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POSITIVE GENETIC CORRELATION BETWEEN PARASITE RESISTANCE AND BODY SIZE IN A FREE-LIVING UNGULATE POPULATION

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Abstract.—Parasite resistance and body size are subject to directional natural selection in a population of feral Soay sheep (*Ovis aries*) on the island of St. Kilda, Scotland. Classical evolutionary theory predicts that directional selection should erode additive genetic variation and favor the maintenance of alleles that have negative pleiotropic effects on other traits associated with fitness. Contrary to these predictions, in this study we show that there is considerable additive genetic variation for both parasite resistance, measured as fecal egg count (FEC), and body size, measured as weight and hindleg length, and that there are positive genetic correlations between parasite resistance and body size in both sexes. Body size traits had higher heritabilities than parasite resistance. This was not due to low levels of additive genetic variation for parasite resistance, but was a consequence of high levels of residual variance in FEC. Measured as coefficients of variation, levels of additive genetic variation for FEC were actually higher than for weight or hindleg length. High levels of additive genetic variation for parasite resistance may be maintained by a number of mechanisms including high mutational input, balancing selection, antagonistic pleiotropy, and host-parasite coevolution. The positive genetic correlation between parasite resistance and body size, a trait also subject to sexual selection in males, suggests that parasite resistance and growth are not traded off in Soay sheep, but rather that genetically resistant individuals also experience superior growth.

Key words.—Growth, helminth, heritability, nematode, *Ovis aries*, sheep, trade-off.

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The assumption that there is significant additive genetic variation for parasite resistance is a linchpin for many theoretical models in evolutionary biology, including life-history evolution (Møller 1997), sexual selection (Hamilton and Zuk 1982), the maintenance of genetic variation (Haldane 1949), and the evolution of sex (Hamilton et al. 1990). For example, the Hamilton-Zuk hypothesis for the evolution of sexually selected traits assumes that genetically resistant males can afford to invest more in costly secondary traits, and therefore females gain resistance genes for their offspring by mating with attractive males (Hamilton and Zuk 1982). Despite great interest in the evolutionary role of parasites, very few studies have actually investigated the heritable genetic component to parasite resistance in natural populations (Goater and Holmes 1997; Sorci et al. 1997). Furthermore, the concept that parasite resistance is costly and must be traded off against investment in other traits is widely held (Gustafsson et al. 1994; Sheldon and Verhulst 1996; Norris and Evans 2000), yet no studies have estimated the extent to which variation in resistance is genetically correlated with other fitness-related traits in the wild.

A widely held expectation, derived from Fisher's fundamental theorem of natural selection (Fisher 1930), is that selection should deplete additive genetic variation for traits closely associated with fitness by driving favorable alleles to fixation. Fitness-related traits such as life-history characters are therefore expected to have lower heritability than morphometric traits that are weakly associated with fitness (Falconer 1981; Gustafsson 1986; Charlesworth 1987; Mousseau and Roff 1987; Roff and Mousseau 1987; Merilä and Sheldon 2000; but see also Price and Schluter 1991; Houle 1992). Accordingly, if parasites detrimentally affect survival in nature, then parasite resistance may be expected to have low additive genetic variance. However, previous studies have demonstrated significant heritable variation for immune response parameters and ectoparasite loads in natural bird populations (Møller 1990; Boulinier et al. 1997; Brinkhof et al. 1999), and many studies from laboratory and domestic animals have demonstrated significant additive genetic variance for endoparasite resistance (Bishop et al. 1996; Goater and Holmes 1997). We have also previously demonstrated significant heritable variation for resistance to gastrointestinal nematodes in Soay sheep, *Ovis aries* (Smith et al. 1999), yet nematode infection adversely affects overwinter survival (Gulland 1992). How has additive genetic variation for resistance been maintained despite selection?

Many general mechanisms for the maintenance of additive genetic variation have been suggested, including mutation-selection balance, heterozygote advantage, balancing (or frequency-dependent) selection, and environmental heterogeneity (Roff 1997). Additive genetic variation for a selected trait may also be maintained if many of the genes underlying variation in the selected trait have adverse effects on other fitness-related traits (antagonistic pleiotropy); these will not be eliminated or driven to fixation as rapidly as alleles with mutually negative or positive effects by selection (Roff 1996). This scenario can result in the development of a negative genetic correlation between two traits under selection. The concept that life-history evolution is constrained by negative genetic correlations, or trade-offs, between fitness com-

ponents, is thus central to life-history theory (de Jong and van Noordwijk 1992; Roff 1992; Stearns 1992; but see also Reznick et al. 2000) and is relevant to the evolution of parasite defenses (Sheldon and Verhulst 1996). Some empirical evidence suggests that the activation of immune defense uses resources that would otherwise be invested in some other function (Svensson et al. 1998; Ilmonen et al. 2000; Lochmiller and Deerenberg 2000; Norris and Evans 2000). Other laboratory studies have also demonstrated that trade-offs between life-history traits and parasite resistance have a genetic basis (Fellowes et al. 1998; Webster and Woolhouse 1999).

