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ABSTRACT

In this paper, we present a comprehensive study of gestation length (GL) in 16 cattle breeds by using large genotype and animal record databases. Data included over 20 million gestations since 2000 and genotypes from one million calves. The study addressed the GL variability within and between breeds, estimation of its direct and maternal heritability coefficients, association with fitness and several economic traits, and QTL detection. The breed average GL varied from 279.7 to 294.4 d in Holstein and Blonde d'Aquitaine breeds, respectively. Standard deviations per breed were similar and ranged from 5.2 to 5.8 d. Direct heritability (i.e., for GL defined as a trait of the calf) was moderate to high ($h^2 = 0.40$–0.67), whereas the maternal heritability was low (0.04–0.06). Extreme breeding values for GL were strongly associated with a higher mortality during the first 2 d of life and were associated with milk production of dams for dairy breeds and precocity of females. Finally, several QTL were detected affecting GL with cumulated effects up to a few days, and at least 2 QTL were found to be shared between different breeds. Our study highlights the risks that would be associated with selection toward a reduced GL. Further genomic studies are needed to identify the causal variants and their association with juvenile mortality and other economic traits.

Key words: gestation length, cattle, genetic parameters, GWAS

INTRODUCTION

Gestation length (**GL**) is a trait of increasing interest to the cattle industry, as a way to manage calving periods in seasonal reproduction systems (Norman et al., 2009; Washburn and Mullen, 2014; LIC, n.d.). Differences in average GL are also a source of competition between breeds, either for the choice of purebred mating and above all for beef-on-dairy crossbreeding, where shorter GL are preferred to reduce nonproductive time and the risk of dystocia (Berry, 2021; Basiel et al., 2024). For these reasons, over the past 20 years, several breeding organizations have developed genetic evaluations for GL (Haile-Mariam and Pryce, 2019), proposing either targeted use of bulls with shorter gestation breeding values (for example, in New Zealand; Winkelman and Spelman, 2001) or selecting for an intermediate optimum objective (Hansen et al., 2004; Norman et al., 2011; Eaglen et al., 2013).

Gestation length can be easily measured as the interval between successful insemination or mating and the calving date, and probably for this reason it is one of the oldest traits to arouse interest in animal science, with the first article on the subject being published in 1899 (Andersen and Plum, 1965). Since then, several studies (Gilleland et al., 2021; Stachowicz et al., 2023) have been devoted to the statistical and genetic analysis of GL in several breeds. In particular, the large number of breeds reared in France, combined with the centralization of livestock records in a unique national database, has allowed 4 comparative studies to be carried out over the last 50 years (Bougler and Derveaux, 1969; Marion, 1995; Guerrier et al., 2007; Ledos and Moureaux, 2013). The latter reported a high variability in mean GL across 23 breeds, ranging from about 280 d for Holstein to 295 d for Blonde d'Aquitaine. The ranking of breeds was particularly stable over time (Brakel et al., 1952; Signoret et al., 1956; Andersen and Plum, 1965; Bougler and Derveaux, 1969; Marion, 1995; Guerrier et al., 2007; Ledos and Moureaux, 2013), as was the variability within breeds, with SD ranging from 5 to 6 d. However, this variability hides extreme phenotypes that have often been associated with adverse effects on calf survival or subsequent milk production and reproductive disorders of the dam (Hansen et al., 2004; Norman et al., 2011; Jenkins et al., 2016; Vieira-Neto et al., 2017; Corbeau et al., 2024).

The list of standard abbreviations for JDS is available at adsa.org/jds-abbreviations-24. Nonstandard abbreviations are available in the Notes.

The direct heritability (as a calf trait) of GL has been reported to be moderate in approximately a dozen breeds with h^2 estimates ranging from 0.2 to 0.5 (Wray et al., 1987; Mujibi and Crews, 2009; Norman et al., 2009; Kumar et al., 2016), whereas the maternal genetic effect has been less studied and found to be of lesser magnitude (~0.05). Finally, with the development of genomic evaluations and the availability of growing genotype datasets, several articles have been published in the last decade dedicated to the detection of QTL for GL (e.g., peak in BTA18 in Maltecca et al., 2011; Fang et al., 2019; and Purfield et al., 2019).

In this article, we present a comprehensive analysis of GL in 16 cattle breeds, taking advantage of the wealth of records (i.e., dates of insemination, births, and deaths) and genotype data generated for genomic evaluation in France. In particular, we present genetic parameters for direct and maternal effects, report environmental factors influencing GL, investigate the possible consequences of a selection using GEBV, and perform individual GWAS and a meta-analysis to identify QTL influencing direct GL.

MATERIALS AND METHODS

Phenotypic Data

Insemination and calving dates, as well as additional information (breed, pedigree over 3 generations, herd ID, age and parity of the cow, stillbirths, twinning events, embryo transfer, milk production, and type traits measured after calving) were obtained from the French national cattle database.

Gestation Length

The dates of AI and subsequent calving were compared for each female to calculate GL. Calving events occurring between January 1, 2000, and December 31, 2021, in parity 1 to 5 for dairy breeds and 1 to 10 for beef breeds were considered. For each calving, the GL record with the value the closest to the breed reference (Ledos and Moureaux, 2013) was kept. If 2 AI had the same gap from the reference GL, only the second one was considered. Gestation lengths within ± 17 d of this reference were retained, as it is classically done in France for parentage certification. Data from twin births were excluded because their GL is shorter than for single births by 3.2 to 6.2 d, depending on the breed (Ledos and Moureaux, 2013), and it is not possible to identify which calf induced parturition. Pregnancies following embryo transfer were also excluded. The declared sire of the calf had to be the same as the bull used in the selected AI, and the parents had to be of the same breed. This resulted in 39,955,142 GL records. Note that during this period, most AI in France were made by AI center technicians, and AI dates were very accurately recorded. Errors in the estimation of GL are therefore expected to be low. The distribution between breeds is shown in Table 1.

Calving events between 2000 and 2009 were used only for long-term statistics, in order to observe the trends in GL change over several years. All other analyses were performed with data corresponding to calves born between 2010 and 2021. This edit was made with the aim of analyzing animals that are genetically close to the current population, and because the number of genotyped animals born before 2010 was small. As the datasets were already large, this time limitation also limited the computational burden.

Genotypic Data

A SNP genotyping dataset of 2,205,594 animals was used, of which 1,321,383 had a direct GL phenotype. These genotypes were obtained from different Illumina SNP arrays over time (LD [7k; 1.8%], custom LD [10–20k; 29.3%], BovineSNP50 [50k; 10.1%], EuroGMD [63k; 58.6%] and HD [777k; 0.2%]). Raw genotypes were all phased and imputed for 53,469 autosomal SNPs (including those genotyped with larger density panels) using Fimpute3 (Sargolzaei et al., 2014), as part of the French routine bovine genomic evaluation, as described in Mesbah-Uddin et al. (2019). The genomic markers used were mapped according to the current ARS-UCD1.2 bovine genome assembly (Rosen et al., 2020).

