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MAPPING QUANTITATIVE TRAIT LOCI UNDERLYING FITNESS-RELATED TRAITS IN A FREE-LIVING SHEEP POPULATION

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We searched for quantitative trait loci (QTL) underlying fitness-related traits in a free-living pedigree of 588 Soay sheep in which a genetic map using 251 markers with an average spacing of 15 cM had been established previously. Traits examined included birth date and weight, considered both as maternal and offspring traits, foreleg length, hindleg length, and body weight measured on animals in August and jaw length and metacarpal length measured on cleaned skeletal material. In some cases the data were split to consider different age classes separately, yielding a total of 15 traits studied. Genetic and environmental components of phenotypic variance were estimated for each trait and, for those traits showing nonzero heritability ($N = 12$), a QTL search was conducted by comparing a polygenic model with a model including a putative QTL. Support for a QTL at genome-wide significance was found on chromosome 11 for jaw length; suggestive QTL were found on chromosomes 2 and 5 (for birth date as a trait of the lamb), 8 (birth weight as a trait of the lamb), and 15 (adult hindleg length). We discuss the prospects for refining estimates of QTL position and effect size in the study population, and for QTL searches in free-living pedigrees in general.

KEY WORDS: **Birth date, birth weight, body size, Soay sheep, QTL, variance components.**

The maintenance of quantitative genetic variation in natural populations has been the focus of intensive debate. Because natural selection is often directional, that is, it favors the individuals at one end of the phenotypic distribution of a trait (Endler 1986), it is expected that selection depletes disadvantageous alleles and leads to the fixation of favorable variants. Eventually, this process should remove the genetic diversity in a population, and the reduction of variability should be faster for traits more closely related to fitness (Fisher 1958). A survey of quantitative genetics parameters from a number of free-living, outbred animal populations has confirmed that the more closely related a trait is to fitness, the lower its heritability (Mousseau and Roff 1987; Roff

and Mousseau 1987; Roff and Simons 1997). However, in contrast to predictions, if the additive genetic variances of different traits are standardized by the trait mean rather than by the total variation, it appears that fitness-related traits tend to have *higher* additive genetic and nonadditive genetic components than traits less closely related to fitness (Houle 1992; Kruuk et al. 2000; Merila et al. 2001; McCleery et al. 2004). This counterintuitive finding suggests that fitness traits have a broad biological and genetic basis that confers high additive genetic variation, and it is the high environmental variation in fitness-related traits that result in their having relatively low heritability (Houle 1992).

The study of quantitative traits is traditionally based on a theoretical framework, the infinitesimal model, in which no knowledge of the number and location of the genes that underlie them is required (Fisher 1918). With respect to gene distribution and action across the genome, it is sufficient to assume that many genes are segregating in a given population, and that their individual allelic differences are small relative to the effects of the environment. Although the infinitesimal model is applicable to a wide variety of studies including natural populations, it fails to capture the complexity of genetic variation in terms of the number of genes involved, their relative effect, and their action and interaction. As early as 1973, for example, Elston and Stewart (1973; Stewart and Elston 1973) realized that a continuous normal phenotypic distribution is not necessarily generated by many additive loci but it can result from the action of a small number of genes interacting with the environment. Determining the nature of complex traits would help in understanding the action of selection because different evolutionary trajectories may result from different genetic architectures (Carlborg et al. 2006).

The development of techniques to generate and screen large numbers of molecular markers in many individuals has opened the way to investigating the whole genome to test whether specific regions (quantitative trait loci, QTL) affect variation in a trait more than the average background. The most insightful successes in QTL mapping have been obtained using experimental populations (Paterson et al. 1991; Kroymann and Mitchell-Olds 2005) based on divergent and often inbred lines grown under uniform conditions (Lynch and Walsh 1998). A typical experiment aimed at mapping QTL starts with crossing inbred lines that have been selected to diverge for the trait of interest; consequently, the selected lines are expected to be homozygous for the alleles conferring the extreme phenotypes. The mapping individuals, often F2 or backcross progenies, are then raised under controlled and uniform conditions designed to enhance the expression of the target phenotype and to reduce environmental heterogeneity (Lynch and Walsh 1998). Because the probability of QTL detection increases with the heritability of the study trait (Williams and Blangero 1999), such experimental designs offer high statistical power to map QTL: in the segregating progeny the additive genetic variance is maximized whereas the environmental variance is reduced.

Unfortunately, the findings discovered with these approaches cannot be readily used to interpret natural variation in the wild because the experimental conditions are often oversimplified or unrealistic. Inbred line crosses have reduced genetic diversity because only the alleles carried by the parental lines are screened in the segregating progeny. Another approach using interspecific crosses may generate variation (i.e., segregating QTL) at loci that do not segregate within a population in the wild. In addition, interactions between genotype and environment are probably altered. Although different strategies have been devised to overcome these limitations, such as the crossing and growing of wild individuals under controlled conditions (e.g., Lexer et al. 2003), the direct study of natural populations in their own environment would be the least dependent on compromising assumptions and constraints.

Variance components QTL analysis, the statistical method applied in this project, is particularly suitable for complex pedigrees. Different experimental and statistical strategies have been devised for mapping QTL using crosses of inbred or outbred lines of animal or plant populations (Haley et al. 1994; Zeng 1994; Lynch and Walsh 1998). However, these methods are less suitable for QTL mapping in large, complex pedigrees because they are designed for analysis of relatively simple pedigrees or single families, and consequently do not fully exploit the information of the range of pedigree relationships. In contrast, variance components analysis makes use of all the possible genetic relationships in the pedigree (Almasy and Blangero 1998; Williams and Blangero 1999). Furthermore, it is robust to deviations from assumptions such as missing or unbalanced data and departure from normality.

Despite its recognized interest, few projects have been undertaken to dissect natural genetic variation through QTL mapping because of the difficulties in collecting suitable phenotypic and genotypic datasets (for an exception see Slate et al. 2002; for reviews see Erickson et al. 2004 and Slate 2005). The human population can be considered "wild" and under natural selection in many respects such as disease resistance (Olson 2002; Sabeti et al. 2002; Bamshad and Wooding 2003), and linkage mapping in humans has proved to be a useful strategy to understand the genetic basis of complex traits, especially medical conditions (Complex Trait Consortium 2003; Botstein and Risch 2003). However, the use of medical treatments and ethical constraints make it hard to study the action of natural selection in modern humans.