In contrast, good-genes models for the evolution of sexually selected characters (Hamilton and Zuk 1982; Folstad and Karter 1992) suggest a positive genetic correlation between parasite resistance and sexually selected traits, such that genetically more resistant individuals are able to express more elaborate characters. Many empirical studies have demonstrated that high parasite loads are phenotypically correlated with reduced trait expression (Thompson et al. 1997; Roulin et al. 2001). However, evidence that these correlations have a genetic basis is more elusive (Kurtz and Sauer 1999). Recently, Barber et al. (2001) found that sticklebacks (*Gasterosteus aculeatus*) sired by brightly colored males were more resistant to parasites; however, the fish also suffered reduced growth. Barber et al. suggested that the genetic tradeoff with early growth might provide a mechanism for the maintenance of additive genetic variation for parasite resistance or male sexual coloration.

From these findings, it is difficult to predict the sign of the genetic correlation between parasite resistance and body size or growth in a wild population. The energetic costs of resistance may have to be traded off against investment in somatic growth, or genetically resistant individuals may be able to afford to invest relatively more resources in growth. Ultimately, the sign of the genetic correlation may also depend on environmental conditions, such as resource abundance (Reznick et al. 2000), thus making generalization problematic.

Here, we present estimates of quantitative genetic parameters for three traits under strong selection in a free-living population of Soay sheep: resistance to infection from gastrointestinal nematodes and two morphometric traits, skeletal size and body weight. All three of these traits are known to be associated with overwinter survival in the Soay sheep, with directional selection favoring increased resistance (Illius et al. 1995; Coltman et al. 1999a), body size (Coltman et al. 1999b; Milner et al. 1999a), and weight (Milner et al. 1999a). Body size is also positively correlated with seasonal mating success (Preston et al. 2001) and lifetime breeding success in males (Coltman et al. 1999b). Previous studies have found there to be significant additive genetic variation for both parasite resistance (Smith et al. 1999) and morphometric traits (Milner et al. 2000). In this study, we employ the animal model, which uses restricted maximum likelihood to estimate genetic parameters using all of the available pedigree and phenotypic information (Meyer 1991; Lynch and Walsh 1998). The animal model estimates the genetic value of all measured individuals in a pedigree. This is the first study to use these methods to estimate genetic parameters for parasite resistance in a free-living animal.

The primary objective of this study is to estimate the genetic correlations between parasite resistance and morphometric traits under natural conditions: whether parasite resistance is traded off against growth or whether genetically more resistant sheep experience improved growth. In addition to the fundamental importance to evolutionary theory of estimating the genetic covariance between disease resistance and growth or quality, this parameter is also of great significance to the animal breeding community, because gastrointestinal nematodes are the most economically important parasites of domestic sheep (Beh and Maddox 1996; Woolaston and Baker 1996). Anthelmintic resistance has evolved independently in many populations worldwide (Prichard 1994), thus, there is considerable interest in improving genetic resistance through selective breeding (Beh and Maddox 1996; Bishop et al. 1996; Woolaston and Baker 1996). This study offers the unique opportunity to unravel the genetic architecture of parasite resistance for a population in which resistance has evolved under natural selection and in which untreated animals have experienced competition for food in their natural environment. In domestic sheep, studies have reported both positive (Bishop et al. 1996; Bouix et al. 1998) and negative (Douch et al. 1995; Eady et al. 1998; Morris et al. 2000) genetic correlations between parasite resistance and production-related traits. However, generalization from these results is difficult due to the variation between studies in sheep breed, selection history, parasite species, infection intensity, and anthelmintic treatment. Differences in environmental conditions between studies are also likely to be important—positive genetic correlations may be more likely to occur under conditions of sustained and abundant resource availability (Reznick et al. 2000). Because the Soay sheep is a relatively ancient sheep breed that has not been subject to artificial selection for production-related traits for many generations, has not been subject to anthelmintic treatment, and has evolved resistance under naturally fluctuating environmental conditions, the genetic correlation between parasite resistance and body size in this breed may represent the ancestral, or wild-type, condition.

The second objective of this study is to disentangle maternal effects and permanent environmental effects from the additive genetic variance for parasite resistance. Maternal effects on parasite resistance may be an important source of variation, for example, if offspring are more likely to graze on the same pasture as their mother and thus experience similar exposure to infective larvae (Bishop et al. 1996). Maternal effects may have inflated previous heritability estimates obtained using mother-daughter regression and maternal sibling analyses (Smith et al. 1999). Also, through the use of repeated observations on individuals, it is possible to quantify any further between-individual variation beyond that to that due to additive genetic variation, such as permanent environmental effects and nonadditive genetic variation that persist throughout the lifetime. Combined with the additive genetic variance, this gives the upper limit to which variation in parasite resistance is under genetic control.

