Review

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Trypanotolerance Sheko cattle: an option for sustainable control of bovine trypanosomiasis

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Abstract: Trypanosomiasis is an impediment to cattle production and other agricultural development in tsetse-infested areas. It is a severe parasitic disease that causes loss in the production and performance of cattle. Hence, the aim of this paper is to review trypanosomiasis control options with emphasis on the use of trypanotolerant Sheko cattle breed for sustainable management of bovine trypanosomiasis in tsetse infested areas. Several methods have been used to control trypanosomiasis through the use of trypanocidal drugs and the management of the vector, tsetse fly. Tsetse fly controls require expensive insecticides and have adverse environmental consequences. Trypanocidal drugs are commonly used and considered a practical trypanosomiasis control method. However, the rise in trypanocidal drug resistance has rendered this option ineffective. The possibility of developing and using a vaccine against trypanosomiasis currently remains out of reach as *Trypanosoma* periodically undergo antigenic variation. In the absence of a vaccine, presence of trypanocidal drug resistance, and the lack of sustainable tsetse fly control measures demand the need to use trypanotolerant cattle breeds. The Sheko breed which is found only in southwestern Ethiopia displays considerable natural resistance to tsetse-transmitted trypanosomiasis. This genetic resource provides sustainable solution for challenges related to trypanosomiasis. These cattle have a low level of parasitemia and are able to maintain a good packed cell volume (PCV) compared to other indigenous breeds. As several trypanosomiasis control methods are

ineffective, the use of trypanotolerance cattle like Sheko breed in tsetse-fly-challenged areas was suggested.

Keywords: Cattle, Sheko breed, Trypanocidal drugs, Trypanosomiasis, Trypanotolerance.

1 Introduction

Considerable numbers of African cattle are at risk of trypanosomiasis caused by a unicellular protozoan parasite that belongs to the genus *Trypanosoma* [1, 2]. Trypanosomiasis is the major cattle production constraint, especially in sub-Saharan countries. It is mainly caused by *T. congolense*, *T. vivax*, and *T. brucei* [3, 4]. The disease is transmitted from infected animals to healthy animals by the tsetse fly (Genus *Glossina*) as vectors [5, 6]. *Trypanosoma evansi* is also an important but non-tsetse transmitted cause of trypanosomiasis [7]. The usual consequence of *Trypanosoma* infection is anemia, weight loss, low milk yield, infertility, abortion and paralysis. If not treated (trypanocidal drugs for therapeutic and prophylactic purpose), it can lead to the death of the host [8]. This disease has a major economic impact accounting for an estimated annual loss of US\$ 5 billion in Sub-Saharan countries [9].

In Ethiopia, trypanosomiasis is still causing the highest production losses in the cattle industry in tsetse-infested areas [10]. The disease causes both direct and indirect loss. The direct loss mostly results from mortality, morbidity, infertility of the infected cattle, and the cost of controlling the disease. Seyoum *et al.* [11] estimated an annual US\$200 million direct loss caused by mortality, morbidity and control costs attributed to trypanosomiasis. The indirect losses include the lack of use of livestock and animal power for crop production in productive land in tsetse infested areas is more significant than the direct loss. Trypanosomiasis is a major constrain to achieving food security and poverty alleviation [12, 13].

The disease is widespread in cattle and large areas of land are infested with *Glossina* species in Ethiopia [14].

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Due to a lack of effective control methods, the disease remains the biggest constraint to cattle production and the overall development of agriculture in the country [10]. There is a growing body of evidence that certain breeds of cattle can survive and thrive in tsetse infested areas whereas other breeds rapidly succumb to trypanosomiasis. This unique and promising trait has been termed as trypanotolerance [15].

Currently, trypanosomiasis control techniques target the vector (tsetse fly control) and the parasite (the use of chemotherapy). Vector control requires the widespread use of insecticide and other technologies, which are very expensive and have adverse environmental consequences. Chemotherapy requires the use of trypanocidal drugs that are also costly and are not always readily available [16, 17]. Furthermore, these drugs are limited and resistance of the parasite to these drugs has been reported [18]. Efforts to develop a vaccine against trypanosomiasis have been unsuccessful due to the unique ability of the parasite to evade the host immune system by use of antigenic variation, the periodic switching of its variant surface glycoprotein coat [4, 19].