Statistical Analyses: Genetic Parameters

Genetic parameters were estimated by restricted maximum likelihood within each breed using Wombat (version 25-02-2020; Meyer, 2007). As GL is influenced by the calf and by its dam, the animal model included correlated genetic direct and maternal effects. The model included the fixed effects of the combinations of herd-birth year, region-month-year, and calf sex with parity and dam age, and the random permanent environment effect of the dam:

$$\mathbf{y} = \mathbf{X\beta} + \mathbf{Zd} + \mathbf{Vm} + \mathbf{Wp} + \mathbf{\epsilon},$$

where $\mathbf{y}$ is the vector of GL phenotypes; $\mathbf{\beta}$ is the vector of fixed effects as defined above; $\mathbf{d}$ is the vector of random direct genetic additive effects; $\mathbf{m}$ is the vector of random maternal genetic effects; $\mathbf{p}$ is the vector of random permanent maternal environmental effects; $\mathbf{X}$, $\mathbf{Z}$, $\mathbf{V}$, and $\mathbf{W}$ are the corresponding incidence matrices; and $\mathbf{\epsilon}$ is the vector of random errors. Genetic effects d and m were assumed to be normally distributed with 0 mean and

Table 1. Summary of breed statistics for gestation lengths (GL, in days) completed between 2010 and 2021 (breeds are sorted from shortest to longest GL)

Breed	Total Average GL	SD	N	Male calves Average GL	SD	N	Female calves Average GL	SD	N	Primiparous dams Average GL	SD	N	Multiparous dams Average GL	SD	N
Holstein	279.7	5.3	13,905,357	280.3	5.4	6,632,828	279.2	5.2	7,272,529	278.6	5.1	5,071,359	280.4	5.9	8,833,998
Jersey	282.4	5.2	63,380	283.5	5.4	20,185	281.9	5.1	43,195	280.8	5.2	19,553	283.2	5.0	43,827
Aubrac	283.2	5.6	67,952	283.9	5.5	33,918	282.5	5.6	34,034	282.2	5.6	21,334	283.6	5.5	46,618
Normande	285.3	5.5	1,802,299	285.8	5.5	891,532	284.7	5.4	910,767	284.5	5.4	614,552	285.7	5.5	1,187,747
Salers	285.9	5.5	49,954	286.6	5.5	24,235	285.3	5.5	25,719	285.2	5.6	16,219	286.3	5.4	33,735
Montbéliarde	286.3	5.5	2,969,904	287.1	5.5	1,300,395	285.7	5.4	1,669,509	285.5	5.4	963,254	286.7	5.5	2,006,650
Tarentaise	286.4	5.4	54,771	287.2	5.4	26,996	285.6	5.3	27,775	285.6	5.3	17,374	286.7	5.4	37,397
Charolaise	286.5	5.7	1,259,281	287.2	5.7	641,561	285.9	5.6	617,720	285.9	5.7	483,121	287.0	5.7	776,160
Parthenaise	287.1	5.6	88,851	287.9	5.6	44,501	286.3	5.5	44,350	286.5	5.6	34,650	287.6	5.6	54,201
Rouge des Prés	287.3	5.6	48,984	287.7	5.6	25,242	286.9	5.5	23,742	286.4	5.5	21,786	288.1	5.5	27,198
Abondance	287.7	5.8	151,873	288.3	5.8	73,314	287.2	5.7	78,559	286.9	5.8	41,901	288.0	5.7	109,972
Simmental	287.9	5.6	127,219	288.6	5.6	63,288	287.1	5.5	63,931	286.8	5.6	39,441	288.4	5.6	87,778
Vosgienne	288.7	5.3	14,095	289.5	5.4	6,721	288.1	5.2	7,374	287.6	5.3	4,211	289.2	5.3	9,884
Brown Swiss	289.1	5.6	121,565	290.1	5.6	54,299	288.2	5.5	67,266	288.1	5.5	42,031	289.6	5.6	79,534
Limousin	289.7	5.7	434,830	290.4	5.6	218,085	289.1	5.6	216,745	289.3	5.7	161,055	289.9	5.6	273,775
Blonde d'Aquitaine	294.4	5.8	458,354	295.2	5.7	231,167	293.7	5.7	227,187	293.4	5.8	182,940	295.1	5.6	275,414

$$\mathrm{var}\begin{bmatrix} \mathbf{d} \\ \mathbf{m} \end{bmatrix} = \mathbf{A} \otimes \begin{bmatrix} \sigma^2_{g,d} & \sigma_{g,dm} \\ \sigma_{g,dm} & \sigma^2_{g,m} \end{bmatrix},$$ where $\mathbf{A}$ is the pedigree-based relationship matrix, $\sigma^2_{g,d}$ is the direct genetic variance, $\sigma^2_{g,m}$ is the maternal genetic variance, and $\sigma_{g,dm}$ is the direct-maternal genetic covariance. To limit the computational burden, 3 generations (the calf itself, and its parents and grandparents) were traced in the pedigree. For genetic parameter estimation in the Holstein, Montbéliarde, Normande, Charolaise, Limousin, and Blonde d'Aquitaine breeds, a random sample was drawn in the phenotype dataset. This sampling based on herd ID aimed at keeping the number of animals in the pedigree below 2 million.

Direct and maternal GEBV were calculated for each animal using a single step animal model with the HSSG-BLUP software (version 26; Tribout et al., 2020).

Association with Other Traits

To estimate the potential impact of GL as a trait on other selected traits in cattle, GEBV were distributed into 9 classes defined by breed-specific genetic SD (i.e., <-3.5, -3.5 to -2.5, -2.5 to -1.5, -1.5 to -0.5, -0.5 to 0.5, 0.5 to 1.5, 0.5 to 1.5, 1.5 to 2.5, 2.5 to 3.5, and ≥ 3.5) and the class mean was calculated for each trait analyzed.

Mortality Rates. Juvenile mortality rates were calculated separately for the perinatal (0–2 d), postnatal (3–14 d), preweaning (15–55 d), and postweaning (56–365 d) periods, as described in Besnard et al. (2023).

Growth and Age at AI. The relationship between the direct GEBV of each female calf and its own age at the first insemination was then computed. We hypothesized that age at first insemination would be linked to growth, because on dairy farms, breeders are advised to manage the age at first insemination based on heifer weight. Inseminations are typically performed when the heifer reaches 60% of her estimated adult weight (Le Cozler et al., 2008), which led us to consider age at first insemination as a proxy for growth.

Milk Production. The effect of the GL calf GEBV class on the 305-d milk yield of the dam following calf birth was analyzed. Milk yield was first corrected with a model that included the fixed effects of age at first calving, herd, and year of calving. Only lactations of 305 d or more were considered. Annual correlations are calculated and summarized as a weighted average based on the number of events recorded each year (i.e., calving of the cow or birth of the calf).

Genome-Wide Association Studies

For each breed, a GWAS at the 50k SNP level (using the 53,469 autosomal SNP dataset that is routinely used

for national genomic evaluation) was performed for GL as a calf trait using the GCTA software (version 1.26; Yang et al., 2011). Yield deviation corrected for the fixed effects were obtained as a byproduct of the genomic evaluation. For large breeds, we limited the size of the cohort to 20,000 genotyped individuals randomly selected across the dataset.

