



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/196970/>

Version: Published Version

Article:

Gauzere, J., Pemberton, J.M., Slate, J. et al. (2023) A polygenic basis for birth weight in a wild population of red deer (*Cervus elaphus*). *G3 Genes|Genomes|Genetics*, 13 (4). jkad018. ISSN: 2160-1836

<https://doi.org/10.1093/g3journal/jkad018>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

A polygenic basis for birth weight in a wild population of red deer (*Cervus elaphus*)

Julie Gauzere,^{1,2,*} Josephine M. Pemberton,¹ Jon Slate,³ Alison Morris,¹ Sean Morris,¹ Craig A. Walling,¹ Susan E. Johnston ¹

¹Institute of Evolutionary Biology, University of Edinburgh, Edinburgh EH9 3FL, UK

²AGAP, Université Montpellier, CIRAD, INRAE, Institut Agro, 34090 Montpellier, France

³School of Biosciences, University of Sheffield, Sheffield S10 2TN, UK

*Corresponding author: Bâtiment ARCAD 10, rue Arthur Young 34090 Montpellier, France. Email: gauzere.ju@gmail.com

Abstract

The genetic architecture of traits under selection has important consequences for the response to selection and potentially for population viability. Early QTL mapping studies in wild populations have reported loci with large effect on trait variation. However, these results are contradicted by more recent genome-wide association analyses, which strongly support the idea that most quantitative traits have a polygenic basis. This study aims to re-evaluate the genetic architecture of a key morphological trait, birth weight, in a wild population of red deer (*Cervus elaphus*), using genomic approaches. A previous study using 93 microsatellite and allozyme markers and linkage mapping on a kindred of 364 deer detected a pronounced QTL on chromosome 21 explaining 29% of the variance in birth weight, suggesting that this trait is partly controlled by genes with large effects. Here, we used data for more than 2,300 calves genotyped at >39,000 SNP markers and two approaches to characterise the genetic architecture of birth weight. First, we performed a genome-wide association (GWA) analysis, using a genomic relatedness matrix to account for population structure. We found no SNPs significantly associated with birth weight. Second, we used genomic prediction to estimate the proportion of variance explained by each SNP and chromosome. This analysis confirmed that most genetic variance in birth weight was explained by loci with very small effect sizes. Third, we found that the proportion of variance explained by each chromosome was slightly positively correlated with its size. These three findings highlight a highly polygenic architecture for birth weight, which contradicts the previous QTL study. These results are probably explained by the differences in how associations are modelled between QTL mapping and GWA. Our study suggests that models of polygenic adaptation are the most appropriate to study the evolutionary trajectory of this trait.

Keywords: genome-wide association study, genomic prediction, GenPred, genomic relatedness, heritability, maternal effects, *Cervus elaphus*

Introduction

Many quantitative traits appear to be subject to selection and yet show substantial levels of genetic variation in nature (Mousseau and Roff 1987; Kingsolver et al. 2001). Understanding how evolutionary forces act on genetic variation remains one of the most fundamental goals in evolutionary biology (Johnson and Barton 2005; Mitchell-Olds et al. 2007; Kruuk et al. 2008). To address this question, we need to understand the nature of quantitative trait variation, i.e. the number and identity of genes underlying trait variation, their physical location in the genome, and their interactions with each other. This detailed knowledge of genomic architecture can also help us to determine how a trait will respond to new selection pressures. For instance, a trait with an oligogenic architecture (i.e. affected by relatively few large effect loci) can evolve faster than a trait with a polygenic architecture (affected by many genes of small effect), but its genetic variation can also be quickly eroded with potential adverse effect on population

viability in the long-term (Kardos and Luikart 2021). Yet, to date, there are still few descriptions of the genomic architecture of quantitative fitness-related traits in wild populations (for exceptions see Bérénos et al. 2015; Santure et al. 2015; Duntsch et al. 2020).

Since the development of molecular markers, quantitative genetic studies have sought to identify the individual loci responsible for trait variation (quantitative trait loci, QTL). Until recently, the main procedure for mapping genes was through “linkage mapping”, which conducted linkage analyses between markers and QTLs, usually performed using microsatellite markers and large half-sibling families, which limited its application in wild populations (Slate et al. 2010; but for an exception see e.g. Slate et al. 2002). With the genomic revolution, and reduced cost of sequencing and genotyping, genome-wide association studies (GWAS), which detect statistical associations between SNP markers and QTL that are sufficiently closely linked, have become increasingly

Received: October 07, 2022. Accepted: January 13, 2023

© The Author(s) 2023. Published by Oxford University Press on behalf of the Genetics Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

accessible. This approach is more flexible than linkage mapping, but it requires much higher marker densities and sample sizes, which ultimately allow us to map QTLs with greater precision (Jensen et al. 2014; Gienapp et al. 2017). Most importantly, the development of GWAS in wild populations means that, in principle, we can now uncover the genomic basis of the large standing variation measured within natural populations. Nonetheless, this task remains challenging because a large proportion of phenotypic variation in nature is usually caused by non-genetic factors (e.g. due to environmental fluctuation; Kruuk 2004; Kruuk and Hadfield 2007), which needs to be accounted for in association analyses.

Until recently, genetic mapping and GWAS have been mainly performed in humans and model organisms. Their results strongly support the idea that most quantitative traits have a polygenic basis (Sella and Barton 2019). In humans, for instance, GWAS have discovered thousands of variants associated with complex traits and diseases (e.g. Goddard and Hayes 2009; Visscher et al. 2012; Yengo et al. 2018), each having a small effect on the trait's value and explaining a very small fraction of the trait heritability. Long-term individual-based studies of wild vertebrates have greatly enhanced our understanding of the genetic basis of fitness-related traits in nature (Kruuk et al. 2008; Slate et al. 2010; Charmantier et al. 2014). Using these data sets, some genetic mapping studies have reported major effect loci, with QTLs explaining more than 20% of the heritability of quantitative traits (e.g. Slate et al. 2002; Poissant et al. 2012). However, these results could be an artefact due to the relatively small sample sizes available in non-model organisms (Slate 2013). Indeed, a well-known statistical bias is the inflation of QTL effect sizes when analysing moderate sample sizes (the Beavis effect; Beavis 1994). Replication of studies with larger data sets is therefore essential to validate the QTLs found in this literature.