Since many control methods for trypanosomiasis are failing, there is necessity for other and supportable solution. One of the promising and worthwhile solution is to use trypanotolerant cattle breeds that are found in several African countries [20]. Trypanotolerance is describes as the relative capacity of the animal to control the development of the parasite and to limit its' pathological effect [15]. Specifically packed cell volume (PCV) and parasitaemia are the major indicators of trypanotolerance. This is strongly correlated with cattle performance especially, reproductive performance and overall cattle productivity. A genetic factor can also determine trypanotolerance [21]. It is thought to involve a strong immune response towards the parasite antigens as well as cytokine synthesis with lethal effect on *Trypanosoma* proliferation [22]. The use of these breeds in tsetse fly-infested areas would significantly improve both cattle and agricultural production these areas. In West Africa, Shorthorn and N'Dama breeds are known to exhibit different levels of trypanotolerance. They are known for their ability to produce milk and reproduce even under high *Trypanosoma* pressure [23]. Sheko cattle which is found only in southwest Ethiopia are more productive compared to other breeds in tsetse-infested areas. Studies indicated that Sheko breed is more trypanotolerant than other breeds found in Ethiopia and other African countries. The tolerance attributes of Sheko are believed to be associated with its taurine genetic background [24, 25]. If implemented as a control strategy, trypanotolerance

could have a major positive effect on long term food security for the country. Therefore, the objective of this paper is to review trypanosomiasis control options with emphasis on the use of trypanotolerant Sheko cattle breed for sustainable management of bovine trypanosomiasis in tsetse infested areas. This review builds on our prior work in defining key aspects of the epidemiology of trypanosomiasis in Ethiopia (10).

2 Trypanosomiasis

Trypanosomiasis is a complex disease caused by several species of unicellular protozoa parasite of genus *Trypanosoma* under Trypanosomatidae family [26]. It is mainly transmitted cyclically by the tsetse flies (genus *Glossina*) and affects various species of animals [27]. *Trypanosoma* lives in the blood and other body fluids of vertebrate animals but undergoes cyclical development the tsetse fly, an arthropod vector [28]. *Trypanosoma* species occur in a variety of genotypes with different strains, virulence, immunogenicity, and response to the chemotherapeutic agent [29]. *Trypanosoma congolense*, *T. vivax*, and *T. brucei* are the most important pathogenic species of *Trypanosoma* to cattle. *Trypanosoma vivax* can cause disease outside of the tsetse belt area [3] suggesting that it can be mechanically vectored by other biting flies. *Trypanosoma congolense* is a group of small *Trypanosoma* with medium-sized marginal kinetoplast, having no free flagella and poorly developed undulating membranes whereas *T. vivax* is species of *Trypanosoma* parasite which has a large terminal kinetoplast, distinct-free flagella, and inconspicuous undulating membrane. *Trypanosoma brucei* is polymorphic *Trypanosoma* happening as short, stumpy organisms with no flagella, long slender organisms with distinct flagella, and intermediate forms that are usually flagellated [30].

2.1 Epidemiology

The distribution of *Trypanosoma* of veterinary important varies with locality and depends upon the interaction between tsetse flies, the parasite, and domestic and wild animals [31, 32]. The epidemiology of trypanosomiasis is very complex since parasite infects different species of domestic and wild animals that can constitute the reservoirs of the disease. The degree of risk trypanosomiasis poses to farm animals depends upon the species and population density of the tsetse, the infection rate in the tsetse,

species and strain of trypanosomes, source of infection, and feeding preference of the flies [33]. Trypanosomiasis is a vector-borne disease known to be transmitted by tsetse flies and mechanically by a number of biting flies of genus Diptera such as *Tabanus*, *Hematopota*, *Chrysops* and *Stomoxys* [34, 35]. Transmission of this trypanosomiasis by tsetse fly could be a complicated mechanism within which the fly remains a long carrier [35]. In the tsetse fly, Trypanosome undergoes many morphologically distinct stages (amastigotes, promastigote, and epimastigote) until it reaches the trypomastigote (metacyclic stage) which is infective for animals [31]. The tsetse becomes infected with trypanosomes once it consumes the blood of a diseased animal. Once the trypanosomes are ingested they lose the surface coat, develop a mitochondrion and undergo a number of biological stages before they become infective to the mammalian host. Though the development stages are similar for the three species of trypanosomes, the sites in the tsetse fly that they occur are different. In general, the occurrence of this disease is affected by the host, environment, and pathogenic factors [36]. Several studies have shown trypanosomiasis is widespread parasitic disease in Ethiopia (Table 1).