The mixed linear model association (**MLMA**) approach was used. The genomic relationship matrix was built with all 50k markers with minor allele frequencies (**MAF**) larger than 0.02. The MLMA analysis was carried out on all markers, but results were interpreted only for variants with at least 20 copies of the minor allele in the sample (i.e., MAF had to be 0.001 for large breeds with >20,000 animals, and 0.05 if the number of data points available was only 400). This level of MAF was fixed to avoid false discovery in small breeds and allow discovering rare variants in large breeds.

To account for the multiplicity of tests, a Bonferroni correction was applied. The significance threshold ($P = 0.05$) was adjusted for 53,469 tests, resulting in a $-\log_{10}(P\text{-value})$ of 6.03. The inflation factor was estimated from the median of P-values as follows: $\left[\lambda = \chi_1^2\left(\text{median }P\text{-value}\right)\middle/\chi_1^2\left(0.5\right)\right]$. Inflation is considered as not significant if this factor is below 1.10 (Sahana et al., 2023).

The GWAS results were then combined in a meta-analysis using the fixed effects approach as implemented in the METAL software (version 2011-03-25; Willer et al., 2010). In this approach, the fixed effects from each within-breed analysis are combined with weights equal to the inverse of their standard errors. The new estimates are divided by the square root of their new error variance to define new t-tests. The fixed effect approach is especially appropriate here because it is slightly more powerful than the z-score and because the trait is defined exactly in the same way in the different breeds.

Genes in the detected regions and that may contain variants associated with variability in GL were listed using the UCSC Genome Browser (https://genome.ucsc.edu/). We then searched literature data that mention gestation length, parturition, fetal growth, juvenile mortality, and affiliated (i.e., any disease or characteristic that could lead to these losses).

RESULTS AND DISCUSSION

Basic Statistics on Raw Data and Determination of Factors Influencing GL

Results from the raw GL data of more than 21.6 million cattle from 16 breeds born in France between 2010 and 2021 were consistent with those from studies on older cohorts (Brakel et al., 1952; Signoret et al., 1956; Andersen

and Plum, 1965; Bougler and Derveaux, 1969; Marion, 1995; Guerrier et al., 2007; Ledos and Moureaux, 2013; Figure 1), with mean GL ranging from 279.7 ± 5.3 d in Holstein to 294.4 ± 5.8 d in Blonde d'Aquitaine (Table 1; Supplemental Figures S1 to S16; see Notes). However, our estimates are all lower than these references and on average 1.2 d shorter than those of Ledos and Moureaux (2013). We hypothesize that the difference with Ledos and Moureaux may be because we filtered out extremely long gestation, possibly due to errors in AI records, which does not seem to be the case in their study. This observation led us to look at the evolution of GL means per breed over the last 2 decades. Overall, their trend has been stable to slightly decreasing (Supplemental Table S1; see Notes) possibly because of coselection with other traits. The biggest change concerns the Simmental breed, whose mean GL decreased from 290.7 d in 2006 to 287.2 d in 2018 (Student t-test $P < 2.2 \times 10^{-16}$). For Holstein, the GL decreased from 282.0 d in 2001 to 279.5 in 2014 ($P < 2.2 \times 10^{-16}$) and seems to have stabilized thereafter. The Jersey breed is the only exception, with a significant increase from 280.6 d in 2002 to 282.9 d in 2021 ($P < 2.2 \times 10^{-16}$). It is noteworthy that this breed has expanded strongly in France during this period, with 1,092 calvings recorded in 2002 to 8,984 in 2021, and the gene pool of the breed may have changed in the meantime.

Our study also confirmed and strengthened previous findings on the effect of various factors influencing GL (Figure 2). The sex of the calf contributes to a difference of about 1.2 d (Supplemental Figures S1C to S16C) and up to 1.8 d in Brown Swiss cattle. On average, gestation is longer for male calves than for female calves in all breeds. GL is one day shorter if birth occurs in spring and summer than in fall and winter. Cow parity is also an important factor, with a difference of up to 2 d between primiparous and multiparous cows (Supplemental Figures S1F to S16F). In almost all breeds, primiparous cows had significantly shorter GL than multiparous cows. Moreover, the youngest quartile of first-calving females had a systematically shorter GL than the oldest across the 16 breeds (Supplemental Figures S1E to S16E). Thus, the real effect behind the effect of the parity on the GL appears to be caused by the age at calving, as the oldest first-calving females have a longer GL by ~3 d than the opposite group. Taken together, these results support an effect of maternal stature (and thus of the space left to the developing fetus) on GL in cattle, as previously reported in humans (Myklestad et al., 2013).

Genetic Parameters

Estimates of genetic parameters are shown in Table 2. Estimates of direct heritability ranged from 0.40 in Holstein to 0.67 in the regional Vosgienne breed (mean and
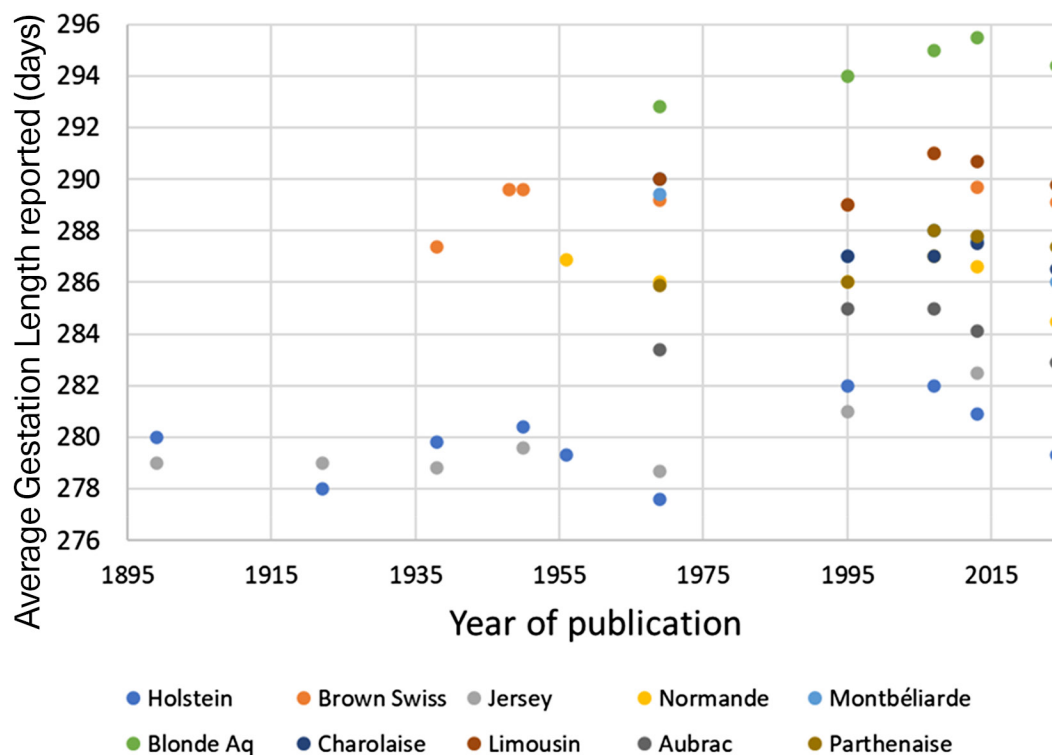
Figure 1. Average gestation length for 12 breeds in the literature data and in the present results across breeds and studies (Brakel et al., 1952; Signoret et al., 1956; Andersen and Plum, 1965; Bougler and Derveaux, 1969; Marion, 1995; Guerrier et al., 2007; Ledos and Moureaux, 2013; our results for 2024). Blonde Aq = Blonde d'Aquitaine.

