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Genome-wide association study of health traits in Fleckvieh cattle

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Vienna, June 2011

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Summary

Genome-wide association study (GWAS) has become an important methodology to detect QTLs affecting phenotypic variations of traits, especially for traits with low heritability. Many health traits in cattle display low heritability and conventional genetic improvements often yield unsatisfying selection responses. In this study, single-SNP and multiple-SNP GWAS analyses were conducted to find SNPs for longevity, fertility and cystic ovaries in Fleckvieh cattle. The daughter yield deviations of progeny tested bulls were used as phenotypes and genotypes of each individual were scored for a total of 41008 SNPs distributed over the whole genome. Bonferroni correction and false discovery rate (FDR) for multiple testing were applied to adjust the significance threshold in the single-SNP analyses. Based on analyses of simulated data, Waldmann et al. (in prep) have shown that penalized multiple regression with the elastic net (penalty weight $\alpha = 0.05$) expressed a very good trade-off between Type I and Type II error. Therefore, the elastic net method ($\alpha = 0.05$ and 1000-fold cross validation) was used in the multiple-SNP analyses. The Bonferroni correction resulted in 4 significant SNPs for longevity and 19 SNPs for fertility. With the FDR method, number of detected SNPs was 270 and 726 for longevity and fertility, respectively. 143 SNPs were identified for longevity in the multiple-SNP analyses and 183 SNPs were detected for fertility. No SNPs were found for cystic ovaries in neither single-SNP nor multiple-SNP analyses. Hence, we can conclude that the single SNP analyses either under- or over-estimate the number of associated SNPs, and that there seems to be a potential for using genomic selection of longevity and fertility in Fleckvieh cattle.

Introduction

The genetic improvement of cattle during the recent decades has been heavily focused on production traits, especially milk production traits (Kuhn et al. 2003). An increase in productive capability potentially results in problems with cattle welfare due to negative genetic correlation between production and health-related traits. Longevity and fertility are health-related traits; they have particularly become an interest of breeders not only because their negative genetic correlation with production traits but also because an increase in public attention concerning ethical and animal welfare (Kuhn et al. 2003). Another health-related trait is the cystic ovarian disease (cystic ovaries) which can have negative effects on fertility and longevity. Unfortunately, the conventional genetic improvement by phenotype and pedigree-based selections only contribute to small progress because of the low heritability of longevity, fertility and cystic ovaries (Schulman et al. 2008).

Longevity is a trait that only can be observed in the late phase of the life of cattle. It is defined in several ways, for example as risk of culling, length of productive life or number of daughters with first lactation (Kuhn et al. 2003). Moreover, the definition of longevity varies among countries due to different focus on which traits to include in the selection index. For example, Denmark put an emphasis on functional traits rather than production traits, whereas Canada mainly is interested in production and conformation traits (Jakobsen et al. 2005).

Fertility is a trait that indicates the pregnancy ease of cows. Selection to improve production traits (e.g. milk production) is normally observed together with a decrease of fertility due to negative genetic correlations (Schulman et al. 2008). This means more difficulties of cows to become pregnant after insemination or less calves surviving until the productive age. Poor fertility would eventually decrease marginal profits and lead to the need of either cost reduction or expanding herd size (Veerkamp & Beerda 2007). The increased effort only on production system management, thus, is less likely to maintain a satisfactory level of fertility. Heritabilities of fertility between 0.01 and 0.14 have been reported in Veerkamp & Beerda (2007) and in Koeck et al. (2010).

Cystic ovarian disease (cystic ovaries) mainly occur in high productive cows causing fluid-filled cysts in ovaries. It prolongs the postpartum period which increases the risk of culling (Peter 2000). Heritability of cystic ovaries was reported in the range of 0.04 to 0.1 in some studies (Hooijer et al. 2001; Zwald et al. 2004b; Heringstad 2010; Koeck et al. 2010).