The red deer population of the Isle of Rum, Scotland, has been intensively studied since 1972. Previous quantitative genetic studies have estimated the heritability of a variety of traits, as well as their association with fitness (Kruuk et al. 1999). Birth weight is a particularly interesting trait for evolutionary studies, as it is positively associated with juvenile survival and male reproductive success (Kruuk et al. 1999; Gauzere et al. 2022) and shows a moderate heritability, with $h^2 = 0.30$ (0.23; 0.41) (Gauzere et al. 2020). We estimated that maternal effects, i.e. the influence of mother's phenotype on the phenotype of her offspring (over and above the direct effect of genes inherited from her), largely contributed to this heritability value, these effects being mainly genetic in origin (Gauzere et al. 2020). Maternal genetic effects indeed explained half of this heritability value, the other half being due to the direct genetic effects. In a previous study, Slate et al. (2002) performed a QTL scan for birth weight using phenotypic, genotypic (90 microsatellites and 3 allozymes), pedigree and linkage map data in a kindred of 364 deer. The authors detected three potential QTL including a pronounced QTL on chromosome 21 explaining 29% of the genetic variance for birth weight. Here, we re-evaluate the genetic architecture of birth weight using a GWA approach, providing a more precise understanding of how genetic variation is distributed throughout the genome. The main drawback of this approach is that it did not allow us to decompose the direct and maternal genetic effects on birth weight, meaning that part of the genetic variance explored here is also due to maternal genetic effects.

In this study, we used data for more than 2,300 individuals and 39,000 SNPs evenly distributed across the genome to estimate the heritability of birth weight based on genomic relatedness. Next,

we used GWA to search for genomic regions associated with birth weight. The model included a genomic relatedness matrix (GRM) to account for potential confounding effects of population structure (Price et al. 2006). Finally, we used the genomic prediction model BayesR (Moser et al. 2015) to analyse the distribution of SNP effect sizes and the proportion of variance explained by the SNPs on each chromosome. Our approach followed a similar recent study on the Soay sheep on St Kilda, which showed high accuracy to predict genomic estimated breeding values (GEBVs; Ashraf et al. 2021). Although genomic prediction analyses are usually used to estimate GEBVs, they can also be used to describe the genomic architecture of quantitative traits, such as the SNP-based heritability, the proportion of variance explained by large effect loci or by individual chromosomes. Here, we applied this approach for the first time in the wild red deer population.

Material and methods

Study population and SNP data set

The red deer living in the population in the North Block of the Isle of Rum, Scotland (57° 03' N, 06° 21' W), have been intensively monitored since 1972. The calving period generally extends over 6 weeks, from mid-May to late June. Most calves born within the 12 km² study area are caught soon after birth (often within 24 h), weighed, tagged, and sampled for DNA (via an ear punch). DNA is also routinely extracted from post-mortem tissues and cast antlers.

All sampled individuals within the study area have been genotyped at an attempted 51,248 SNP markers (Huisman et al. 2016) on the Illumina Cervine BeadChip using an Illumina iScan instrument (Illumina Inc., San Diego, CA, USA). SNP genotypes were clustered using the Illumina GenomeStudio software and quality control was carried out using PLINK v1.9 with the following thresholds: SNP genotyping success >0.99, minor allele frequency >0.01 and individual genotyping success >0.99 (following Johnston et al. 2017). A linkage map specific to the Rum population is available, with 38,083 SNPs assigned to linkage groups corresponding to the 33 deer autosomes and X chromosome (Johnston et al. 2017). Estimated SNP positions are based on this linkage map. In total, $n = 3,067$ individuals were genotyped at 39,587 SNPs.

Model of birth weight and GRM-based heritability

We analysed the weight (kg) of calves caught within 7 days of birth and born before August 1 (following Gauzere et al. 2020) and modelled it as a Gaussian trait. The model of birth weight accounted for the effect of calf sex, age at capture (hours), effects related to maternal condition, namely maternal age (years) and maternal reproductive status (as categorized in five levels), and the effect of birth location (categorized into six regions; see Gauzere et al. 2020). We also considered two random effects to account for the phenotypic variance in birth weight explained by variance in additive genetic effects (σ_a^2) and variance due to cohort effects (σ_c^2). Models of genetic architecture, especially genomic prediction models, do not easily accommodate different sources of genetic effects (e.g. maternal genetic effects). For this reason, we did not fit a maternal effect for birth weight here or in the following methods (more details can be found in the [Supplementary Information SI](#)). In a model omitting maternal effects, the maternal effect variance will mainly be confounded with additive genetic variance leading to inflated h^2 estimates (Kruuk and Hadfield 2007). We know that maternal effect variance in birth weight is mainly due to genetic effects (Gauzere et al. 2020); maternal genetic effects explain 35% of the total phenotypic variance in birth weight

and maternal environmental effects only explain 8% of the phenotypic variance. For this reason, we believe our models will not be biased by uncontrolled environmental effects.

We estimated the heritability of birth weight using an animal model and genomic information derived from a genome-wide relatedness matrix (GRM), namely a GRM-based heritability (h^2_{GRM}). The GRM was estimated using the `—make-grm` function in GCTA v1.90.2 (Yang et al. 2011). This GRM was adjusted to account for imperfect linkage disequilibrium (LD) between markers using the `—grm-adj 0` function. The estimated GRM was used to specify the covariance structure of the additive genetic effects in the birth weight model. The animal model was fitted using the R-package ASReml-R v3 (Gilmour et al. 2006).

