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NEWS AND COMMENTARY

Gems from the Heredity archive

Scrapie genetics before the discovery of prions

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Transmissible spongiform encephalopathies are a form of infectious disease caused by a self-replicating modified form of a protein that accumulates in the central nervous system, leading to death. Examples include kuru in humans, bovine spongiform encephalopathy ('mad cow disease'), chronic wasting disease in deer, and scrapie in sheep and goats. In 1982, Prusiner (1982) purified the protein that causes sheep scrapie and later named it a prion; he subsequently won the Nobel Prize for Physiology or Medicine. In its unmodified form (denoted PrP^{C}) the prion protein is expressed in all vertebrates, and the gene that encodes it seems to be under strong functional constraint. The modified form of protein (PrP^{Sc}) is responsible for the pathology of scrapie and is tolerant to proteolysing agents and UV radiation. In many organisms, including sheep (Goldmann *et al*., 1990), deer (O'Rourke *et al*., 1999) and humans (Mead *et al*., 2003), host susceptibility to a transmissible spongiform encephalopathies is dependent on its genotype at the prion protein gene (*PRNP*).

This particular 'Gem' from the Heredity archive (Parry, 1962) concerns the genetics of scrapie in sheep. The paper was published 20 years before prions had been isolated, and used extensive field data collected over the previous decade, including records of over 1000 scrapie-affected sheep from closely monitored and pedigreed flocks. The author, Parry (1983) dedicated over 20 years of his research career to scrapie, culminating in a monograph that was published posthumously, after extensive editing by his friend and colleague DR Oppenheimer. For most of his career Parry's ideas on scrapie were regarded as being at odds with the consensus view (that scrapie was exclusively transmissible by an infectious agent). Interestingly, although the paper has been cited over 150 times (Figure 1), it has never been cited more than 10 times in a year, and in fact was cited fewer times between 1962 and 1986 than in the following 23 years (bovine spongiform encephalopathy was first confirmed in 1987). Its influence and impact have been steady rather than instant. The main points of the paper are that (i) scrapie is a heritable disease caused by a recessive allele; (ii) affected animals contain transmissible agents, which can be artificially made infectious and (iii) that the recessive allele must also confer some form of selective advantage or scrapie would not have remained in European sheep populations since the early 1700s.

Why was this paper controversial and how robust do the findings look in light of contemporary understanding of scrapie? In 1962, it was known that scrapie could be artificially transmitted by inoculation of the brain material from an affected sheep into a lamb. Indeed, Parry's paper describes just such an experiment. However, the bulk of the paper concerns analyses of crosses between rams and ewes of known disease status. Notably, when both parents had scrapie, nearly all lambs developed the disease (the exceptions can be attributed to the fact that scrapie can be late-onset), whereas progeny of other crosses had a 0–50% incidence. The data are a very good fit to a simple model in which scrapie is caused by a recessive allele at a single gene, and Parry thereafter advocated the 'recessive-gene hypothesis' for scrapie transmission. He argued that natural transmission of scrapie was always genetic, although he suggested that the scrapie gene determined a pro-virus, which could be transmitted by experimental inoculation. The strongest criticism of Parry came from a paper by Dickinson *et al*. (1965), also published in this journal. They argued that scrapie was caused by an infectious agent and that Parry's data could be explained by the fact that the agent was maternally transmissible, which he had mistakenly interpreted as evidence of a single locus heritable trait. They argued that although there may be some genetic variation in susceptibility to disease, 'this is probably not controlled by a major gene'.

It wasn't until well after Parry's death that the hitherto conflicting 'recessive-gene' and infective agent hypotheses were reconciled. We now know that the infective agent is PrP^{Sc}, but that susceptibility to scrapie after exposure to PrP^{Sc} is determined by genotype at *PRNP* (Goldmann *et al*., 1990; Hunter, 1997). Three nonsynonymous polymorphisms at codons 136, 154 and 171 largely determine susceptibility. The usual genotype notation refers to the amino acid at each codon (136 = A or V, 154 = R or H and 171 = R, H or Q). The ARR haplotype is the most resistant (there are very few cases of ARR homozygous sheep developing scrapie), whereas ARQ (which is ancestral) and, in particular, VRQ are the most susceptible. Selective breeding for resistance among UK flocks was formally introduced with the National Scrapie Plan in 2001 and similar schemes were part of EU policy by 2003. These measures have been largely successful, with the incidence of scrapie declining to the extent (Table 1) that the ram genotyping scheme has now closed in the UK. Therefore, although *PRNP* genetics and scrapie susceptibility don't exactly match Parry's recessive-gene hypothesis, we generally get a close correspondence between his model and contemporary data if we regard the recessive allele (*s*) as being all haplotypes other than ARR. Furthermore, Parry actually anticipated selective breeding to eradicate scrapie, and showed success in this area (Parry, 1979).

