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THE PRESENT OF SCRAPIE AND THE RESULT OF BREEDING PROGRAM IN EUROPE AND CYPRUS

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Abstract

Scrapie is a fatal neuro-degenerative disease of sheep and goats belongs to the group of transmissible spongiform encephalopathy (TSEs). Classical scrapie resistance and susceptibility are closely related to PrP Gene polymorphism (ARR, ARQ, VRQ, and AHQ ARH) in sheep. The ARR / ARR genotype is the most resistant. Subsequent annual testing campaigns among the animals at risk were done in Europe from 2001 to 2015 showed that the goat had at least 16 silent mutation of a specific study of PrP distribution. In 2014, the test in sheep and goats carried out under the frame work of the TSE monitoring programs in E.U showed that 1015 out 325530 sheep and 1437 out of 127016 goats turned out positive to classical Scrapie. There are Scrapie cases reported in both south and north Cyprus. Infected herds in Southern Cyprus represent 22.6% (2014) of total active sheep and goat herds. It has been also known that there are Scrapie cases in Northern Cyprus although there is no official data recorded. Some sheep breeds have the highest ARR / ARR allele like Canadian Arcott with 39.3%, Dorset Down with 28.9%, and Polypay with 26.8%. Among the sheep breeds, the Chios has the highest level of ARR allele with 38% in Turkey and 32.5% in North Cyprus while the lowest level (5.9%) was seen in Awassi in Turkey. In the TSE eradication program applied in Europe (2015): 1.When BSE cannot be excluded, all animals > 18 months killed for destruction shall be tested for TSE.2. When TSE and atypical Scrapie can be excluded, option A; Killing and complete destruction or slaughter for human consumption (SHC) of all animals. Option B: Killing and complete destruction of the susceptible animals only. Option C: No mandatory killing and complete destruction of animals. In Europe, selected male animals which have ARR / ARR gene are used in breeding program. As a result of the breeding programs implemented in Europe; 1108 Scrapie cases reported in 2002 decreased to 685 in 2016.

Keywords: Scrapie, TSE, Ovine, Caprine, Europe, Cyprus

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1. Introduction

Scrapie is a deadly neurodegenerative disease of the sheep and goat. The disease belongs to the group of infectious spongiform encephalopathy (TSEs), together with large Bovine Spongiform encephalopathy (BSE) in cattle and Creutzfeldt-Jakob disease (CJD) in humans

(Papasavva-Stylianou et al., 2011).Scrapie disease was first reported in England in 1732, and in 1938 it spread from England to Canada (Anonymous, 2006).

The TSEs are characterized by the accumulation of the pathological protease-resistant isoform (PrP Sc) of the host-encoded cellular prion protein (PrP C) in the central nervous system of essentially affected entities (Oesch et al., 1985). Abnormal protein can also accumulate in the lymphocytic system and other tissues or body fluids (Bucalossi et al., 2011).

Several biochemical tests have been approved for differentiation between BSE and Scrapie, and immunohistochemical procedures have been performed for lymphoid tissue and central nervous system with the same purpose (Acutis et al., 2012, Corbière et al., 2013).

2. Genetic Resistant to Scrapie Disease

2.1. Sheep

PCR and sequence sequencing methods are used to detect the PrP gene. In sheep, various polymorphisms of the PrP gene are associated with differences in phenotypic expression of prion diseases such as incubation period, pathology and clinical manifestations. Although more than 30 polymorphisms have been identified, only a few of them are closely related to resistance or susceptibility to classical Scrapie (Belt et al., 1995). Three PrP polymorphisms have a particularly strong connection with both natural and experimental formation. These are codon 136 valine (V) or alanine (A), 154 histidine (H) or arginine (R) and codon 171 arginine (R) or glutamine (Q). Of these polymorphisms, only five of the 12 alleles formed are common. These are: 136 R 154 R 171 (here after ARR), ARQ, VRQ, AHQ and ARH (Belt et al., 1995). ARR allele is associated with resistance and VRQ is associated with susceptibility (Belt et al., 1995). The sensitivity of the ARQ / ARQ genotype is more complex and varies by sheep type. This is the most common genetic type in the Suffolk sheep (Hunter et al., 1997). In the UK, sheep with the VRQ allele are known to almost guarantee that any sheep with the homozygous genotype (VRQ / VRQ) will develop the Scrapie disease. The main alerted identified by these three codons, ARR <AHQ <ARQ ≈ ARH <VRQ such as increased risk. Recently, an Atypical Scrapie (AS) form has been identified and challenged such programs; because animals that are genetically resistant to Classical Scrapie (CS) have been affected (Fediaevsky et al., 2010). In the United Kingdom in 2001, the National Scrapie Plan (NSP) was launched to help sheep breeding to reduce the frequency of sensitive genotypes. In NPU Cheviot run with endemic Natural Scrapie, 100% of VRQ / VRQ animals succumb to Scrapie in about 2 years old (Hunter et al., 1996). In animals with the VRQ / VRQ gene the incubation time of the disease is 150 days, with VRQ / ARQ genes having 256 days and VRQ / ARR 259 days ((Hunter, 2007).