SD across the 16 breeds: 0.51 and 0.07, respectively), which was consistent with previous studies (e.g., Norman et al., 2009). Despite relatively high heritability coefficients, the genetic variability was low, with a genetic SD of about 3.5 d and a genetic coefficient of variability (genetic SD/mean) of less than 1%. Maternal heritability was low but significantly different from 0, ranging from 0.04 in Jersey to 0.10 in Vosgienne (mean and SD equal to 0.06 and 0.02, respectively). These results indicate that the genetics of the calf have a much greater effect on its own GL than the genetics of its dam. In addition, the direct and maternal genetic effects appeared to be slightly negatively correlated, with values ranging from −0.05 to −0.37 in all breeds except Holstein, for which this correlation was +0.05. Only 5 coefficient estimates ranging from −0.24 to −0.37 were significantly different from zero (Table 2). This balance between direct and maternal effects has been reported previously in cattle (Hansen et al., 2004; Ibi et al., 2008; Mujibi and Crews, 2009) and in other species, such as horses (Vassilev et al., 2002). However, the magnitude of this negative correlation is moderate and consistent across our datasets and weaker than that reported in Ibi et al. (2008) in Japanese black cattle (−0.73).

Interestingly, several breeds of common ancestry and geographic origin showed close direct and maternal h².

This was the case, for example, with the Alpine breeds (Abondance, Simmental, and Montbéliarde), or for the Northwestern breeds, that used Durham bulls in the 19th century (Normande and Rouge des Prés [formerly Maine-Anjou]).

The genetic change in GL over the years was estimated by averaging the EBV per year of birth. Among the dairy breeds (Figure 3), the direct GL of the Simmental breed decreased by more than 2 genetic standard deviations since 2000. The Holstein breed followed a similar trend. Conversely, the level of the maternal genetic effect has increased, which is consistent with the observed negative correlation previously reported. Furthermore, the change in Holstein is in agreement with the observations of Galluzzo et al. (2024) and Stachowicz et al. (2023), who found that the genetic trend of direct GL genetic level decreased by approximately 1 to 6 d between 1995 and 2020 depending on the country of evaluation.

Relationships with Other Traits

Because the relationship between GL and other traits of interest is suspected to be nonlinear, we preferred to study the evolution of these traits according to GL GEBV categories. In all breeds, reduced GL was associated with increased perinatal mortality. For example, in the Hol-
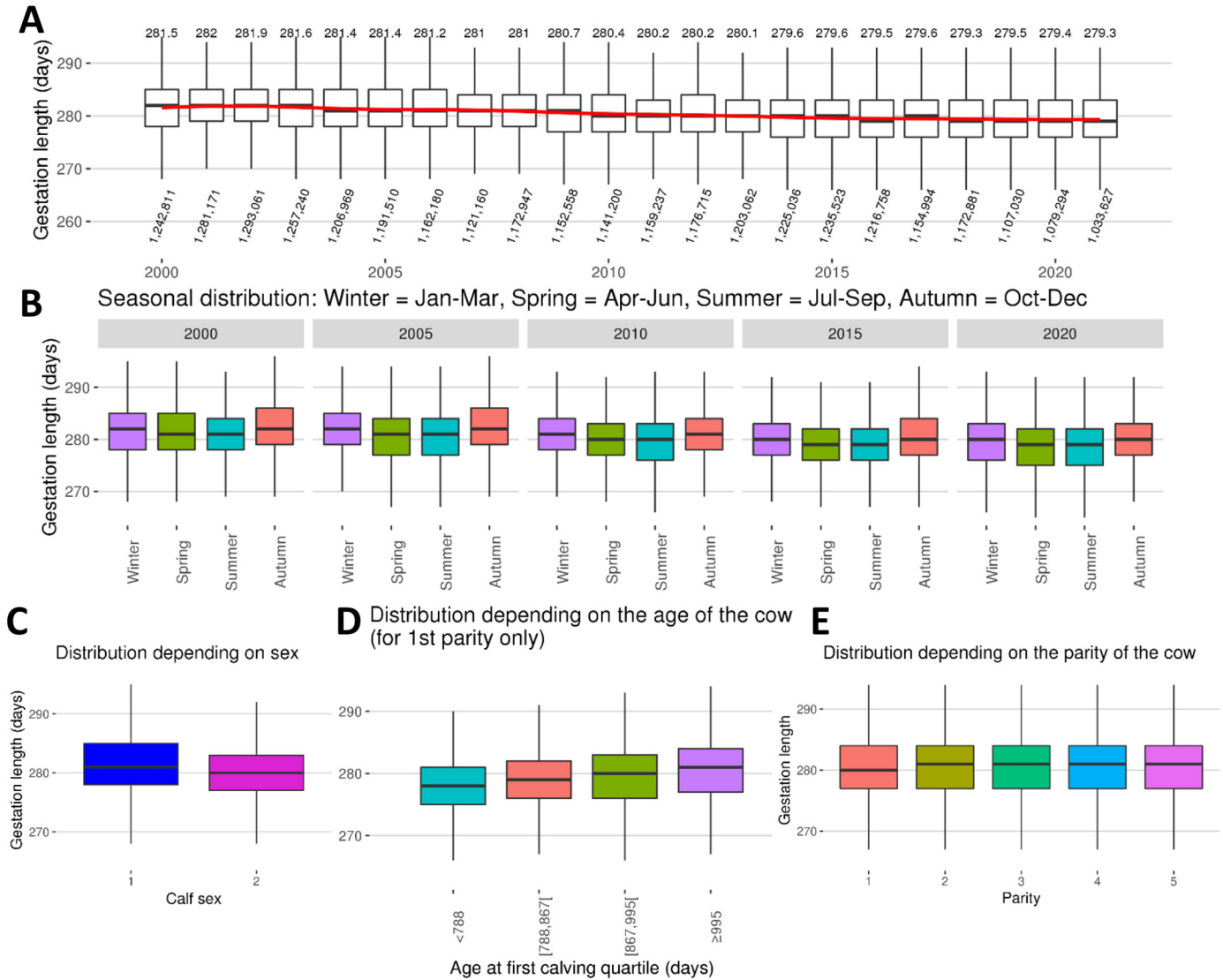
Figure 2. Factors influencing the gestation length (GL) of the Holstein breed. (A) Change in GL by year of birth of the calves since 2000 (number of births considered listed below boxes [1,033,627 < n < 1,293,061]; yearly average listed above boxes and represented by the red curve). (B) Seasonal change in GL (yearly order: winter, spring, summer, autumn). (C) Change in GL according to the sex of the calf (1 = male calf; 2 = female calf). (D) Distribution of GL by age at first calving (divided by breed-specific quartiles). (E) Change in GL as a function of cow parity. Midlines of boxes indicate median values, upper and lower edges indicate the 0.25 and 0.75 quantiles, and whiskers represent 99% of the values.