Finally, we also examine genetic parameters for parasite resistance measured under different environmental conditions representing periods of energetic or physiological stress. Several hypotheses predict that the expression of genetic vari-

ation may increase or decrease under unfavorable conditions (Hoffmann and Merilä 1999). For males, we compare genetic parameters for parasite resistance measured during the rut, when males reduce feeding, increase their activity in mate competition, and have elevated levels of testosterone, to resistance measured during the summer, when forage in plentiful. For females, we compare resistance measured in the spring, when lactating ewes experience a rise in fecal egg count (FEC; the periparturient rise) to resistance measured in the summer. The periparturient rise in FEC is believed to result from a temporary reduction in host immunocompetence as a result of seasonal hormonal changes (Lloyd 1983). We hypothesize that energetically stressful or potentially immunosuppressive conditions will exacerbate the phenotypic differences between genetically resistant and susceptible individuals, resulting in an increase in both the phenotypic and additive genetic variances.

Materials and Methods

Study Population

The Soay sheep study population is located on the island of Hirta (636 ha) in the St. Kilda archipelago, located approximately 80 km west of the Outer Hebrides, Scotland (57°49′N, 08°34′W). The Hirta population was founded in 1932, following the evacuation of the human population, when 107 sheep were introduced from the adjacent island of Soay. Since 1932 the Soay sheep have existed in an unmanaged state on Hirta, and the total island population size has fluctuated between 600 and 2000 individuals. Life histories of tagged individuals living with the Village Bay study area (175 ha) have been monitored since 1985 (Clutton-Brock et al. 1991, 1992).

The Soay sheep population experiences periodic overwinter crashes following years of high population density and harsh winter weather conditions (Grenfell et al. 1998; Coulson et al. 2001). Crash mortality is proximately caused by starvation, however, it is exacerbated by protein and nutrient deficiency caused by strongyle nematodes, primarily *Teladorsagia circumcincta* (Gulland 1992; Gulland and Fox 1992). Overwinter survival probability is negatively associated with FEC measured in the previous August (Illius et al. 1995; Coltman et al. 1999a), and animals that have been experimentally relieved of their nematode burdens show significantly improved crash survival (Gulland 1992; Gulland and Fox 1992).

Phenotypic Data Collection

Since 1985, over 95% of the sheep born in the Village Bay study area have been individually marked, sampled for genetic analyses, and monitored throughout their lives. Phenotypic data are collected at three times each year. During the spring (April and early May), lambs are caught, tagged, and sampled for genetic analyses. Multiple fecal samples are also taken from ewes during the periparturient rise (Gulland et al. 1993). Each year since 1988, approximately 50% of the Village Bay population are caught in the summer (mid-August) and detailed morphometric measurements and a single fecal sample from each individual are taken. Body weight is measured to the nearest 0.1 kg, and hindleg length is measured to the nearest 1 mm from the tubercalcis of the fibular tarsal bone to the distal end of the metatarsus using callipers. In the autumn, multiple fecal samples are taken from free-ranging males during observations of the rut. Strongylid nematode eggs in feces are determined to the nearest 100 per gram using a modification of the McMaster technique (MAFF 1971). Counts are predominately made up of *T. circumcincta* (Gulland and Fox 1992). We interpret FEC as a measure of nematode parasite infection for the following reasons: (1) FEC is positively correlated with worm burden (both number and mean size of nematodes in the gut) in domestic sheep (Stear et al. 1996) and in Soay sheep (Grenfell et al. 1995); (2) the correlated response to selection for low FEC in domestic sheep includes increased immunological measures of resistance such as parasite specific antibody titre (Shaw et al. 1999); (3) FEC is negatively correlated with overwinter survival (Illius et al. 1995; Coltman et al. 1999b; Milner et al. 1999b) and antibody titres in Soay sheep (Coltman et al. 2001); and (4) Soay sheep treated with anthelmintics have reduced FEC, worm burden, and improved overwinter survival (Gulland 1992; Gulland and Fox 1992; Gulland et al. 1993). Individuals that had previously been treated with either anthelmintics (Gulland and Fox 1992) or hormones (Stevenson and Bancroft 1995) in other experimental studies were excluded from this study.

Pedigree Determination

Maternal relationships were known for 1690 of 2020 lambs born and sampled between 1985 and 1999 from field observation. Single-locus protein and microsatellite markers were used to determine paternity using a likelihood-based method implemented by the CERVUS program (Marshall et al. 1998). For details about paternity determination in the Soay sheep system see Pemberton et al. (1999). Paternal relationships were determined for 1374 lambs at an estimated 80% confidence level. The pedigree contains 456 mothers (mean maternal sibship size = 3.71, range 1–15) and 433 sires (mean paternal sibship size = 3.19, range 1–36). Full-siblings are relatively rare (40 pairs, four trios and one set of four).