Genome-wide association study

A GWAS was performed to test for association between trait and SNP genotypes using the R-package RepeatABEL v1.1 (Rönnegård et al. 2016). First, we used the `“preFitModel”` function to fit the model of birth weight, with the fixed and random effects listed above, but without the SNP effects. We then used the `“rGLS”` function to test the effect of each SNP genotype on birth weight, accounting for the variance components previously estimated and the list of fixed effects. This model also accounted for population structure by fitting the GRM as a random effect. *P*-values for each SNP were computed using Wald statistics, distributed as χ^2 with 1 degree of freedom. We divided these statistics by the genomic inflation factor λ to account for potential inflation due to population structure not captured by the GRM, where λ is defined as the median observed χ^2 statistic divided by the median χ^2 statistic as expected from a null distribution (Devlin and Roeder 1999). A previous study by Johnston et al. (2018) on this dataset established the genome-wide significance threshold at a *P*-value of 1.42×10^{-6} after correcting for multiple testing and accounting for nonindependence due to linkage disequilibrium between SNP markers. In total, we analysed $n=2,317$ calves.

Estimation of SNP effect sizes and chromosome partitioning

The BayesR method implemented in the BayesR v0.95 software package (Moser et al. 2015) was used to infer the phenotypic variation explained by SNPs in different effect size groups and their contribution per chromosome. This method also estimated the SNP-based heritability (h^2_{SNP}). The SNP-based heritability differs from the GRM-based heritability as it estimates the proportion of variance accounted for by linear regression of a set of genotyped SNPs on the trait value (de los Campos et al. 2015). BayesR models SNP effects as a number of distributions of different effect sizes, including one of zero effect. Here, we ran the model with four distributions of effect size of 0, 0.0001, 0.001, and 0.01 (as a proportion of the phenotypic variance). BayesR does not allow for the inclusion of any fixed or random effects. Consequently, we first fitted the model of birth weight with lme4 (not considering any additive genetic effects) and we used the residuals of this model as phenotypes in Bayes R (following Ashraf et al. 2021; see Supplementary Information Part 1 for more information).

We first ran the model using a training population containing 95% of phenotyped and genotyped individuals (randomly selected). We then predicted genomic estimated breeding values (GEBVs) in the remaining 5%. We repeated this operation with a randomized 95% subset 10 times. The accuracy of the model was estimated as the Pearson correlation between the GEBVs and the observed phenotypic values, divided by the square root of the trait's heritability (estimated using an animal model with

a GRM; h^2_{GRM}) (Ashraf et al. 2021). Finally, we used all the phenotypic and genomic information available to characterise the genomic architecture of birth weight using the estimated distribution of effect sizes. We estimated the proportion of variance explained by each chromosome using the allele frequencies and effect sizes of the mapped SNPs. We tested for the association between chromosome size and variance explained using a linear model. For polygenic traits, we expect the proportion of genetic variance explained by each chromosome to be directly related to its size (i.e. the number of genes it contains). The MCMC chains were run for a total of 120,000 iterations with a burnin of 20,000 and a thinning interval of 100, to sample 1,000 posterior samples for each parameter and individual.

Estimation of effective population size and power calculation

The accuracy of association-based methods critically depends on the existence of linkage disequilibrium (LD) between causal loci and genetic markers. The effective population size (N_e) directly affects the pattern of LD across the genome. For this reason, genomic prediction shows low accuracy in wild populations with large effective population sizes (N_e) in comparison to domesticated species (Gienapp et al. 2019). Peters et al. (2022) have recently described the genome-wide LD pattern in the study population, and showed a relatively slow decay of LD across the genome. However, no study had yet used genomic data to estimate historical N_e in the red deer population. Here, we used the SNeP model developed by Barbato et al. (2015) to estimate N_e from LD information. This software considers squared Pearson's product-moment correlation coefficient between pairs of loci to define LD. We fitted SNeP with default parameters.

We also performed a power analysis to evaluate the capacity of our GWA study to detect biologically meaningful QTLs (i.e. explaining $\geq 5\%$ of genetic variance in birth weight). We conducted this analysis using an analytical method developed by Wang and Xu (2019), which uses as input the kinship matrix (GRM), the ratio of the additive genetic variance to the residual variance (estimated by the GWA model), and the sample size ($n=2,317$). This calculation gives the power to detect association when the causative variant is typed. The power at the marker locus thus also depends on the coefficient of LD between the marker and causative variant (Pritchard and Przeworski 2001). Therefore, we adjusted the sample size to the effective sample size (n') accounting for the linkage disequilibrium between neighbouring markers ($r^2=0.2$; Peters et al. 2022), so that $n'=463.4$.

Results

Analysis of power to detect QTL

We estimated that there is relatively good power to detect biologically meaningful QTLs ($\text{power}=0.72$ for $h^2_{\text{locus}}=0.05$, and $\text{power} \geq 0.99$ for $h^2_{\text{locus}} \geq 0.10$). Therefore, if birth weight has an oligogenic basis (as suggested by the previous QTL mapping study; Slate et al. 2002), we would be able to detect it. Based on genome-wide LD information, we estimated a relatively low effective population size of $N_e=175$, which suggested that genomic prediction models are relevant to investigate and predict the genetic evolution of complex traits in the study populations.

GRM-heritability and GWAS

The variance partitioning approach using an animal model and a GRM showed that birth weight had a significant and moderate heritability with $h^2_{\text{GRM}}=0.38$ (0.32; 0.44) (point estimate and 95%