2.2. Goat

PrP amino acid polymorphisms in codon 21 are described in goats; (V → A), 23 (L → P), 49 (G → S), 142 (I → M), 143 (H → R), 154 (R → H), 168 (P → Q), 220 (Q → H), 240 (S → P). 42 (a → g), 107 (g → a), 138 (c → t) and 207 (g → a) cords are silent mutations (Billinis et al., 2002). These nine alleles are an important data set for assessing the resistance levels to Scrapie for S127, M142, R143, D145, D146, S146, H154, Q211 and K222 goats. (Ricci et al., 2017). K222, D146 and S146 alleles, which are resistant to the disease, are used in the European goat population.

K222 polymorphism confers resistance to Classical Scrapie isolates on many Scrapie strains. However, there is no conclusive evidence that K222 carriers will be resistant to all TSE strains present in the EU goat population (Ricci et al., 2017).

3. Eradication Program Implemented in Countries

3.1. Monitoring Program in Europe

In 1987, 442 animals that are infected with Scrapie were reported in England. In 1992, the number of animals that are infected with Scrapie was reported as 37301. This number was reported as 1123 in 2002 and 610 animals in 2013. After 2013, 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 this year the disease peaked. Scrapie disease in France was first reported in 1993. In 2002, 240 patients were reported. The first case was reported in Germany in 1991. The number of animals reported in 2002 was 7, while in 2001, 125 animals were reported. (EFSA, 2016). The first case of Scrapie in Spain was reported in 1987, and in 2001 it was observed that the number of infected animals has been increased (Acin 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 et al., 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 second case was diagnosed after 11 years. The second case was seen near the region where the first case was seen. This is 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 (EU report, 2014). Number of Scrapie cases in European countries was given in Figure 1 and total number of Classical Scrapie cases in sheep by country and year between 2001 and 2016 in the EU and other reporting countries was given in Figure 2. Europe eradication program were given Table 1.

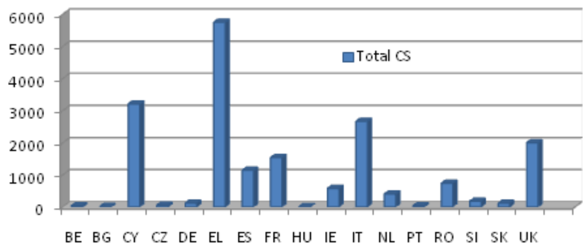

Figure 1. Number of Scrapie cases in European countries (EFSA, 2017)

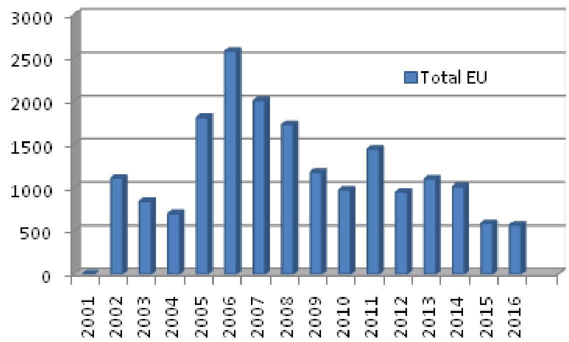

Figure 2. Total number of Classical Scrapie cases in sheep by country and year between 2001 and 2016 in the EU and other reporting countries, (EFSA, 2017)

Table 1. TSE surveillance and control options in small ruminant for 2015 (EFSA, 2016)

