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Research Article

Valuing the investigation of Prion diseases in Ethiopia

Abstract

Cellular Prion proteins have a wide variety of function from the birth of a cell to its programmed death. Prion protein can be the cause for a number of lethal animal and human diseases when misfolded. Furthermore, prion infection is transmissible. Polymorphisms of prion gene at different loci are associated with prion diseases development, the onset of symptoms and incubation period. Indel polymorphism in the promoter region of PRNP gene is found to be accoaited to BSE in cattle while the haplotype ARR at positions 136,154 and 171 is resistant to scrapie in sheep. Taking into account the severity of prion disease and its potential entrance to the food chain, genetic and clinical studies continued to be conducted in a different course of time in many countries. Even though African countries in general and Ethiopia in particular, are highly dependent on animals and animal products as food and income source, there are neither epidemiologic nor genetic studies addressed prion diseases yet. Moreover, high animal product consumption and poor regular animal health inspection are among the many good reasons to study prion in Ethiopia. Prion disease survey and prion gene profiling boldly contribute to the provision of prion-free animals to the market for local consumption and for export. Thus, the main objective of this work is to uncover the extent of the importance of prion-related studies in Ethiopia considering livestock management, food quality safeguard and contribution of the work for further study.

Introduction

Prion protein which is expressed by *PRNP* gene is highly conserved in mammals [1]. However, the conservation is not as absolute as it is expected. There are variations in the biochemistry of prion across species not to mention its genetic makeup even in the same species. The variation comes from nucleotides change within and among species which in turn affects the number, type and sequence of amino acids [2]. By principle a change in amino acid has effect in protein higher order structures and further posttranslational modifications. In most cases a change in protein structure affects its biological function directly or by altering its basic structure so that it either become highly interactive with other proteins or unable to interact and has to be degraded without being functional if not already causing pathology [3]. A misfolded prion protein results in the most debilitating diseases, which is in most case, is transmissible [4]. The infectivity in most Prion pathologies is due to the protein either gain a new toxic function that brutally affects cellular functions, loses its protective function or its function become subverted by already dysfunctional Prion [5]. For the most part, formation of misfolded aggregate called amyloid plaque and associated inflammatory cytokines are the most noticeable pathomechanisms that kill neural cells and result neurodegeneration [6].

Though prion expressed in many tissues, brain cells are the major site where prion harbors [7]. Upon conversion to infective form, truncated prion mostly affects midbrain, thalamus, and cerebellum [8]. Apart from gliosis and amyloid formation, spongiform changes in this brain parts are hallmarks of prion diseases [9].

Decades have passed since the discovery of misfolded protein as the sole cause of prion diseases. Some of prion diseases are sporadic, some are acquired and some have genetic bases. The oldest of all is scrapie in sheep. Bovine Spongiform Encephalopathy (BSE) in cattle and Creutzfeldt-Jacob disease (CDJ) in human are also most studied prion disease. However, there are also others which are already archived as prion disease like familial Creutzfeldt-Jacob disease (fCJD), fatal familial insomnia (FFI) and Gerstmann–Sträussler–Scheinker syndrome (GSS) in human while chronic wasting disease (CWD) in deer and elk [10]. The most pronounced sign and symptoms of prion diseases are ataxia, tremor, behavioral changes (hyperesthesia, hyperexcitability, aggressiveness, depression, and restlessness), cannibalism and loss of wool & decreased product particularly in animal [8].

There are ample mount of information on genotypes of *PRNP* gene of multiple species [11]. Susceptibility and incubation period of prion infection varies from species to

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species. ARR genotype at 136,154 and 171 positions is resistant to scrapie in sheep [12,13]. Homozygosity to Methionin at position 129 predisposes individuals to sporadic CJD [14,15]. Similar studies were also documented for different prion caused neurodegenerative disease in wide variety of species [16,17]. An indel polymorphisms across the promoter region of *PRNP* gene is also associated to BSE in cattle [18-20].

The above-mentioned studies enriched our understanding on prion from different perspectives especially from public health and selective animal breeding strategy point of view. However, none of the previous prion related epidemiologic surveys and genetic characterization studies address Africa, which is the very important source of evolutionary lineages. The extent of scientific interest from evolution perspective towards east Africa could have been a good reason to include those regions in such important studies. Especially genetic variability which is best evidenced and deep rooted in Africa shall indeed be a more than enough reason to give a slight attention to genetic studies in the region [21]. The main objective of this work is to give sound reasons on the value of investigating prion in Ethiopia. Besides, this work uncovers the importance of *PRNP* gene characterization in native breeds of Ethiopia to increase quality and quantity of livestock resources.

What is known about prion across the globe?

Prion diseases once were burden in most developed countries especially in the UK (Belay and Schonberg 2004). According to a report by BBC, BSE was first identified in 1986 and in 1995 the first known victim of vCJD was diagnosed [22,23]. EuroCJD, CDC and other organizations extensively made surveillances across Europe and in their major economic allies in Asia and Both North and South America [24]. In countries where Prion diseases detected, mass killing and incineration of farm animals were performed [25], resulting especially in economic crises beside to public health inconveniences. In USA and most part of Canada, the ministry of health ordered animal health inspection in every farmer's farmyard and forced them to eliminate their animals if suspected for prion disease [26]. Since then, in most developed countries, there have been uninterrupted studies on prion. Molecular basis of prion-associated diseases and genetic studies that focuses on prion gene characterization, mutation, and polymorphisms for identifying resistant and risk alleles are being conducted particularly in developed countries. However, in the history of prion studies, neither a broad nationwide disease survey nor genetic characterizations were addressed developing countries [27], especialy African countries. However there was partial surveillance studies in North Africa limited to diagnosis of suspected Dromedary camels [28].