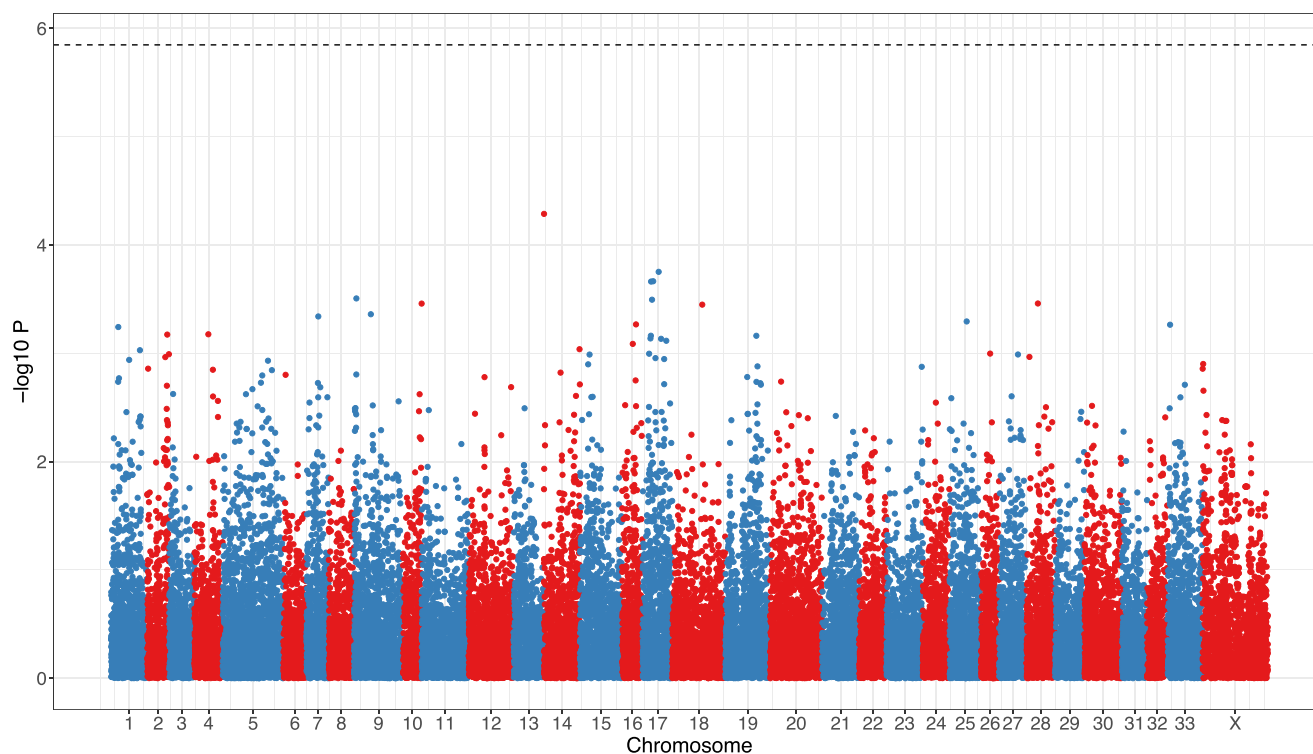


Fig. 1. Manhattan plot for the association between birth weight and SNPs. Top dashed line: significance threshold equivalent to $\alpha = 0.05$. Points are coloured by chromosomes (blue: odd numbers; red: even numbers). We only show results for the SNPs with known map positions. Previous potential QTLs found by [Slate et al. \(2002\)](#) were on chromosomes 12, 14 and 21 but not mapped with sufficiently good precision to be represented here.

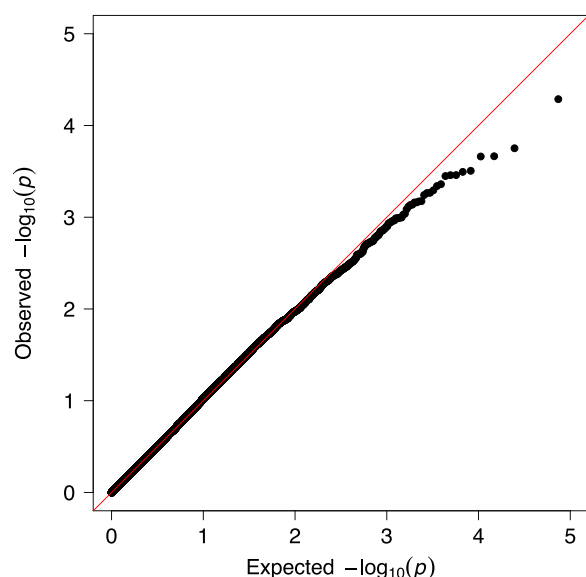


Fig. 2. Quantile-quantile (Q-Q) plot of GWAS P-values for birth weight (shown in the Manhattan plot). This is a graphical representation of the deviation of the observed P-values from the null hypothesis. We found no P-values larger than expected under the null hypothesis (there are not points above the 1:1 diagonal).

confidence intervals). This GRM-based heritability is very similar to a pedigree-based one with a model also omitting maternal effects ($h^2_{\text{PED}} = 0.45$; see [Supplementary Information, Part 1](#)).

The GWAS revealed a flat association landscape with no SNP significantly associated with birth weight ([Fig. 1](#)). The Q-Q plot showed that the P-values from the model were distributed as

expected under a null model, and no obvious outliers were detected ([Fig. 2](#)). The genomic control inflation parameter was moderate, with $\lambda = 1.34$, and was used to adjust our test statistics to properly account for population structure. The top 10 SNPs with the lowest P-values are listed in [Supplementary Table 1](#).

Genomic prediction accuracy, distribution, and quantification of SNP effect sizes

The genomic prediction model had a high accuracy to predict the genomic estimated breeding values (GEBVs) in the red deer population. This is an important finding, as models such as BayesR have not yet been tested and validated on many wild animal data sets (see e.g. [Gienapp et al. 2019](#); [Ashraf et al. 2021](#)). The mean model accuracy was 0.71, with a minimum of 0.44 and a maximum of 0.88 ([Fig. 3](#)). The estimated heritability using the genomic prediction model was $h^2_{\text{SNP}} = 0.38$ (0.26; 0.49) (95% credible intervals), very similar to the GRM- and pedigree-based heritabilities estimates above.