Regardless of low heritability, one problem that still obstructs the improvement of traits is the late availability of performance records, for instance longevity, and traits that can not be measured directly such as fertility. Consequently, less accurately estimated breeding values or longer generation intervals due to low-heritable trait selections would contribute to less genetic gain at the end of breeding programs.

The Bovine (*Bos taurus*) genome was a few years ago, within the Bovine genome project, completely sequenced (Eck et al. 2009). With the advent of high throughput genotyping technologies, the discovery of cattle SNPs and the development of commercial cattle SNP-chips with many thousands polymorphic markers have become straightforward. SNP-chips can be used for genome-wide association studies (GWAS) to find SNPs that are in linkage disequilibrium (LD) with a quantitative trait loci (QTL) behind a trait of interest. The main purpose of a GWAS is to identify chromosome regions that harbor the gene(s) that contribute to the phenotypic variation of a trait, which then could serve as putative regions of QTL for further studies (Sahana et al. 2010). In genomic selection, SNPs with high effects in GWAS can be selected to obtain more accurate breeding values even for individuals without phenotypic observations. Moreover, because of the high density of SNPs in GWAS, it is better suited for fine-mapping of QTLs compared to traditional linkage analysis which usually estimates QTLs within very large chromosome intervals (Goddard & Hayes 2009). Hence, GWAS can be expected to have higher power than linkage studies to detect QTLs behind quantitative traits that are influenced by many genes of small effects (Cordell & Clayton 2005; Sahana et al. 2010).

GWAS can be categorized into SNP-based and haplotype-based analyses. A haplotype-based analysis is generally appreciated as a powerful approach to detect rare causative variants. Nevertheless, statistical analyses in current GWAS mostly focus on SNP-based analyses because of problems with

unclear solutions generally occurred in haplotype-based analyses, for example, the loss of power due to many degrees of freedom, an uncertainty to define haplotype phases or unsuitable assumptions commonly used to impute missing phases (Balding 2006; Meng & Fingerlin 2008; Wason & Dudbridge 2010). Single-SNP and multiple-SNP (multipoint-SNP) analyses are common approaches of SNP-based analyses. Although multiple-SNP analyses mainly are computationally more demanding, they are superior in power to single-SNP analyses or even as powerful as complicated haplotype-based analyses (Balding 2006; Meng & Fingerlin 2008; Wason & Dudbridge 2010).

QTL mapping of longevity and fertility have been conducted in several studies of various cattle breeds (Heyen et al. 1999; Van Tassell et al. 2000; Kuhn et al. 2003; Ashwell et al. 2004; Sahana et al. 2010). However, most of the studies have located QTLs with linkage analyses and used different trait definitions. Although genetic studies of reproductive disorders, fertility and production traits have been reported, there is no up to date study of these traits using GWAS in Fleckvieh cattle. This study aims to identify putative SNPs that are associated with longevity, fertility and cystic ovaries in Fleckvieh (Simmental) cattle. Both single-SNP and multiple-SNP analyses are applied to detect SNP associations and facilitate further comparison between the different methods.

Material and methods

Phenotypic and genotypic data

The daughter yield deviations (DYDs; provided by The Federation of Austrian Cattle Breeders (ZAR) and ZuchtData EDV-Dienstleistungen GmbH) of longevity, fertility and cystic ovaries were recorded for 2500 Fleckvieh progeny tested bulls. The number of bulls in association tests differed among traits because not all phenotypic records of the bulls were available. In total, DYD data from 1953 bulls for longevity, 1695 bulls for fertility and 1238 bulls for cystic ovaries was used in the association tests. Genotypes of the bulls were scored as -1, 0 and 1 based on data from the Illumina bovine 54K SNP chip. The quality of genotypic data was checked for the minimum call rate and the minor allele frequency (MAF $\geq$ 1%). Missing alleles were replaced with an average allele frequency. A total of 41008 SNPs were used in the final analyses.

