

raised recurrently. Experimental studies of evolution in natural conditions have become feasible in the past ten years, and applications to the evolution of dispersal are eagerly awaited, as is the integrated book³ financed by the International Union of Biological Sciences (IUBS) and DIVERSITAS that will synthesize results of this Conference.

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Adaptive cycles: parasites selectively reduce inbreeding in Soay sheep

Sometimes, we can predict the consequences of inbreeding or the cost of an infectious disease outbreak on the survival of free-ranging populations, but actually demonstrating the interplay of the two is another thing. The interactions between variant immune defences, parasite load, population demography, and life history parameters (e.g. age, sex and breeding structure) are likely to determine a population's response to new diseases, but tracking and evaluating these parameters has always been an elusive prospect. However, a new study of feral Soay sheep (*Ovis aries*), in the face of harsh versus mild winters' influence on an endemic fatal nematode, paints a graphic portrait of partitioned fitness components that bear on whether this small island population survives¹. By simultaneously considering several interacting ecological factors that mediate relative survival or mortality in this population, Coltman *et al.*¹ integrate demographic, molecular genetic, and epidemiological analyses to reveal the regulatory influence of individual and population zygoty.

Genes and outbreaks

Abrupt reduction in population genetic variation because of inbreeding, population bottlenecks, or genetic drift will usually diminish overall fitness or survival and can lead to extinction^{2,3}. Infectious diseases are major threats to a species' survival depending on virulence, pathogenesis, mutability and other components that determine the infectious

agents' spread, morbidity and mortality. A few examples have demonstrated an advantage for maximum heterozygosity, particularly involving the mammalian major histocompatibility complex (MHC), in the face of exposure to fatal viruses such as HIV-1 (Ref. 4) or hepatitis-B (Ref. 5). Several additional host genes have alleles that can restrict a pathogen's virulence⁶. Yet few parameters that monitor the interplay of host population genetic disposition and acute outbreaks have received detailed analysis, mostly because the tools for assessing molecular genetic variation, the knowledge of host restriction genes, and the biological materials collected in field studies during outbreaks have not been widely available. The new Soay sheep study attempts such a task and in the process implicates a critical influence for genome-wide homozygosity – a signal for close inbreeding – on individual sensitivity to parasite dependent mortality, exacerbated during severe winters of food deprivation. By considering the interaction over time of six ecological parameters on population survivorship (Table 1), Coltman *et al.* have shown that the genomic influence emerges in a fascinating manner.

Parasites and severe winters

Soay sheep are a primitive domestic breed introduced to Soay Island in the St Kilda archipelago west of Scotland about 4000 years ago. In 1932, 85 breeding individuals were introduced to the uninhabited Hirta island (638 hectares), where

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today up to 1800 animals reside. A longitudinal study of population's natural history was initiated in 1985 (by T.H. Clutton Brock, S.D. Albon and P.A. Jewell) and has continued to the present. The Soay sheep are afflicted with virulent strongyle nematode parasites (principally *Teladorsagia circumcincta*), which damage the gastrointestinal mucosa and result in nutritional deficiencies. The parasite load (determined by fecal egg counts) varies among individuals with little apparent consequence except during severe winters when sheep with high parasite load preferentially succumb to starvation mortality. The population vacillates from boom to bust years in demographic terms (Fig. 1), with harsh winters (1989, 1992 and 1995) causing 40–70% mortality and mild winters promoting rapid population growth.

Parasite load in the summer preceding the harsh winters is a strong predictor of mortality for all age classes, although lambs and yearlings are the most susceptible (53% and 36% mortality, respectively). There is also a sex difference in mortality, with males dying at twice the rate of females. The yearly fluctuation in parasite load correlates with population density, whereby adults in more dense population (after good years of reproductive increase) have nearly twice the parasite load, on average, than the same populations following severe winters of high mortality. Treatment of a subset of parasitized sheep (N = 121) with antihelminthic therapy abrogated mortality almost completely, linking the parasite's pre-winter incidence directly to survival. Each of these nongenetic parameters dramatically influences survivorship, and now the role of the sheep population genetic structure is being factored into the mix.