We found a positive correlation between the chromosome size and the proportion of additive genetic variance explained by each chromosome ([Fig. 3](#)). Chromosome 9 explained most variation, but this was nevertheless a very low percentage of the total genetic variation (<12.5%). Most SNPs had no effect on birth weight and only 5,805 SNPs were predicted to have a non-zero effect on birth weight. The largest proportion of genetic variance is explained by loci with very small effect sizes ([Table 1](#) and [Supplementary Table 2](#)). Altogether, results from the genomic prediction model are suggestive of a highly polygenic architecture. Nonetheless, one should be cautious when interpreting these estimates, especially regarding the number of SNPs with small effect sizes and proportion of variance explained by these SNPs, which are estimated with a very large uncertainty ([Table 1](#)). As also noted by

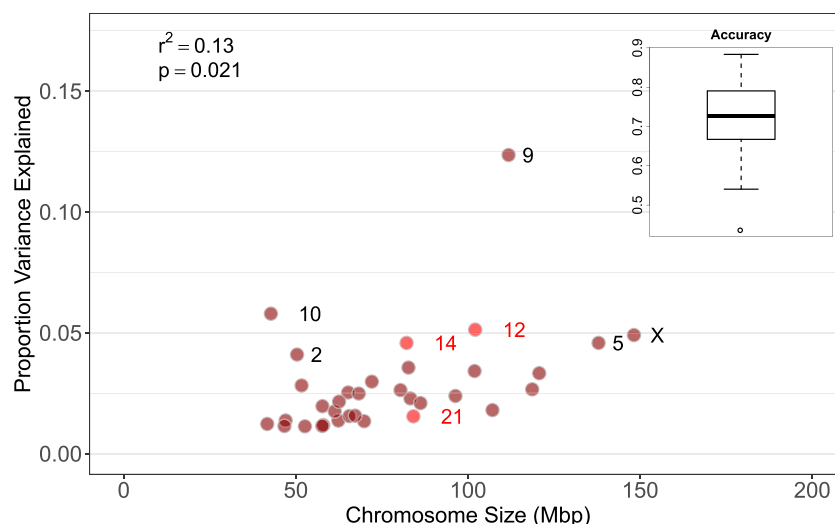


Fig. 3. Chromosome partitioning from the genomic prediction analysis. The proportion of additive genetic variance explained by each chromosome is slightly positively correlated with their size. The genomic prediction model has a high accuracy to predict the breeding values for birth weight, with a mean accuracy of 0.71 (using $h^2_{\text{SNP}} = 0.38$). The previous QTLs reported by [Slate et al. \(2002\)](#) were found on chromosomes 21, 12 and 14 (in red), which respectively explain here 1.5, 5.1 and 4.6% of the genetic variance.

Table 1. Number and effect sizes of SNPs contributing to phenotypic variation.

	Mean estimate	Lower CI	Upper CI
V_A	0.456	0.30	0.66
V_E	0.757	0.67	0.85
N_{SNP}	5,805	1,179	9,432
N_{SNP_0}	33,782	30,155	38,408
$N_{\text{SNP}_0.0001}$	5,402	260	9,392
$N_{\text{SNP}_0.001}$	392	117	951
$N_{\text{SNP}_0.01}$	10	0	37
$\text{PGV}_{0.0001}$	0.54	0.03	0.94
$\text{PGV}_{0.001}$	0.39	0.02	0.93
$\text{PGV}_{0.01}$	0.07	0.00	0.26

Results from the genomic prediction model. N_{SNP} provides the number of non-zero SNPs and N_{SNP_X} the number of SNPs in each effect size groups X. PGV is the proportion of genetic variance assigned to the three non-zero effect size distribution (sum equals 1).

[Ashraf et al. \(2021\)](#), the relatively small sample sizes used in studies in natural populations probably make it difficult to distinguish between zero effect and small effect loci.

Discussion

Two decades of genetic mapping in wild populations have provided contrasting results about the genetic architecture of fitness-related traits ([Slate et al. 2010](#); [Jensen et al. 2014](#)). Some of the earlier works, which showed apparently large effect loci using QTL mapping techniques, need to be reevaluated using high-density genome-wide markers. In this study, we used two different genomic approaches to describe the genetic architecture of birth weight in a natural population of red deer, a trait known to be under strong positive selection ([Kruuk et al. 1999](#); [Gauzere et al. 2022](#)). Both approaches demonstrate that this trait is heritable and has a polygenic architecture. Pedigree and GRM-based heritability estimates were very similar, indicating that the genotyped SNPs are in sufficiently high linkage to represent the recombination events in the study population (as also found by [Peters et al. 2022](#)). Additionally, [Peters et al. \(2022\)](#) recently showed that the linkage disequilibrium among the SNPs present on the red deer SNP

chip is maintained over a distance of up to 1Mb. Such linkage is essential in mapping studies and suggests that we should be able to detect major QTLs, although not necessarily locate them with great precision. These results indicate that pedigree-free approaches offer a promising prospect for measuring the heritability of fitness-related traits in the wild, even when using relatively small sample sizes ([Bérénos et al. 2014](#); [Perrier et al. 2018](#)).

Three different results provide evidence that birth weight has a highly polygenic genetic architecture: (1) there were no significant SNP associated with birth weight in the GWAS, (2) in the BayesR model, most variation was explained by loci with very small effect sizes and (3) in the same analysis, the variance explained by each chromosome scaled with chromosome size. These findings are in line with a number of recent genomic studies usually showing flat association landscapes (e.g. [Hansson et al. 2018](#); [Duntsch et al. 2020](#); [Peters et al. 2022](#)), but contradict a previous study on the genetic architecture of birth weight in the study population, which reported a major effect QTL on chromosome 21 ([Slate et al. 2002](#)). A similar scenario applies in the great reed warbler system, in which a large effect QTL for wing length found using linkage mapping was not found using GWAS, albeit with a very small sample size for GWAS (181 individuals; [Hansson et al. 2018](#)). Here, we confirmed that, with the sample size and number of markers used in this study, we have enough power to detect moderate to large effect size loci affecting birth weight if such major QTLs existed; we can thus confidently exclude this hypothesis.

