natural and acquired immunity (Afshar-Kharghan, 2017; Dunkelberger & Song, 2010; Jagatia & Tsolaki, 2021; Merle et al., 2015; Ogundele, 2001; R. Zhang et al., 2019).

COL19A1 is also called COL9A1L or D6S228E and it is collagen type XIX alpha 1 gene that is involved in pericellular matrix or sphincteric smooth muscle organization, skeletal myogenesis in developing esophagus while also acting as a cross-bridge between fibrils and other extracellular matrix molecules (Calvo *et al*., 2020; Khaleduzzaman *et al*., 1997; Su *et al*., 2017; Sumiyoshi *et al*., 1997). COL19A1 protein is important in neuronal synaptic transmission and it also stimulates or inhibits immune components such as monocytes (Calvo *et al*., 2020; Roumazeilles *et al*., 2018; Su *et al*., 2010). COL19A1L is found in various tissues such as skeletal and epithelial tissues with anti-tumor activity through the protein kinase B route, anti-angiogenic characteristics and matrix metallopeptidase 14 expression (Oudart *et al*., 2017). COL19A1 regulates the phagocytosis of trypanosomes in the animal's blood or tissue important in trypanosome clearance and reducing parasitemia in the trypanotolerant cattle (Roumazeilles *et al*., 2018).

DPF3 is a Double PHD Fingers 3 gene that encodes a protein that plays a significant role in the immune system and it has been identified as a risk factor for breast cancer (Lin et al., 2019). This gene also plays a role in the development of the nervous system and muscle in eukaryotic organisms (Lange et al., 2008). DPF3 has been found to play a role in lipid metabolism where it is involved in the formation of brown fat ((Shapira et al., 2017)Shapira et al., 2017). Brown fat is involved in the generation of energy and the process is modulated by the immune system especially in cases of obesity (Brestoff, 2017; Fu et al., 2021; Moon et al., 2020; van den Berg et al., 2017; Villarroya et al., 2018; Villarroya et al., 2019).

These significant genes in the N'Dama cattle breed are associated with the following metabolic pathways:

hsa04974 Protein digestion and absorption pathway

https://www.genome.jp/kegg-bin/show_pathway?162028856272613/hsa04974.args

hsa04714 Thermogenesis pathway

https://www.genome.jp/kegg-bin/show_pathway?162028856272613/hsa04714.args

hsa05225 Hepatocellular carcinoma pathway

https://www.genome.jp/kegg-bin/show_pathway?162028856272613/hsa05225.args

5.2 Genetic variants identified in non trypanotolerant breed

In the Boran case-control group, see Table 4.3 and Figure 4.3, SUSD1 is a Sushi Domain containing 1 gene that is important in the formation of adhesion and complement proteins that is important in the functioning of the complement system that is involved in immunity. This protein has been shown to play a role in the diseases of the nervous system such as amyotrophic lateral sclerosis and in blood such as chronic myeloid leukemia (Halbach et al., 2016; Ellinghaus et al., 2020; Dervishi et al., 2018). SUSD1 is also associated with neurocognitive disorders (Nilsson et al., 2016). The complement system is important in the enhancement of phagocytosis, the production of antibodies that are necessary in the fight against infections such as trypanosomes and it is part of both natural and acquired immunity (Merle et al., 2015; Dunkelberger et al., 2010; Jagatia, 2021; Afshar-Kharghan et al., 2017; Zhang et al., 2019; Ogundele, 2001).

PAG1 is a pregnancy-associated glycoprotein 1 / pregnancy-specific protein B (PSPB)/ Peptidase A1 domain-containing gene that is an aspartic-type endopeptidase involved in proteolysis and protein catabolism (digestion and absorption) (Gaudet et al., 2011; Rao et al., 1998; Souza et al., 2015). The endopeptidase enzyme is involved in breaking down proteins into amino acids and dipeptides for absorption (Dallas, 2012; Kumar *et al*., 2019; Mamo & Assefa, 2018). PSPB is important in pregnancy preservation and it is used in pregnancy detection in cattle (Giordano *et al*., 2012; Green *et al*., 2000; Huang *et al*., 1999; Northrop *et al*., 2019; Wallace *et al*., 2015). This protein might be the reason for pregnant animals expressing better immunity to infectious diseases than those which are not (Downs *et al*., 2015).