Hardy-Weinberg equilibrium and linkage disequilibrium

The Fisher exact test was used to calculate deviation from Hardy-Weinberg equilibrium for each SNP. Linkage disequilibrium analysis between SNPs was investigated by calculating Pearson correlation coefficients (r^2). Analyses were performed with the genetics package in R.

Single-SNP analyses

Single-SNP associations were analyzed by applying the ordinary linear model one time for each SNP with the genetics packages in R. The Bonferroni correction was applied to control the family-wise error rate (FWER) due to multiple testing, where a global error rate of 0.05 resulted in a Bonferroni threshold of 1.22×10^{-6}. SNPs with smaller p-values than the Bonferroni threshold are considered as significant. The false discovery rate (FDR) was controlled by calculating q-values, which can be interpreted as FDR adjusted p-values (Storey 2002; Storey & Tibshirani 2003). The q-values were calculated based on primary p-values with the qvalue package in R. SNPs were considered significant when their q-values were less than the standard threshold of 0.05.

Multiple-SNP analyses

Multiple-SNP associations were investigated by using the elastic-net method which performs penalized multiple regression by combining the penalties from the lasso and ridge regression (Zou and Hastie 2005). Waldmann et al. (in prep) performed analyses of simulated data and concluded that a penalty weight of $\alpha = 0.05$ in combination with a stopping criteria for regularization parameter λ at MSE plus 1 standard error provided a very good trade-off between Type I and Type II errors. The elastic net analyses were performed using the glmnet package (Friedman et al. 2010) in R with penalty weight $\alpha = 0.05$ and 1000-fold cross validation to find λ at MSE plus 1 standard error.

Results

Hardy-Weinberg equilibrium and linkage disequilibrium

Hardy-Weinberg equilibrium tests resulted in *p*-values that ranged between 5.33×10^{-11} and 1. There were 5467 (longevity), 6304 (fertility) and 2149 (cystic ovaries) SNPs with a *p*-value smaller than 0.05 and 4 (longevity), 19 (fertility) and 0 (cystic ovaries) SNPs with a *p*-value smaller than the Bonferroni threshold. Nevertheless, no SNPs were removed because the data comes from a cattle population that has been subjected artificial selection. Linkage disequilibrium between adjacent SNPs was on average 0.18 ± 0.02 across the whole genome, with the lowest value of 0.15 for BTA19 and BTA28 to the highest of 0.21 for BTA6 (Table 1). The relationship between r^2 values and distance between adjacent SNPs on BTA2 are plotted in Figure 1 (all chromosomes show a similar pattern). There were no obvious decay of LD with longer distance between SNPs, but SNPs with long distance apart seldom display high LD. Some adjacent SNPs were highly correlated. For example, the number of SNP pairs with r^2 values larger than 0.95 were 1175 over all chromosomes.

Table 1 Average linkage disequilibrium (r^2) between adjacent SNPs on each chromosome.