Mapping studies using small sample sizes can overestimate the effect size of significant QTLs and/or identify false positive QTLs due to the Beavis effect ([Slate 2013](#)). The Beavis effect has a biological explanation: fewer recombination events are represented in small sample sizes, hence multiple loci that affect a trait can be misidentified as single QTL with a large effect ([Josephs et al. 2017](#)). This bias likely affected the results of the previous QTL study that used a sample size of about 350 individuals. However, if the previous results were entirely due to the Beavis effect and the co-segregation of multiple QTLs, we would have expected to detect some signal at the chromosome 21. On the contrary, we found that chromosome 21 is among those that explains the smallest amount of variation in birth weight (1.5%). Consequently,

poor resolution does not explain the large effect QTL previously reported. It is most likely that the result by [Slate et al. \(2002\)](#) was due to the fact that microsatellite-based and pedigree-based QTL mapping are more sensitive to spurious associations ([Hansson et al. 2018](#)) and that lower significance thresholds were used. Moreover, the previous analysis was conducted within one specific kindred in the red deer population. A spurious association could therefore have emerged if related individuals in that lineage shared unique alleles at loci on chromosome 21 and also had higher/lower birth weight. Because GWAS and genomic prediction models are fundamentally different methods from QTL mapping that look at the statistical association between genotype and phenotype and do not focus on the co-segregation of markers in a pedigree, they are less sensitive to this bias. Finally, population structure and hidden family structure can also cause false positives in mapping studies ([Price et al. 2006](#); [Wood et al. 2014](#)). GWAS uses a mixed model framework that is flexible enough to allow the inclusion of a genomic relatedness matrix to account for this structure. We also corrected our statistics by the inflation factor to avoid detecting SNPs erroneously associated with birth weight.

When analysing natural populations, one of the biggest challenges is to control for potential environmental covariates that might affect trait variation. Indeed, such covariates might buffer the signal of genotype-phenotype association, which might explain why plant GWAS performed in controlled environmental conditions are usually able to map larger effect QTLs ([Josephs et al. 2017](#)). Here, we controlled for the major environmental effects and covariates known to affect birth weight. We also know that maternal effects are an importance source of phenotypic variance in birth weight (35% of phenotypic variance explained; [Gauzere et al. 2020](#)). However, the approach used did not allowed us to decompose the maternal effect variance from direct genetic variance (see [Supplementary Information Part 1](#) for more details). This is because almost all the maternal effect variance is due to maternal genes ([Gauzere et al. 2020](#)). Decomposing the genetic architecture of direct and maternal genetic effects is a daunting task that requires statistical cross-fostering ([Wolf and Cheverud 2012](#)) or modelling the effect of transmitted and non-transmitted alleles ([Kong et al. 2018](#)), methods that have only been applied in model systems or very large human datasets. Because we found a polygenic architecture for birth weight, we do not believe that decomposing these effects will provide more information than the current analysis. However, one has to keep in mind that part of the genetic variance explored here is due to maternal genetic effects.

Our results highlight the potential of genomic prediction models to study the trait architecture and evolution in this wild population. Indeed, we report a high accuracy to predict GEBVs that is comparable to that found in a similar wild study system, the Soay sheep of St Kilda ([Ashraf et al. 2021](#)), and in plant and animal breeding (e.g. [de los Campos et al. 2013](#); [Bhat et al. 2016](#)). We know that the accuracy of genomic prediction depends, among other things, on the effective population size (N_e), which directly affects LD patterns across the genome ([Visscher et al. 2006](#); [Hill and Weir 2011](#)). Here, we study an island population with a relatively small N_e ($N_e=175$), which explains this high accuracy in comparison to other wild populations (e.g. in birds; [Gienapp et al. 2019](#)). Most importantly, our model is flexible enough to capture different genetic architectures, as it models SNP effects as a mixture of distributions describing large and small effect sizes. Nonetheless, further characterization of the architecture of a polygenic trait such as deer birth weight would require a much

larger data set than the one used here to disentangle small effect sizes from zero effect.

This study uses one of the largest datasets in a wild population, with ~2,300 individuals phenotyped and genotyped, to explore the genetic architecture of a fitness-related trait. This knowledge of the underlying genetic architecture of quantitative traits is most important to understand the origin of genetic variance and how it evolves. According to theory, the evolution of birth weight, a trait with a highly polygenic architecture, will be driven by subtle changes of allelic frequencies at many QTLs and by covariance among QTLs ([Le Corre and Kremer 2003](#)). This polygenic architecture should counteract the loss of genetic variation due to natural selection ([Sella and Barton 2019](#)). The results found here suggest that models of polygenic adaptation that explicitly model the genome-wide covariance between allele frequency changes in temporal or spatial data are the most appropriate to measure the genomic imprint of natural selection (see e.g. [Buffalo and Coop 2020](#)).

Data availability

All the genomic and phenotypic data used in this paper have been deposited on figshare, <https://doi.org/10.6084/m9.figshare.21842130>. [Supplemental material](#) available at G3 online.

Acknowledgements

We thank NatureScot for permission to work on Rum. We thank F. Guinness, M. Baker and many others for collecting field data, J. Huisman, P. Ellis, H. Lemon and P. Jack for DNA extraction, T. Clutton-Brock, S. Albon and L. Kruuk for their contributions to the long-term project, and L. Peters for her help with the calculation of linkage disequilibrium. The SNP genotyping was conducted at the Wellcome Trust Clinical Research Facility Genetics Core in Edinburgh. The UK Natural Environment Research Council funded the long-term project and this research; a European Research Council Advanced Grant to J. M. Pemberton supported most SNP genotyping.

Funding

This research was supported by a Natural Environment Research Council (NERC) grant. NERC reference: NE/R001456/1.

Conflicts of interest statement

The authors declare no conflict of interest.

Author contributions

J.G., S.E.J., C.A.W., and J.M.P. designed the study. A.M. and S.M. collected the data. J.G. ran the analyses and drafted the manuscript. S.E.J. and J.S. provided help and guidance to implement the analyses. J.G., S.E.J., J.S., C.A.W., and J.M.P. discussed and interpreted the findings.