stein breed, animals with a GEBV in the lowest 5% had a mortality rate of 7.4% before 2 d of age, corresponding to a +57% increased risk compared with the intermediate category (4.7%). This effect was not symmetrical: the 10% of calves with the highest GEBV had only a slightly increased mortality rate (5.0%, corresponding to a 6% increased risk). For all breeds, intermediate genetic values (GEBV from −1.5 to +1.5 SD) for GL seem to be optimal to avoid perinatal mortality (Figure 4). For instance, in the Brown Swiss breed, the perinatal mortality rate was 6.7%, 3.9%, and 4.9%, for low, intermediate, and high GL GEBV, respectively. Extreme GL were also

linked with increasing neonatal mortality in the Holstein breed in Nogalski and Piwczyński (2012). Calves with low GEBV are more prone to die in connection with their short gestation, as in humans, where the risks and causes of death associated with late preterm parturition have been extensively studied (Engle, 2011; Parikh et al., 2014). The mortality rate also increases with the highest GEBV, most likely due to calving difficulties associated with a larger size of the calf with longer gestation or placental insufficiency, as it is described in humans (Campbell et al., 1997; Galal et al., 2012). This is consistent with Nogalski and Piwczyński (2012), who demonstrated

Table 2. Estimates of genetic parameters for all the breeds

Breed	Direct h^2 (SE)	Calves (n)	Maternal h^2 (SE)	Dams (n)	Permanent maternal environment	Direct-maternal correlation
Holstein	0.40 (0.01)	393,565	0.05 (0.003)	207,345	0.027	0.05
Jersey	0.47 (0.03)	55,052	0.04 (0.008)	26,007	0.024	−0.07
Aubrac	0.52 (0.04)	58,118	0.06 (0.01)	35,358	0.044	−0.29*
Normande	0.46 (0.01)	350,556	0.05 (0.004)	177,282	0.022	−0.05
Salers	0.49 (0.04)	41,774	0.06 (0.01)	25,353	0.062	−0.34*
Montbéliarde	0.58 (0.02)	370,124	0.09 (0.005)	187,238	0.027	−0.37*
Tarentaise	0.56 (0.04)	48,229	0.07 (0.01)	23,883	0.025	−0.19
Charolaise	0.53 (0.02)	350,699	0.06 (0.005)	182,944	0.037	−0.24*
Parthenaise	0.47 (0.04)	85,447	0.05 (0.01)	45,656	0.035	−0.13
Rouge des Prés	0.41 (0.04)	44,943	0.07 (0.01)	26,351	0.023	−0.06
Abondance	0.54 (0.03)	136,864	0.07 (0.008)	68,729	0.039	−0.29*
Simmental	0.56 (0.02)	119,502	0.07 (0.007)	57,030	0.038	−0.27*
Vosgienne	0.67 (0.07)	11,063	0.10 (0.02)	4,872	0.027	−0.28
Brown Swiss	0.49 (0.02)	103,993	0.05 (0.007)	53,516	0.030	−0.15
Limousin	0.49 (0.02)	329,935	0.07 (0.006)	187,760	0.043	−0.16*
Blonde d'Aquitaine	0.48 (0.02)	338,918	0.07 (0.007)	180,627	0.040	−0.14*

*Genetic direct maternal correlations significantly different from 0 ($P < 0.05$).
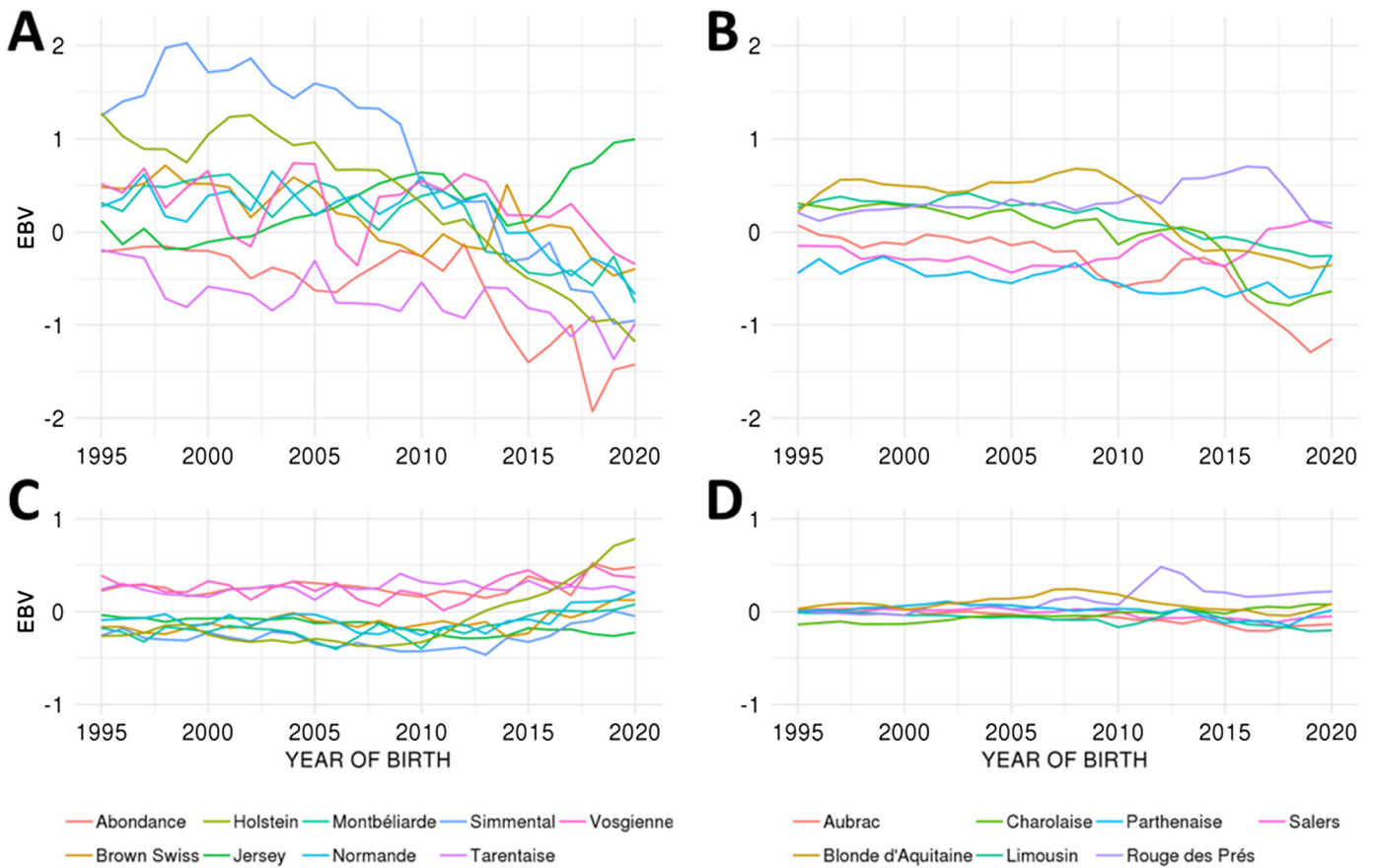