There is an interesting population genetics aspect to the 1962 paper. Parry recognized that his scrapie susceptibility allele must be at high frequency and that, therefore, selection was required to maintain it in the population. He argued, rather anecdotally that many winners of agricultural shows went on to manifest the disease and that, therefore, the recessive allele might be associated with traits favoured by breeders. There have been a number of papers in recent years that have examined the evidence for associations between *PRNP* genotype and morphological traits (Alexander *et al*., 2005; Isler *et al*., 2006; Vitezica *et al*., 2007), although there is no convincing evidence that marker-assisted selection for scrapie resistance has come at a cost of a decline in performance of production traits. However, there remains some indirect evidence that *PRNP* has been under balancing selection. First, there is an apparent genomic signature consis-

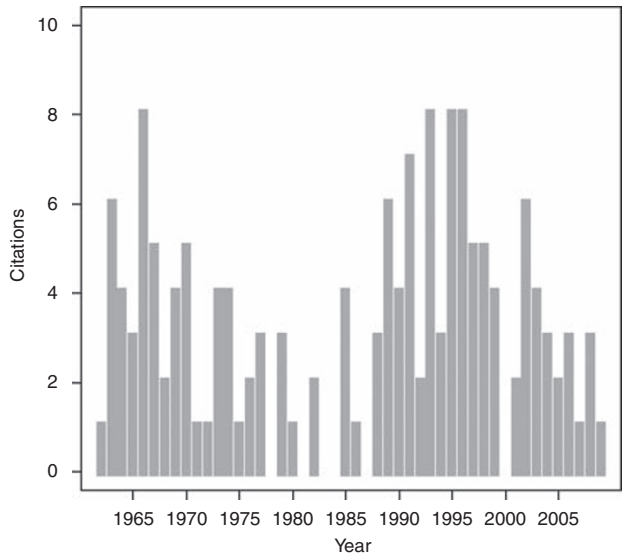

Figure 1 Citations per annum of Parry's 1962 paper.

Table 1 Number of scrapie cases detected by passive surveillance in Great Britain by 30 June 2009

Year	*Cases classical scrapie*	*Cases 'Atypical' scrapie*
2000	568	0
2001	296	0
2002	403	0
2003	379	0
2004	307	0
2005	178	3
2006	97	3
2007	10	2
2008	1	0
2009	1	0

Data from Veterinary Laboratories Agency (http://www.defra.gov.uk/vla/science/sci_tse_stats_sheep.htm).

tent with balancing selection at *PRNP* (Slate, 2005), although that study suffers from a lack of comparison of *PRNP* with other parts of the sheep genome. Second, the emergence of a subclinical strain, termed 'atypical' or Nor98 scrapie, to which sheep resistant to classical scrapie are susceptible (Baylis and McIntyre, 2004), poses the intriguing question of whether variation at *PRNP* has been maintained by negative frequency-dependent selection, that is, when a new scrapie strain arises, it tends to be the rarest host genotypes that are most resistant. Fortunately, atypical scrapie has no known symptoms, but it is unknown whether other strains with more serious effects were present in the past (or at low incidence today).

In summary, Parry's paper may look a little dated in light of later work on prions, but it can be regarded as a forerunner of modern scrapie eradication programs and it also sets the scene for a number of scrapie genetics problems, many of which remain unanswered today. It deserves wider recognition.

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Alexander BM, Stobart RH, Russell WC, O'Rourke KI, Lewis GS, Logan JR *et al.* (2005). The incidence of genotypes at codon 171 of the prion protein gene (PRNP) in five breeds of sheep and production traits of ewes associated with those genotypes. *J Anim Sci* **83**: 455–459.

Baylis M, McIntyre KM (2004). Transmissible spongiform encephalopathies—scrapie control under new strain. *Nature* **432**: 810–811.

Dickinson AG, Young GB, Stamp JT, Renwick CC (1965). An analysis of natural scrapie in Suffolk sheep. *Heredity* **20**: 485–503.

Goldmann W, Hunter N, Foster JD, Salbaum JM, Beyreuther K, Hope J (1990). 2 Alleles of a neural protein gene linked to Scrapie in sheep. *Proc Natl Acad Sci USA* **87**: 2476–2480.

Hunter N (1997). PrP genetics in sheep and the implications for scrapie and BSE. *Trends Microbiol* **5**: 331–334.

Isler BJ, Freking BA, Thallman RM, Heaton MP, Leymaster KA (2006). Evaluation of associations between prion haplotypes and growth, carcass, and meat quality traits in a Dorset x Romanov sheep population. *J Anim Sci* **84**: 783–788.

Mead S, Stumpf MPH, Whitfield J, Beck JA, Poulter M, Campbell T *et al.* (2003). Balancing selection at the prion protein gene consistent with prehistoric kurulike epidemics. *Science* **300**: 640–643.

O'Rourke KI, Besser TE, Miller MW, Cline TF, Spraker TR, Jenny AL *et al.* (1999). PrP genotypes of captive and free-ranging Rocky Mountain elk (Cervus elaphus nelsoni) with chronic wasting disease. *J Gen Virol* **80**: 2765–2769.

Parry H (1983). *Scrapie Disease in Sheep*. Academic Press: London, 191 pp.

Parry HB (1979). Elimination of natural Scrapie in sheep by sire genotype selection. *Nature* **277**: 127–129.

Parry HB (1962). Scrapie: a transmissible and hereditary disease of sheep. *Heredity* **17**: 75–105.

Prusiner SB (1982). Novel proteinaceous infectious particles cause scrapie. *Science* **216**: 136–144.

Slate J (2005). Molecular evolution of the sheep prion protein gene. *Proc R Soc Lond Ser B-Biol Sci* **272**: 2371–2377.

Vitezica ZG, Moreno CR, Lantier F, Lantier I, Schibler L, Roig A *et al.* (2007). Quantitative trait loci linked to PRNP gene controlling health and production traits in INRA 401 sheep. *Genet Sel Evol* **39**: 421–430.