Literature cited

- Ashraf B, Hunter DC, Berenos C, Ellis PA, Johnston SE, Pilkington JG, Pemberton JM, Slate J. Genomic prediction in the wild: a case study in Soay sheep. *Mol Ecol*. 2021;31(24):6541–6555. doi:10.1111/mec.16262.
- Barbato M, Orozco-terWengel P, Tapio M, Bruford MW. *SNep*: a tool to estimate trends in recent effective population size trajectories

- using genome-wide SNP data. *Front Genet.* 2015;6:Article 109. doi:10.3389/fgene.2015.00109.
- Beavis W. 1994. The Power and Deceit of QTL Experiments: Lessons from Comparative QTL Studies. *Proceedings of the Forty-Ninth Annual Corn and Sorghum Research Conference.* 250–266.
- Bérénos C, Ellis PA, Pilkington JG, Lee SH, Gratten J, Pemberton JM. Heterogeneity of genetic architecture of body size traits in a free-living population. *Mol Ecol.* 2015;24(8):1810–1830. doi:10.1111/mec.13146.
- Bérénos C, Ellis PA, Pilkington JG, Pemberton JM. Estimating quantitative genetic parameters in wild populations: a comparison of pedigree and genomic approaches. *Mol Ecol.* 2014;23(14):3434–3451. doi:10.1111/mec.12827.
- Bhat JA, Ali S, Salgotra RK, Mir ZA, Dutta S, Jadon V, Tyagi A, Mushtaq M, Jain N, Singh PK, et al. Genomic selection in the era of next generation sequencing for complex traits in plant breeding. *Front Genet.* 2016;7:Article 221. doi:10.3389/fgene.2016.00221.
- Buffalo V, Coop G. Estimating the genome-wide contribution of selection to temporal allele frequency change. *Proc Natl Acad Sci U S A.* 2020;117(34):20672–20680. doi:10.1073/pnas.1919039117.
- Charmanier A, Garant D, Kruuk L. *Quantitative Genetics in the Wild.* Oxford: Oxford University Press; 2014.
- de los Campos G, Hickey JM, Pong-Wong R, Daetwyler HD, Calus MPL. Whole-genome regression and prediction methods applied to plant and animal breeding. *Genetics.* 2013;193:327–345.
- de los Campos G, Sorensen D, Gianola D. Genomic heritability: what is it? *PLoS Genet.* 2015;11(5):e1005048. doi:10.1371/journal.pgen.1005048.
- Devlin B, Roeder K. Genomic control for association. *Biometrics.* 1999;55(4):997–1004. doi:10.1111/j.0006-341X.1999.00997.x.
- Duntsch L, Tomotani BM, de Villemereuil P, Brekke P, Lee KD, Ewen JG, Santure AW. Polygenic basis for adaptive morphological variation in a threatened aotearoa New Zealand bird, the hihi (*Notiomystis cincta*). *Proc Biol Sci.* 2020;287(1933):20200948.
- Gauzere J, Pemberton JM, Kruuk LEB, Morris S, Morris A, Walling CA. Maternal effects do not resolve the paradox of stasis in birth weight in a wild mammal. *Evolution.* 2022;76(11):2605–2617. doi:10.1111/evo.14622.
- Gauzere J, Pemberton JM, Morris S, Morris A, Kruuk LEB, Walling CA. The genetic architecture of maternal effects across ontogeny in the red deer. *Evolution.* 2020;74(7):1378–1391. doi:10.1111/evo.14000.
- Gienapp P, Calus MPL, Laine VN, Visser ME. Genomic selection on breeding time in a wild bird population. *Evolution Letters.* 2019;3(2):142–151. doi:10.1002/evl3.103.
- Gienapp P, Fior S, Guillaume F, Lasky JR, Sork VL, Csillery K. Genomic quantitative genetics to study evolution in the wild. *Trend Ecol Evol.* 2017;32(12):897–908. doi:10.1016/j.tree.2017.09.004.
- Gilmour A, Gogel B, Cullis B, Thompson R. *ASReml user guide release 2.0.* Hemel Hempstead. Oxford: VSN International Ltd; 2006.
- Goddard ME, Hayes BJ. Mapping genes for complex traits in domestic animals and their use in breeding programmes. *Nat Rev Genet.* 2009;10(6):381–391. doi:10.1038/nrg2575.
- Hansson B, Sigeman H, Stervander M, Tarka M, Ponnikas S, Strandh M, Westerdahl H, Hasselquist D. Contrasting results from GWAS and QTL mapping on wing length in great reed warblers. *Mol Ecol Resour.* 2018;18(4):867–876. doi:10.1111/1755-0998.12785.
- Hill WG, Weir BS. Variation in actual relationship as a consequence of Mendelian sampling and linkage. *Genet Res.* 2011;93(1):47–64.
- Huisman J, Kruuk LEB, Ellis PA, Clutton-Brock T, Pemberton JM. Inbreeding depression across the lifespan in a wild mammal population. *Proc Natl Acad Sci U S A.* 2016;113(13):3585–3590. doi:10.1073/pnas.1518046113.
- Jensen H, Szulkin M, Slate J. *Molecular quantitative genetics. In Quantitative Genetics in the wild.* Oxford: Oxford University Press; 2014.
- Johnson T, Barton N. Theoretical models of selection and mutation on quantitative traits. *Philos Trans R Soc Lond B Biol Sci.* 2005;360(1459):1411–1425. doi:10.1098/rstb.2005.1667.
- Johnston SE, Huisman J, Ellis PA, Pemberton JM. A high-density linkage map reveals sexual dimorphism in recombination landscapes in red deer (*Cervus elaphus*). *G3 (Bethesda).* 2017;7(8):2859–2870. doi:10.1534/g3.117.044198.
- Johnston SE, Huisman J, Pemberton JM. A genomic region containing *rec8* and *rnf212b* is associated with individual recombination rate variation in a wild population of red deer (*Cervus elaphus*). *G3 (Bethesda).* 2018;8(7):2265–2276. doi:10.1534/g3.118.200063.
- Josephs EB, Stinchcombe JR, Wright SI. What can genome-wide association studies tell us about the evolutionary forces maintaining genetic variation for quantitative traits? *New Phytologist.* 2017;214(1):21–33. doi:10.1111/nph.14410.
- Kardos M, Luikart G. The genetic architecture of fitness drives population viability during rapid environmental change. *Am Nat.* 2021;197(5):511–525. doi:10.1086/713469.
- Kingsolver JG, Hoekstra HE, Hoekstra JM, Berrigan D, Vignieri SN, Hill CE, Hoang A, Gibert P, Beerli P. The strength of phenotypic selection in natural populations. *Am Nat.* 2001;157(3):245–261. doi:10.1086/319193.
- Kong A, Thorleifsson G, Frigge ML, Vilhjalmsdottir BJ, Young AI, Thorgeirsson TE, Benonisdottir S, Oddsson A, Halldorsson BV, Masson G, et al. The nature of nurture: effects of parental genotypes. *Science.* 2018;359(6374):424–428. doi:10.1126/science.aan6877.
- Kruuk LEB. Estimating genetic parameters in natural populations using the “animal model”. *Philos Trans R Soc Lond B Biol Sci.* 2004;359(1446):873–890. doi:10.1098/rstb.2003.1437.
- Kruuk L, Clutton-Brock T, Rose K, Guinness F. Early determinants of lifetime reproductive success differ between the sexes in red deer. *Proc Biol Sci.* 1999;266(1429):1655–1661. doi:10.1098/rspb.1999.0828.
- Kruuk LEB, Hadfield JD. How to separate genetic and environmental causes of similarity between relatives. *J Evol Biol.* 2007;20(5):1890–1903. doi:10.1111/j.1420-9101.2007.01377.x.
- Kruuk LEB, Slate J, Wilson AJ. New answers for old questions: the evolutionary quantitative genetics of wild animal populations. *Annu Rev Ecol Evol Syst.* 2008;39(1):525–548. doi:10.1146/annurev.ecolsys.39.110707.173542.
- Le Corre V, Kremer A. Genetic variability at neutral markers, quantitative trait loci and trait in a subdivided population under selection. *Genetics.* 2003;164(3):1205–1219. doi:10.1093/genetics/164.3.1205.
- Mitchell-Olds T, Willis JH, Goldstein DB. Which evolutionary processes influence natural genetic variation for phenotypic traits? *Nat Rev Genet.* 2007;8(11):845–856. doi:10.1038/nrg2207.
- Moser G, Lee SH, Hayes BJ, Goddard ME, Wray NR, Visscher PM. Simultaneous discovery, estimation and prediction analysis of complex traits using a Bayesian mixture model. *PLoS Genet.* 2015;11(4):e1004969. doi:10.1371/journal.pgen.1004969.
- Mousseau T, Roff D. Natural selection and the heritability of fitness components. *Heredity (Edinb).* 1987;59(2):181–197. doi:10.1038/hdy.1987.113.
- Perrier C, Delahaie B, Charmanier A. Heritability estimates from genome-wide relatedness matrices in wild populations: application to a passerine, using a small sample size. *Mol Ecol Resour.* 2018;18(4):838–853. doi:10.1111/1755-0998.12886.
- Peters L, Huisman J, Kruuk LEB, Pemberton JM, Johnston SE. Genomic analysis reveals a polygenic architecture of antler morphology in wild red deer (*Cervus elaphus*). *Mol Ecol.* 2022;31(4):1281–1298.

