# HISTORY OF PRION PROTEIN GENE (*PRNP*) POLYMORPHISM IN SHEEP AND SCIENTIFIC FINDINGS

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**Abstract.** Scrapie is basically a kind of disease that originally was specific to European countries, but from England it spread all over the world to Canada, South Africa, Australia, New Zealand and many other countries. Scrapie is a prion disease which is fatal and results in or can be characterized by the degeneration of the nervous system. It belongs to transmissible spongiform encephalopathies (TSEs) infecting small ruminants including sheep and goat. Sheep susceptibility or resistance to classical scrapie is highly supervised by the polymorphisms at codons 136, 154 and 171 of the *PRNP*. In this review, we found that countries like Romania, Finland, Italy, Slovakia, Germany, Greece, Spain, Poland, Turkey, Iran, Brazil, England, Portugal, Hungary, Austria, and Czech Republic, are susceptible to scrapie, while in Pakistan, China, Algeria, West Africa, America, Burkina Faso, and Niger are those countries where sheep are not susceptible to this disease. From these studies, we can clearly conclude that China and Pakistan are the countries where sheep show more resistance to scrapie. We focused to summarize the *PRNP* polymorphism at 136, 154, and 171 in sheep and some important findings in major parts of the world.
**Keywords:** *scrapie, transmissible spongiform encephalopathies (TSEs), European countries, history, prion*

## Introduction

Approximately, 70.7% of the total sheep population is present in Asia and 35.89% of the total population of sheep is present in China which has become the leading country for sheep products. But in China, no case of scrapie in sheep has been found so far, whereas in the countries like England, Greece, Turkey and other small European countries scrapie is on red alert. Where sheep (*Ovis aries*) and goat (*Capra aegagrus hircus)* have many resemblances, their scientific taxonomy eventually split, have distinct species and genus, whereas sheep and goat have 54 and 60 chromosomes simultaneously. The polymorphism of the *PRNP* gene plays a fundamental role in prion disease. Scrapie is resulting in or characterized by the degeneration of the nervous system affecting sheep and belongs to a group of a prion disease that naturally occurs in sheep. *PRNP* is responsible for negative influence on the financial loss, such as the cashmere yield, wool thickness (Lan et al., 2012) and milk yield (Vitezica et al., 2013) as well as the waistline, body length (Yang et al., 2016), rump length (Yang et al., 2018), and weight. Almost the same mutation of *PRNP* present in sheep, has also been determined in goat (White et al., 2008; Zhou et al., 2013). The only responsible factor for scrapie that has been determined until now is a prion. Scrapie is not like a viral or bacterial disease which have causal agent, rather it is a genetical disease making it difficult to cure. The possibility for the elimination of this disease is wholly associated with polymorphisms of the *PRNP*. Sheep and goat are not the only victims of prion disease as it has been reported in almost all vital living species of animals with different


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names (*Table 1*). The first human victimization to scrapie were the farmers or the sheep owners who were directly affected by the disease. During the 20th century, many ideas on the nature of the causative agent of TSEs were published (*Table 2*) while with the passage of time, the majority of these revealed to be unwarranted. Prion disease affects both animals and humans (Yaman and Ün, 2017) but until 1990s scientists failed to provide any evidence of transmission of disease to humans (Van Duijn et al., 1998).

***Table 1.*** *Affected species with prion diseases (Mabbott, 2017)*

| Disease | Species |
|---|---|
| **Scrapie** | Sheep, goats, mouflon |
| **Iatrogenic Creutzfeldt-Jakob disease (CJD)** | Human |
| **Sporadic Creutzfeldt-Jakob disease** | Human |
| **Variant Creutzfeldt-Jakob disease** | Human |
| **Familial Creutzfeldt-Jakob disease** | Human |
| **Gerstmann-Straussler-Scheinker syndrome** | Human |
| **Kuru** | Human |
| **Fatal familial insomnia** | Human |
| **Bovine spongiform encephalopathy** | Cattle |
| **Chronic wasting disease** | Elk, deer, moose |
| **Transmissible mink encephalopathy** | Mink |
| **Feline spongiform encephalopathy** | Domestic and zoological cats |
| **Exotic ungulate encephalopathy** | Nyala, kudu |

***Table 2.*** *Names of causative agents given by different scientists from 1912 to 1991*

| Year | TSE agents | Reference |
|---|---|---|
| **1914** | Sarcosporidia | M'Gowan (1914) |
| **1938** | A filterable virus | Cuillé and Chelle (1938) |
| **1954** | A slow virus | Sigurdsson (1954) |
| **1966** | A replicating polysaccharide | Alper et al. (1967) |
| **1967** | A protein | Pattison and Jones (1967) |
| **1967** | A replicating membrane | Gibbons and Hunter (1967) |
| **1968** | A DNA-polysaccharide complex | Adams and Caspary (1968) |
| **1972** | A viroid | Diener (1972) |
| **1978** | A lipid | Alper et al. (1978) |
| **1979** | A Spiroplasma sp. | Bastian (1979) |
| **1979** | A virino | Dickinson (1979) |
| **1982** | A prion | Prusiner (1982) |
| **1984** | A virus | Manuelidis (1996) |
| **1989** | Mitochondria (l nucleic acid(s)) | Aiken et al. (1990) |
| **1991** | A holoprion, consisting of abnormal prp (PrP in the scrapie specific conformation, the apoprion) and a (dispensible) nucleic acid (the coprion) | Weissmann (1991) |


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Scrapie is the disease with the maximum and oldest publications as explicit journals allude to a paper going back to the year 1732 as the initial report of scrapie (Detwiler and Baylis, 2003). In 1772 scrapie was accounted for to be known for around 40 years, a point in time going back to the year 1732. This distemper disease is normally said to be remains of almost forty years in England (Comber, 1772). All scholars were devoted to the quest for the origin of the disease. A large number of proposed causes were diagnosed by all methods like the number of prescribed pathogens set forward all through the twentieth century. Since the 1930s, scrapie examination was reinforced when impressive money related misfortunes to the sheep business were brought about by expanding measurements of cases. These harms likewise advance studies on the precise idea of the infective reason, besides parasites (M'Gowan, 1914) and bacteria (Bastian, 1979) as causative agents, virus infection was the most frequently proposed principle, already formulated in 1938 (Cuillé and Chelle, 1938). In 1954, the word of a "slow virus infection" was presented the first time (Sigurdsson, 1954). Though, in 1966, a substitute to the viral origin was hypothesized as the cause, i.e., polysaccharides (Alper et al., 1966; Alper et al., 1967) or lipids (Alper et al., 1978). In 1967, for the first time, a protein was predictable as an infective cause (Pattison and Jones, 1967), and the first "protein-only- hypothesis" was articulated (Griffith, 1967), which was followed in the 1970s by the "virino" theory (Dickinson, 1979). At long last, in light of the opposition of the pathogen, in 1982, "proteinaceous irresistible molecule" (abbreviation: prion) was presented (Prusiner, 1982) and the transformation of a healthy cellular protein (PRPC) into a pathological isoform (PRPSc) as a critical event of TSE pathogenesis was proposed not long after (Oesch et al., 1985).

The investigation of scrapie was complex by the circumstance that in previous times, many new diseases like Drehkrankheit, Kreuzdrehe, and Gnubberkrankheit were confused with scrapie. Numerous scholars believed at least one of them to be indistinct with or separate from scrapie. Some particular authors attempted to recognize "Drehkrankheit," "Gnubberkrankheit," "Kreuzdrehe," and "Traberkrankheit." Whereas a lot of them segregate among "Drehkrankheit" and "Kreuzdrehe" from one viewpoint and "Traberkrankheit" on the other (Frank, 1820; Ribbe, 1821; Hering, 1849; Erdt, 1861; May, 1868), there were other writers who considered "Kreuzdrehe" and "Traberkrankheit" to be the identical but to be dissimilar from "Gnubberkrankheit" (Wagenfeld, 1829). This mistake of terms, just as the indistinct and confounding portrayal of the indications of scrapie and of different diseases, indicating scrapie recognized in the year 1750. Different terms that were utilized to make reference to scrapie are mentioned (*Table 3*).