Characterization of Fixed Effects

Generalized linear models (McCullagh and Nelder 1989) with normal error structure implemented in S-PLUS (MathSoft, Seattle, WA) were used to identify important sources of fixed effect variation for each trait. FEC data were transformed by natural logarithm prior to analysis due to positive skewness; weight and hindleg length were not changed. Terms fitted as fixed effects were age, factor with 10 levels in females for ages 0 through 9+ and as a seven-level factor in males for ages 0 through 6+, with the exception of hindleg length for which age was fitted as a nine-level factor; year, year of capture fitted as a factor; cohort, year of birth fitted as a factor; twin, twin versus singleton versus unknown for morphometric traits, adult versus twin/singleton/unknown status at age 0 for FEC; and date, Julian date of capture fitted as a continuous variable for summer weight, autumn FEC, and as a second order polynomial for spring FEC. Terms were kept in the model if either they were

statistically significant or if they were close to statistical significance ($P < 0.10$) and explained at least 1% of the total variance. Terms identified in this way were fitted as fixed effects in the variance component estimation procedure for the trait in question. Residuals from the GLMs were used to estimate phenotypic correlations between traits within the sexes. For each individual, the mean phenotypic value for a given trait was taken as the mean of the residuals. Phenotypic correlations were then calculated as the Pearson product-moment correlation between mean phenotypic values.

Random Effects and Variance Component Estimation

Variance components, heritabilities, and genetic correlations were estimated in each sex separately using multiple-trait, restricted-estimate, maximum-likelihood models implemented by the program VCE (Groeneveld and Kovac 1990; Groeneveld 1995). An animal model was fitted in which the phenotype of each animal was broken down into components of additive genetic value and other random and fixed effects: $\mathbf{y} = X\mathbf{b} + Z\mathbf{a} + P\mathbf{c} + M\mathbf{d} + \mathbf{e}$, where $\mathbf{y}$ is a vector of phenotypic values; $\mathbf{b}$ is a vector of fixed effects; and $\mathbf{a}$, $\mathbf{c}$, and $\mathbf{d}$ are vectors of additive genetic, permanent environmental, and maternal random effects; $\mathbf{e}$ is a vector of residual values; and X, Z, P, and M are the corresponding design matrices relating records to the appropriate fixed or random effects (Lynch and Walsh 1998). Maternal identity was fitted as random effect to partition shared maternal environmental influences and maternal condition from additive genetic effects. The permanent environmental effect grouped repeated observations on the same individual to quantify any between-individual variance over and above that due to additive genetic or maternal effects; this will be due to long-term environmental and nonadditive genetic effects.

The total phenotypic variance (V_P) was therefore partitioned into four components: the additive genetic variance (V_A), the permanent environmental variance (V_E), the maternal effects variance (V_M), and the residual variance (V_R), thus $V_P = V_A + V_E + V_M + V_R$. Heritability was calculated as $h^2 = V_A/V_P$, the permanent environmental effect as $c^2 = V_E/V_P$, and the maternal effect as $m^2 = V_M/V_P$. The repeatability, R, was taken as the sum of the heritability, maternal, and the permanent environmental effects. Coefficients of additive genetic variation (CV_A) were calculated using variance component estimates and trait means as $CV_A = 100\sqrt{V_A}/\bar{x}$ (Houle 1992). Coefficients of variation for weight were scaled downward by a factor of three to account for their dimensionality (Houle 1992). The genetic correlation between traits x and y was calculated from the genetic covariance estimate ($\mathrm{Cov}[x, y]$) and their additive variances as $r_A = \mathrm{Cov}(x, y)/[(V_{Ax})\ (V_{Ay})]^{0.5}$. The VCE program returns standard errors on all variance components and ratios.

To determine whether measurements made in both sexes at the same time of year should be treated as separate traits, additive genetic variances and the additive genetic covariances between the sexes were initially estimated in a six-trait variance component analysis. For the traits to be considered the same genetically, they should have equal additive genetic variances and a genetic correlation not significantly different from one (Lynch and Walsh 1998). Final genetic parameters for the suite of traits measured in either sex were then estimated in a single multiple trait VCE analysis in males and females separately.

Results

Matched weight, hindleg length, and summer FEC data were available for 493 males ($N = 687$ observations) and 576 females ($N = 1250$ observations; Table 1). The levels of FEC observed in Soay sheep were generally comparable to those observed in untreated domestic hill sheep in Scotland (Morgan et al. 1950). Mean natural log(summer FEC) was considerably higher and relatively less variable in males than in females (CV = 50.5% vs. 90.3%, respectively). In males, average FEC observed in the autumn was lower than that observed in the summer, whereas average spring FEC in females was relatively higher than observed in summer (Table 1).

Age, year, cohort, and twin status explained much of the variation in morphometric traits in both sexes (Table 2), accounting for approximately two-thirds of the total variance in hindleg length and over 80% of the variance in weight, as shown previously (Milner et al. 2000). Summer weight increased with capture date. There were differences between the sexes in the relative importance of each term, for example, cohort and litter size account for more variation in male body size (Table 2). GLMs explained less variation in FEC in both sexes, accounting for up to 53% of the total variance in spring female FEC (Table 2). FEC exhibits considerable interannual variation due to changes in population density (Gulland and Fox 1992) and probably weather. The effects of age on summer-male FEC and cohort on autumn-male and both summer- and spring-female FEC were not quite statistically significant ($0.10 > P > 0.05$), probably due to the large number of factor levels. These terms were kept as fixed effects because they appear to explain relatively large amounts of variation, and the primary objective of the GLM exercise was to identify sources of variation that may be biologically important prior to estimating the genetic parameters. Residuals from all eight models were distributed approximately normally.

