

Variation in the prion protein in Dutch goats for selective breeding to eradicate Scrapie

EAAP 2016

Jack Windig, Jan Priem, Alex Bossers,
Jan Langeveld, Rita Hoving



Scrapie

■ TSE

- Transmissible Spongiform Encephalitis
- Prion protein (PRNP) misfolding
- Neuro-degenerative disease
 - Like BSE, Creutzfeld-Jacob etc.

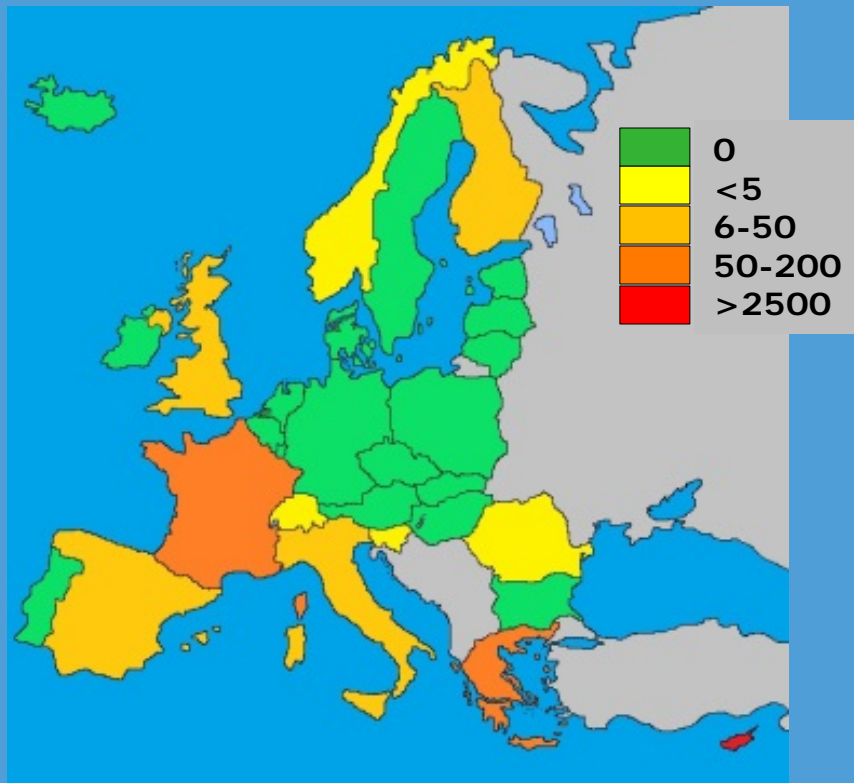
■ Sheep

- Sensitive (VRQ) to Resistant alleles (ARR) in PRNP
- Obligatory breeding program
- VRQ almost disappeared, high levels of ARR
- Scrapie is disappearing in sheep in EU

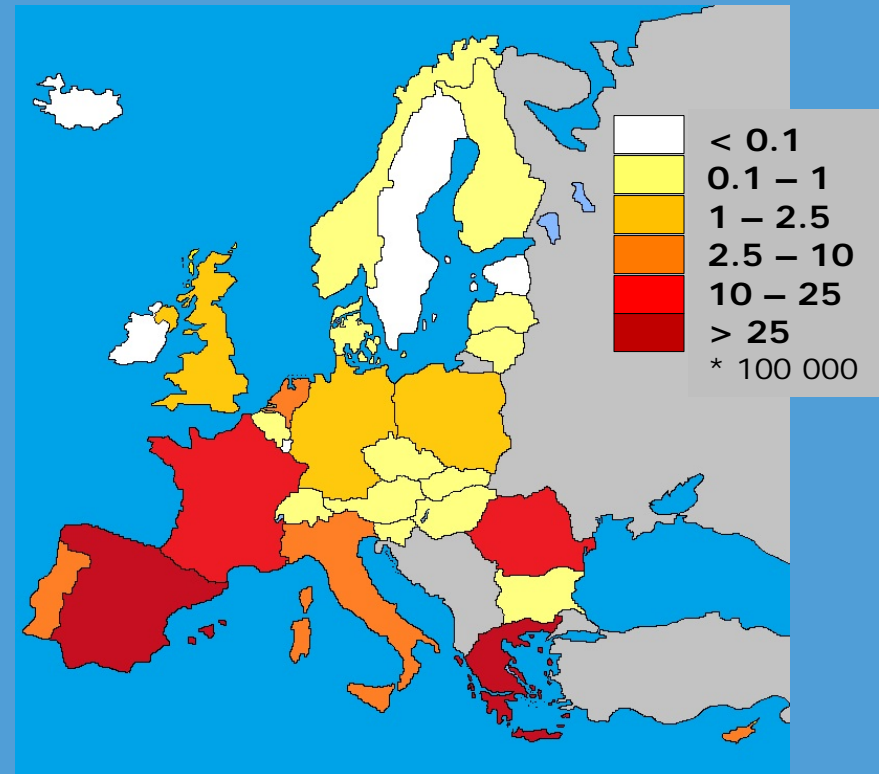


Scrapie cases in goats

Scrapie cases 2002 - 2007



Goat numbers 2010



- Are there resistant alleles in goats?