***Table 3.*** *Historical names of scrapie given by locals in different regions of the world*

| | Name of scrapie | Country | Reference |
|---|---|---|---|
| **1** | Basqvilla Disease | Spain | von Richthofen (1828) |
| **2** | Cuddie Trot | Scotland | Healy et al. (2003) |
| **3** | Drab(en) | Germany | von Richthofen (1827) |
| **4** | Dreb/Deeb | Germany | Frank (1820) |
| **5** | Drehkrankheit | Germany | Schneider et al. (2008) |
| **6** | Gaubber/G(n)aup(p)er | Germany | Schneider et al. (2008) |
| **7** | Gnubberkrankheit | Germany | Cassirer (1898) |
| **8** | Knopper | Germany | Frank (1820) |


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| | | | |
|---|---|---|---|
| **9** | Khujali | India | Katiyar (1962) |
| **10** | Kreu(t)zdrehe(n) | Germany | von Richthofen (1827) |
| **11** | Kreutzschlagen | Germany | Albert and Brunn (1818) |
| **12** | La maladie convulsive | France | Liberski and Jaskólski (2002) |
| **13** | La maladie foll(i)e | France | Beck et al. (1964) |
| **14** | La maladie trotteurs | France | Besnoit (1899) |
| **15** | La prurigo lombaire | France | Liberski and Jaskólski (2002) |
| **16** | La Tremblante | France | Beck et al. (1964) |
| **17** | Mukoo | India | Katiyar (1962) |
| **18** | Petermännchen | Germany | Erdt (1861) |
| **19** | Prurigo lombaire | France | Besnoit (1899) |
| **20** | Prurigo lumbar | Spain | Yam (2003) |
| **21** | Reiberkrankheit | Germany | Beck et al. (1964) |
| **22** | Reiber-Uebel | Germany | von Richthofen (1827) |
| **23** | Rickets | England | Beck et al. (1964) |
| **24** | Rida | Iceland | Palsson (1979) |
| **25** | Rub/Rubbers | England | Beck et al. (1964) |
| **26** | Rubbing disease | England | Parry (1983) |
| **27** | Ruppe | Germany | Frank (1820) |
| **28** | Scabies dorsalis | Germany | Hörnlimann et al. (2001) |
| **29** | Schrucken/Schru(c)kigsein | Germany | Frank (1820) |
| **30** | Scratchie | Scotland | Liberski and Jaskólski (2002) |
| **31** | Shakings | England | Beck et al. (1964) |
| **32** | Shrewcroft | England | Liberski and Jaskólski (2002) |
| **33** | Shrugginess | England | Parry (1983) |
| **34** | Spruckigkeit | Germany | Schneider et al. (2008) |
| **35** | Tempermänner | Germany | Erdt (1861) |
| **36** | Trab(en)/Traberkrankheit | Germany | Beck et al. (1964) |
| **37** | Trotting disease | England | Schneider et al. (2008) |
| **38** | Trzęsawka | Poland | Liberski and Jaskólski (2002) |
| **39** | Wetzkrankheit | Germany | May (1868) |
| **40** | Yeukie pine | Scotland | Healy et al. (2003) |
| **41** | Zitterkrankheit | Germany | May (1868) |

The description of literature is that scrapie was firstly born in Europe in the 18th century but until now the presence of scrapie in Europe is a dangerous sign for all over the world due to the threat of its spreading (*Fig. 1*) from England to all over the world (Detwiler and Baylis, 2003). The evidence of the scrapie in the European Union and the nearby regions from the day first till 2016 (EFSA, 2017) were as follows.

In 1987, 442 animals infected with scrapie were reported in England. In 1992, the number of animals infected with scrapie were reported as 37301. This number was reported as 1123 in 2002 and 610 animals in 2013, after that there were no reports of animals infected with scrapie. In Ireland, 15 animals were reported in 1990, in 2002, a total of 334 animals were reported, and in 2017, the disease showed peak time. Scrapie disease in France was first published in 1993, in 2002, 240 patients were reported. The first case was reported in Germany in 1991, the number of animals


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reported in 2002 were 7, while in 2001, 125 animals were published (EFSA, 2017). The first case of scrapie in Spain was reported in 1987, and in 2001, it was observed that the number of infected animals had been increased (Acín et al., 2004). Spain has started to work on the genotypic characterization of various races in this sense, to develop different strategies for each race and to prepare the laws governing these programs (Ugarte and Gabina, 2004). The first case of scrapie in Greece was settled in the north of the country in 1986, and the second case was diagnosed in 1997, the latter case was diagnosed after 11 years. The second case was seen near the region where the first case was observed, which was the evidence that the implemented eradication program is inadequate (Leontides et al., 2000). In 2001, there were 18 cases reported in Greece. According to the eradication program in Greece, the herds with the disease were massacred (Billinis et al., 2004). As a result of the breeding policies observed in Europe, the number of scrapie cases has decreased since 2009 (EFSA, 2014). In sheep, 933 scrapie cases were reported in the EU in 2017, which is an increase of 36.2% compared with 2016 (EFSA, 2018). In *Figure 2*, Cosseddu showed us the presence of scrapie in all over the world in 2007.

## Resistance and susceptibility

Sheep can be resistant and susceptible to the disease and the majority of susceptible sheep are in European countries. Every one of these discernments lead to the European Union (EU) keeping on developing breeding projects focused at developing the frequency of safe alleles in breeds from all member-states. These European programs are established on five groups of genotypes, from extremely resistant to extremely sensitive, whose alleles ARR and VRQ are considered highly resistant and susceptible to scrapie, respectively (Hunter, 1997).