Quantitative genetic parameters for weight, hindleg length, and summer FEC were first estimated in a multiple-trait model including data from both sexes (Table 3). Similar additive genetic variances in each sex were observed for each trait, and in each case there was a significant positive genetic covariance between the traits measured in each sex. However, all three genetic correlations between the sexes were significantly less than one (t-test, $P < 0.001$ for all), indicating that the traits should be considered separately for further analyses.

Genetic parameters were estimated for the four traits measured in each sex separately in multiple trait models (Table 1). Estimates of V_A and CV_A for weight and hindleg length were very similar to those previously reported by Milner et al. (2000) in an analysis of a slightly smaller dataset. Morphometric traits had similar levels of additive genetic variance in males and females, but lower heritability in males due to higher levels of residual variance and permanent environmental variance. Maternal effects, expressed either as

TABLE 1. Means, standard deviation (SD), sample sizes (*N*, observations/individuals), and variance components (±SE) for all traits considered in separate-sex, multiple-trait models. Figures in bold indicate a value significant difference from zero by *t*-test ($P < 0.01$).

Trait	Mean	SD	*N*	V_A	V_E	V_M	V_R	CV_A	h^2	c^2	m^2	*R*
Males												
Hindleg (mm)	171.8	15.1	687/493	**22.8 ± 3.6**	**43.2 ± 4.6**	**17.5 ± 3.4**	**11.0 ± 1.5**	**2.8 ± 0.2**	**0.24 ± 0.04**	**0.46 ± 0.04**	**0.18 ± 0.03**	**0.89**
Weight (kg)	19.7	8.5	687/493	0.79 ± 0.40	**3.5 ± 0.8**	**1.9 ± 0.5**	**4.1 ± 0.4**	1.5 ± 0.8	0.07 ± 0.04	**0.34 ± 0.06**	**0.18 ± 0.05**	**0.59**
Log_eFEC (summer)	1.63	0.82	687/493	**0.039 ± 0.009**	**0.015 ± 0.005**	**0.024 ± 0.007**	**0.27 ± 0.02**	**12.2 ± 1.3**	**0.11 ± 0.02**	**0.04 ± 0.01**	**0.07 ± 0.02**	**0.22**
Log_eFEC (autumn)	1.33	0.87	836/306	**0.041 ± 0.010**	**0.025 ± 0.008**	**0.019 ± 0.007**	**0.23 ± 0.02**	**15.1 ± 1.6**	**0.13 ± 0.03**	**0.08 ± 0.02**	**0.06 ± 0.02**	**0.27**
Females												
Hindleg (mm)	172.5	12.8	1250/576	**24.3 ± 1.2**	**27.5 ± 1.5**	**10.4 ± 0.9**	**7.5 ± 0.3**	**2.9 ± 0.1**	**0.35 ± 0.21**	**0.40 ± 0.02**	**0.15 ± 0.01**	**0.89**
Weight (kg)	18.7	5.1	1250/576	**1.46 ± 0.10**	**1.7 ± 0.1**	**0.40 ± 0.07**	**1.7 ± 0.1**	**2.1 ± 0.08**	**0.28 ± 0.02**	**0.32 ± 0.02**	**0.08 ± 0.01**	**0.68**
Log_eFEC (summer)	0.92	0.83	1250/576	**0.029 ± 0.003**	**0.023 ± 0.003**	**0.014 ± 0.002**	**0.16 ± 0.01**	**18.6 ± 0.8**	**0.13 ± 0.01**	**0.11 ± 0.01**	**0.06 ± 0.01**	**0.30**
Log_eFEC (spring)	1.54	1.14	2294/348	**0.073 ± 0.006**	**0.072 ± 0.006**	**0.046 ± 0.007**	**0.35 ± 0.01**	**17.6 ± 0.7**	**0.14 ± 0.01**	**0.13 ± 0.01**	**0.09 ± 0.01**	**0.36**

m^2 or CV_M, were similar for hindleg length and slightly higher in males for body weight.

Heritability estimates for FEC fell within a very narrow range (0.11–0.14). In females, spring FEC had higher V_A than summer FEC, yet similar heritability and CV_A due to a higher V_R and mean. Differences between the sexes in genetic parameters for FEC were relatively small overall. Compared to morphometric traits, FEC traits generally had lower heritability yet higher levels of additive genetic variance when expressed relative to the mean (Fig. 1).

Genetic and phenotypic correlations between the morphometric traits were positive and high in both sexes (Table 4). Phenotypic correlations between FEC measurements made at different times of year were positive and moderate. The genetic correlation between autumn and summer FEC in males was very high (+0.71). In contrast, the genetic correlation between spring and summer FEC in females was quite low (+0.28). All phenotypic and genetic correlations between FEC and morphometric traits were negative. All four genetic correlations between FEC and hindleg length were statistically significant, and two of four genetic correlations between FEC and weight were significant.