NVL is a Nuclear (Valosin-containing-protein) VCP Like gene also called CDC48 that codes for a protein that catalyzes the release of specific assembly factors in the ribosome through the

ATPase activity. This gene has been implicated in nervous disorders such as Schizophrenia (Wang et al., 2015; Lingaraju et al., 2019; Fujiwara et al., 2011; Sehrawat et al., 2021). NVL plays a role in the immunity of cattle towards Mycobacterium bovis and it is important in protozoan infections as well by contributing to the inflammatory process that is initiated (Jone et al., 2011; Xu et al., 2019). Valosin-containing protein is essential for the degradation of proteins in cells apart from causing cell death (Yeo et al., 2016; Yeo, 2016 b; Jia et al., 2018; Zhu et al., 2018).

WDR11 is a Tryptophan- aspartic acid (WD) repeat containing 11 gene that is also referred to as DR11/ HH14/ SRI1/ BRWD2/ WDR15, it is involved in the hedgehog (Hh) pathway for cilia formation, control of Zinc finger protein (GLI3) lysis, hormonal release in the endocrine system and vesicle binding for the degradation of cytoplasmic materials (Humke *et al*., 2010; Navarro Negredo *et al*., 2018; Niewiadomski *et al*., 2014; Taylor & Mossman, 2015). The Hh pathway enhances multiplication of antibody producing cells in infection and cancer (Benson, 2004; Chan *et al*., 2006; Grund-Gröschke *et al*., 2019; Shen *et al*., 2017; Smelkinson, 2017). During viral infections, this protein enhances parasite multiplication whereas its role in trypanosomiasis is yet to be described and it's also involved in cancer development inhibition (Kim *et al*., 2018; Stamou *et al*., 2015; Taylor & Mossman, 2015; Teng *et al*., 2015; Wei *et al*., 2017).

These significant genes in the Boran cattle breed are associated with the following metabolic pathway:

hsa03008 Ribosome biogenesis pathway

https://www.genome.jp/kegg-bin/show_pathway?162028821787328/hsa03008.args

5.3 Genes identified in hybrid cattle

In the N'Dama X Boran case-control group, ZZZ3 is a Zinc Finger ZZ-Type Containing 3 gene that is involved in the regulation of transcription in the cells and it also binds to chromatin. It has also been shown to interact with the ADA Two A Containing (ATAC) complex (Mi et al., 2018; Zhang et al., 2019; Arede et al., 2020; Kobow et al., 2013). ZZZ3 also is implicated in some cancers and it plays a crucial role in the development of the immune system of animals (Arede et al., 2020; Yue et al., 2019; van der Kolk, 2019). The ATAC complex is important in the immune

cells that are required for mounting an immune response against the invading trypanosomes (Guelman et al., 2009; Lee et al., 2013).

SEMA3A is a Semaphorin 3A gene that regulates the neuronal growth and distributed in other mammalian tissues (Eastwood *et al*., 2003; Hanchate *et al*., 2012; Quintremil *et al*., 2019; Tapia *et al*., 2008; Ufartes *et al*., 2018). SEMA3A protein has inflammatory activity and it blocks the movement of phagocytic cells and stimulate antibody producing immune cells required for infection and cancer control (Chapoval, 2018; Chen & Cuang, 2019; Feinstein & Ramkhelawon, 2017; Lepelletier *et al*., 2006; Takamatsu *et al*., 2010; Takamatsu & Kumanogoh, 2012). SEMA3A controls infection progression by modulating interaction between the pathogens and immune cells (Kumanogoh, 2003; Papic *et al*., 2018; Sabag *et al*., 2014; Vadasz & Toubi, 2018).

ZFYVE28 also referred to as LYST2/ LST2 is a Lateral signaling target protein 2 homolog gene that controls epidermal growth factor receptor (EGFR) pathway (Kropp *et al*., 2017; McFerrin & Atchley, 2011; Zambrano *et al*., 2018). This pathway is important in modulating immune activity by maintaining the normal role of Tregs in the pathogenesis of cancer and infectious diseases (Abdelhamed *et al*., 2016; Bauer *et al*., 2012; Lim *et al*., 2016; MacDonald & Zaiss, 2017; Sasada *et al*., 2016). This pathway interacts with others like extracellular signal regulated kinase (ERK) in immune cells to control the progression of contagious diseases in animals (Kedzierski *et al*., 2017).

PTPRS also known as PTP-NU3 is a Protein tyrosine phosphatase receptor type S protein gene that controls interferon release which is important in viral immunity, it also activates neuronal outgrowth in response to heparan sulphate and it regulates the endocrine system (Bunin et al., 2015; Hendriks & Pulido, 2013; S. Mamo et al., 2012; Senis & Barr, 2018; Stewart et al., 2013). PTPRS protein activates immunity by controlling crucial signaling pathways in disease conditions like tumors (Davis *et al*., 2018). It is also implicated in infectious diseases by controlling necrobiosis in the host cells (Curtis et al., 2019; Sclip & Südhof, 2020; Stewart et al., 2017).