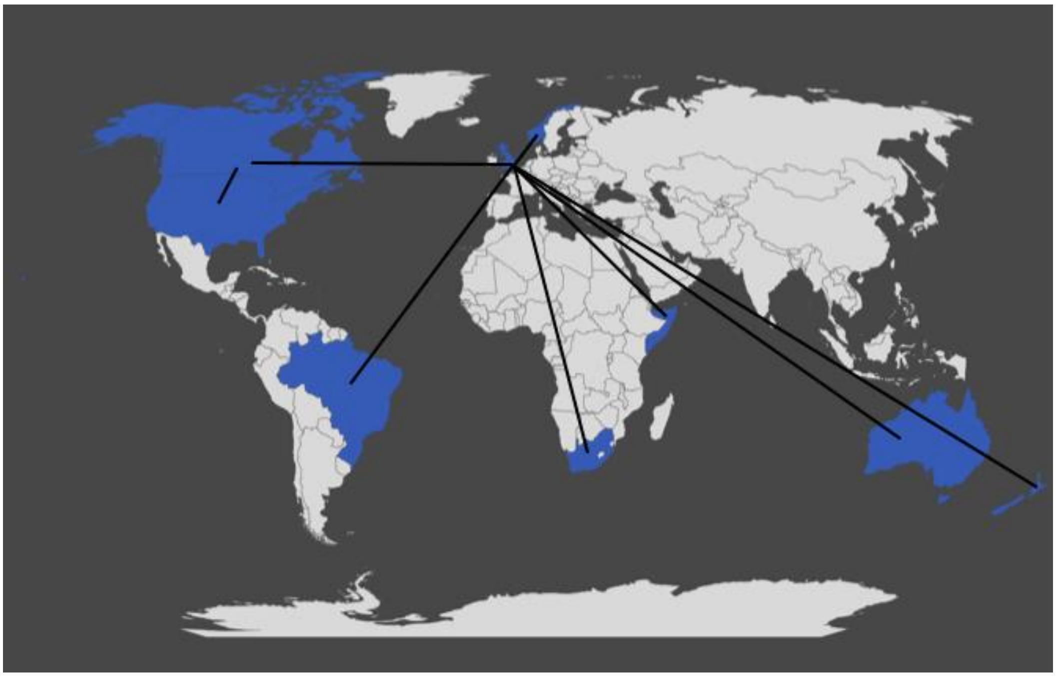

***Figure 1.*** *Spread of scrapie from England to the major parts of the world in 2003 (Detwiler and Baylis, 2003)*


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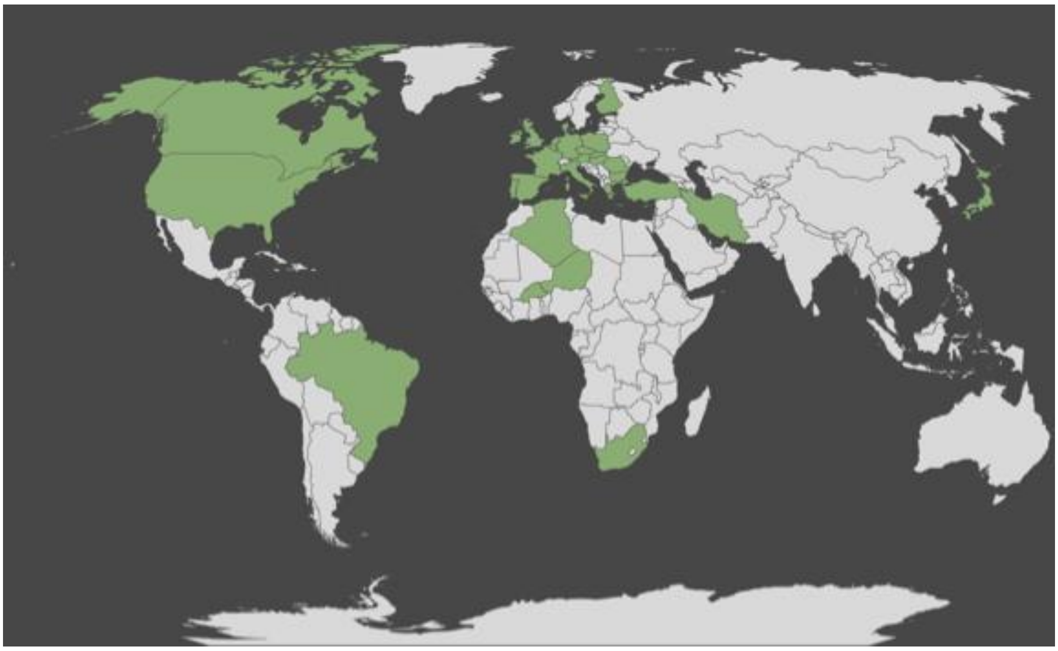

***Figure 2.*** *Scrapie distribution in all over the world in 2007 (Cosseddu et al., 2007)*

As it is clear that polymorphisms at residues 136, 154, and 171 are associated with susceptibility to both, experimental and natural scrapie (Hunter, 1997). In sheep, breeding projects have been set up in a few European nations to expand the ARR allele as much as possible. To evade the negative outcomes of scrapie-safe alleles, it is indispensable to know their populace recurrence. Some programs are still working on the frequencies to get rid of the susceptible alleles. In *Table 4* we can see the genotype groups and the intensity of risk.

## Prions and scrapie

Scrapie is a protein misfolding where the normal prp misfolds into abnormal prp that is extremely resistant to enzymatic breakdown within the cell and accumulates, ultimately leading to neurodegeneration. The disease is experimentally transmissible to cattle, goats, and laboratory animals *via* oral, parenteral, and intracerebral routes using homogenates of a brain or lymphoid tissues from infected animals (Pattison et al., 1961). Squirrel monkey was infected by feeding infected tissues and many other species like rats, mice, chimpanzees and many others were infected as well (de Mouton, 2007). The mode of transmission from ewe to lamb or between adults in field environments is not clear. However, oral exposure to fetal membranes or to pastures grazed by infected animals has been implicated as a possible route of vertical and horizontal transmission (Brotherston et al., 1968). Susceptibility to ovine scrapie is controlled by a combination of host genetics. During the course of a prion disease, a largely protease-resistant aggregated form of prp designated abnormal prp, accumulates mainly in the brain, and maybe the main or only constituent of the prion but in some species little or no signs of accumulation other than brain were found (de Mouton, 2007). The alteration of the normal prp into the abnormal prp is the vital route of transmission and pathogenesis of the prion disease in sheep. Transgenic studies say that abnormal prp acts as a template


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on which normal prp is refolded into a nascent abnormal prp molecule through a process facilitated by another protein. Because no differences in the primary sequence were found between normal prp and abnormal prp, the two species are believed to differ only in their conformation. After normal prp is synthesized in the endoplasmic reticulum, it transits through the Golgi to the cell surface where it is bound by a glycophosphatidyl inositol (GPI)-anchor. At or near the cell surface, normal prp is either metabolized or converted into abnormal prp (Benke et al., 2007). Normal prp seems to re-enter cells through caveolae-like domains (CLDs), a subcellular compartment defined biochemically by membranes rich in cholesterol and glycosphingolipids; this compartment also contains many GPI-anchored proteins. Polymorphisms in the prion protein gene (*PRNP*) determine the amino acid sequence of the host's prion protein and play a major role in relative susceptibility or resistance to classical scrapie. Prion protein (*PRNP*) gene is well known for affecting mammal transmissible spongiform encephalopathies (TSE) and is also reported to regulate phenotypic traits (e.g., growth traits) in healthy ruminants. As the vital control gene of fatal prion diseases or transmissible spongiform encephalopathies (TSE), the prion protein (*PRNP*) gene will always be a focus of ovine research (Houston et al., 2015; Stepanek and Horin, 2017). The *PRNP* gene encodes the prion protein (PrP), which plays a major role in the disease process (Goldmann, 2008; Houston et al., 2015). In sheep, amino acid polymorphisms at many positions (89, 94, 101, 112, 127, 128, 132, 134, 135, 136, 137, 138, 141, 143, 145, 146, 149, 151, 152, 154, 157, 159, 160, 163, 164, 167, 168, 169, 171, 172, 174, 175, 176, 180, 183, 184, 185, 189, 193, 195, 196, 199, 211, 213, 220, 224, 241) have been described (Oner et al., 2011), but the polymorphisms at codons 136, 154 and 171 have been demonstrated to be of major importance, as they modulate the susceptibility/resistance of sheep for scrapie (Clouscard et al., 1995; Hunter et al., 1996).

These polymorphisms are Alanine (A), Valine (V) or Threonine (T) at codon 136, Arginine (R) or Histidine (H) at codon 154 and Glutamine (Q), R, H or Lysine (K) at codon 171. The five most common haplotypes are ARR, ARQ, AHQ, ARH, and VRQ. New haplotypes (TRQ, ARK, VRR, AHR, VHQ, and TRR) have been reported so far. Haplotype alleles encoding three other forms of PrP (ARQ, AHQ, and ARH, where H is histidine) have intermediate associations with classical scrapie disease progression following exposure to the transmissible agent (Goldmann, 2008). Over 30 SNPs already showed that the ovine prion gene (PrP) shows an unusually high level of genetic variation (Goldmann et al., 2005). The ovine *PRNP*, mapped to chromosome 13, is a highly polymorphic gene consisting of three exons, among which only the third is translated (Lee et al., 1998). Single nucleotide polymorphisms (SNPs) leading to amino acid change in PrP were observed in over 20 codons, but most of them are rare and unrelated to disease development (Goldmann et al., 2005). It was established that polymorphisms A136V (Alanine, GCC → GTC, Valine), R154H (arginine, CGT → CAT, histidine) and Q171R (glutamine, CAG → CGG, arginine) are associated with susceptibility or resistance to scrapie (Baylis et al., 2004). Additionally, some studies reported another polymorphic variant coding for histidine at codon 171, but it is very rare (Acín et al., 2004). The combination of these polymorphisms results in the creation of 3-locus haplotypes and diploid genotypes, among which A136R154Q171 (hereafter ARQ) haplotype and AA136RR154QQ171 (hereafter ARQ/ARQ) genotype are thought to be wild-type variants. With the help of *Table 4,* we can see the severity or intensity of genotypes.


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***Table 4.*** *According to the intensity of risk, scientists has classified the risk groups (Cosseddu et al., 2007)*

| Risk class | Genotype | Risk intensity |
|---|---|---|
| **1** | ARR/ARR | Sheep are highly resistant to scrapie |
| **2** | ARR/AHQ<br>ARR/ARH<br>ARR/ARQ | Sheep are resistant to scrapie, thus require particular attention in breeding programs |
| **3** | ARQ/ARH<br>ARQ/AHQ<br>AHQ/AHQ<br>ARH/ARH<br>AHQ/ARH<br>ARQ/ARQ | Sheep with low genetic resistance to scrapie. Their use in breeding programs must be avoided |
| **4** | AHQ/ARH | Sheep are sensitive to scrapie |
| **5** | AHQ/VRQ<br>ARH/VRQ<br>ARQ/VRQ<br>VRQ/VRQ | Sheep are highly sensitive to scrapie, thus must be castrated or culled |

The rapid dissemination of scrapie over the previous limited years led to the development of a specific eradication program, based on the polymorphisms within the prion protein gene (*PRNP*). The current approach encourages the selection of animals carrying the resistant ARR/ARR genotype, while other genotypes are considered not preferable. Although the strategy seems to be working quite well, farmers are concerned whether this will affect sheep productivity and subsequently decrease net profits. Current scrapie eradication program includes genotyping and subsequent selection of animals on the ARR/ARR genotype.