DISCUSSION

Heritable Variation for Parasite Resistance

Our results clearly show there to be significant heritable variation for FEC in both sexes measured under varying environmental and physiological conditions. Both heritability and the coefficients of additive genetic variation for FEC fell within very narrow ranges (h^2 range = 0.11–0.14, CV_A range = 12.2–18.6%) overall. For males, the high genetic correlation between FEC measured during the summer and the autumn suggest that the genetic basis of resistance at these times of year is very similar. Sources of stress related to the rut do not appear to strongly affect the expression of genetic variation in parasite resistance in males as measured by FEC. Alternately, there may be genetic variation for the immunosuppressive effects associated with rutting (Grossman 1985; Schuurs and Verheul 1990) that lead to increased establishment of infective larvae, but not necessarily to increased FEC during the period that we are able to collect fecal samples. In females there was significantly higher additive genetic and residual variance for FEC in the spring than in the summer, and a low genetic correlation between summer and spring FEC. This suggests that the energetic and hormonal stresses of parturition and lactation do affect the expression of genetic resistance to nematodes in females in a manner consistent with the idea that genetic differences between individuals are exacerbated under conditions of environmental stress (Hoffmann and Merilä 1999).

The heritability estimates for FEC reported here are approximately 50% lower than previous estimates made using parent-offspring regression and sibling analyses (mean h^2 = 0.26; Smith et al. 1999), but all are significantly different from zero at $P < 0.01$. In contrast, only eight of the 31 estimates presented in Smith et al. (1999) were significant at $P < 0.05$. By considering the similarity between an individual and all other individuals in the pedigree to which it is related (Lynch and Walsh 1998), the animal model provides a much

TABLE 2. Sources of fixed effect variation identified by generalized linear modeling of fecal egg count (FEC) and morphometric trait measurements. Traits were analyzed separately in males and females, and statistical significance assessed by *F*-tests.

	Males											
	Hindleg length $N^1 = 687$, 67.9% of variance explained			Weight $N = 687$, 88.3% of variance explained			Summer FEC $N = 687$, 29.0% of variance explained			Autumn FEC $N = 995$, 32.0% of variance explained		
Term	k^2	%[3]	*F*	*k*	%	*F*	*k*	%	*F*	*k*	%	*F*
Age	10	37.7	24.1***	7	52.4	61.6***	7	3.3	2.1	7	16.5	8.2***
Year	12	4.6	2.1*	12	10.1	6.5***	12	15.3	4.5***	9	8.4	3.1**
Cohort	14	8.5	3.2***	14	13.1	7.1***	14	6.5	1.6	12	6.0	1.6
Twin	3	17.1	38.1***	3	10.1	35.7***	4	3.8	6.1**			
Date				C	2.5	17.6***				C	1.1	3.2
	Females											
	Hindleg length $N = 1250$, 71.2% of variance explained			Weight $N = 1250$, 83.5% of variance explained			Summer FEC $N = 1250$, 39.9% of variance explained			Spring FEC $N = 2294$, 53.1% of variance explained		
Term	*k*	%	*F*	*k*	%	*F*	*k*	%	*F*	*k*	%	*F*
Age	10	57.4	96.2***	10	74.4	159.4***	10	7.6	5.1***	9	6.2	8.4***
Year	12	1.3	1.8*	12	2.7	4.7***	12	20.0	9.8***	10	31.3	32.8***
Cohort	16	2.9	2.9***	16	2.2	2.8***	16	8.8	3.2***	13	2.0	1.6
Twin	3	9.6	72.6***	3	3.7	35.6***	3	3.5	9.6***	4	3.4	15.9***
Date				C	0.6	10.8**				C	7.2	68.4***
(Date)[2]										C	3.0	28.1***

[1] Number of observations.
[2] Factor level or C, continuous variable.
[3] Percent of variation explained (see Methods).
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

more efficient use of pedigree data, resulting in considerably lower standard errors (typically 10–20% of the mean compared to an average standard error of 109% of the mean reported in Smith et al. 1999) and greater accuracy. This study has high statistical power to estimate low heritability values as a consequence of both the large sample size (Palmer 2000) and the use of the animal model.

There are several reasons why previous estimates of the heritability of FEC in this population may have been upwardly biased. First, there is a significant maternal effect on parasite resistance, equivalent to about 50% of the additive genetic variance in either sex (Table 1). Maternal effects on FEC have been previously reported in domestic sheep (Bishop et al. 1996), and may be caused by a tendency toward shared pasture use or forage selectivity between mothers and offspring, or they may be a consequence of environmentally determined maternal quality. Second, Smith et al. (1999) used mean values from the repeated FEC measures on each individual. This will both reduce the measurement error variance and remove genuine year-to-year variance within an individual, and thus inflate the heritability estimate. Using the animal-model approach, we were able to use repeated measures to estimate the permanent environmental effect. The permanent environmental effects variance was significantly different from zero, but tended to be lower than either the additive genetic or maternal effects variance for FEC. Part of this variance is likely to be due to dominance genetic variance, as we have previously demonstrated that inbreeding adversely affects parasite resistance in this population (Coltman et al. 1999a). However, to some extent the permanent environmental effect will be confounded with maternal effects (e.g., through the effects of a shared home range or pasture use).