The free-living Soay sheep population on Hirta, St. Kilda, U.K., is the subject of a long-term project aimed at addressing a wide range of ecological and evolutionary issues (extensively documented in Clutton-Brock and Pemberton 2004). The population dynamics are characterized by periodic fluctuations in the number of individuals. The population size increases until the density of animals exceeds the winter carrying capacity and, as a result, a

large proportion of individuals die in the following winter mainly due to starvation (Coulson et al. 2001; Clutton-Brock et al. 2004). Previous studies have investigated the genetic basis of a variety of traits associated with fitness in Soay sheep (Clutton-Brock and Pemberton 2004). Traits measured in early development, that is, birth date and birth weight, contribute to total fitness in Soay sheep (Clutton-Brock et al. 1992; Jones et al. 2005) and in other mammals such as red deer (Kruuk et al. 1999). In Soay sheep, lambs born heavier and later in the season have better survival in the first few months of life (Wilson et al. 2005b). Early development continues to influence survival during the first winter, when early-born and below average weight neonates are more likely to die, especially if the population density is high (Clutton-Brock et al. 1992; Milner et al. 1999). A detailed analysis of selection acting via mothers and offspring suggests there are differences in trait optima for mothers and offspring (Wilson et al. 2005b). In common with other mammal populations such as bighorn sheep (Coltman et al. 2002) and red deer (Kruuk et al. 1999), fitness of Soay sheep is positively correlated with adult body size measured either as body weight or hindleg length (Milner et al. 1999). In winters characterized by high mortality, directional selection favors heavier and longer-legged individuals (Milner et al. 1999). Heavier females are more fecund and more successful at rearing offspring (Clutton-Brock et al. 1997). Larger males (in terms of both body weight and hindleg length) have higher reproductive success, through an increased ability to monopolize receptive females (Preston et al. 2003).

Previous quantitative genetic analyses in the Soay sheep population indicate that the fitness-related traits discussed above harbor additive genetic variation. Heritability estimates for birth date and weight are 0.06 and 0.08, respectively, but in each case there is also a relatively substantial maternal genetic component (0.28 and 0.12, respectively, as a proportion of phenotypic variance) (Wilson et al. 2005a). These two traits also show substantial genetic correlation ($R_G = 0.962 \pm 0.375$ [SE]). In two studies using different data subsets, estimates for the heritability of body weight at age four months and above were 0.24 and 0.28 for females and 0.12 and 0.07 for males (Milner et al. 2000; Coltman et al. 2001) and heritability estimates for hindleg length were 0.26 and 0.35 for females and 0.20 and 0.24 in males (Milner et al. 2000; Coltman et al. 2001). These two traits again show substantial genetic correlation (R_G estimates for females 0.74 ± 0.09 and 0.80 ± 0.02 and for males 0.78 ± 0.10 and 0.78 ± 0.05).

Altogether, the large volume of phenotypic, pedigree, and environmental data that has been collected since 1985 makes the Soay sheep suitable for linkage mapping projects. Elsewhere we have described the construction of a genetic map for the study population and the mapping of three Mendelian traits segregating in Soay sheep (Beraldi et al. 2006). Here we report the result of variance components analyses and genome scans aimed at identifying QTL for neonatal traits (birth weight, birth date), and body size (body weight, hind and fore leg length, jaw length, and metacarpal length). The results presented constitute one of the first attempts to dissect the complexity of quantitative traits in the wild, and the methods here applied, based on an extension of methods developed for complex traits in humans (Amos 1994; Almasy and Blangero 1998; Williams and Blangero 1999; George et al. 2000), should be suitable for the analysis of any natural population with a pedigree of similar or even higher complexity.

Materials and Methods

STUDY POPULATION

The Soay sheep on the islands of Soay and Hirta (St. Kilda archipelago, North West Scotland, U.K., 57°49′ N, 08°34W) are feral populations of a breed regarded as the most primitive in Europe (Campbell 1974; Doney et al. 1974); nowadays, the sheep population of Hirta varies between 600 and 2000 individuals. Since 1985 regular expeditions have been sent to St. Kilda to monitor the population dynamics and to record the life histories of individuals living in Village Bay, Hirta (Clutton-Brock and Pemberton 2004). No predators are present on St. Kilda.

MAPPING PEDIGREE AND LINKAGE MAP

The whole Soay sheep pedigree file numbers more than 3900 animals. Within this pedigree maternal links were assigned through observation of the animals in the field, whereas paternal links were inferred through molecular analysis (Overall et al. 2005). From the total pedigree, a panel of 588 animals was genotyped at 247 microsatellite and four isoenzyme markers. This subset comprised all the sibships with 10 or more offspring and their common parents. Figure 1 shows part of the mapping pedigree (107 animals) as an example of its overall complexity. Ancestors of the genotyped individuals and animals linking different sibships ($n = 294$) were not genotyped, but they were included in the mapping pedigree to improve the estimates of the kinship and identity by descent (IBD) coefficients in the variance components analysis. A more thorough description of the mapping pedigree and selection criteria is included in Beraldi et al. (2006). The Soay sheep map covers approximately 90% of the genome with an average intermarker spacing of 15 cM. Further details of the map characteristics and of the technical procedures can be found in Beraldi et al. (2006).

PHENOTYPIC DATASET

Phenotypic records of the animals in the mapping pedigree were retrieved from the Soay sheep database in which data for more than 6000 sheep are stored. The data analyzed in this study were collected between 1988 and 2005 from animals born between 1978 and 2002. Sample sizes and summary statistics for each trait are reported in Table 1.

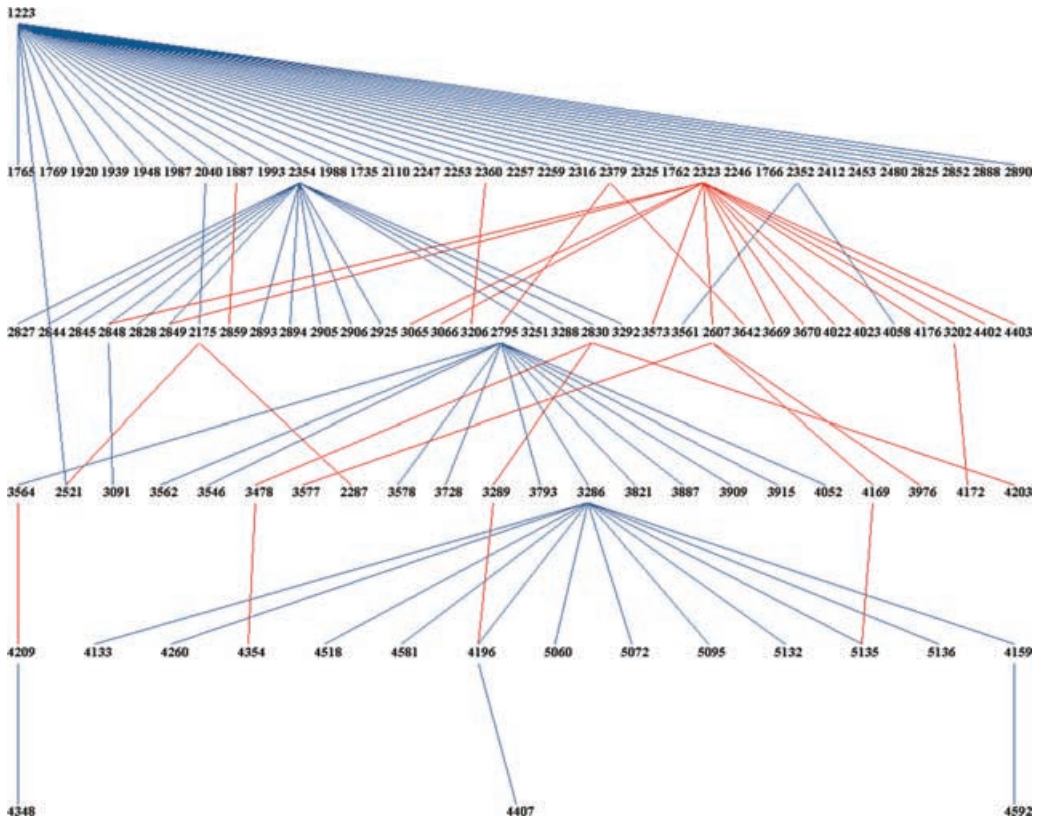

Figure 1. Graphical representation of part of the mapping pedigree: only sire 1223 (top left) and his descendants are shown. This subset contains 107 individuals out of the 882 of the whole mapping pedigree.