Genetic analysis studies

As per our knowledge, there are no nationwide prion-associated studies in Ethiopia. Many studies in prion are limited to a specific part of the world. In this mini review, we highlighted genetic studies focusing on susceptible and resistant alleles both in human and animals across the globe.

A study on the molecular genetics of prion in France revealed that their subjects were homologous to methionine at codon 129 [29]. In a study conducted on sCDJ patients in Italia majority were found to possess excess methionine at codon 129 [30]. In the same country, a second the study indicated some other alleles which are protective against scrapie in goat [31]. Major homozygosity at codon 129 for methionine was recorded in almost all patients of sCJD in the UK [32]. Polymorphism at codon 141 was showed in sheeps with Nor98 cases [33]. Homozygosity to valine at codon 136 was reported in a research conducted in Norwegian scrapie infected sheep [34]. Another study on native Spanish sheep's *PRNP* gene also showed diverse polymorphism of prion protein [35]. A study on selected German cattle identified more than 60 PrP polymorphism [20]. A triangulated data revealed polymorphism in both healthy and scrapie-affected Greek goats and sheep [36,37]. A study on native Turkish sheep breeds revealed that the most frequent PRNP haplotype was was ARQ [38]. A different study on native Turkish sheep breeds also indicated the existence of a highly variable PrP polymorphism [39]. An in23/in12 variant also discovered on promoter and intron 1 indel among Anatolian water buffalo by the same investigator [40]. Indel polymorphism on *PRNP* promoter was also found among native Turkish cattle indicating Turkish breed are resistant to BSE infection [39]. A study on Japanese cattle breed and Holstein cattle indicated the existence of a number of variants [41]. High allelic and polymorphic variants of *PRNP* were also detected in Chinese native cattle [42,43]. Among the many types of research in North America, a research on CWD showed the resistant variant to the disease in white-tailed deer at codon 96 [44].

The above sampled genetic studies were conducted for the sole purpose of identifying resistant/risk variant. Now that those countries have genetic profile on their native animal breeds, there is an increased chance of taking prion disease under control as quick as possible. Moreover there is a high possibility of safeguarding quality and quantity of livestock in case of prion diseases through selective breeding strategy.

The importance of prion studies in Ethiopia

Studies revealed that Prion could infect a wide variety of species horizontally and vertically [45]. Variant CJD is a glaring evidence for the possibility of even cross-species infectivity. Moreover, yet the absence of any kind of treatment makes prion critical research issue for many years. For the most part, the dependency of human on farm animals and their products makes it even more precautious. African countries, which are largely dependent on farm animals, need to consider prion from animal well-being and public health point of view.

Ethiopia has a long history of agriculture. According to WHO 85% of the country's economy is based on agriculture [46]. Livestock is always being the greatest source of in-country consumption and economy through product export. History is a witness that land is everything for any Ethiopian farmer. Together with land, farm animals are their source of daily food consumption, income, power and transportation. Animals are traditionally the standard of wealth and they are

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saving accumulations [47]. In the last few decades, the growth of cattle population increased from 38 million to 52 million, which might be true for small ruminants as well. That indicates Ethiopia is the leading livestock resources for Africa market [48,49]. Apart from the exports, domestic meat consumption keeps increasing. The long history of Ethiopian tradition of consuming raw and cooked meat from specific animal sources like cattle and small ruminants based on the recommendation by religious denominations. Religious festivals are accompanied by slaughtering of animals by municipal abattoir and by individuals. Often, slaughtering of the animal takes place in the backyards of individuals. And, the sources of those animals are the rural part of the country where in most cases animal health inspection is rarely performed [50].

Considering livestock's sociocultural and economic importance for farmers and the country at large, it is worth to increase the quality and quantity animal and animal products. Selective and crossbreeding though community based breeding programs to increasing the quality and quantity of livestock in different part of the country [51]. However, animal management is a notable weakness for the majority of the farmers [52]. Poor animal feeding, housing, regular health examination are major drawbacks [53]. Despite there are some improvements, most of the efforts are not indeed supported by current technologies [54]. Infectious diseases are the major cause of animal loss. Endo and Ectoparasites are frequently reported as a major challenge in livestock production. There are many unreported cases, which may be are infectious, lethal and need to be taken seriously [55].

Despite it is a major economic sector of the country, stakeholders and government agencies [53], has loose monitoring and controlling strategies over livestock. Beside to official export, animal and animal products have been in market crossing borders illegally [56]. The report by IGAD on their policy brief series stated that cross-border trade affects the economy of the country. Apart to that, there is a high tendency for acquisition of potential cross-border infectious diseases in to and out of the country.

Currently, there is no evidence for the absence of prion diseases in Ethiopia. At the same time, there is also no research conducted to investigate the presence or the absence of the case which is true for most developing countries. Considering high consumption of animal & animal products and the absence of prior epidemiologic studies, it is worth considering studying prion diseases and PRNP genotyping in Ethiopia. Taking in to account the lethality of prion diseases and its public health burden, for a country like Ethiopia which is highly populated prion studies are undeniably crucial [57]. Besides the wellbeing of animal and human, genotyping is indeed necessary to guarantee the quality of animal and animal products that are presented to the market.

Recommendation

As mentioned before, prion has been the area of research across the globe significantly. Thus, it is highly recommended giving an insight into prion and prion-like diseases in Ethiopia and Africa at large. The detection of prion disease in Algeria is an alerting signal for immediate need for prion disease surveillance across the continent. Epidemiologic survey shall be a starting point in order to confirm the absence of prion disease in the country both in animal and in human. Further genotyping native farm animals are worth important to identify breeds that are more resistant to disease there by the information will be a base line data for selective breeding programming.

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