## Genotype and haplotype

Observing the development of *PRNP* genotype and haplotype is a powerful pointer of choice weight, which is evaluated in reference class creatures alongside ages so as to dodge predisposition, while the advancement in the common populace is assessed depending on scientific models. In countries where the scrapie incidence was statistically significant (see *Tables 5* and *6*), such as from Romania (Lacaune) the genotype frequencies are (ARR/ARR: 15.1) and (ARQ/VRQ: 12.6) (Otelea et al., 2011); from Romania (Turcana) (ARR/ARR: 14.64) and (ARQ/VRQ: 12.2) (Coşier et al., 2011); from Finland (Finnish Landrace) (ARR/ARR: 1.3) and (ARQ/VRQ: 10.3) (Hautaniemi et al., 2012); from Italy (Biellese rams) (ARQ/VRQ: 1.4) and (ARQ/VRQ: 9.9) (Acutis et al., 2004); from Slovakia (Orava) (ARR/ARR; 10.9) and (ARQ/VRQ: 9.0) (Tkáčiková et al., 2003); from Slovakia (Valachian) (ARR/ARR; 10.9) and (ARQ/VRQ: 9.0) (Tkáčiková et al., 2003); rom Slovakia (Spiš) (ARR/ARR; 10.8) and (ARQ/VRQ; 8.9) (Tkáčiková et al.,


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2003); from Germany (Texel) (ARR/ARR; 11.7) and (ARQ/VRQ; 7.8) (Kutzer et al., 2002); from Greece (Greek Dairy Breed) (ARR/ARR; 2.2) and (ARQ/VRQ; 5.4) (Boukouvala et al., 2018a); from Spain (Rasa Aragonesa) (ARR/ARR; 2.0) and (ARQ/VRQ; 5.0) (Acín et al., 2004); from Poland (Pomorska) (ARR/ARR; 13.3) and (ARQ/VRQ; 3.3) (Lühken et al., 2008); from Poland (Pomorska) (ARR/ARR; 13.3) and (ARQ/VRQ; 3.3) (Acín et al., 2004); from Spain (Roya Bilbilitana) (ARR/ARR; 2.0) and (ARQ/VRQ; 3.0) (Acín et al., 2004); from Poland (Kaminieniecka) (ARR/ARR; 35.3) and (ARQ/VRQ; 2.9) (Szkudlarek-Kowalczyk et al., 2010); from Germany (Nolana) (ARR/ARR; 32.4) and (ARQ/VRQ; 2.8) (Kutzer et al., 2002); from Turkey (Imroz) (ARR/ARR; 29.9) and (ARQ/VRQ; 2.7) (Oner et al., 2011); from Brazil (Santa Ines sheep) (ARR/ARR; 7.4) and (ARQ/VRQ; 2.2) (Andrade et al., 2018); from Greece (Crossbred) (ARR/ARR; 7.3) and (ARQ/VRQ; 1.9) (Kioutsioukis et al., 2018); from Greece (Chios crossbred) (ARR/ARR; 2.7) and (ARQ/VRQ; 1.6) (Kioutsioukis et al., 2018); from Brazil (Dorset sheep) (ARR/ARR; 11.6) and (ARQ/VRQ; 1.5) (Andrade et al., 2018); from Iran (local sheep) (ARR/ARR; 38) and (ARQ/VRQ; 1.2) (Karami et al., 2011); from Greece (chios) (ARR/ARR; 1.2) and (ARQ/VRQ; 1.2) (Kioutsioukis et al., 2018); from Poland (Ile de France) (ARR/ARR; 72.0) and (ARQ/VRQ; 1.1) (Wisniewska and Mroczkowski, 2009); from Poland (Polish Merino) (ARR/ARR; 7.1) and (ARQ/VRQ; 1.0) (Wiśniewska et al., 2006); from Turkey (Kivircik) (ARR/ARR; 1.41) and (ARQ/VRQ; 0.7) (Oner et al., 2011); from Greece (Chios) (ARR/ARR; 0.4) and (ARQ/VRQ; 0.5) (Psifidi et al., 2011); from England (15 scrapie affected flocks) (ARR/ARR; 14.8) and (ARQ/VRQ; 0.2) (Tongue et al., 2004); from Pakistan (Kajli) (ARR/ARR; 1.9) (Babar et al., 2009); from China (Gansu Alpine Merino sheep) (ARR/ARR; 20.7) (Liu et al., 2017); from the Czech Republic (Charollais) (ARR/ARR; 61.5) (Stepanek and Horin, 2017). Breeding programs planned to increase the RR171 genotype in sheep populations and eliminate affected animals, to considerably decrease the number of classical scrapie cases in America and in the European Union (Greenlee, 2019). This is cleared that these genotypes and haplotypes are the backbone in the resistance and susceptibility of scrapie, which can be low or high. From *Table 5* we can clearly say that, in Romania, Finland, Italy, Slovakia, Germany, Greece, Spain, Germany, Brazil, Iran, Poland, Turkey, Greece, England, Portugal and Hungary sheep are highly sensitive to scrapie, therefore must be eliminated or separated and in countries like Pakistan and China resistance to scrapie was observed.

The writers propose that arginine/glutamine replacement in the 171st position of the sheep *PRNP* might have affected the scrapie incubation period. In some countries the haplotype is very significant, that can be seen in *Table 6*, like the ARR in German Blackheaded Mutton; 87.0 which is the highest ARR frequency recorded and the highest VRQ frequency is recorded in Lacunae from Romania 18.9. The countries where the VRQ frequencies are found are Romania, Poland, Greece, Germany, Italy, Slovakia, Czech Republic, Finland, Germany, Austria, Spain, Turkey, Finland, Iran, Hungary; these are highly sensitive to scrapie, thus sheep must be eliminated and breeding programs must be introduced.

From these two tables and from the graphical presentation in *Figures 3* and *4*, we can see the clear difference between the countries where the scrapie is present, or the chance of scrapie is severe. The countries like China and Pakistan must take some important steps like proper breeding programs, before doing meat or any kind of trade associated with sheep with countries like Romania, Greece and the other countries found susceptible to scrapie.


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***Table 5.*** *Genotypic frequencies of PRNP gene at codon 131, 154 and 171 in various breeds of sheep in major parts of the world*

| # | Country | Breed | N | ARR/ ARR | ARR/ ARQ | ARQ/ ARQ | ARR/ AHQ | ARQ/ AHQ | AHQ/ AHQ | ARR/ VRQ | VRQ/ VRQ | ARQ/ VRQ | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Romania | Lacaune | 159 | 15.1 | 33.3 | 20.1 | 5.0 | 5.7 | | 6.3 | | 12.6 | Otelea et al. (2011) |
| **2** | Romania | Turcana | 123 | 14.64 | 32.52 | 28.46 | 0.81 | 1.63 | | 5.69 | | 12.2 | Coşier et al. (2011) |
| **3** | Finland | Finnish Landrace | 232 | 1.3 | 15.9 | 68.8 | | 0.4 | | | 0.4 | 10.3 | Hautaniemi et al. (2012) |
| **4** | Italy | Biellese rams | 1207 | 1.4 | 11.4 | 56.3 | 0.7 | 5.5 | 0.2 | 1.2 | 0.7 | 9.9 | Acutis et al. (2004) |
| **5** | Slovakia | Orava | 366 | 10.9 | 45.4 | 19.4 | 5.7 | 4.9 | 0.8 | 3.6 | 0.3 | 9.0 | Tkáčiková et al. (2003) |
| **6** | Slovakia | Valachian | 735 | 10.9 | 45.2 | 19.3 | 5.7 | 4.9 | 0.7 | 3.5 | 0.3 | 9.0 | Tkáčiková et al. (2003) |
| **7** | Slovakia | Spiš | 369 | 10.8 | 54.0 | 19.2 | 0.5 | 4.9 | 0.5 | 3.5 | 0.3 | 8.9 | Tkáčiková et al. (2003) |
| **8** | Germany | Texel | 231 | 11.7 | 19.5 | 25.1 | 0.4 | 2.2 | | 6.5 | 0.4 | 7.8 | Kutzer et al. (2002) |
| **9** | Greece | Greek Dairy Breed | 4382 | 2.2 | 24.2 | 32.4 | | 12.5 | 2.0 | 1.23 | 0.3 | 5.4 | Boukouvala et al. (2018b) |
| **10** | Spain | Rasa Aragonesa | 296 | 2.0 | 21.0 | 51.0 | 2.0 | 6.0 | 0.0 | 0.0 | | 5.0 | Acín et al. (2004) |
| **11** | Poland | Pomorska | 30 | 13.3 | 36.7 | 16.7 | 6.7 | 6.7 | | 3.3 | 3.3 | 3.3 | Lühken et al. (2008) |
| **12** | Spain | Ojinegra | 182 | 2.0 | 21 | 56 | 0.0 | 1 | 0.0 | 1.0 | | 3.0 | Acín et al. (2004) |
| **13** | Spain | Roya Bilbilitana | 96 | 2.0 | 34 | 53 | 1.0 | 0 | 0.0 | 1.0 | | 3.0 | Acín et al. (2004) |
| **14** | Poland | Kaminieniecka | 102 | 35.3 | 33.3 | 2.9 | | | | 6.9 | | 2.9 | Szkudlarek-Kowalczyk et al. (2010) |
| **15** | Germany | Nolana | 71 | 32.4 | 33.8 | 18.3 | | | | 4.2 | | 2.8 | Kutzer et al. (2002) |
| **16** | Turkey | Imroz | 147 | 29.9 | 33.3 | 19.0 | 6.1 | 5.4 | | | 0.7 | 2.7 | Oner et al. (2011) |
| **17** | Brazil | Santa Ines sheep | 94 | 7.4 | 21.3 | 47.8 | | 17 | | 1.1 | | 2.2 | Andrade et al. (2018) |