Two neonatal traits were considered. Daily observations allow us to identify *birth date* for each lamb to the nearest day, measured as the number of days from January 1. Newborn lambs are captured, tagged, and weighed to obtain *birth weight*; in this analysis we included measurements collected within four days of birth. Both birth date and birth weight were first analyzed as traits of the lamb and then analyzed as maternal traits. In the latter case the trait represented the average lambing date and the average offspring birth weight for each dam.

Sheep older than four months of age are regularly captured, especially during an annual August catch up and also at lower frequency during spring and autumn. At each capture *body weight* is obtained. Due to large seasonal variation, the body weight data analyzed here were restricted to data collected in August. *Foreleg length* measured in mm as the length of the metacarpal bone measured when both the knee joint and the hoof joint are bent away from it and *hindleg length* measured in mm from the tubercalcis of the fibular tarsal bone to the distal end of the metatarsus is also collected at each capture and post mortem. The genetic basis of variation in body weight and hindleg length varies over ontogeny (Wilson et al., in press) and so these traits, together with foreleg length, were analyzed in three different data subsets defined by the age of the animals included. The first (unrestricted) dataset included animals of all ages (minimum 47 days, maximum 15 years, mean 3.8 years); the second dataset included only those animals younger than nine months (referred to as lambs), and the third dataset included only animals older than nine months (referred to as adults). This classification was applied because for the two leg length measures it separates the juvenile period when heritability is low but maternal effects are strong from the adult period when heritability is high and maternal effects are no longer detectable.

Two additional measures of body size were available from cleaned skeletal material. *Metacarpal length* was measured as the distance between the proximal and distal canal foramina on the dorsal side of the metacarpus. *Jaw length* was measured as the distance between the gonion caudale and the most aboral indentation of the mental foramen. For both measures, all data were for adult animals (i.e., older than nine months).

DEFINITION OF FIXED EFFECTS

Fixed effects known to influence the study traits were fitted in the variance components models (see below). Table 2 lists the effects fitted for each trait and reports the number of degrees of freedom used by each effect. A general linear model analysis implemented in Minitab 14.1 (Minitab, Inc., State College, PA) was applied to

Table 1. Characteristics and estimated variance components of the study traits (NS: nonsignificant).

Trait	Dataset	Number of records[a]	Number of animals (genotyped)	Mean (SD)[b]	V_A^c (SE)[b]	CV_A^d (%)	h^{2e} (SE)[b]	V_M^f (SE)[b]	CV_M^g (%)	m^{2h} (SE)[b]	V_C^i (SE)[b]	CV_C^j (%)	c^{2k} (SE)[b]	V_E^l (SE)[b]	CV_E^m (%)	E^{2n} (SE)[b]
Birth date [days] (lamb)	Neonatal	710	710 (526)	111 (8)	6.467 (4.042)	2.29	0.07 (0.04)	63.946 (7.944)	7.19	0.69 (0.04)	NS	NS	NS	22.434 (3.299)	4.26	0.24 (0.04)
Birth date [days] (mother)	Neonatal	1901	311 (136)	140 (8)	19.700 (6.274)	3.16	0.28 (0.08)	NS	NS	NS	10.776 (5.107)	2.34	0.16 (0.07)	38.756 (0.393)	4.44	0.56 (0.03)
Birth weight [kg] (lamb)	Neonatal	601	601 (507)	2.30 (0.61)	0.022 (0.012)	6.44	0.16 (0.09)	0.034 (0.009)	8.06	0.25 (0.06)	NS	NS	NS	0.079 (0.010)	12.26	0.58 (0.08)
Birth weight [kg] (mother)	Neonatal	1708	306 (133)	2.22 (0.73)	0.048 (0.007)	9.86	0.27 (0.03)	NS	NS	NS	NS	NS	NS	0.131 (0.005)	16.34	0.73 (0.03)
Foreleg length [mm]	All	2242	737 (509)	124 (10)	6.977 (2.491)	2.14	0.16 (0.06)	1.116 (0.908)	0.86	0.03 (0.02)	18.334 (2.423)	3.47	0.44 (0.06)	15.418 (0.584)	3.18	0.37 (0.02)
	Lambs	401	377 (308)	113 (8)	NS	NS	NS	5.679 (3.103)	2.10	0.13 (0.07)	28.507 (4.346)	4.70	0.66 (0.10)	8.833 (2.531)	2.62	0.20 (0.06)
	Adults	1841	659 (436)	126 (9)	12.437 (3.004)	2.80	0.32 (0.07)	NS	NS	NS	11.954 (2.405)	2.75	0.30 (0.06)	14.968 (0.626)	3.08	0.38 (0.02)
Hindleg length [mm]	All	2379	740 (512)	177 (12)	17.884 (4.873)	2.40	0.25 (0.06)	10.777 (2.259)	1.86[b]	0.15 (0.03)[o]	32.891 (4.101)	3.24	0.47 (0.06)	8.834 (0.329)	1.68	0.12 (0.01)
	Lambs	425	400 (329)	162 (10)	NS	NS	NS	9.897 (4.999)	1.95	0.14 (0.07)	55.045 (6.029)	4.59	0.77 (0.07)	6.831 (1.952)	1.62	0.10 (0.03)
	Adults	1954	659 (436)	180 (10)	25.421 (5.074)	2.80	0.46 (0.08)	NS	NS	NS	21.132 (3.618)	2.55	0.38 (0.07)	8.459 (0.337)	1.61	0.15 (0.01)
Body weight [kg]	All	1672	579 (407)	21.62 (6.45)	1.650 (0.699)	5.94	0.12 (0.05)	3.736 (0.929)[o]	8.94[b]	0.26 (0.05)[0]	4.323 (0.703)	9.62	0.30 (0.05)	4.559 (0.211)	9.88	0.32 (0.03)
	Lambs	401	380 (314)	13.78 (2.98)	NS	NS	NS	1.104 (0.511)	7.62	0.20 (0.09)	3.211 (0.578)	13	0.59 (0.11)	1.086 (0.356)	7.56	0.20 (0.07)
	Adults	1297	396 (228)	23.95 (5.20)	2.475 (0.948)	6.57	0.23 (0.08)	NS	NS	NS	4.282 (0.885)	8.63	0.40 (0.08)	3.963 (0.191)	8.31	0.37 (0.03)
Metacarpal length [mm]	Adults	450	449 (332)	78 (6)	7.204 (2.076)	3.44	0.45 (0.11)	NS	NS	NS	NS	NS	NS	8.762 (1.611)	3.79	0.55 (0.11)
Jaw length [mm]	Adults	566	565 (396)	112 (13)	7.824 (2.155)	2.48	0.39 (0.10)	NS	NS	NS	NS	NS	NS	12.113 (1.753)	3.09	0.61 (0.10)

[a]Total number of measurements in the dataset; [b]standard error; [c]additive genetic variance; [d]coefficient of additive genetic variation; [e]heritability; [f]maternal genetic variance; [g] coefficient of maternal genetic variation; [h]maternal effect; [i]permanent environmental variance; [j]coefficient of permanent environmental variation; [k]permanent environmental effect; [l]residual variance; [m]coefficient of residual variation; [n]residual effect; [o]maternal effect fitted on lambs only (animals younger than 9 months).