2.2 Control options for trypanosomiasis

The complexity of the epidemiology of trypanosomiasis and coupled with the limitation of currently available control methods make disease management difficult [35]. The control method of trypanosomiasis in the

enzootic countries mainly involves control of the tsetse fly population, chemoprophylaxis, the use of trypanotolerant animals, or a combination of them [55, 56].

2.2.1 Tsetse fly control

Several tsetse fly control methods have been applied separately or in combination with varying levels of success in Ethiopia and other parts of Africa [35, 57]. Control of tsetse fly has led to successful results, however reinvasion is frequent in poorly utilized land. Newer ways concerned the use of insecticides applied strategically in the form of ground and aerial spraying (by the use of aircrafts) over large expanses of land [58, 59]. As tsetse fly is sensitive to insecticides and no resistance has developed, significant successes were achieved in some countries. However, spraying insecticides is costly and harmful to the surroundings [60]. These harmful effects are significantly reduced if the insecticides, for instance, synthetic pyrethroids, are applied to the animal in form of spray or pour-on formulation. Other effective ways involve targets impregnated with insecticides and traps that attract and catch glossina species. These methods are simple and low-cost that can be made by local communities. Moreover, there are not pollute the environment and are appropriate for both small and large-scale fanning [57, 61].

Another technique is that the sterile insect technique. Since female tsetse fly mates only once in lifetime, this method is theoretically eradicating a targeted tsetse species in areas wherever alternative methods reduce its

Table 1: Distribution of bovine trypanosomiasis in Ethiopia

Study area	Sample size	Diagnostic technique	Prevalence (%)	References
Omo-Ghibe	1508	Concentration	7.80	[37]
Didessa district	384	Concentration	5.50	[38]
Dara district	384	Concentration	14.80	[39]
Gidami district	930	Concentration	14.10	[40]
South-west	7021	Concentration	9.61	[41]
Mareka district	384	Concentration	8.30	[42]
Metekel zone	1260	Concentration	12.14	[43]
Oda Buldigilu district	395	Concentration	11.89	[44]
Shebe-sombo district	780	Concentration	14.23	[45]
Nyangatom district	384	Concentration	26.30	[46]
Sayonole district	599	Concentration	16.90	[47]
Asossa District	202	Concentration	22.80	[48]
Kindo Koisha district	1008	Concentration	15	[49]
Hawa-Gelan district	389	Concentration	10.80	[50]
Metekel and Awi zones	540	Concentration	12.41	[51]
Didess river basin	1517	Concentration	5.41	[52]
Buno Bedele zone	1046	Concentration	3.44	[53]
Jimma zone	2088	Concentration	13.36	[54]

density but it's expensive [61]. Finally, it ought to be stated that the development of the land for agriculture, industries, highways, etc. can effectively destroy the habitat for tsetse fly flies [32, 55]. The difficulty of sustaining tsetse fly management has increased the requirement to enhance trypanotolerance through selective breeding either within breeds or through cross-breeding [21].

2.2.2 Trypanocidal drug

The diagnosis and treatment of trypanosomiasis are less practical to control the disease in heavily tsetse-infested areas. As a result, the use of trypanocidal drugs is a common method for trypanosomiasis management in which all animals at risk will be treated to control *Trypanosoma* transmission in an area. Trypanocidal drugs such as homidium (bromide and chloride salts), isomethamidium, and diminazene aceturate were used as prophylaxis along with other methods in high tsetse fly-infested areas [62]. The prophylactic effect is supplemented by the development of host immunity and the duration can range from weeks to months depending on the type and dose of drugs, and level of trypanosomiasis challenge [63]. Prophylactic use of trypanocidal drugs has been one of the most important and beneficial control methods of trypanosomiasis. However, the widespread use and misuse of trypanocidal drugs for the therapeutic and prophylactic purpose has led to the emergence and widespread occurrence of drug resistance [18, 30]. Some trypanocidal compounds have even been withdrawn from the market because of the emergence of drug resistance [16]. Worryingly, despite the importance of animal trypanosomiasis there is no new trypanocidal drug on the pipeline to counter the drug resistance challenge. This increases the challenge of drug resistance demands the need to adopt the combinations of other disease management strategies such as reduced exposure to the vectors, strategic treatment of exposed animals, and the use of trypanotolerant animals [35].

2.2.3 Vaccination

The complex epidemiology of trypanosomiasis makes eradication of the entire *Trypanosoma* reservoir unattainable. This indicates that anti-*Trypanosoma* vaccination needs to be considered as an ultimate option in the fight against the disease [64]. The first vaccine trial against trypanosomiasis targeted the Variant Surface Glycoprotein (VSG), a surface coat of the parasite.