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| # | Country | Breed | N | ARR/ ARR | ARR/ ARQ | ARQ/ ARQ | ARR/ AHQ | ARQ/ AHQ | AHQ/ AHQ | ARR/ VRQ | VRQ/ VRQ | ARQ/ VRQ | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **18** | Greece | Crossbred | 483 | 7.3 | 28.2 | 31.5 | 5.6 | 12.7 | 1.0 | 0.4 | 0.00 | 1.9 | Kioutsioukis al. (2018) |
| **19** | Greece | Chios crossbred | 633 | 2.7 | 18.9 | 40.8 | 2.0 | 9.9 | 0.8 | 0.6 | 0.3 | 1.6 | Kioutsioukis et al. (2018) |
| **20** | Brazil | Dorset sheep | 69 | 11.6 | 43.5 | 39.1 | | | | 4.3 | | 1.5 | Andrade et al. (2018) |
| **21** | Iran | Local sheeps | 250 | | 38 | 43.2 | | | | | | 1.2 | Karami et al. (2011) |
| **22** | Greece | chios | 340 | 1.2 | 13.2 | 52.9 | 2.1 | 7.1 | 0.6 | 0.3 | 0.00 | 1.2 | Kioutsioukis et al. (2018) |
| **23** | Poland | Ile de France | 93 | 72.0 | 6.5 | | | | | 17.2 | 3.2 | 1.1 | Wisniewska and Mroczkowski (2009) |
| **24** | Poland | Polish Merino | 98 | 7.1 | 54.1 | 35.7 | | | | 2.0 | | 1.0 | Wiśniewska et al. (2006) |
| **25** | Turkey | Kivircik | 142 | 1.41 | 24.65 | 30.28 | 1.41 | 7.75 | | | | 0.7 | One et al. (2011) |
| **26** | Greece | Chios | 1013 | 0.4 | 11.4 | 56.0 | 0.5 | 15.0 | 0.1 | | | 0.5 | Psifidi et al. (2011) |
| **27** | England | 15 scrapie affected flocks | 3732 | 14.8 | 30.7 | 15.7 | 7.8 | 8.2 | 1.5 | 7.6 | 0.8 | 0.2 | Tongue et al. (2004) |
| **28** | Portugal | Merino Branco | 62 | 0.194 | 0.387 | 0.306 | 0.065 | 0.016 | 0.00 | 0.016 | | 0.00 | Mesquita et al. (2010) |
| **29** | Portugal | Saloia | 52 | 0.096 | 0.231 | 0.442 | 0.038 | 0.135 | 0.00 | 0.019 | | 0.019 | Mesquita et al. (2010) |
| **30** | Portugal | Serra da Estrela | 69 | 0.174 | 0.420 | 0.304 | 0.014 | 0.014 | 0.00 | 0.014 | | 0.029 | Mesquita et al. (2010) |
| **31** | Portugal | Bordaleira entre Douro e Minho | 64 | 0.078 | 0.250 | 0.469 | 0.047 | 0.047 | 0.0 | 0.016 | | 0.047 | Mesquita et al. (2010) |
| **32** | Portugal | Churra Badana | 58 | 0.052 | 0.345 | 0.517 | 0.017 | 0.052 | 0.0 | 0.00 | | 0.00 | Mesquita et al. (2010) |
| **33** | Portugal | Churra Galega Mirandesa | 71 | 0.014 | 0.253 | 0.549 | 0.0 | 0.099 | 0.014 | 0.00 | | 0.056 | Mesquita et al. (2010) |
| **34** | Portugal | Churra Mondegueira | 19 | 0.053 | 0.105 | 0.737 | 0.0 | 0.00 | 0.00 | 0.00 | | 0.00 | Mesquita et al. (2010) |
| **35** | Portugal | Merino da Beira-Baixa | 65 | 0.092 | 0.231 | 0.523 | 0.0 | 0.31 | 0.00 | 0.031 | | 0.077 | Mesquita et al. (2010) |


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| # | Country | Breed | N | ARR/ ARR | ARR/ ARQ | ARQ/ ARQ | ARR/ AHQ | ARQ/ AHQ | AHQ/ AHQ | ARR/ VRQ | VRQ/ VRQ | ARQ/ VRQ | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **36** | Hungary | Hungarian Tsigai | 392 | 0.27 | 0.4 | 0.2 | 0.06 | 0.02 | 0.0 | 0.02 | 0.06 | 0.06 | Mari (2016) |
| **37** | Greece | Karagouniko | 100 | | 14.5 | 32 | | 6.0 | | | 7.9 | | Billinis et al. (2004) |
| **38** | Austria | Carynthian sheep | 24 | 4.2 | 37.5 | 41.6 | | 4.2 | | | 4.2 | | Sipos et al. (2002) |
| **39** | Turkey | Chios | 124 | 15.32 | 22.58 | 20.16 | 1.61 | 7.26 | 1.61 | | 0.8 | | Oner et al. (2011) |
| **40** | Poland | Olkuska | 174 | 35.1 | 60.9 | 4.0 | | | | | | | Kaczor et al. (2011) |
| **41** | Poland | Gorska | 31 | 12.9 | 51.6 | 22.6 | 3.2 | 9.7 | | | | | Lühken et al. (2008) |
| **42** | Poland | Wrzosowka | 31 | 6.5 | 48.4 | 9.7 | 19.3 | 12.9 | 3.2 | | | | Lühken, Lipsky et al. (2008) |
| **43** | Finland | Kainuu | 48 | | 16.7 | 83.3 | | | | | | | Hautaniemi et al. (2012) |
| **44** | Germany | Suffolk | 87 | 14.9 | 20.7 | 54.0 | 1.1 | 1.1 | | | | | Kutzer et al. (2002) |
| **45** | Pakistan | Awassi | 21 | | 4.8 | 92.2 | | | | | | | Babar et al. (2009) |
| **46** | Pakistan | Buchi | 35 | | | 100 | | | | | | | Babar et al. (2009) |
| **47** | Pakistan | Hissardale | 20 | 5 | | 70 | | | | | | | Babaret al. (2009) |
| **48** | Pakistan | Kajli | 52 | 1.9 | 9.6 | 84.6 | | | | | | | Babaret al. (2009) |
| **49** | Pakistan | Lohi | 50 | | 10 | 88 | | | | | | | Babaret al. (2009) |
| **50** | Pakistan | Pak-Karakul | 19 | | 36.8 | 63.2 | | | | | | | Babaret al. (2009) |
| **51** | Pakistan | Sipli | 41 | | | 65.9 | | | | | | | Babaret al. (2009) |
| **52** | Pakistan | Thalli | 40 | | 25 | 100 | | | | | | | Babaret al. (2009) |
| **53** | Pakistan | kachi | 30 | | | 100 | | | | | | | Babaret al. (2009) |
| **54** | China | Gansu Alpine Merino sheep | 111 | 20.7 | 27 | 46 | | | | | | | Liu et al. (2017) |