Table 2. Fixed effects for the study traits fitted in the polygenic and QTL models. Numbers are the degrees of freedom used by each effect (NF: not fitted).

Trait	Dataset	Mean	Sex	Litter size	Mother's age	Birth date	Birth year	Capture year	Capture age	Cohort
Birth date (lamb)	Neonatal	1	1	NF	10	NF	25	NF	NF	NF
Birth date (mother)	Neonatal	1	1	2	NF	NF	20	NF	NF	24
Birth weight (lamb)	Neonatal	1	1	1	10	NF	16	NF	3	NF
Birth weight (mother)	Neonatal	1	1	1	10	1[a]	19	NF	1[a]	NF
Foreleg length	All ages	1	1	2	NF	NF	24	17	24	NF
	Lambs	1	1	2	NF	NF	14	NF	1[a]	NF
	Adults	1	1	2	NF	NF	24	17	16	NF
Hindleg length	All ages	1	1	2	NF	NF	24	17	24	NF
	Lambs	1	1	2	NF	NF	14	NF	1[a]	NF
	Adults	1	1	2	NF	NF	24	17	16	NF
Body weight	All ages	1	1	2	NF	NF	23	17	16	NF
	Lambs	1	1	2	NF	NF	14	NF	1[a]	NF
	Adults	1	1	2	NF	NF	22	17	10	NF
Metacarpal length	Adults	1	1	2	NF	NF	22	NF	11	NF
Jaw length	Adults	1	1	2	NF	NF	24	15	15	NF

[a]Effect fitted as covariate.

determine the fixed effects significantly contributing to variation in the study traits. Sex was fitted with two levels (male or female); litter size with either two (twin or singleton) or three levels (twin, singleton, unknown). The age of the mother was classified into 11 levels (one year old to 10 or more, plus one level for unknown age). Although the age of the mother is a continuous variable, the fitting of mother's age as multilevel factor rather than as a covariate allowed better correction of the study traits and allowed the use of records in which the age of the mother was unknown. Birth date was fitted as a covariate and was measured as days from January 1 of the year of birth. Birth year and capture year had one level for each year to control for differences in environmental conditions (e.g., population density) at the time of birth or measurement. Capture age accounted for the growth of the animal and was fitted as a covariate in lamb foreleg and hindleg length, in lamb body weight, and in birth weight as trait of the mother. In birth weight as trait of the offspring, capture age was fitted as factor with four levels, one for each day from birth. In the other traits capture age was divided into 11 levels for age from zero to one year (one level for each month) and 14 levels after the first year of age (one level for each year). Mother's cohort was fitted as a factor in which each level was a different year of birth of the mother.

VARIANCE COMPONENTS ESTIMATION

Under the null hypothesis of no segregating QTL (i.e., major genes whose effect stands out from the average genetic background), it is assumed that the additive genetic variation is represented by a number of genes with small effect randomly scattered across the genome, and for this reason this design is called the polygenic model. The polygenic model provides the log likelihood against which to test the alternative hypothesis of linkage. In addition, it yields information about the relative weight of the different variance components on the total variation.

Under a polygenic model, fixed effects can be included to account for known influences on the phenotypic mean, whereas the remaining variance is partitioned among specified random effects (Lynch and Walsh 1998; Williams and Blangero 1999). In the simplest case the random effects will include just the additive genetic value such that

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{a} + \mathbf{e}$$

where $\mathbf{y}$ is a vector of records on individuals, $\boldsymbol{\beta}$ is a vector of fixed effects, $\mathbf{a}$ is a vector of additive genetic effects (or breeding values) estimated on the basis of the coefficient of co-ancestry between any pair of individuals in the pedigree, and $\mathbf{e}$ is a vector of residual effects. $\mathbf{X}$ and $\mathbf{Z}$ are design matrices relating records to the appropriate fixed or random effects. The appropriate fixed effects were determined separately for each trait (see above and Table 2). Additional components responsible for the total variation (random effects), such as permanent environment and maternal effect, were fitted if they significantly improved the likelihood of the models (likelihood ratio test, the test statistic under the null hypothesis that the variance component is zero is a 50:50 mixture of zero and a χ^2 with 1 df). The additive genetic relationship matrix created from the pedigree file incorporated information from all known and inferred relatives, of both sexes, correctly weighted for relatedness. Where different measurements of the same trait,

on the same individual, were available at different life stages, the permanent environmental effect grouped the repeated measurements to determine the environmental variance between individuals who arose from long-term or nonlocalized conditions. Finally, the maternal effect removed variation due to the contribution of the mother's phenotype and genotype on the offspring's trait. It should be noted that if the maternal effect is not explicitly modeled, its variation is included in the additive genetic component, thus leading to possibly biased results.

Heritability (h^2), maternal effect (m^2), permanent environment effect (c^2), and residual effect (e^2) were calculated as the ratio of the relative variance component (V_A, additive genetic variance; V_M, maternal genetic variance; V_C, permanent environmental variance; V_E, residual variance) to total phenotypic variance (V_P), i.e.$h^2 = V_A/V_P$; $m^2 = V_M/V_P$; $c^2 = V_C/V_P$; $e^2 = V_E/V_P$.

The coefficient of variation (CV) standardizes the variance by the trait mean instead of the total variance, and it is calculated as the ratio of the standard deviation (square root of the variance) to the mean times 100, therefore,

$$CV_i = 100V_i^{1/2}/\bar{x},$$

where the subscript i stands for the additive genetic (A), maternal effect (M), permanent environment (C), and residual components (E) and x is the trait mean.

Variance components were estimated by the restricted maximum likelihood (REML) procedure (Lynch and Walsh 1998) implemented in the software package ASReml (Gilmour et al. 2002).

QTL MAPPING

To map putative segregating QTL, an IBD matrix estimated at any given map position was fitted in the polygenic model described above as an additional random effect (George et al. 2000):

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Za} + \mathbf{Zq} + \mathbf{e}$$

where $\mathbf{q}$ is a vector of additive QTL effect. The IBD matrix at a given chromosomal position contains all the pairwise probabilities that that chromosomal region is identical by descent between any pair of individuals in the pedigree file. The IBD matrices, calculated using marker data and pedigree structure (see below), can be thought as the genetic make-up of the mapping population. The QTL mapping task, therefore, is to test whether the study trait (phenotype) co-varies with the IBD probability at any map position. If, after the removal of fixed and random effects, individuals consistently share the same phenotypic and IBD state, then the chromosomal region where the IBD was calculated contains one or more QTL.