- Poissant J, Davis CS, Malenfant RM, Hogg JT, Coltman DW. QTL mapping for sexually dimorphic fitness-related traits in wild bighorn sheep. *Heredity*. 2012;108(3):256–263.
- Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*. 2006;38(8):904–909. doi:10.1038/ng1847.
- Pritchard JK, Przeworski M. Linkage disequilibrium in humans: models and data. *Am J Hum Genet*. 2001;69(1):1–14. doi:10.1086/321275.
- Rönnegård L, McFarlane SE, Husby A, Kawakami T, Ellegren H, Qvarnström A. Increasing the power of genome wide association studies in natural populations using repeated measures—evaluation and implementation. *Methods Ecol Evol*. 2016;7(7):792–799. doi:10.1111/2041-210X.12535.
- Santure AW, Poissant J, De Cauwer I, van Oers K, Robinson MR, Quinn JL, Groenen MA, Visser ME, Sheldon BC, Slate J. Replicated analysis of the genetic architecture of quantitative traits in two wild great tit populations. *Mol Ecol*. 2015;24(24):6148–6162. doi:10.1111/mec.13452.
- Sella G, Barton NH. Thinking about the evolution of complex traits in the era of genome-wide association studies. *Annu Rev Genomics Hum Genet*. 2019;20(1):461–493. doi:10.1146/annurev-genom-083115-022316.
- Slate J. From beavis to beak color: a simulation study to examine how much QTL mapping can reveal about the genetic architecture of quantitative traits. *Evolution*. 2013;67(5):1251–1262.
- Slate J, Santure AW, Feulner PG, Brown EA, Ball AD, Johnston SE, Gratten J. Genome mapping in intensively studied wild vertebrate populations. *Trends Genet*. 2010;26(6):275–284.
- Slate J, Visscher PM, MacGregor S, Stevens D, Tate ML, Pemberton JM. A genome scan for quantitative trait loci in a wild population of red deer (*Cervus elaphus*). *Genetics*. 2002;162(4):1863–1873. doi:10.1093/genetics/162.4.1863.
- Visscher PM, Medland SE, Ferreira MAR, Morley KI, Zhu G, et al. Assumption-free estimation of heritability from genome-wide identity-by-descent sharing between full siblings. *PLOS Genetics*. 2006;2(3):e41.
- Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. *Am J Hum Genet*. 2012;90(1):7–24.
- Wang M, Xu S. Statistical power in genome-wide association studies and quantitative trait locus mapping. *Heredity (Edinb)*. 2019;123(3):287–306. doi:10.1038/s41437-019-0205-3.
- Wolf J, Cheverud JM. Detecting maternal-effect loci by statistical cross-fostering. *Genetics*. 2012;191:261–277.
- Wood A, Esko T, Yang J, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genetics*. 2014;46:1173–1186.
- Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet*. 2011;88(1):76–82.
- Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, Frayling TM, Hirschhorn J, Yang J, Visscher PM, et al. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Hum Mol Genet*. 2018;27(20):3641–3649.

Editor: M. Rockman