Table 1. Factor implication in Soay sheep survival and parasite load

| Modulating co-factor | Sensitive individuals | Resistant individuals |
|-----------------------------|-------------------------------|--------------------------------|
| Nongenetic | | |
| Year (climatic extreme) | In 1989, 1992 and 1995 | In other years |
| Age | < 1 yr old | > 1 yr old |
| Sex | Males | Females |
| Survival of previous crash | Naive | Previous survivors |
| Density | Those at high density | Those at low density |
| Anthelmintic therapy | Untreated | Treated |
| Genetic | | |
| MHC microsatellites | OLADRB-205, -257, -267 | OLDRB-263 |
| Genome-wide microsatellites | Those with low heterozygosity | Those with high heterozygosity |

A role for genomic diversity

In 1998, Paterson⁷ reported that three microsatellite loci within the class II region of the ovine MHC displayed unusually 'even' allele distributions compared with adjacent microsatellite loci outside the MHC. The MHC region microsatellite loci were in strong linkage disequilibrium (the tendency of alleles at linked polymorphic loci to be associated or occur together non-randomly in populations) with each other. The even allele distributions plus the linkage disequilibrium are indicators that powerful selective pressures operate on functional genes within the MHC even today. A subsequent study⁸ demonstrated that certain

microsatellite alleles within the MHC are associated with parasite load resistance and with juvenile survival, whereas alternative alleles are more prevalent among susceptible sheep with high parasite loads and increased mortality.

These observations are provocative, particularly in light of our growing understanding of the role of natural selection in reinforcing extensive allele heterozygosity at MHC loci as a defence against infecting microbes. MHC class II gene products recognize invading parasites in hosts, present them to T-helper cells, and assist in mounting a humoral immune response against them. That younger lambs (<6 months) in Paterson *et al.*'s

study⁸ failed to show the MHC effects on survival⁸⁻¹⁰ actually supports a role for MHC genes because immune responses depend on exposure and time-dependent immune development.

The new study¹ on Soay sheep suggests that inbreeding itself, by homogenizing polymorphic loci over the entire genome, produces homozygous lambs that are preferentially eliminated by the parasite-harsh winter combination.

Coltman *et al.*¹ monitored individual genomic heterozygosity by genotyping up to 14 (average 9.7) microsatellite loci and relating diversity to parasite load and survival, but factoring the effects of age, density and winter severity. In nearly every case, genomic homozygosity is associated with higher parasite load and lower survival in harsh winter years. Apparently, the parasite epidemic itself confers selective pressure against homozygosity (inbreeding was actually demonstrated in several individuals), by eliminating less heterozygous sheep preferentially.

When sheep are treated with anthelmintics in the summers preceding harsh winters, overall genome heterozygosity shows no relationship with survival, providing a powerful control population. Untreated animals display genomic heterozygosity-dependent pathogen resistance, whereas treated animals, apparently relieved of the parasite selective pressure, show no mortality difference among heterozygosity classes. As a consequence of strong selective advantage for increased heterozygosity with every harsh winter, heterozygosity actually increases with age in the surveyed survivors of the population crashes (Fig. 1).

Implications and prospects

Coltman *et al.*'s genetic study tracked 1867 sheep over a 10-year interval, providing a valiant attempt to quantify multifactorial genetic and nongenetic regulation of species survival. It is the first study to implicate a fatal parasite outbreak as a selective agent against increased genomic homozygosity, although there have been other examples of recessive genetic influence for specific genes on infectious disease outcomes⁶. We are used to thinking that genetic drift on islands leads to increased genetic loss and homozygosity; but in these sheep the parasite load actually reverses the process.

There are two remarkable aspects of this study. First Coltman *et al.*¹ provide a comprehensive epidemiological analysis of the interaction of genome-wide zygosity with nongenetic parameters that regulate the likelihood of survival in different ways (Fig. 1, Table 1). Second, they demonstrate that the association of survival with genetic heterozygosity vanishes when the parasite