TSE suspect animals	Ovine	Caprine
Surveillance in holdings under TSE control and eradication measures (EM)	Different options of flock management are provided.	Different options of flock management are provided.
When BSE cannot be excluded	All animals > 18 months killed for destruction shall be tested for TSE.	All animals > 18 months killed for destruction shall be tested for TSE.
When herd have not TSE and atypical Scrapie	Option 1: Killing and complete destruction or slaughter for human consumption (SHC) of all animals. Animals > 18 months killed for destruction: a sample tested for TSE based on the actual number of animals killed. If derogations are applied: all animals > 18 months SHC shall be tested for the presence of TSE.	Option 1: Killing and complete destruction or SHC of all animals. Animals > 18 months killed for destruction: a sample tested for TSE based on the actual number of animals killed. If derogations are applied: all animals > 18 months SHC shall be tested for the presence of TSE.
	Option 2: Killing and complete destruction of the susceptible animals only. Animals of selected genotypes killed for destruction > 18 months: a sample tested for TSE based on the actual number of animals killed. If derogations are applied: all animals > 18 months SHC shall be tested for the presence of TSE.	
	Option 3: No mandatory killing and complete destruction of animals.	Option 3: No mandatory killing and complete destruction of animals.
Surveillance in ovine and caprine animals slaughtered for human consumption (SHC)		
Annual survey	Minimum sample size of animals > 18 months of age, if the population of ewes and ewe lambs put to the ram is >750,000: 10,000	Minimum annual sample size of animals > 18 months of age, if the population of goats that have already kidded and goats mated is > 750,000: 10,000
When herd have not TSE and atypical Scrapie	After application of Option 2 and during a period of 2 years of TSE intensified monitoring: animals (except ARR/ARR) which were kept in the holding at the time when the TSE case was confirmed and which have been slaughtered for human consumption shall be tested for the presence of TSE. After application of Option 3 or derogations (point 2.2.2 b ii and iii) of option 2 and during a period of 2 years of TSE intensified monitoring: all animals > 18 months (except ARR/ARR) which have been slaughtered for human consumption must be tested for the presence of TSE.	After application of Option 3 and during a period of 2 years of TSE intensified testing of all animals > 18 months which have been slaughtered for human consumption.

Table 1. TSE surveillance and control options in small ruminant for 2015 (EFSA, 2016) (Continue)

TSE suspect animals	Ovine	Caprine
When atypical Scrapie is confirmed	During a period of 2 years of TSE intensified testing of all ovine animals > 18 months and slaughtered for human consumption.	After application of Option 3 and during a period of 2 years of TSE intensified testing of all animals > 18 months which have been slaughtered for human consumption.
Surveillance in ovine and caprine animals not slaughtered for human consumption (NSHC)		
Annual survey	Minimum sample size of dead ovine animals > 18 months of age, if the population of ewes and ewe lambs put to the ram is: > 750,000: 10,000 100,000–750,000: 1,500 40,000–100,000: 100% up to 500 < 40,000: 100% up to 100	Minimum sample size of dead caprine animals > 18 months of age, if the population of goats that have already kidded and goats mated is: > 750,000: 10,000 250,000–750,000: 1,500 40,000–250,000: 100% up to 500 < 40,000: 100% up to 100
When BSE and atypical Scrapie can be excluded	In the case of an infected flock where either option 1, 2, 3 or derogations (point 2.2.2 b ii and iii) has been applied, during the 2-year period of TSE intensified monitoring: all animals (except ARR animals) > 18 months which have died or been killed on the holding but which were not killed in the framework of a disease eradication campaign shall be tested for the presence of TSE.	In the case of an infected flock where either option 1 or 3 has been applied, during the 2-year period of TSE intensified monitoring: all animals > 18 months which have died or been killed on the holding but which were not killed in the framework of a disease eradication campaign shall be tested for the presence of TSE.
When atypical Scrapie is confirmed	During a period of 2 years of TSE intensified monitoring, all ovine animals > 18 months which have died or been killed on the holding.	During a period of 2 years of TSE intensified monitoring, all caprine animals > 18 months which have died or been killed on the holding.

4. PrP Gene Polymorphism and Eradication Program in Turkey and Cyprus

4.1. Turkey

A very high ARR / ARR genotype was observed in the Chios sheep while an important VRQ subspecies were found in the Imroz sheep in Turkey. The ARR / ARQ genotype was the most common genotype are found in Gökçeada breed and Chios breed whereas the ARQ / ARQ genotype was the highest is in Kıvırcık breed. ARQ / ARQ genotypes are in Gökçeada and Chios breeds and ARR / ARQ genotypes are found in Kıvırcık breed(Oner et al., 2011). Native breeds in Turkey (Kıvırcık, Chios and Imroz) were determined eight different polymorphisms. Most of the different polymorphisms were observed in Kıvırcık sheep breeds (Un et al., 2008). The findings also support the opinion that the predominant allele of the native breeds of ARQ allele Turkey (Bulut et al., 2014).

The most durable Turkish goat race can be Damascus. The dominant proportion of the resistant PrP variants of the Damascus herds was found, while others such as the Imroz and Maltese breeds were not goat in this category. The non-native Saanen breed is cultivated in the southern part of Turkey, with seven kinds of species have emerged as the most variable species and hybridization with native breeds may be advantageous from the perspective Scrapie (Meydan et al., 2017).

4.2. Cyprus

1019 Scrapie epidemics have been diagnosed in Southern Cyprus since 1985. It has been reported that the majority of outbreaks are sheep and goats in mixed herds. There was a sudden increase in the number of outbreaks in 2002, 2003, 2004 and 2005 and the breeding program started in 2004 As a result of the breeding program applied to all herds that raised sheep, the resistance in the sheep has been observing to increase. In 2009, the implementation of a breeding program for Scrapie in the Cypriot goat was initiated (EU report, 2014). From 2009 to 2014 there are 722 Scrapie infected flocks were operating. These surveys represent 22.6% of total active sheep and goat farming. These numbers have been constantly changing because the old outbreaks have been closing and new outbreaks have added to the known infected herds (EU report, 2014).