Figure 3. Genetic changes in gestation length (GL) over time. Estimated breeding values for direct effect on GL in dairy (A) and beef (B) breeds. Estimated breeding values for maternal GL in dairy (C) and beef (D) breeds (year of birth on x-axis). The number of observations considered in these graphs ranged between 100 and 1,337,572.
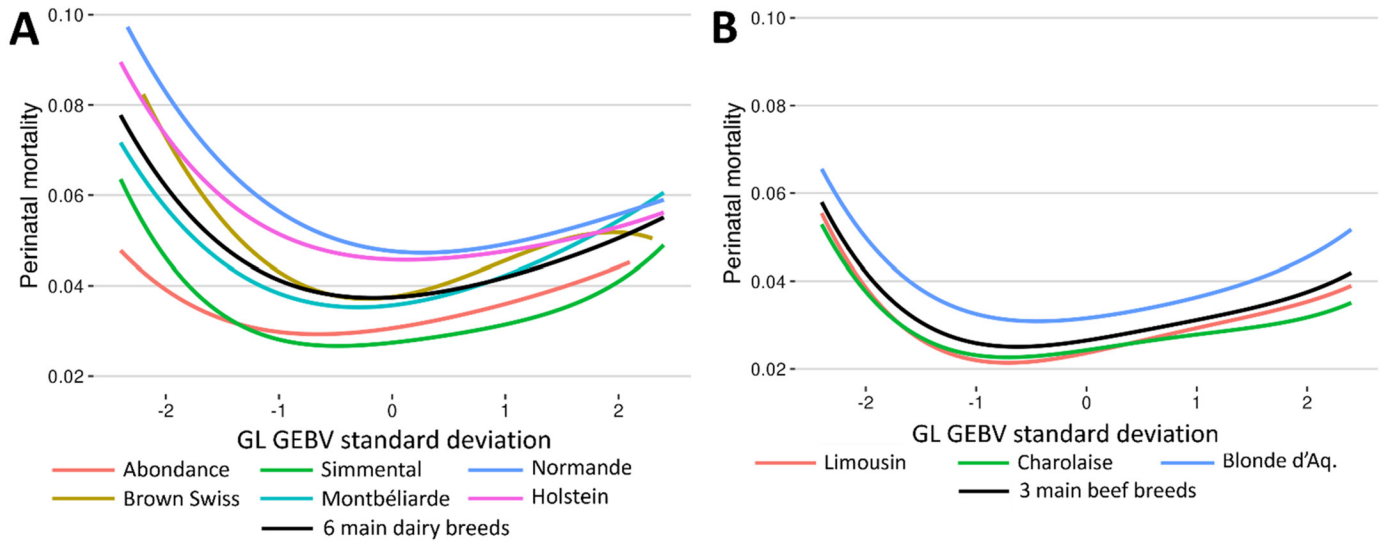
Figure 4. Perinatal mortality (0–2 d) rates as a function of gestation length genomic direct estimated breeding values for 9 breeds with >100,000 births since 2010: (A) for 6 dairy breeds; (B) for beef breeds. Blonde d'Aq. = Blonde d'Aquitaine.

that long gestations require human assistance more often than short gestations.

The analysis of the mortality rates for periods later than the first 2 d of life (i.e., postnatal, preweaning, and postweaning periods) showed no association with the GL GEBV categories considered.

To conclude on this section, a selection to reduce or increase gestation length is not recommended because the association between extreme GL and perinatal mortality with its economic and social consequences outweighs the small potential gain in preterm birth. Still, mating animals for producing calves that are genetically intermediate for GL could contribute to reducing mortality during the first 2 d of life.

Using age at first insemination as a proxy, we then focused on the growth of females as a function of their own GL GEBV. A significant positive association was observed for the 3 main dairy breeds (Holstein, Montbéliarde, and Normande), whereas it was negative for 2 of the major beef breeds (Charolaise and Blonde d'Aquitaine) reared in France. However, these correlations are very low, e.g., 0.037 and −0.029 for Holstein and Blonde d'Aquitaine heifers, respectively (Figure 5 and Supplemental Figures S1H to S16H). On average, Holstein females in the lowest GL GEBV decile are inseminated 25 d earlier than those in the highest decile. For Blonde d'Aquitaine heifers, the highest percentile has an advantage of 12 d. Taken together, these results indicate that the impact of GL on the age at first insemination in the population scale is moderate. In a previous study, Bourdon and Brinks (1982) also found a negative correlation between GL and growth traits in 2 beef breeds, namely Angus and Hereford.

Finally, we studied the influence of the calf's GL on its dam's milk production during the lactation following this birth. For the first lactation, we found significant correlations close to zero for most breeds, with the highest correlation being −0.053 for the Simmental breed, which means that the shortest gestations lead to an increased yield. For the Holstein calves and their dams, the correlation was also negligible (0.025). The results are similar for the second lactation, with correlations close to zero for most breeds (from −0.042 for Holstein to 0.040 for Jersey; Figure 6). Among the dairy breeds, we found a clear trend toward a low but positive correlation between calf GL GEBV and dam milk production (Supplemental Figures S1I to S14I). The possible small positive effect in some breeds may not be sufficient to offset the negative aspects of the mortality.

As a conclusion to the correlations with other traits, we would like to highlight the potentially detrimental consequences of a genetic decrease in GL. Indeed, there is a major risk of increasing the mortality rate of young calves. In dairy breeds, the effects of short GL on age at first insemination of the heifer progeny (a proxy for their growth) or on dam milk production are generally unfavorable, but the link is negligible. In short, selection to reduce GL should not be undertaken until the biological processes are fully understood.