PCSK6 is a Proprotein convertase subtilisin/kexin type 6 protein gene that affects cellular secretory pathway where it processes proteins and transports peptide precursors in the cells

ensuring the normal functioning of the female reproductive system and endocrine system (Mekonnen et al., 2019; Mujoomdar et al., 2011; Southey et al., 2009; Y. Wang et al., 2014). PCSK6 modulates necrobiosis, a pathway that is important in natural immunity of animals and it is sometimes affected by the infecting parasites (Cotzomi-Ortega *et al*., 2018; Farhan & Rabouille, 2011; Sharp & Estes, 2010; Sitia & Rubartelli, 2020; Stanley & Lacy, 2010). Various pathogens such as bacteria and viruses interact with this pathway in the host animal with an effect on the mounted immune activity (Belov *et al*., 2007; Mages *et al*., 2008; Nanbo, 2020).

These significant genes in the N'Dama X Boran cattle breed are associated with the following metabolic pathway:

hsa04360 The axon guidance pathway.

https://www.genome.jp/kegg-bin/show_pathway?1620890323106138/hsa04360.args

Chapter 6

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The genes that contain the significant SNPs enhance the immune responses for phagocytosis and the production of antibodies that is required for the elimination of the trypanosomes in trypanotolerant Sheko and N'Dama cattle to reduce parasitemia.

In this study, we suggest that in the N'Dama cattle, the SUSD1 gene that is involved in the thermogenesis pathway has a mutation that enhances the inflammatory process and other immune responses including those that are mediated by lymphocytes that play a role in the development of cancer. A mutation in the DPF3 gene that is involved in the hepatocellular carcinoma pathway promotes the immune activity against the invading pathogens. This leads to the killing of the trypanosomes that are in circulation that are then degraded in cells whose COL19A1 gene mutation has helped enhance protein digestion and absorption pathway

In the Boran cattle, we suggest that this breed of cattle is attempting to use the mutation in the NVL gene to enhance the ribosome biogenesis pathway so that it can be able to withstand the trypanosomiasis challenge that it is exposed to in its environment. Ribosomes are important in forming proteins that are involved in the immune processes during an infection and they may independently play a role in pathological process during trypanosome infections

In the N'DamaXBoran cattle, the mutation in the SEMA3A and PTPRS genes are crucial in modulating the functioning of the axon guidance pathway during trypanosomiasis infections. This helps to reduce the effect of the infection on the nervous system of these hybrid cattle

In the Sheko cattle, the ribosome biogenesis, cAMP signaling and vitamin digestion and absorption pathways may be playing a crucial role in the expression of the trypanotolerance trait although hormonal pathways and nucleic acid degradation pathways are implicated. The key

genes have mutated to enhance the killing of the trypanosomes and enhance their degradation in the host organism to help reduce parasitemia

6.2 Recommendations

- Expression studies should be performed to determine the role of the identified key genes in the trypanotolerance trait mechanism.

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APPENDICES

Appendix 1: The distribution of samples according to the cattle breed and its continent of origin (sample size n=1199 from 44 breeds).

Continent	Breed	Sample size
Africa	Sheko	20
	Tuli	16
	Senepol	80
	Ankole-Watusi	12
	N'Dama	59
	N'DamaXBoran	83
	Boran	44
Europe	Sussex	11
	Belted Galloway	11
	Marchigiana	13
	Romagnola	36
	Brown Swiss	17
	Chianina	14
	Piedmontese	36
	Dexter	11
	Jersey	17
	Scottish Highland	15
	Guernsey	17
	Gelbvieh	15
	Salers	12
	Welsh Black	9
	Pinzgauer	12
	Norwegian Red	28
	Montbeliard	12
	South Devon	10
	Blonde d'Aquitaine	12
	Belgian Blue	11
	Red Angus	22
	Galloway	11
	Tarentaise	12
	Simmental	162
	Kerry	10
	English	10

	Longhorn	
	Shorthorn	105
	Red Poll	11
	White Park	10
	Devon	10
	Maine Anjou	11
South America	Corriente	12
	Romosinuano	15
Asia	Gir	32
	Sahiwal	17
North America	Brahman	105
Australia	Murray Gray	11
	44 breeds	N=1199