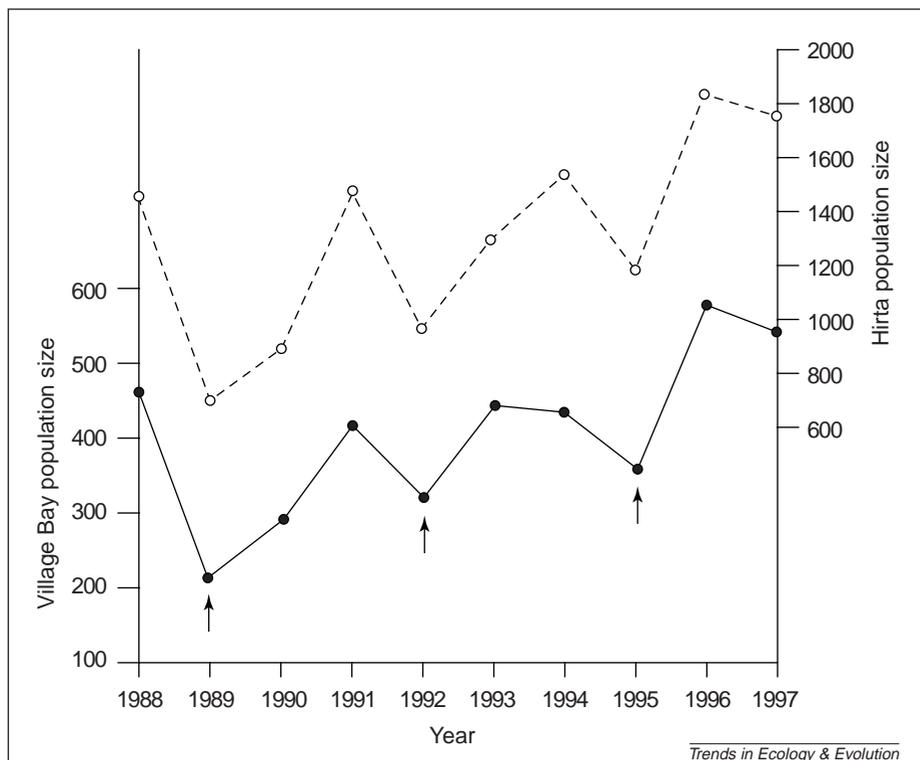


Fig. 1. Annual fluctuations in the Soay sheep (*Ovis aries*) population on Hirta Island (UK; open circles) and in a smaller subset of this study population (Village Bay; filled circles). Severe winters of increasing starvation mortality were evident in 1989, 1992 and 1995 where the sample and entire population showed similar large mortalities (indicated by arrows). Reproduced, with permission, from Ref. 1.

selective pressures are eliminated by anti-helminthic treatment. It is not often we catch such a glimpse of the consequence of both factor-dependent mortality and acute selective pressures exerted by infectious diseases in an isolated free-ranging natural population.

A puzzle that comes from this study is which of the specific sheep genes are responsible for the heterozygosity relationship? The studies by Paterson *et al.*^{7,8} reveal that the sheep MHC shows signals of historic and recent heterozygote advantage (historic evidence is an excess of nonsynonymous variants among compared MHC class II alleles; recent evidence is the 'even' allele distribution of MHC linked microsatellite loci). Nevertheless, specific MHC loci (e.g. class I, class II, TNF, *Tap*, or any of a hundred genes in the MHC) were not genotyped and analysed epidemiologically. Somewhat perplexing is the simultaneous association for MHC region and for whole-genome heterozygosity with survival in the same population. Is it possible that the genome-wide homozygosity is a marker for MHC effect? Alternatively, could MHC effects be surrogates for genome-wide homozygosity? MHC diversity is frequently used to screen for historic inbreeding in natural popu-

lations. Yet, in at least one case, MHC gene homozygosity influence on infectious disease progression (AIDS) was uncoupled with MHC linked and with overall genome-wide microsatellite zygosity⁴.

The identification of gene variants that drive these critical population events should soon be possible. With a full-length sequence of both the human and mouse genomes only a few years away, the power of comparative genomics will allow genome scans to pinpoint responsible genes¹¹. A sheep genetic map including integrated coding (Type I) and microsatellite loci is rapidly developing. The Soay sheep population might be one of the first in which interacting population genetic methods, gene-map driven analyses and ecological insight are employed to describe what until recently have been called stochastic variables. Is it possible that these fluctuations can become deterministic as field ecologists harness the power of comparative molecular genetics? It will not be long.

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