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| # | Country | Breed | N | ARR/ ARR | ARR/ ARQ | ARQ/ ARQ | ARR/ AHQ | ARQ/ AHQ | AHQ/ AHQ | ARR/ VRQ | VRQ/ VRQ | ARQ/ VRQ | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **55** | Algeria | Barbarine | 20 | | 20 | 40 | | | | | | | Djaout et al. (2018) |
| **56** | Algeria | Berbere | 20 | 5 | 20 | 20 | | | | | | | Djaout et al. (2018) |
| **57** | Algeria | Hamra | 27 | | 19 | 11 | | | | | | | Djaout et al. (2018) |
| **58** | Algeria | Ouled Djellal | 35 | 8 | 17 | 11 | | | | | | | Djaout et al. (2018) |
| **59** | Algeria | Rembi | 40 | 8 | 20 | 18 | | | | | | | Djaout et al. (2018) |
| **60** | Algeria | Sidaou | 30 | | 3 | 23 | | | | | | | Djaout et al. (2018) |
| **61** | Algeria | Taadmit | 10 | 20 | 10 | 10 | | | | | | | Djaout et al. (2018) |
| **62** | Algeria | Tazegzawt | 31 | | 10 | 23 | | | | | | | Djaout et al. (2018) |
| **63** | Czech Republic | Berrichone du Cher | 445 | 54.6 | | | | | | | | | Stepanek and Horin (2017) |
| **64** | Czech Republic | Charollais | 3219 | 61.5 | | | | | | | | | Stepanek and Horin (2017) |
| **65** | Czech Republic | East Friesian sheep | 1864 | 56.5 | | | | | | | | | Stepanek and Horin (2017) |
| **66** | Czech Republic | German Blackheaded Mutton | 628 | 75.3 | | | | | | | | | Stepanek and Horin (2017) |
| **67** | Czech Republic | Kent Romney) | 5995 | 38.0 | | | | | | | | | Stepanek and Horin (2017) |
| **68** | Czech Republic | Merinolandschaf | 2057 | 33.1 | | | | | | | | | Stepanek and Horin (2017) |
| **69** | Czech Republic | Oxford Down | 1044 | 59.5 | | | | | | | | | Stepanek and Horin (2017) |
| **70** | Czech Republic | Romanov sheep | 3281 | 44.2 | | | | | | | | | Stepanek and Horin (2017) |
| **71** | Czech Republic | Sumavka | 3358 | 23.1 | | | | | | | | | Stepanek and Horin (2017) |
| **72** | Czech Republic | Suffolk | 12987 | 73.9 | | | | | | | | | Stepanek and Horin (2017) |


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| # | Country | Breed | N | ARR/ ARR | ARR/ ARQ | ARQ/ ARQ | ARR/ AHQ | ARQ/ AHQ | AHQ/ AHQ | ARR/ VRQ | VRQ/ VRQ | ARQ/ VRQ | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **73** | Czech Republic | Texel | 3142 | 72.7 | | | | | | | | | Stepanek and Horin (2017) |
| **74** | Czech Republic | Valachian sheep | 1301 | 55.9 | | | | | | | | | Stepanek and Horin (2017) |
| **75** | Czech Republic | Zwartbles | 1791 | 39.6 | | | | | | | | | Stepanek and Horin (2017) |
| **76** | West Africa | Burkina-Sahel | 46 | | 6.5 | 80.4 | 2.2 | 10.9 | | | | | Traoré et al. (2012) |
| **77** | West Africa | Djallonké | 50 | | | 86.0 | | 12.0 | 2.0 | | | | Traoré et al. (2012) |
| **78** | West Africa | Mossi | 46 | | 6.5 | 76.1 | | 15.2 | 2.2 | | | | Traoré et al. (2012) |
| **79** | West Africa | Touareg | 20 | | | 40.0 | | 55.0 | 5.0 | | | | Traoré et al. (2012) |
| **80** | Finland | Grey race sheep | 48 | | 16.7 | 83.3 | | | | | | | Hautaniemi et al. (2012) |
| **81** | Finland | Aland sheep | 56 | | 23.2 | 48.2 | | 19.6 | 8.9 | | | | Hautaniemi et al. (2012) |
| **82** | Finland | Taxel | 71 | 1.4 | 31.0 | 33.8 | | 8.5 | | | | | Hautaniemi et al. (2012) |
| **83** | America | Suffolk | 128 | 36.72 | 43.75 | 17.19 | | | | | | | DeSilva et al. (2003) |
| **84** | America | Montadale | 47 | 17.02 | 23.40 | 19.15 | | | | | | | DeSilva et al. (2003) |
| **85** | America | Hampshire | 91 | 20.88 | 52.75 | 26.37 | | | | | | | DeSilva et al. (2003) |
| **86** | America | Dorset | 62 | 9.68 | 38.71 | 38.71 | | | | | | | DeSilva et al. (2003) |
| **87** | Austria | Tyrolean mountain | 35 | 2.9 | 40.0 | 40.0 | 5.7 | 11.4 | | | | | Sipos et al. (2002) |
| **88** | Austria | Forest sheep | 26 | 111.5 | 15.4 | 57.7 | | 11.5 | | | | | Sipos et al. (2002) |
| **89** | Austria | Tyrolean stone sheep | 27 | | 29.6 | 40.7 | | 22.2 | | | | | Sipos et al. (2002) |


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***Table 6.*** *Haplotypic frequencies of PRNP gene at codons 136, 154 and 171: alanine (A), arginine (R), histidine (H), glutamine (Q) and valine (V) in various breeds of sheep in major parts of the world*

| # | Country | Breed | N | ARR | ARQ | AHQ | VRQ | Reference |
|---|---|---|---|---|---|---|---|---|
| **1** | Romania | Lacaune | 159 | 15.1 | 60.4 | 5.0 | 18.9 | Otelea et al. (2011) |
| **2** | Poland | Ile de France | 93 | 83.8 | 3.8 | | 12.4 | Wisniewska and Mroczkowski (2009) |
| **3** | Greece | Greek Dairy Breed | 4382 | 0.1 | 9.4 | 10 | 11.9 | Boukouvala et al. (2018b) |
| **4** | Romania | Turcana | 123 | 34.1 | 53.7 | 1.2 | 8.9 | Coşier et al. (2011) |
| **5** | Poland | Pomorska | 30 | 40.0 | 40.0 | 6.7 | 8.3 | Wiśniewska et al. (2006) |
| **6** | Germany | Texel | 231 | 28.8 | 44.4 | 1.9 | 8.2 | Kutzer et al. (2002) |
| **7** | Italy | Biellese rams | 2414 | 8.3 | 74.4 | 3.8 | 6.8 | Acutis et al. (2004) |
| **8** | Slovakia | Valachian | 735 | 38.4 | 48.7 | 6.0 | 6.5 | Tkáčiková et al. (2003) |
| **9** | Czech Republic | Valachian sheep | 1301 | 74.3 | | | 5.7 | Stepanek and Horin (2017) |
| **10** | Finland | Finnish Landrace | 464 | 9.5 | 83.4 | 0.2 | 5.6 | Hautaniemiet al. (2012) |
| **11** | Germany | Nolana | 71 | 52.8 | 36.6 | | 5.6 | Kutzer et al. (2002) |
| **12** | Poland | Kaminieniecka | 102 | 63.2 | 21.6 | | 5.4 | Szkudlarek-Kowalczyk et al. (2010) |
| **13** | Poland | Zelanienska | 31 | 46.8 | 43.6 | 4.8 | 4.8 | Lühken et al. (2008) |
| **14** | Austria | Carynthian sheep | 24 | 23.0 | 64.6 | 4.2 | 4.2 | Sipos et al. (2002) |
| **15** | Spain | Rasa Aragonesa | 296 | 15.0 | 70.9 | 4.8 | 2.9 | Acín et al. (2004) |
| **16** | Spain | Roya Bilbilitana | 96 | 21.4 | 72.4 | 1 | 2.6 | Acín et al. (2004) |
| **17** | Czech Republic | Romanov sheep | 3281 | 66.3 | | | 2.5 | Stepanek and Horin (2017) |
| **18** | Turkey | Imroz | 147 | 50.0 | 40.1 | 5.8 | 2.4 | Oner et al. (2011) |
| **19** | Greece | Chios crossbred | 633 | 15.0 | 63.4 | 7.7 | 1.7 | Kioutsioukis et al. (2018) |
| **20** | Czech Republic | Zwartbles | 1791 | 63.7 | | | 1.6 | Stepanek and Horin (2017) |
| **21** | Greece | Crossbred | 483 | 25.7 | 55.9 | 11.3 | 1.5 | Kioutsioukis et al. (2018) |
| **22** | Poland | Polish Merino | 98 | 35.2 | 63.3 | | 1.5 | Wiśniewska et al. (2006) |
| **23** | Finland | Taxel | 144 | 17.6 | 64.1 | 4.2 | 1.4 | Hautaniemiet al. (2012) |
| **24** | Czech Republic | Charollais | 3219 | 79.6 | | | 1.3 | Stepanek and Horin (2017) |
| **25** | Turkey | Kivircik | 142 | 30.64 | 39.52 | 6.83 | 0.8 | Oner et al. (2011) |
| **26** | Greece | Chios | 340 | 10 | 71.5 | 5.8 | 0.7 | Kioutsioukis et al. (2018) |