Our results suggest that parasite resistance, as measured by FEC, has lower heritability than most morphometric traits (Fig. 1). However, this was not a consequence of the depletion of additive genetic variance due to selection, because parasite resistance traits have considerable additive genetic variance

TABLE 3. Residual variances, additive genetic variances, and covariances (±SE) of traits measured simultaneously in both sexes estimated jointly in a multiple-trait variance component estimation model. Figures in parentheses give *P*-values for *t*-tests of difference from zero.

	Males ($N = 493$ individuals)		Females ($N = 576$ individuals)		Between sex	
Trait	V_R	V_A	V_R	V_A	COV_A	r_a
Hindleg length	9.0 ± 0.7 (<0.001)	19.3 ± 3.2 (<0.001)	7.5 ±0.3 (<0.001)	22.1 ± 2.5 (<0.001)	8.3 ± 0.07 (<0.01)	0.40 ± 0.14 (<0.01)
Weight	4.3 ± 0.2 (< 0.001)	0.89 ± 0.23 (<0.001)	1.66 ±0.09 (<0.001)	1.18 ± 0.30 (<0.001)	0.43 ± 0.06 (<0.01)	0.42 ± 0.09 (<0.01)
FEC (summer)	0.26 ± 0.02 (< 0.001)	0.032 ± 0.007 (<0.001)	0.16 ± 0.01 (<0.001)	0.030 ± 0.004 (<0.001)	0.009 ± 0.004 (<0.05)	0.27 ± 0.13 (<0.05)

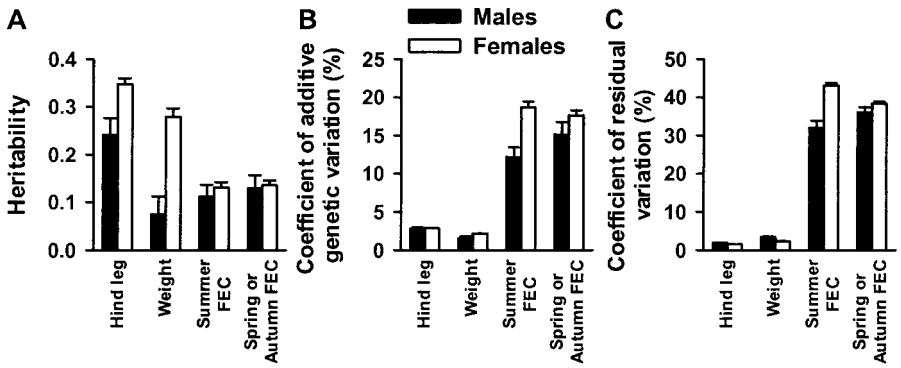

FIG. 1. (A) Heritabilities, and coefficients of (B) additive genetic and (C) residual variation for fecal egg count (FEC) and morphometric traits measured in male and female Soay sheep. Bars represent one standard error. Error bars for morphometric trait coefficients of variation are very small in relation to the axis scale.

when measured by the coefficient of additive genetic variance (Fig. 1). Rather, the low heritability of parasite resistance is more a consequence of high residual variance (Table 1, Fig. 1), and considerable additive genetic variation for FEC exists in the Soay sheep population despite strong selection. Furthermore, positive genetic correlations exist among six of the eight pairwise comparisons of morphometric traits and parasite resistance considered in this study, indicating that selection on morphometric traits reinforces selection in favor of parasite resistance indirectly (Table 4). This indicates that growth and parasite resistance are not traded off, but rather that genetically resistant individuals experience better growth. Why might parasite resistance have up to six-fold greater levels of additive genetic variation, as measured by the CV_A, than morphometric traits that are subject to similar selection intensity (Coltman et al. 1999b; Milner et al. 1999a)?

Maintenance of Genetic Variation for Parasite Resistance

A number of mechanisms may play a role in maintaining additive genetic variation for parasite resistance. First, parasite resistance is likely to be under control of a large number of genes, and therefore may have high additive genetic variance due to high net mutational input (Houle et al. 1996). A review by Houle et al. (1996) found that life-history traits have six-fold greater mutational variability than morphological traits. Like life-history traits, parasite resistance is a composite of variation at numerous loci. This may include loci underlying immunological parameters such as the major histocompatibility complex (MHC), genes encoding and regulating cytokine function, and other background genes (Stear and Wakelin 1998), as well as genes that may affect feeding behavior patterns that may determine exposure to infective larvae (Hutchings et al. 1999). Three loci have been shown to be associated with resistance to nematode infection in Soay sheep. One allele at the adenosine deaminase locus is correlated with both with reduced FEC and increased survival probability (Gulland et al. 1993). Paterson et al. (1998) found that variation at microsatellite loci associated with functional MHC genes is also correlated with juvenile FEC and survival. Variation in the interferon gamma gene, a cytokine that plays a critical role in regulating the type 1 versus type 2 immune responses in vertebrates (Wakelin 1996), is correlated with FEC in Soay sheep (Coltman et al. 2001).