Considerable investigation has been carried out to harness the advantage of this VSG, potent immune-stimulatory molecules to develop a vaccine against it. However, the effort to develop a vaccine against trypanosomiasis is challenged by a phenomenon of antigenic variation, a process used by the parasite to evade host adaptive immunity [65]. Anti-trypanosome vaccination such as anti-FP, anti-tubulin, Invariant surface glycoprotein (ISG), Sialidase and Cysteine Protease (CP) were developed in the past year. The hope to develop a vaccine targeted against these VSGs of the parasite has waned mainly because of the countless possible antigenic molecules that the parasite can produce through gene conversion and the short-lived type of IgM immunoglobulin isotype they elicit [15].

3 Trypanotolerance Sheko breed

Trypanotolerance is the comparative ability of cattle to manage the proliferation of the *Trypanosoma* parasite and prevent their effect on the hosts [15]. Other authors describes this breed as the type of cattle that tolerates it to continue production in trypanosomiasis-infected areas [66, 67]. Similarly, trypanotolerant cattle are describes as cattle that do not get disease as often, and while diseased, they survive and produce better than susceptible cattle [20]. These meanings are wide and might be related to various factors spanning from cattle' coat color that doesn't attract the fly, to antibodies targeting the trypanosomes [15].

Trypanotolerant cattle are a consequence of natural selection where cattle and trypanosomes have to live for a long time. The differences between breeds and breed groups are explained by the way cattle arrived on (origin introduced from Asia) the African region. *Bos taurus* was the first cattle on African region. Nevertheless, taurine cattle breed has over the years acquired hardiness to harsh climates and resistance to different disease among which trypanotolerance is the most notable one. Trypanotolerance traits were found in taurine cattle breeds while indicus breeds are more trypano-susceptible [66]. Cattle breeds such as N'Dama cattle are the most known trypanotolerant breeds in West Africa. N'Dama cattle are characterized by small body size and low production [28].

Trypanotolerance results from various biological mechanisms under multigenic control which are related either to the control of trypanosome infection, as measured by parasitemia [68] or the control of the

pathogenic effects of the parasites, the most prominent of which is anemia. The capacity to regulate anemia is an important characteristic of trypanotolerant cattle and this is associated with the entire production and reproduction performance. Following the first hemolysis of RBC and reduced PCV, trypanotolerant cattle become healthy while susceptible cattle remain to have a lower PCV (Figure 1). Regulate of anemia in trypanotolerant cattle is not influenced by the acquired immune response [20].

Trypanotolerant animals limit anemia through an innate mechanism that controls growth and the haematopoietic system [20]. The response of bone marrow is a key determinant factor of trypanotolerance in cattle since it determines the capacity of animals

for haematopoietic cell regeneration and control of anemia. These are considered the key differences between trypanotolerant and trypanosusceptible cattle. This is further supported by the effects of macrophage activation in the bone marrow which is found greater in trypanotolerant cattle [21]. Trypanotolerance cattle control *Trypanosoma* parasite by two factors: complement-dependent and clone-specific lytic activities, and compliment-independent trypanocidal activities that are not restricted to *Trypanosoma* clone and species [69]. Trypanotolerant animals have antitrypanosomal activities in their blood that inhibit the replication of the trypanosome parasite. Serum xanthine oxidase, serum catalase, and trypanosome-specific immune responses also play roles

Figure 1: The activation state of myeloid cells associated with anemia development during trypanosomiasis in trypanotolerance and trypano-susceptible cattle [71]. **(A)** Anemia development in trypanosusceptible (green) and trypanotolerant (blue) animals during the course of infection. Anemia progression can be divided into (i) an acute phase characterized by a rapid drop in red blood cell (RBC) numbers (i.e., consumptive anemia) followed by a partial recovery phase, (ii) a late stage characterized in the susceptible model by a progressive decline in RBC numbers (below that of the acute phase) and host death. In the tolerant model, this decline is less pronounced and leads to (iii) a chronic phase (i.e., progressive anemia), whereby RBC numbers keep on declining till finally reaching levels of that of the acute phase. **(B)** Throughout the course of infection progressive hepatosplenomegaly occurs, whereby the onset of splenomegaly precedes hepatomegaly. At the late/chronic stage of infection, splenomegaly is more pronounced than hepatomegaly. **(C)** During the different stages of infection, the host produces different mononuclear phagocyte system (MPS) polarizing molecules. During the early/acute stage, both trypanosusceptible (upper, green) and trypanotolerant (lower, blue) animals produce IFN- γ (green line) required to trigger the induction of classically activated macrophages (M1), which is followed by a moderate induction of IL-10 (blue line) to dampen the pathogenic effects of the M1. Only in the trypanotolerant model, there is a second progressive increase in IL-10 during the late/chronic phase of infection, which is required to induce alternatively activated macrophages (M2). **(D)** Occurrence of M1 and M2 during the course of aggressive *Trypanosoma brucei* or *T. brucei* attenuating strategies (GPI-based strategy or AAV-10/anti-CD28) or less virulent *T. brucei* PLC-/-/*Trypanosoma congolense* infection.