IBD sharing statistics were estimated using pedigree relationships, marker data, and map distances and are described in detail in Beraldi et al. (2006). For an initial scan, IBD matrices and variance components were estimated every 10 cM. Putative QTL regions were then scanned every 1 cM. All the markers present on a chromosome were simultaneously used to generate the IBD matrices relevant for that chromosome. The IBD sharing analysis was performed by a Markov chain Monte Carlo (MCMC) procedure, which is based on a stochastic process (gene-drop simulations) and as such does not provide an exact result, but allows the handling of very large and complex pedigrees. After a burn-in period of 1000 cycles, 100,000 MCMC iterations were performed and sample statistics were stored every 10 iterations. This process was implemented in the program Loki (Heath 1997). The IBD matrices were then inverted and fitted one by one in ASReml using a program written by one of the authors (AFM) to automate the process of inputting and storing the results. Logarithm of the odds (LOD) scores were calculated as the difference in log likelihood between QTL and polygenic model according to the equation

$$\mathrm{LOD} = (L_1 - L_0)/\ln(10)$$

where L_1 is the natural log likelihood of the QTL model and L_0 is the natural log likelihood of the polygenic model.

The significance thresholds adopted in this study to declare evidence of a QTL correspond to those suggested by Lander and Kruglyak (1995) for human pedigrees; this decision was taken on the basis that the size of the Soay sheep and human linkage maps are very similar (about 3300 cM). The LOD value of 3.3 denotes the *genome-wide* significance, that is, the probability of finding a false positive every 20 genome scans; the value 1.9 corresponds to the *suggestive* linkage that is the evidence expected to occur once at random in a genome scan (Nyholt 2000). Confidence intervals for the presence of a putative QTL were defined by the map range within a one-LOD score drop from the peak value, this is equivalent to approximately 95% confidence (Lander and Botstein 1989).

Results

VARIANCE COMPONENTS ANALYSIS

Under the null hypothesis with no QTL effects, variance components analysis provides estimates of various population parameters and these are reported in Table 1. Consistent with Wilson et al. (2005a) we found that birth date had a low heritability ($h^2 = 0.07$) as a trait of the lamb, but a substantial maternal effect ($m^2 = 0.69$), and when analyzed as a trait of the mother showed a much higher heritability ($h^2 = 0.28$, Table 1). Similarly birth weight had a lower additive genetic component than maternal component when analyzed as a trait of the lamb ($h^2 = 0.16$, $m^2 = 0.25$) but a higher heritability as a trait of the mother ($h^2 = 0.27$; Table 1). The coefficient of variation for birth weight was approximately three times higher than that for birth date (as a trait of the lamb: $CV_A = 6.44$ for birth weight vs. $CV_A = 2.29$ for birth date; as a

trait of the mother: $CV_A = 9.86$ for birth weight vs. 3.16 for birth date; Table 1).

With respect to body size traits measured on individuals older than neonates, the analysis of foreleg and hindleg length and body weight across all ages showed a moderate to low heritability (h^2 foreleg length = 0.16, h^2 hindleg length = 0.25, body weight = 0.12; Table 1) whereas the maternal effect, fitted only for animals of up to nine months of age, explained 3% of the variation in fore leg length, 15% of the variation in hindleg length, and 26% of the variation in body weight (Table 1). When the data were restricted to measurements taken on lambs (< nine months of age), no additive genetic component was detected for any of the three measures of body size, but a maternal effect was found for all three traits (Table 1). When the data were restricted to measurements taken on adults (≥ nine months of age), heritability was moderately high for leg length ($h^2 = 0.32$ for foreleg length and 0.46 for hindleg length) and moderate for body weight ($h^2 = 0.23$), and no maternal effect was detected (Table 1).

Both skeletal measurements had substantial heritabilities ($h^2 = 0.45$ for metacarpal length $h^2 = 0.39$ for jaw length; Table 1) and, consistent with the other traits when measured on individuals greater than nine months of age, no maternal effects were detected in these traits (Table 1).

Where multiple measurements on the same individual were recorded, the permanent environmental effect could be estimated and, in most cases, explained a substantial proportion of the variation (Table 1). The c^2 ranged from 0.16 for birth date as trait of the mother to 0.77 for hindleg length in lambs. CV_C ranged from 2.34 for birth date as trait of the mother to 13 for body weight in lambs (Table 1).

GENOME SCANS

Genome scans were performed for the traits having an additive genetic component greater than zero; therefore, leg length and body weight in lambs were not investigated further. The LOD score profiles of the whole genome are shown in Figures 2 and 3.

The highest LOD score values identified for each trait are listed in Table 3 along with the variance components estimates and the map characteristics of the region containing the peaks.

Suggestive evidence of a QTL was detected on chromosomes 2 and 5 for birth date as a trait of the lamb (LOD = 2.70 and 2.16, respectively) and on chromosome 8 for birth weight as a trait of the offspring (LOD = 2.54). In all these case cases the suggestive QTL accounted for all of the additive genetic variation. Chromosome 15 showed suggestive evidence of a QTL for hindleg length in adults (LOD = 2.89), which explained 36% of the variation (residual genetic variation: $h^2 = 0.09$). Finally, a genome-wide significant QTL was detected for adult jaw length on chromosome 11 (LOD = 3.59). The IBD matrix corresponding to the position harboring the QTL explained 29% of the phenotypic variation, thus reducing the residual genetic variation to $h^2 = 0.15$. The LOD profiles of these chromosomes are shown in more detail in Figure 4. QTL confidence intervals derived from the 1-LOD drop support correspond to approximately 30 and 20 cM for birth date (lamb) for chromosomes 2 and 5, respectively, 40 cM for birth weight (lamb), 40 cM for hindleg length, and 20 cM for jaw length (Fig. 4, Table 3).

Discussion

We have performed one of the first genome-wide scans in a wild population, the free-living Soay sheep on St. Kilda, to investigate the genetics of fitness-related traits. The traits targeted in this project represent different aspects of early development and body size, and several of them have documented relationships with total fitness (see Introduction) (Clutton-Brock et al. 1992; Milner et al. 2000; Jones et al. 2005). Such quantitative traits are probably the raw material for microevolutionary change. Our results suggest that at least one genomic region is likely to carry genes of biological and evolutionary relevance and four other regions have suggestive QTL, although their validity has to be confirmed by further analyses.

VARIANCE COMPONENTS QTL ANALYSIS

The mapping panel used in this study presents a probably unprecedented level of complexity for a QTL genome scan. Furthermore, in common with many long-term studies of natural populations, there is missing information in the Soay sheep pedigree, genotype, and phenotype files. All of the 882 pedigree members were related to each other, although they belonged to several different half-sibling families and spanned up to seven generations including many inbreeding loops (175 loops detected by Loki). As explained in the Introduction, variance components QTL analysis, the statistical method applied in this project, is particularly suitable for complex pedigrees. Following George et al. (2000), we performed a two-step variance components analysis in which the first step involved the estimation of IBD matrices using an MCMC procedure. The MCMC sampling method allowed the handling of the entire pedigree to exploit the genetic relationship between all possible pairs of individuals. In the second step, the phenotypic, pedigree, and IBD information was combined in a REML framework to estimate the parameters of interest.