Additive genetic variation may also be maintained through coevolution between the host and parasite (Haldane 1949; Anderson and May 1982). A host genotype may confer resistance to certain parasite strains, but this situation may change due to the selection exerted by the host immune system on the parasite gene pool and the associated evolutionary response by the parasite. As the host evolves resistance to infection or reduced virulence, parasites evolve to keep virulence and infectivity at an optimum level for continued survival and propagation (Ebert and Hamilton 1996). The ad-

TABLE 4. Additive genetic (below diagonal) and phenotypic (above diagonal) correlations (±SE) between traits analyzed in separate-sex, multiple-trait models.

Males	Hindleg length	Weight	FEC (summer)	FEC (autumn)
Hindleg length	—	+0.69 ± 0.05***	−0.16 ± 0.05***	−0.10 ± 0.07
Weight	+0.78 ± 0.05***	—	−0.15 ± 0.05***	−0.17 ± 0.07*
FEC (summer)	−0.23 ± 0.08**	−0.30 ± 0.25	—	+0.32 ± 0.07***
FEC (autumn)	−0.31 ± 0.13*	−0.39 ± 0.19*	+0.71 ± 0.09***	—
Females	**Hindleg length**	**Weight**	**FEC (summer)**	**FEC (spring)**
Hindleg length	—	+0.72 ± 0.04***	−0.16 ± 0.04***	−0.13 ± 0.06*
Weight	+0.80 ± 0.02***	—	−0.20 ± 0.04***	−0.16 ± 0.06**
FEC (summer)	−0.26 ± 0.02***	−0.05 ± 0.04	—	+0.26 ± 0.06***
FEC (spring)	−0.22 ± 0.04***	−0.14 ± 0.04***	+0.28 ± 0.04***	—

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

ditive value of a particular variant at a locus may not remain constant. In this way, additive genetic variation at some loci may be maintained by negative frequency-dependent or balancing selection, and there is evidence for the past action of balancing selection on MHC variants in Soay sheep (Paterson 1998).

Antagonistic pleiotropy may play a role in the maintenance of additive genetic variation for disease resistance. In mammals, resistance to intercellular pathogens such as gastrointestinal nematodes frequently depends on an elevated type 2 immune response (Else et al. 1994; Grencis 1997). The type 2 response is mediated by the action of cytokines such as interferon gamma and interleukin 5, and these cytokines play a direct role in down-regulating the type 1 immune response, or cell-mediated immunity, directed against intracellular pathogens such as bacteria and viruses. Sheep that are genetically resistant to nematode infection have a strong type 2 immune response (Gill et al. 2000), and therefore may be more susceptible to infection from intracellular pathogens. In Soay sheep, the interferon gamma resistance allele is associated with reduced FEC and increased titre of immunoglobin A specific to infective third stage *T. circumcincta* larvae (Coltman et al. 2001), a result consistent with the idea that enhanced type 2 immune response associated with parasite resistance in ruminants is genetically determined (Gill et al. 2000), perhaps in part by a polymorphism affecting the expression or efficacy of interferon gamma or a closely linked unidentified gene (Crawford and McEwen 1998). The resistant allele was not, however, associated with increased overwinter survival probability. One clear possibility that warrants future research is that sheep who are relatively resistant to nematodes are more prone to infection from viruses and bacteria due to depressed type 1 immune response, such that polymorphism at this locus could be maintained in the Soay sheep by antagonistic pleiotropy.

Implications for Animal Breeding

The results of this study may have important implications for breeding sheep genetically resistant to gastrointestinal parasites. First, our data indicate that there is considerable additive genetic variance for parasite resistance, and therefore potential for a continued response to selection, in an unmanaged population that has experienced continual directional selection for resistance over many generations. Second, because our data come from a relatively ancient sheep breed resembling Neolithic domestic sheep, they suggest that a positive genetic correlation between parasite resistance and body size or growth may be the wild-type condition and that selection for improved parasite resistance may not usually compromise production related traits.

Of course, extrapolation of our results to domestic sheep in general should be viewed cautiously. For one, Soay sheep are predominately infected by *T. circumcincta,* the most important parasite of domestic sheep in temperate areas of the world; however, our results may not necessarily bear on resistance to other nematodes such as *Haemonchus contortus* and *Trichostrongylus nematodirus,* which are more important in the Southern Hemisphere. Secondly, all domestic sheep breeds have been subject to different selective breeding histories and genetic drift, and therefore may be expected to have different allele frequencies at the loci underlying quantitative trait variation. It is perhaps for this reason that positive genetic correlations between parasite resistance and production traits have been found in some flocks (Douch et al. 1995; Eady et al. 1998; Morris et al. 2000) and positive correlations in others (Bishop et al. 1996; Bouix et al. 1998). Furthermore, estimates of the heritability of FEC made in domestic sheep, which typically range from 0.2 to 0.4, tend to be higher than our estimates in Soay sheep, but comparisons of heritability between the Soays and domestic sheep are problematic for many reasons including differences in environment, age structure, treatment history, and parasitological methods. Our pedigree will also contain errors in paternal assignments that will cause a downward bias in the estimate of additive genetic variance. For these reasons we have not directly compared our heritability estimates with those made in domestic sheep, however, it would seem likely that the level of additive genetic variation for parasite resistance in Soay sheep is as high as that of most domestic sheep flocks.

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