Potentially resistant haplotypes in PRNP protein in Goats

Codon #	127	142	146	154	211	222	240	
wildtype	G	I	N	R	R	Q	S	
P ₂₄₀	-	-	-	-	-	-	P	Most frequent
S ₁₂₇	S	-	-	-	-	-	P	
M ₁₄₂ P	-	M	-	-	-	-	P	
M ₁₄₂ S	-	M	-	-	-	-	-	
S ₁₄₆	-	-	S	-	-	-	P	Resistant
H ₁₅₄	-	-	-	H	-	-	-	
Q ₂₁₁	-	-	-	-	Q	-	-	
K ₂₂₂	-	-	-	-	-	K	-	Very Resistant



This study

■ Aim

- Determine frequencies of PRNP haplotypes in the Netherlands
- Identify animals carrying resistant haplotypes, useful for breeding

■ Expectation

- High frequencies possible by
 - Selection -> absent in NL -> low frequency expected
 - Genetic drift -> high in rare breeds -> frequency may be high or low



Random samples

- National scrapie surveillance
 - 2005, 2008, 2012
 - N = 766, 768, 300
 - Random samples
 - Slaughter houses (2005, 2008)
 - National destruction unit (2005, 2008, 2012)
 - Breed not registered
 - DNA sequenced and analysed for haplotypes



Results random samples

Allele frequency (%)

	2005	2008	2012
wildtype	25.9	32.0	35.9
P ₂₄₀	48.3	41.4	33.5
S ₁₂₇	6.5	3.8	5.0
M ₁₄₂ P	0.0	1.2	2.0
M ₁₄₂ S	11.9	17.2	10.3
S ₁₄₆	0.1	0.0	0.3
H ₁₅₄	0.5	0.2	1.0
Q ₂₁₁	3.8	2.5	8.7
K ₂₂₂	3.1	2.5	3.3

- Resistant alleles rare
- Q/K₂₂₂ not in HWE
 - Excess of homozygotes
 - Possibly local breeding
 - Within breeds
 - Within farms



Targeted breed samples winter 2012/2013

- Main breeds in the Netherlands
- Main breeders that provide bucks for most other farms sampled
 - Per farm: all bucks (except full brothers or father/sons)
 - Possibly unrelated females

Breed	Registered herd book 2012-2013	Sampled # animals	Sampled # herds
White goat	1219	162	12
Dutch pied	885	38	3
Dutch Toggenburger	699	32	3
Nubian	317	21	2
Boer	357	29	2
Dutch landrace	790	10	Gene bank



Result breed samples 2012/2013

Haplotype	White goat	Dutch pied	Toggen burger	Boer	Nubian	Land race
wildtype	19.1	22.4	26.6	48.3	52.4	100
P ₂₄₀	63.2	69.7	21.9	20.7	38.1	0.0
S ₁₂₇	2.5	0.0	3.1	0.0	0.0	0.0
M ₁₄₂ ^P	0.6	0.0	0.0	0.0	2.4	0.0
M ₁₄₂ ^S	8.3	1.3	0.0	0.0	0.0	0.0
S ₁₄₆	0.0	0.0	0.0	31.0	7.1	0.0
H ₁₅₄	1.2	1.3	0.0	0.0	0.0	0.0
Q ₂₁₁	4.6	0.0	12.5	0.0	0.0	0.0
K ₂₂₂	0.3	5.3	35.9	0.0	0.0	0.0



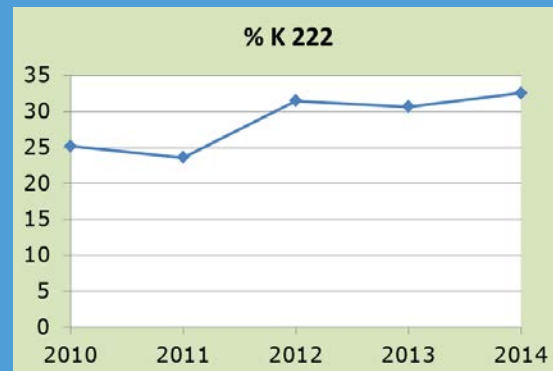
K₂₂₂ in Toggenburger en White Goat

- Extra effort in 2014/2015 to locate K₂₂₂ carriers
- Only tested for Q/K₂₂₂ codon
- Toggenburger
 - 220 animals in 20 herds sampled, including animals unrelated to those sampled before
 - Probability of genotype estimated for unsampled animals based on pedigree and genotypes of related animals (REML)
- White goat
 - 942 animals in AI centre plus 11 herds



Results K222 in Toggenburger & White Goat

- Allele frequency Toggenburger
 - 25.0% (2014/2015 sampled animals)
 - 29.2% (estimated whole pedigree)
 - Slight increase from 2010 – 2014



- White goat
 - 3.1% (59 heterozygotes)



International perspective

- Low frequencies are generally the rule
 - Saanen derived breeds K_{222} around 3% as in White goats
- Some exceptions
 - African breeds high frequency of S_{146} as in Dutch Nubian and Boer goats
 - K_{222} in southern Italian breeds (22%)
 - Selection (?)
- Dutch Toggenburger exceptionally high
 - Started around 1900 with import from Switzerland and crossed with local landrace
 - Bottlenecks and popular sires -> genetic drift high
 - Rare breed harbouring unique diversity



Future

- No need for obligatory breeding in NL
 - Scrapie absent
 - Low frequency: potential for high inbreeding rates, genetic drift and unwanted change in other traits
- Breeding on a voluntary basis
 - Publish genotypes of animals
 - Possibly interesting for export



Conclusions

- Unexpectedly High frequency resistant K_{222} allele in Dutch Toggenburger
- Low frequency or absence of resistant alleles in other breeds
- Possibilities for breeding more resistant animals