NEONATAL TRAITS

Consistent with Wilson et al. (2005a), we found that in Soay sheep birth date and birth weight are determined more by the maternal performance (maternal effect) than by the offspring. Consistent with this observation, in the mapping panel we found a heritability of 0.07 and 0.28 as a trait of the lamb and trait of the mother, respectively (Table 1). Likewise, we found a heritability of 0.16

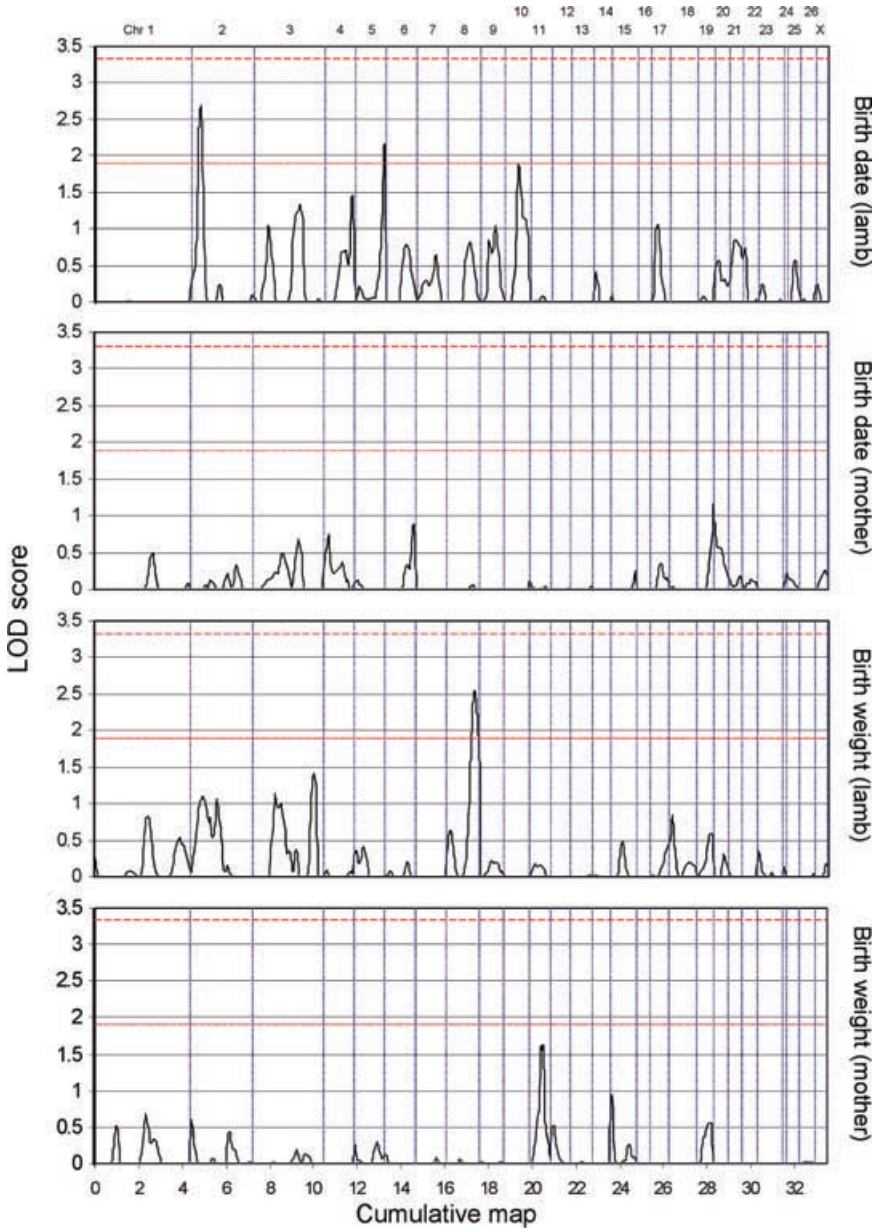

Figure 2. **Whole genome scans of neonatal traits. Top to bottom: birth date as a trait of the lamb and of the mother and birth weight as a trait of the lamb and of the mother. LOD score values (ordinates) were plotted against genetic position (abscissas, Morgan scale). Dotted lines show the genome-wide significance threshold (3.3); dashed lines are the suggestive significance threshold (1.9). Vertical lines mark the chromosome boundaries and chromosome names are displayed at the top.**

and 0.27 for birth weight as a trait of the lamb and trait of the mother, respectively (Table 1). Therefore, we scanned the genome to detect QTL affecting birth weight and birth date as a trait of both the lamb and the mother. We found two suggestive linkages (LOD = 2.70 and 2.16 on chromosomes 2 and 5, respectively) for birth date as a trait of the lamb and a suggestive linkage (LOD = 2.54) for birth weight as a trait of the lamb on chromosome 8. A previous study in a commercial sheep breed did not examine birth weight as a trait but identified suggestive QTL on chromosomes 2, 3, and 18 for weight at 8 weeks of age (Walling et al. 2004), but these results had limited significance and could not be replicated (Johnson et al. 2005). In cattle suggestive QTL for birth weight have been detected on chromosomes 21 and 26 (Casas et al. 2003, 2004), which are homologous to chromosomes 4 and 18, respectively, in sheep. At the moment, we are not aware of any published genome scans performed to identify QTL for birth date in sheep or cattle. The scans for birth date and birth weight as traits of the mother did not produce any particular evidence for QTL, the highest LOD score being 1.16 and 1.63, respectively. This is perhaps a reflection of the fact that the power of analysis was reduced by