The project for struggling with Scrapie in Cyprus has been successfully implemented in Agricultural Research Institute (ARI) with the use of genetic methods breeding in Chios sheep. There was Chios sheep unit in Athalassa where is natural park in Nicosia in South Cyprus. That herd has been transformed into a nucleus herd of Scrapie resistant genotypes. All the sheep in the herds has ARR/ARR genotypes, which are considered to be 100% resistant to the disease. That sheep has been breeding in Athalassa Park and delivered to the farmers. At the end of both lambing season in a year, a large number of young rams and more females are given to the farmers to increase the genetic density and productivity of their herds and to increase the frequency of resistant genotypes in the population of Cypriot sheep. Over the last 15 years, more than 4,700 Scrapie-resistant sheep have been given to farmers for growth and milk production.

In mid-2008, a research program was launched to transform the Cyprus Damascus goat breed into 300 adapt-universal-resistant genotyping nuclei, through targeted mapping. This program allows ARI to give increasing number of animals to farmers. These animals have superior genetic stigma and are also considered to be resistant to the disease. In this context, ARI has contributed decisively to the national struggle against Scrapie in the Cypriot population (Republic Of Cyprus Agricultural Research Institute, 2018).

Evidence from Scrapie control studies of goats in Cyprus suggests that the S146 and D146 alleles protect against Scrapie (Papasavva-Stylianou et al, 2007).

Animals that have been seized since 2009; animals with suspicious clinical indications consist of animals that were not slaughter off for human consumption due to the PrP genotype or age. As a result of the application of the breeding program for durability in sheep, the number of animals has been constantly decreasing. On the contrary, the number of seized goats has been increasing. Ram not having an ARR / ARR alleline under the breeding program in sheep is not used as studs. Ram who do not have ARR alleles are either dealt with or culled (FAO, 2013). That kind of breeding program of Cyprus is unique for eradication program among to the EU countries.

There is still no official eradication program in Northern Cyprus but eradication program applied in 2003 and approximately 3000 sheep had killed and paid compensation to the farmers. After that this couldn't be sustainable because of the economic difficulties. The farmers where lives in Northern Cyprus have bought ram which has ARR/ARR genotypes from the farmers of Southern Cyprus as unofficial. Depending on this issue, the incidence of Scrapie disease is decreasing in Northern Cyprus.

The project which was genetic identification of TRNC sheep breeds in terms of resistance to Scrapie disease had carried out in sheep and goats in Northern Cyprus with Turkey Food and Agriculture Ministry of Livestock and TRNC Food and Agriculture Ministry of Livestock. In accordance with the project results, 16 % very resistant ARR / ARR, 21% resistant single allele ARR genotype and 62% partially resistant genotype were found in the risk group (TAGEM, 2012). Allele frequencies in PrP and PrP gene in sheep were given in Table 2, among three sheep breeds in Northern Cyprus.

Table 2. PrP gene in sheep breeds of TRNC (TAGEM, 2012)

Risk Group	Genotype	Hybrid (n:50)		Chios (n: 49)		Awassi (n:50)		Total	
		n	%	n	%	n	%	n	%
R1	ARR/ARR	1	2	5	10.20	-	-	6	4.02
R2	ARR/AHQ	-	-	-	-	-	-	-	-
	ARR/ARH	2	4	2	4.08	2	4	6	4.02
	ARR/ARQ	6	12	20	40.81	3	6	29	19.46
R3	AHQ/AHQ	-	-	-	-	-	-	-	-
	AHQ/ARH	-	-	-	-	-	-	-	-
	AHQ/ARQ	-	-	-	-	-	-	-	-
	ARH/ARH	1	0.5	-	-	3	6	4	2.68
	ARH/ARQ	14	-	2	4.08	13	26	29	19.49
	ARQ/ARQ	26	-	20	40.81	27	54	73	-
R4	ARR/VRQ	-	-	-	-	-	-	-	-
R5	VRQ/ARH	-	-	-	-	1	2	1	0.67
	VRQ/AHQ	-	-	-	-	-	-	-	-
	VRQ/ARQ	-	-	-	-	1	2	1	0.67
	VRQ/VRQ	-	-	-	-	-	-	-	

R1= the most resistant sheep to Scrapie, R2= genetically resistant to Scrapie but careful selection should be made if it is used in the rearing, R3= genetically less resistant to Scrapie, R4= genetically sensitive to Scrapie, R5= genetically sensitive to Scrapie.

Conflict of interest

The authors declare that there is no conflict of interest.

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