GWAS Results

To gain insight into the genetic background of GL, we performed a GWAS using 50K SNP array genotypes for direct effects on GL in each of the 16 breeds independently. Of these, 12 showed significant associations (P
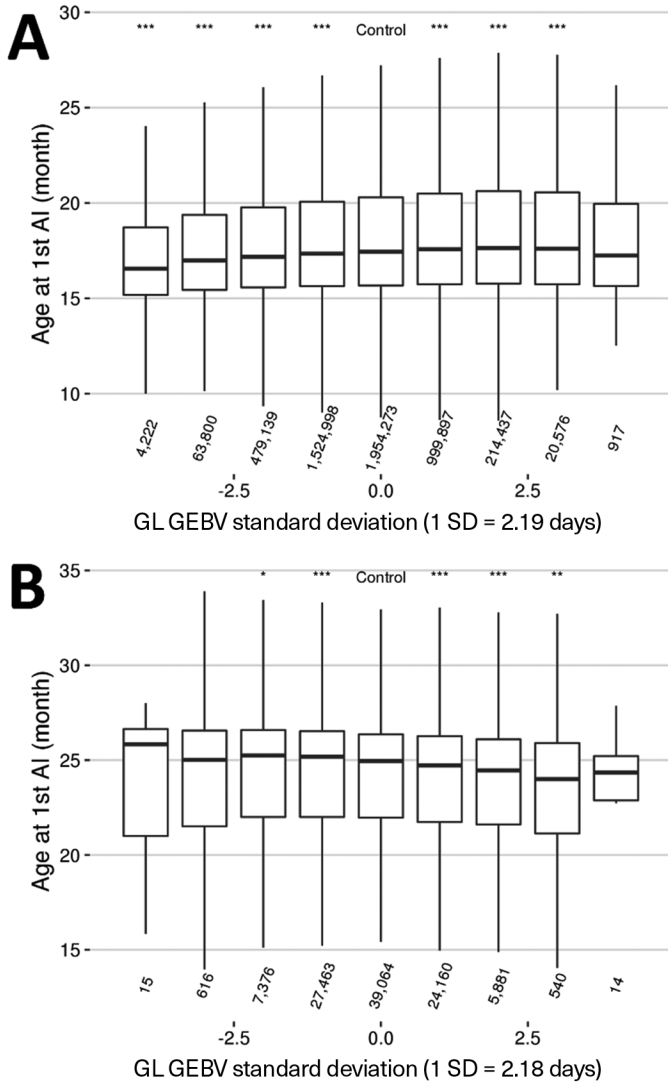
Figure 6. Relationship between calf's genomic estimated breeding values and dam's milk production in Holstein second-lactation cows. Number of births indicated below boxes; significance level indicated compared with controls (i.e., intermediate animals): ***$P < 0.001$. Midlines of boxes indicate median values, upper and lower edges indicate the 0.25 and 0.75 quantiles, and whiskers represent 99% of the values.

Figure 5. Distribution of age at first insemination according to gestation length direct genomic estimated breeding values. (A) Holstein. (B) Blonde d'Aquitaine. Classes are defined by 0.5 genetic SD intervals; significance expressed from controls (intermediate gestation length): ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$; number of animals in each class are represented below bars. Midlines of boxes indicate median values, upper and lower edges indicate the 0.25 and 0.75 quantiles, and whiskers represent 99% of the values.

$< 10^{-5}$; except those performed in Aubrac, Salers, Rouge des Prés, and Parthenaise, where the number of genotypes was too small to provide sufficient power). The GWAS performed in Jersey and Tarentaise had no peak reaching the corrected minimum P-value. Inflation estimates for the breeds that had at least 1 significant SNP were all below 1.10 (ranging from 1.015 for the Limousin breed to 1.099 for Montbéliarde). Thus, no inflation factor was applied to adjust P-values.

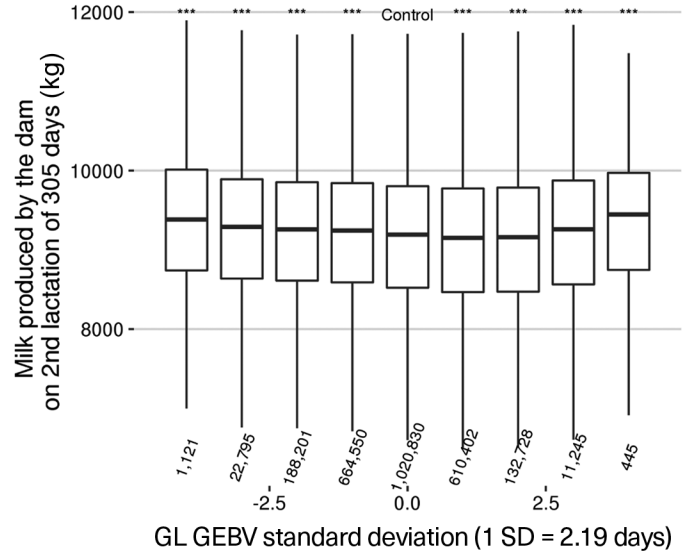Considering the reduction potential in each breed, some breeds could potentially reduce their GL by 1 wk by fixing short GL segregating alleles (Table 3). Regarding the 3 main dairy breeds in France (Holstein, Montbéliarde, and Normande), the GL reduction potential would be higher in Montbéliarde, which currently has the longest GL of the 3 breeds. Only 2 peaks were found in Blonde d'Aquitaine, which has a particularly long GL, and its reduction potential would be only 3.2 d. This breed, as a specialized beef breed, has a low number of available genotypes, which reduces the power of a GWAS approach. In this approach, we considered each peak separately from the others. In the facts, we assume some possible epistatic interactions, and therefore the real reduction that would be achieved by a selection would be lower than suggested in Table 3.

We found 39 peaks reaching the Bonferroni corrected P-value, 24 of which were located on only 4 chromosomes (Figure 7; Supplemental Table S2 and Supplemental Figures S1J to 16J, see Notes). We found that 8 breeds showed a QTL at the beginning of BTA21, which, to our knowledge, had not been reported in any of the previous studies. The 95% CI of this peak encompassed 4 genes, including *MKRN3*, which is known to be highly expressed at birth and paternally imprinted in mice (Abreu et al., 2013). In addition, some variants in this gene were found to be involved in body mass and advanced puberty in humans (Perry et al., 2014), which may also indicate an accelerated in utero development. For the Holstein breed, which has been the subject of most previous studies, we

Table 3. Effects of significant SNP for each breed; most significant peak and peaks with −log10(P-value) > 10[1,2]

Breed	Peak considered (chr:position)	−log(P)	Effect (β value)	Frequency of short GL allele	Potential phenotypic effect of selecting for the strongest peak
Abondance	21:2,109,801	18.1	−0.90	0.44	−1.7
Brown Swiss	7:51,106,002	9.1	0.69	0.37	−0.4
Limousin	21:2,702,004	7.4	−0.62	0.28	−1.1
Simmental	21:2,049,253	13.9	−0.99	0.45	−1.6
Charolaise	21:489,512	17.4	0.52	0.65	−0.5
Montbéliarde	9:101,768,658	21.1	−1.02	0.14	−1.9
	21:2,416,354	35.9	1.26	0.58	−1.4
Normande	13:77,131,352	25.7	0.32	0.09	−1.5
	21:489,512	21.6	0.72	0.69	−0.6
Vosgienne	3:104,094,726	8.9	1.11	0.71	−0.6
Holstein	19:28,726,588	10.0	0.46	0.59	−0.3
Blonde d'Aquitaine	2:94,432,972	12.0	−1.32	0.06	−2.1

[1]Other peaks are presented in Supplemental Table S2.

[2]chr = chromosome.

found very similar peaks to Fang et al. (2019), Purfield et al. (2019), and Maltecca et al. (2011). In particular, we confirmed the QTL on BTA18 around position 57.7 Mb, for which they proposed *ZNF613* as a functional candidate because this gene is involved in the regulation of cell fate commitment in mice (Oliver et al., 2012). However, with a frequency in Holstein of 0.98 of the SNP favoring short gestations, the variant involved is probably major in the breed. If the mutant allele is the one favoring short gestation, it is unlikely to be deleterious for other phenotypes.