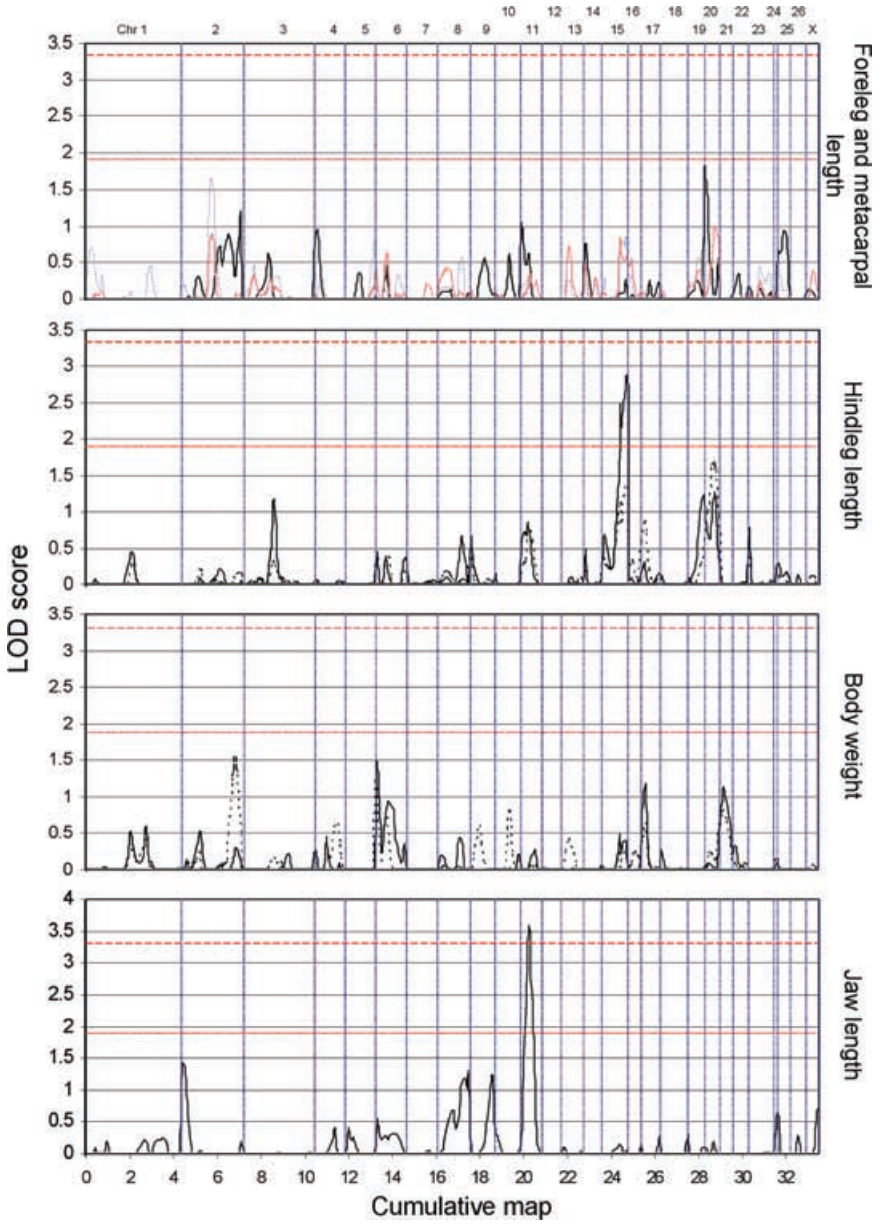

Figure 3. **Whole genome scans of body size traits. Top to bottom: foreleg length (continuous line, metacarpal length; dotted line, adults; hatched line, animals of all ages), hindleg length (continuous line, adults; dotted line, animals of all ages), body weight (continuous line, adults; dotted line, animals of all ages), and jaw length. Graph legend as in Figure 2.**

the small number of genotyped mothers ($n = 136$ for birth date, $n = 133$ for birth weight) compared with genotyped offspring ($n = 526$ for birth date, $n = 507$ for birth weight; Table 1). To the best of our knowledge, no previous studies have been undertaken to detect QTL affecting birth date or birth weight as traits of the mother in sheep.

BODY SIZE TRAITS

The phenotypic datasets for foreleg, hindleg length, and body weight were initially analyzed including animals of all ages and then re-analyzed to include only lambs or only adults. This strategy was pursued to define traits with a higher proportion of genetic variance. In the pedigree analyzed in this study, there was no additive genetic variation for either leg length or body weight in lambs, whereas adults had significant heritable variation for leg length and body weight. Overall, this trend suggests that the same trait has different sources of additive genetic or environmental variation at different ontogenic stages. Body size, for example, was more strongly affected by the permanent environmental effect in lambs than in adults, especially with respect to hindleg length (hindleg length $c^2 = 0.77$ in lambs, $c^2 = 0.38$ in adults,

Table 3. QTL LOD scores above suggestive significance for the study traits and their estimated parameters.

Trait	Dataset	LOD	Chromosome	Position (cM)	Flanking markers (cM)[a]	1-LOD drop support (cM)	q^2 (SE)[b]	h^2 (SE)[c]	m^2 (SE)	c^2 (SE)
Birth date (lamb)	Neonatal	2.70*	2	53	LPLP2 (12) McM505 (1)	30	0.14 (0.04)	0.00 (0.00)	0.70 (0.03)	–
		2.16*	5	136	CSRD134 (17) BMS1247 (2)	20	0.11 (0.04)	0.00 (0.00)	0.69 (0.03)	–
Birth date (mother)	Neonatal	1.16	20	1	BM1815 (1) OLADRB2 (24)	–	0.34 (0.08)	0.00 (0.00)	–	0.10 (0.06)
Birth weight (lamb)	Neonatal	2.54*	8	130	URB024 (16) BMS1967 (8)	40	0.21 (0.07)	0.00 (0.00)	0.26 (0.06)	–
Birth weight (mother)	Neonatal	1.63	11	61	MCM120 (3) ETH3 (10)	–	0.26 (0.03)	0.00 (0.00)	–	–
Foreleg length	All	0.99	20	54	BM1818 (2) BM1905 (18)	–	0.12 (0.07)	0.06 (0.08)	0.03 (0.02)	0.43 (0.05)
	Adults	1.65	2	145	BM81124 (12) CP79 (10)	–	0.22 (0.10)	0.10 (0.12)	–	0.30 (0.06)
Hindleg length	All	1.69	20	45	OMHC1 (10) BM1818 (12)	–	0.21 (0.08)	0.07 (0.10)	0.15 (0.03)	0.44 (0.06)
	Adults	2.89*	15	113	BMS2076 (13) MCM105 (6)	40	0.36 (0.11)	0.09 (0.13)	–	0.39 (0.07)
Body weight	All	1.55	2	253	BM6444 (0) BM2113 (26)	–	0.13 (0.04)	0.00 (0.00)	0.26 (0.05)	0.29 (0.04)
	Adults	1.50	6	1	BM9058 (1) MCM0204 (4)	–	0.22 (0.07)	0.00 (0.00)	–	0.41 (0.07)
Metacarpal length	Adults	1.82	20	7	BM1815 (7) OLADRB2 (18)	–	0.45 (0.10)	0.00 (0.00)	–	–
Jaw length	Adults	3.59**	11	37	CSSME70 (9) SRCRSP6 (1)	20	0.29 (0.10)	0.15 (0.13)	–	–

[a]The distance (cM) of the flanking markers from the QTL peak is given in parentheses; [b]QTL heritability (QTL variance/total phenotypic variance); [c]Heritability due to polygenic effect after having fitted a QTL effect (residual heritability); *LOD score chromosome-wide significant (LOD > 1.9); **LOD score genome-wide significant (LOD > 3.3).

$c^2 = 0.47$ in all ages combined; Table 1). In general, the linear traits (leg lengths, metacarpal, and jaw length) had high values of h^2 and low values of CV_A whereas body weight had lower h^2 but higher CV_A (Table 1). To make a specific comparison, although the heritability of adult hindleg length was found to be more than twice that of adult body weight, the coefficient of variation was higher for body weight than for hindleg length (CV_A= 2.80 vs. 6.57). With respect to the permanent environmental effect, V_C had a similar value in both traits in terms of the proportion of total variation explained ($c^2 = 0.38$ hindleg length vs. 0.40 body weight). However, the coefficient of variation of VC for body weight was more than three times that of hindleg length ($CV_C = 2.55$ vs. 8.63). This trend confirms the intuition that body weight is composed of several underlying traits that confer a higher overall genetic contribution to the trait, but also a higher residual variation which in turn results in a lower ratio V_A/V_P (i.e., heritability).