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| # | Country | Breed | N | ARR | ARQ | AHQ | VRQ | Reference |
|---|---|---|---|---|---|---|---|---|
| **27** | Iran | Local sheeps | 250 | | 67.8 | | 0.6 | Karami et al. (2011) |
| **28** | Czech Republic | East Friesian sheep | 1864 | 76.1 | | | 0.5 | Stepanek and Horin (2017) |
| **29** | Czech Republic | Sumavka | 3358 | 46.1 | | | 0.5 | Stepanek and Horin (2017) |
| **30** | Greece | Chios | 1013 | 6.9 | 76.1 | 8.2 | 0.4 | Psifidi et al. (2011) |
| **31** | Turkey | Chios | 124 | 17.25 | 56.69 | 5.63 | 0.4 | Oner et al. (2011) |
| **32** | Czech Republic | Berrichone du Cher | 445 | 75.5 | | | 0.4 | Stepanek and Horin (2017) |
| **33** | Spain | Ojinegra | 182 | 14.6 | 73.9 | 3 | 0.3 | Acín et al. (2004) |
| **34** | Greece | Random breeds | 5815 | 47.7 | 44.9 | 3.9 | 0.3 | Boukouvala et al. (2018b) |
| **35** | Czech Republic | Texel | 3142 | 85.9 | | | 0.2 | Stepanek and Horin (2017) |
| **36** | Czech Republic | Suffolk | 12987 | 86.28 | | | 0.1 | Stepanek and Horin (2017) |
| **37** | Czech Republic | Merinolandschaf | 2057 | 59.3 | | | 0.1 | Stepanek and Horin (2017) |
| **38** | Czech Republic | Kent Romney) | 5995 | 63.5 | | | 0.1 | Stepanek and Horin (2017) |
| **39** | Hungary | Hungarian Tsigai | 569 | 0.5 | 0.4 | 0.05 | 0.01 | Mari (2016) |
| **40** | Czech Republic | German Blackheaded Mutton | 628 | 87.0 | | | 0.0 | Stepanek and Horin (2017) |
| **41** | Czech Republic | Oxford Down | 1044 | 79.2 | | | 0.0 | Stepanek and Horin (2017) |
| **42** | Finland | Grey race sheep | 96 | 8.3 | 91.7 | 0 | 0 | Hautaniemiet al. (2012) |
| **43** | Finland | Aland sheep | 112 | 11.6 | 69.6 | 18.8 | 0 | Hautaniemiet al. (2012) |
| **44** | Poland | Olkuska | 174 | 65.5 | 34.5 | | | Kaczor et al. (2011) |
| **45** | Poland | Polish Mountain | 31 | 40.3 | 53.2 | 6.5 | | Wiśniewska et al. (2006) |
| **46** | Poland | Wrzosowka | 31 | 41.9 | 38.7 | 19.4 | | Lühken et al. (2008) |
| **47** | Finland | Kainuu | 48 | 8.3 | 91.7 | | | Hautaniemi et al. (2012) |
| **48** | Greece | Karagouniko | 100 | 28.5 | 66.0 | 3.0 | | Billinis et al. (2004) |
| **49** | Germany | Suffolk | 87 | 27.0 | 67.2 | 1.1 | | Kutzer et al. (2002) |
| **50** | China | Xinjiang Sheeps | 222 | 9.0 | 75.2 | 2.3 | | Lan et al. (2006) |
| **51** | Algeria | Barbarine | 20 | 15 | 65 | | | Djaout et al. (2018) |
| **52** | Algeria | Berbere | 20 | 18 | 48 | 3 | | Djaout et al. (2018) |
| **53** | Algeria | Hamra | 27 | 11 | 41 | 7 | | Djaout et al. (2018) |
| **54** | Algeria | Ouled Djellal | 35 | 26 | 31 | 3 | | Djaout et al. (2018) |


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| # | Country | Breed | N | ARR | ARQ | AHQ | VRQ | Reference |
|---|---|---|---|---|---|---|---|---|
| **55** | Algeria | Rembi | 40 | 24 | 43 | 3 | | Djaout et al. (2018) |
| **56** | Algeria | Sidaou | 30 | 8 | 45 | 2 | | Djaout et al. (2018) |
| **57** | Algeria | Taadmit | 10 | 30 | 30 | 10 | | Djaout et al. (2018) |
| **58** | Algeria | Tazegzawt | 31 | 8 | 47 | 3 | | Djaout et al. (2018) |
| **59** | Burkina Faso | Burkina-Sahel | 46 | 4.4 | 89.1 | 6.5 | | Traoré et al. (2012) |
| **60** | Burkina Faso | Djallonké | 50 | | 92.0 | 8.0 | | Traoré et al. (2012) |
| **61** | Burkina Faso | Mossi | 46 | 3.2 | 87.0 | 9.8 | | Traoré et al. (2012) |
| **62** | Niger | Touareg | 20 | | 67.5 | 32.5 | | Traoré et al. (2012) |
| **63** | Austria | Tyrolean mountain | 35 | 25.8 | 65.7 | 8.6 | | Sipos et al. (2002) |
| **64** | Austria | Forest sheep | 26 | 19.2 | 71.2 | 5.8 | | Sipos et al. (2002) |
| **65** | Austria | Tyrolean stone sheep | 27 | 14.8 | 70.3 | 11.1 | | Sipos et al. (2002) |
| **66** | China | Lanzhou large-tailed sheep | 30 | 0 | 26 | 0 | | Lan et al. (2014) |
| **67** | China | Mongol sheep | 30 | 0 | 26 | 0 | | Lan et al. (2014) |
| **68** | China | Tan sheep | 30 | 0 | 25 | 0 | | Lan et al. (2014) |
| **69** | China | Gaoyuan sheep | 30 | 0 | 32 | 0 | | Lan et al. (2014) |
| **70** | China | Guide fur sheep | 30 | 0 | 28 | 0 | | Lan et al. (2014) |
| **71** | China | Oula sheep | 30 | 0 | 30 | 0 | | Lan et al. (2014) |
| **72** | China | Lowland sheep | 30 | 0 | 28 | 0 | | Lan et al. (2014) |
| **73** | China | Sishui fur sheep | 30 | 0 | 21 | 0 | | Lan et al. (2014) |
| **74** | China | Small-tailed Han sheep | 30 | 0 | 22 | 0 | | Lan et al. (2014) |
| **75** | China | Hu sheep | 30 | 2 | 25 | 0 | | Lan et al. (2014) |
| **76** | China | Tong sheep | 30 | 1 | 25 | 0 | | Lan et al. (2014) |
| **77** | China | Duolang sheep | 30 | 1 | 27 | 0 | | Lan et al. (2014) |
| **78** | China | Diqing sheep | 30 | 2 | 30 | 1 | | Lan et al. (2014) |
| **79** | China | Tengchong sheep | 30 | 1 | 12 | 17 | | Lan et al. (2014) |
| **80** | China | Zhaotong sheep | 30 | 1 | 7 | 22 | | Lan et al. (2014) |
| **81** | China | Tibetan sheep | 30 | 3 | 27 | 0 | | Lan et al. (2014) |