in the regulation of parasitemia in these animals [70]. There are variations in antibody response (complement and cytokine expression) between trypanotolerant and trypano-susceptible cattle (Figure 1). However, it is not clear whether these variations are the reason for resistance to trypanosomiasis or not [20]. In addition, some studies found a correlation between plasma lipid levels between trypanotolerance and trypano-susceptible cattle. This is also assumed to play role in *Trypanosoma* growth, differentiation and pathology of the disease. A genetic factor can also determine trypanotolerance [20]. The genetic ability of certain breeds to live normally and remain productive in tsetse-fly-challenged areas might be related to two different pools of genes [8].

Currently, consideration is given to the use of trypanotolerant breed of cattle as a sustainable approach to livestock development in tsetse-infested areas, because of a number of inherent limitations in other prevention and control methods [15]. Some cattle breeds have a capacity to survive and are productive in glossina troubled areas without any intervention. Trypanotolerance has usually been attributed to the taurine breeds of cattle N'Dama in the west and central African, Shorthorn in West African, and Sheko in Ethiopia [8, 24]. The significant difference in resistance to trypanosomiasis occurs among various breed of cattle in tsetse-infested areas that required regular treatment or are found solely on the fringes of the fly belt. Imported

breeds cannot be maintained even in areas of low tsetse risk without intensive drug therapy [20].

The geographical distribution of Sheko breed is mainly restrict to Bench-Sheko zone and partly in the adjoining parts of Keffa and Sheka zones of southwest Ethiopia. This breed local named as “*Godda*” (meaning hornless or polled) [72]. The Sheko breed is believed to have a different and longer evaluation history [73], perhaps associated with a different pattern of natural selection for adaptation under harsh environmental condition of warm and humid climate of southwest Ethiopia and continual exposure for trypanosomiasis (Figure 2).

Sheko breed is trypanotolerance cattle that have greater potential for survival in trypanosomiasis challenging areas [15]. This breed is the single well-known cattle of taurine group and classifies as a humpless Shorthorn breed in eastern Africa. It is believed that the taurine background of the Sheko is linked to its trypanotolerance characteristic [24]. This taurine admixture is likely a legacy of the first taurine occurrence of the African region [74]. Sheko breed is disease resistant and adaptation to extreme environments would possibly prove vital to food security for the current human generation [72]. Farmers breed these cattle because of their unique natural resistance to disease, notably to tsetse transmitted trypanosomiasis. Sheko cattle are better trypanotolerant than other local cattle breeds and the most important for sustainable cattle production in tsetse infested areas in Ethiopia [15].

Figure 2: Map showing location of Sheko cattle (Bench-Sheko, Keffa and Sheka zones), SNNPR: Southern Nations Nationalities and Peoples Region.

Sheko cattle had a low level of *Trypanosoma* infection, need the fewest number of trypanocidal treatment doses, and able to maintain a good PCV value compared to other breeds (Abigar, Horro, and Gurage). It found that the Sheko breed had the highest level of trypanotolerance than other breeds [27, 44]. Stein *et al.* [15] found that the average PCV value in Sheko cattle (25.1) was higher than in Abigar cattle (20.0), whereas Lemeche *et al.* [75] found that Abigar and Sheko had higher PCV value than other breeds. Sheko cattle also had a lower level of parasitaemia (6%) and needed fewer trypanocidal treatments (1%) compared to the other three breeds [15]. In addition, cattle keepers considered trypanosomiasis to be less of a problem in Sheko cattle than in the other breeds [76]. These cattle performed well with regard to survival rate, reproduction, and production in trypanosomiasis endemic areas. The Sheko cattle were also the most preferred cattle than local zebu or other breeds [77]. The Sheko cattle have favorable characteristics and the most trypanotolerant breed out of other breeds [15]. The genetic resource of this breed provides sustainable and environmentally friendly solutions for the management of trypanosomiasis. These natural innate resistances to the disease possessed by Sheko breed make them an important approach of trypanosomiasis control programs in tsetse-infected areas [15]. Trypanotolerance is also a breed characteristic of a heritable trait within this breed. Moreover, the genetic difference within trypanotolerance breed has opened opportunities for improved productivity through selection for the trypanotolerance [21].