Genome scans were conducted on all body size traits except in lamb datasets (animals of age up to nine months) due to the absence of heritable variation (see above). In adults, the most significant result for hindleg length was identified on chromosome 15 (LOD = 2.89, Table 3). Unfortunately, the scan performed by Walling et al. (2004) in commercial sheep did not include chromosome 15 so that it is not possible to compare the results. Hindleg length in all ages combined produced the highest LOD score on chromosome 20 (LOD = 1.69, Table 3) where putative QTL for fat depth have been recorded (Walling et al. 2004). The same region harbors the MHC, a gene complex involved in the immune response and affecting parasite resistance in Soay sheep (Paterson et al. 1998). The two highest LOD score peaks identified for body weight were located on chromosomes 2 (LOD = 1.55, animals of all ages) and 6 (LOD = 1.50, adults, Table 3). The peak on chromosome 6 corresponds to the region identified by Walling et al. (2004) for muscle depth. The genome scan for jaw length produced a genome-wide significant QTL with LOD score of 3.59. This trait represents a component of body size and, as such, is probably under selection (Milner et al. 1999). As far as we are aware, no other studies of this trait have been conducted in ruminants.

Improved modeling of traits for which multiple measures are available at different ages, such as body size, could be achieved by applying a random regression analysis to allow for the change of the genetic effect over time (Macgregor et al. 2005). We pursued this strategy by fitting in the variance component model the first-degree polynomial of the QTL effect. Although the random regression model was no better than the model with constant QTL effect (results not shown), this does not preclude the possibility that better modeling of longitudinal traits may improve the performance of the analysis.

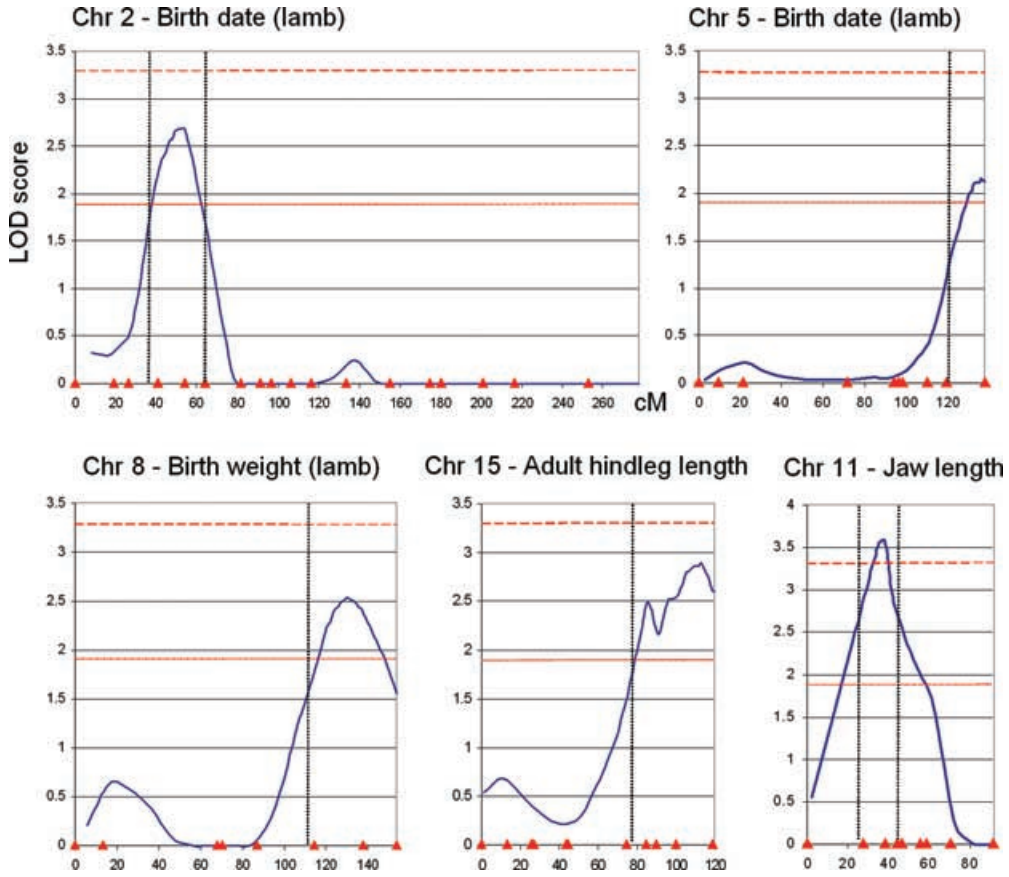

Figure 4. **Detailed map positions of the candidate QTL identified by the genome scans. Vertical lines define the 1-LOD drop confidence intervals. Triangles on the abscissas (chromosome maps) show the marker positions. Dotted and dashed horizontal lines represent the suggestive and significant linkage thresholds as in Figure 2.**

EFFECT SIZES

Although we report estimated effect sizes in Table 3 to provide a comparison with similar studies, these estimates are inevitably inflated. In fact, the estimation of the QTL heritability and effect from a genome scan aimed at mapping is upwardly biased and probably unrealistic, especially when the QTL has weak effect (Goring et al. 2001). This is because the maximum likelihood procedure provides the highest statistical evidence of linkage (LOD score) in which the parameters (QTL effect) are maximized. Therefore, independent datasets should be analyzed if both QTL position and effect are desired (Goring et al. 2001).

Furthermore, in the case of studies focused on natural selection, a case can be made that effect sizes should be estimated without fitting fixed effects in the analysis, because selection only "sees" raw variation. For sake of QTL detection, removing fixed effects offsets the limited sample size and time range of a typical study. However, if the goal is to estimate the effect size of a (confirmed) QTL, removing fixed effects would bias effect size estimation. This is because natural selection operates on the whole phenotype and uncoupling the target traits from other characters would modify the trait under selection.

FUTURE DEVELOPMENTS

The key challenge now is to follow-up this work to confirm the validity of the putative QTL detected. Genotyping of additional markers around the putative QTL documented here in the existing pedigree will be conducted to improve the estimates of the IBD-sharing probabilities and hence the resolution of the confidence intervals and to confirm or reject the hypothesis of linkage. Second, an independent set of families genotyped at the putative QTL regions will allow confirmation of the presence of QTL and more realistic estimation of QTL effect sizes.

Previous simulation studies have established that linkage disequilibrium in Soay sheep probably declines rapidly with genetic distance and that the overall linkage disequilibrium background is likely to be low (McRae et al. 2005). This pattern of linkage disequilibrium should allow the fine mapping of QTL through association analysis if the target region can be enriched with markers to a resolution equal to or less then 2 cM/marker (McRae et al. 2005). Such a marker density could be achieved combining microsatellites and single nucleotide polymorphism (SNP) markers and by typing a larger number of individuals than were used here. We have previously managed to fine map Mendelian trait loci by

linkage disequilibrium mapping (Gratten et al., unpubl. ms.) and similar efforts are underway to fine map quantitative traits.

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