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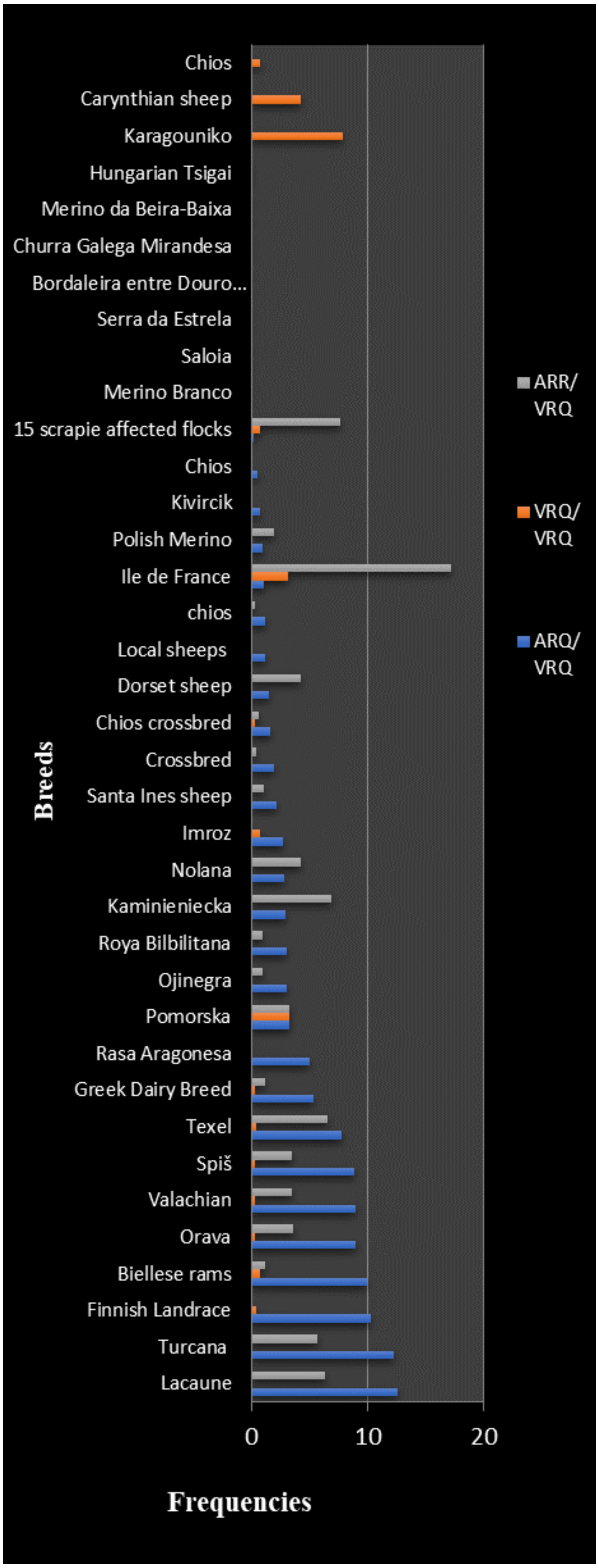


***Figure 3.*** *Genotype frequencies of PRNP gene at codons 136, 154 and 171. (Constructed from Table 5)*


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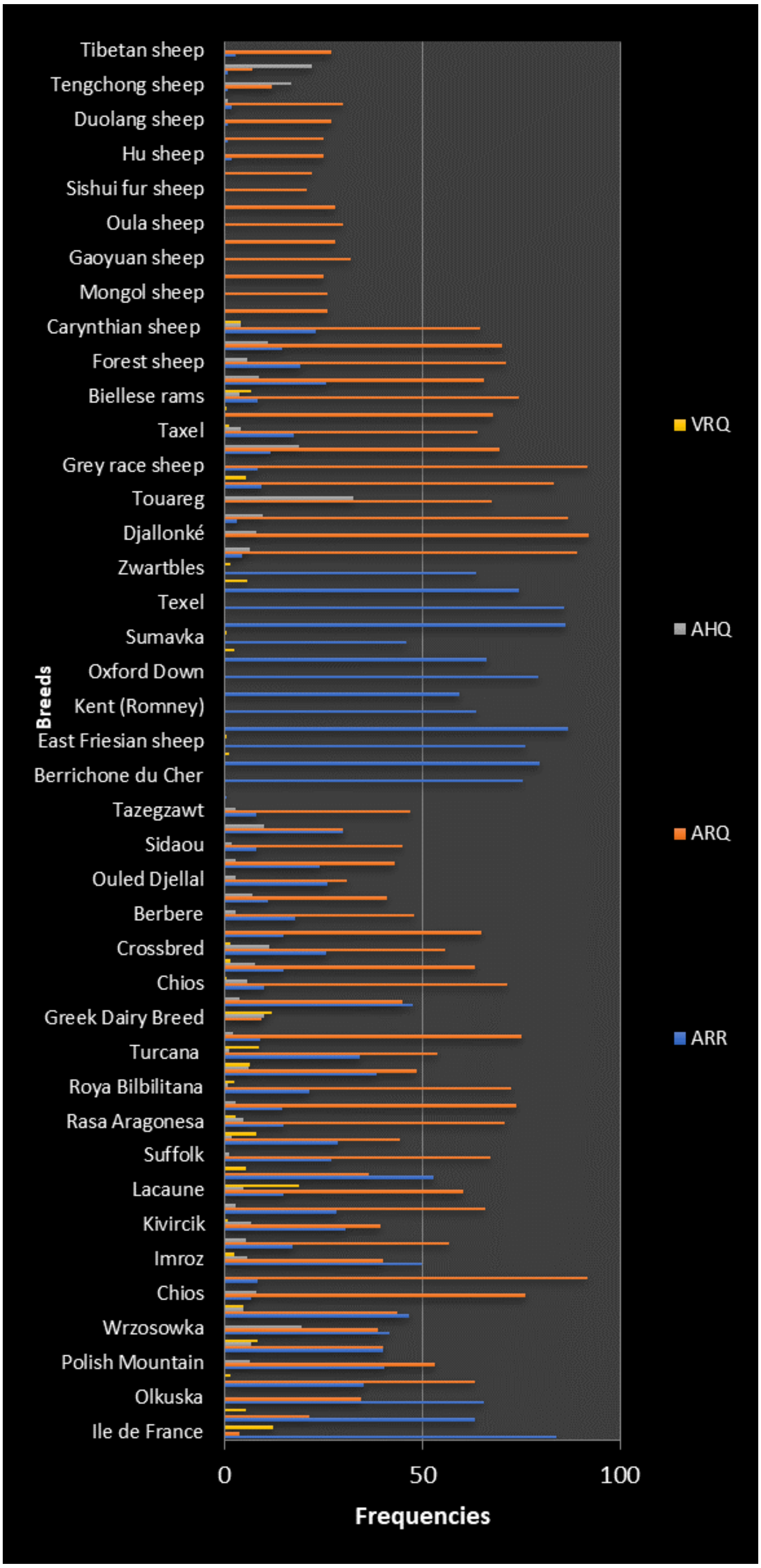


***Figure 4.*** *Haplotype frequencies of PRNP gene at codons 136, 154 and 171. (Constructed from Table 6)*


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## Summary

The purpose of this review is to highlight the countries where scrapie is causing problems and provide some information about the countries where scrapie is not present but there is possibility of its occurrence because scrapie is a prion disease and scientists still do not know how to cure the disease. It is very difficult to get rid of this if once entered in a country, the complete rid is only possible with the help of special breeding programs. Almost every country is working hard on breeding programs to get rid of scrapie, because these breeding programs showed positive signs in countries like Australia and New Zealand which are now scrapie free. But actual facts of scrapie in many parts of the world remain unknown due to the unsatisfactory passive surveillance system, because of which we cannot get consistent results or conclusion. As already described scrapie or any other prion disease do not have any treatment, so the only way to protect the animals is taking proper precautionary measures. The causative agent of the scrapie has still not been fully identified. All routes of transmission and their relative importance are still unknown. Animal health is directly related to humans, for the safety of humans, we must try to find some serious solutions for the well-being of animals. Like in humans, for the early diagnosis of sCJD many scientists have preferred the polysomnogram to detect earlier changes in sCJD patients may be praiseworthy. In humans, the accessory examinations of magnetic resonance imaging (MRI), electroencephalography (EEG), combined with this evidence and clinical symptom; scientists made a clinical diagnosis of sCJD. Though various drugs have been tried *in vitro* and/or *in vivo*, only four drugs have been studied in larger-scale observational or placebo-control trials: flupirtine, quinacrine, pentosan polysulfate (PPS), and doxycycline (Trevitt and Collinge, 2006). In sheep scientists must try some special drugs, any kind of hormonal changes which can prolong the survival or try to find any other way by which animal can show the clinical signs on early stage so that they can be culled or separated from healthy animals. Continuous study and research programs are needed to clear risk factor especially those affecting for human health. Yet, we do not have effective results which can lead us to the solution. The only possible solution is to carry out proper breeding programs. Continuity investigation is needed on this research for the well-being of the mankind and for the well-being of the animals. Further studies are needed to clarify the transmission of scrapie to humans.

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