There is evidence indicating that host genetic factor play a significant role in determining an individual's resistance status to *Trypanosoma* infection [78].

Trypanotolerance of Sheko cattle can be associated with genomic region known as trypanotolerance candidate regions. Recent study identified 15 candidate signature genes that are associated with trypanotolerant attributes in Sheko breed [24]. Specifically, polymorphisms in or nearby the MIGA1, CDAN1, HSPA9 and PCSK6 genes in the genome of Sheko cattle might be associated the evolutionary response against anemia. The MIGA1 gene is associated with iron deficiency anemia and immunity [80]. Another candidate signature gene are related with anemia is CDAN1. Polymorphisms in this gene are associated with congenital dyserythropoietic anemia type1 [80]. Moreover, hsp70 protein family and the heat shock 70KDa protein (HSPA9) gene play a role as a downstream mediator of erythropoietic signaling and contribute to normal erythropoiesis [81]. The mutation in this gene is associated with sideropoiesis anemia [82] while the PCSK6 gene is involved in iron homeostasis and hence related with iron deficiency anemia [83]. Mekonnen *et al.* [24] also identified the SPAG11B, RAET1G, PPP1R14C and TTC3 genes which are involved in immune tolerance in Sheko breed. Likewise, the candidate signature genes that associated with trypanotolerant attributes in Sheko cattle were described in Table 2.

Immunity-related genes within the candidate region (LTA4H, IL7, IL15, FCN, LTA4H and NFAM1) were identified by Bahbahani *et al.* [25] which are potential targets of natural selection. An immunity-related gene identified in Sheko Rsb candidate region on BTA5 is leukotriene A-4 hydrolase (LTA4H). This gene is associated with immune response regulation and inflammation response in mammals. Two interleukin genes (IL7 and IL15) were

Table 2: Candidate signature genes play a major role in the natural tolerance attributes of Sheko breed against trypanosomiasis. Modified from Mekonnen *et al.* [24].

Genes	Methods	CHR	Association	Position (UMD31) start-End (bp)
MIGA1	Rsb	3	Anemia, immune tolerance and neurological dysfunction	6706504-67137909
CDAN1	CLR	10	Anemia	38138863-38151656
HSPA9	Rsb	7	Anemia	51506219-51521515
PCSK6	iHS	21	Anemia	29553201-29673109
SPAG11B	iHS	27	Immune tolerance	4920083-4942958
RAET1G	Rsb	9	Immune tolerance	88232044-88408862
PPP1R14C	Rsb	9	Immune tolerance	88384683-88500749
TTC3	Rsb	1	Immune tolerance and Neurological dysfunction	151034217-151141015
ERN1	Rsb	19	Immune tolerance and Neurological dysfunction	48924511-48971838
CAPG	CLR	11	Immune tolerance and Neurological dysfunction	49423731-49438680
TTBK2	CRL	10	Neurological dysfunction	38159317-38248606
POLR3B	iHS	5	Neurological dysfunction	70062608-70178439
GNAS	iHS and CRL	13	Neurological dysfunction	58010287-58049012
CHAT	Rsb	28	Listlessness	44143145-44187239
AP1M1	iHS	7	Listlessness	7820650-7850254

identified in zebu-excess and zebu-deficient region on B- and T-cell. Whilst, Interleukin-15 mediates is the activation of natural killer cell [84, 85].

4 Conclusion

Since many control methods of trypanosomiasis are not successful, there is a requirement for different and sustainable solution. Using trypanotolerant cattle is a preferable and cost-effective control method of trypanosomiasis. Trypanotolerant cattle, like sheko breed, have been shown to effectively survive, reproduce, and produce in trypanosomiasis challenging areas without any intervention. Hence, it is important to introduce and use Sheko cattle or crossbreed between Sheko and Zebu breed, to other areas with high *Trypanosoma* challenge, as this might be an essential factor in the attempt to effectively manage the challenge of cattle trypanosomiasis in tsetse-infested areas. Moreover, detail study should be done to identify and characterize the genetic traits of trypanolerant Sheko cattle.

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