The frequencies of the alleles under the peaks we found are difficult to discuss because they are certainly in linkage disequilibrium with the variant involved in the biological process of the variability, which has a different frequency. Nevertheless, 23 of the peaks had an MAF higher than 0.25, which could be a sign of a necessary balance between the variants due to the correlated consequences of short or long gestation.

In a second step, to focus on the most important QTL across breeds, we performed a meta-analysis by combining the GWAS results of the 16 breeds (Figure 7A). The
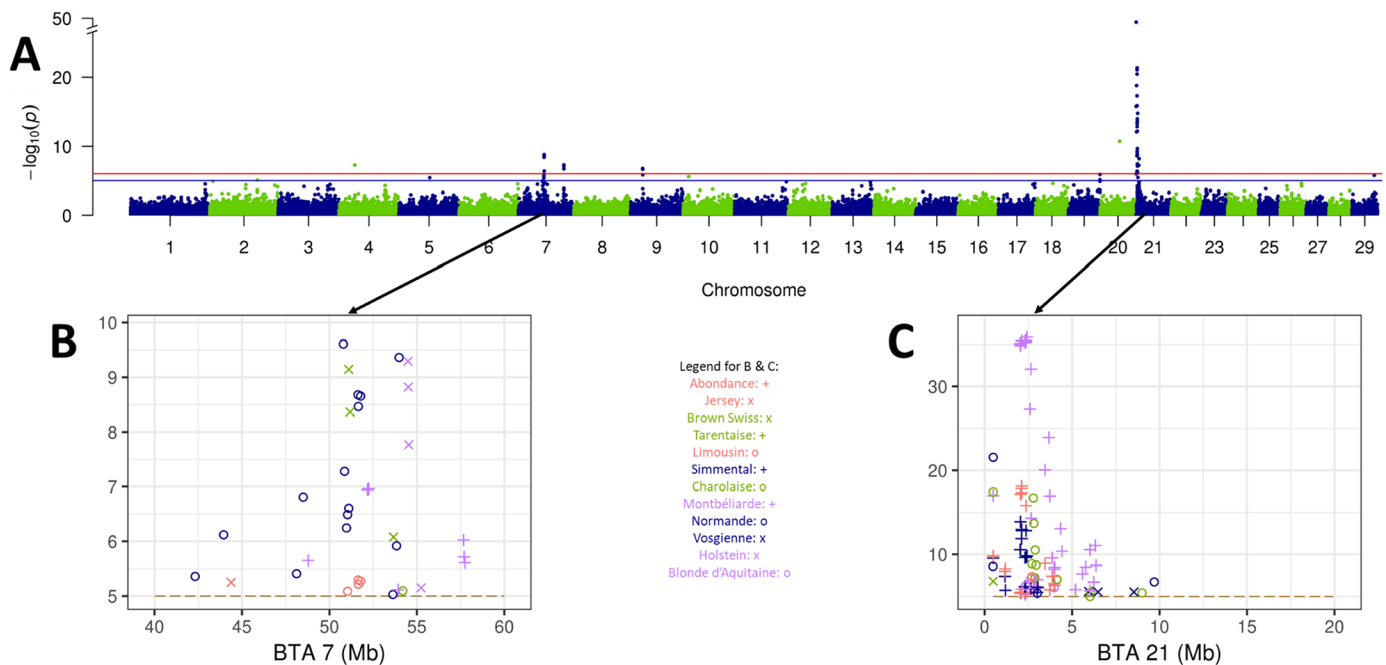

Figure 7. Results of GWAS meta-analysis. (A) Meta-analysis of the 16 GWAS. The blue and red lines correspond to −log10(P) =10^{-5} and 10^{-6}, respectively. (B, C) Focus on regions on chromosome 7 and 21, respectively. Dashed lines correspond to −log10(P) = 10^{-5}.

results highlighted the 2 main regions that segregate in several breeds. The most significant peak was located in a large interval between 478,537 bp and 6,330,388 bp on BTA21 (Figure 7C). Within this region, *SNORD116* and *UBE3A* are very good candidate genes. For the first of these, a publication on mice explains that an induced heterozygous knockout leads to a decreased development with no implication in behavior, aging, and reproductive system (Ding et al., 2008). Note that this induced mutation in mice was under maternal imprinting. These phenotypes would be consistent with an effect of a mutant allele in cattle that would affect the fetal development and induce variability in the maturity of the calf and the parturition. *UBE3A* polymorphisms have also been extensively studied in mice, but knockouts regarding this gene seem to result in abnormal phenotypes (Dindot et al., 2008; Meng et al., 2013), and homozygous carriers die at the juvenile stage in large proportions (Jiang et al., 1998). We did not search for an association with morphologically deviant phenotypes in our study, but the risk of mortality in case of homozygosity could be a genomic evidence for the high neonatal mortality rates observed in all the breeds. The second most significant peak was found to have a significant effect in 8 breeds and was found in BTA7 (50,974,963–51,785,251 bp; Figure 7B). In this region are located 3 genes (*NRG2*, *CYSTM1*, *IK*). Variants in each of these have been described in mice, and some consequences of these mutations may be interesting in our case. A homozygous targeted knockout in *NRG2* led to decreased body and litter size and postnatal lethality (Britto et al., 2004). In *IK*, embryonic and preweaning mortality rates were increased in a homozygous mutant (IMPC, 2014). Also, from Mouse Genome Informatics (https://informatics.jax.org/), *CYSTM1* was described as causing problems in body mass and fat, as well as respiratory quotient. Another peak in BTA7 (90,855,265 bp) was close to *ARRDC3*, which is involved in decreased body mass and increased basal metabolism in heterozygotes, complemented by perinatal lethality in homozygous animals (Patwari et al., 2011). These different annotations are not clearly related to parturition and the potential implication of these genes remains to be demonstrated. Only *CYSTM1* has been highlighted by Purfield et al. (2019). A last significant peak in BTA9 (24,163,108 bp) held our attention, as it is located in *RSP3*, which has mutations involved in embryo growth, vascular development, and lethality in mice (Kazanskaya et al., 2008; Neufeld et al., 2012; Cambier et al., 2014).

Using 50K genotypes, we cannot postulate on causal variants. Deepening the GWAS results at the imputed whole-genome sequence level with a larger number of individuals would allow us to identify candidate variants in these regions and could also highlight peaks that are missed with the medium density of the current study.

CONCLUSIONS

We report one of the most comprehensive genetic studies of GL in cattle. By analyzing 20 million births and 1.3 million 50K genotypes from 16 breeds, we highlighted the high variability of this trait between breeds, with 2 wk separating the longest average from the shortest. Calculation of genetic parameters showed high direct and moderate maternal heritability, suggesting the possibility of selection for GL, although the potential for reduction is limited. In addition, quantitative selection for the trait would result in increased juvenile mortality. If selection for GL is to be planned, the first step should be to examine the effect of each QTL individually and retain only those that do not negatively affect calf fitness.

NOTES

Nonstandard abbreviations used: Blonde Aq = Blonde d'Aquitaine; GL = gestation length; MAF = minor allele frequency; MLMA = mixed linear model association.

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