BTA	r^2	BTA	r^2
1	0.20	16	0.20
2	0.20	17	0.18
3	0.19	18	0.19
4	0.20	19	0.15
5	0.18	20	0.17
6	0.21	21	0.19
7	0.20	22	0.18
8	0.19	23	0.15
9	0.18	24	0.18
10	0.17	25	0.15
11	0.19	26	0.17
12	0.17	27	0.15
13	0.17	28	0.15
14	0.18	29	0.17
15	0.17	Mean	0.18
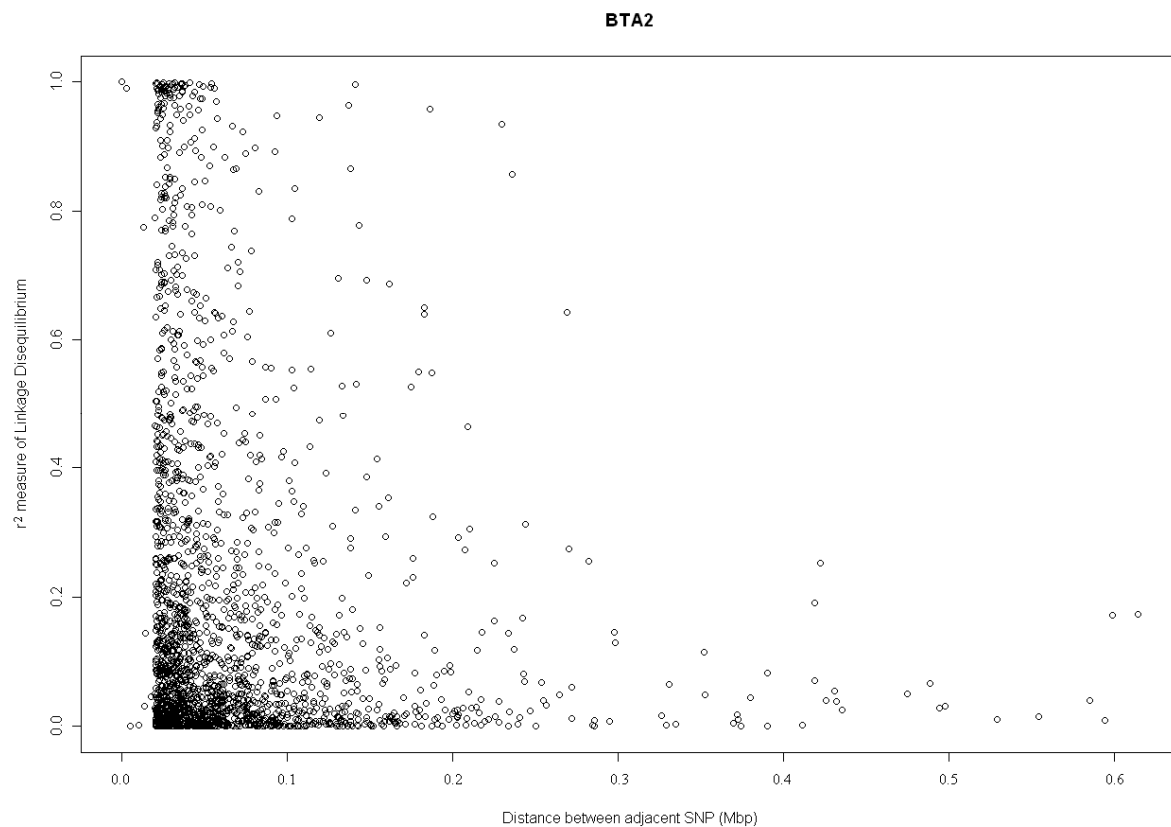
Figure 1 Relationship between linkage disequilibrium (r^2) and distance (Mbp) between adjacent SNPs on BTA2.

Single-SNP analyses

In the single-SNP analyses, 4 SNPs showed significant associations with longevity on BTA7, 15 and 16 after applying the Bonferroni correction (p-value $< 1.22 \times 10^{-6}$). 270 SNPs were detected as significant when correcting with FDR (q-value < 0.05; Table 2). These 270 SNPs were spread across the whole genome (Table 3). For fertility, the number of significant SNPs after Bonferroni correction was 19 and located on BTA1, BTA3, BTA4, BTA5, BTA9, BTA10, BTA23 and BTA24. With FDR, 726 SNPs were found to be significantly associated with fertility (Table 2) and distributed across the whole genome (Table 3). No significant association was observed for cystic ovaries after the Bonferroni and FDR corrections.

Multiple-SNP analyses

The number of SNPs detected with the elastic net method was 143 and 183 for longevity and fertility, respectively. The regression coefficients of detected SNPs were in the range of - 0.005 to 0.0048 for longevity, and from - 0.1755 to 0.168 for fertility. Also there was no SNP associated with cystic ovaries. Only 3 SNPs on BTA8, BTA19 and BTA20 showed an association with both longevity and fertility (Table 4). The details of the SNPs associated with longevity and fertility are presented in the Appendix.

Table 4 SNPs detected in both longevity and fertility.

SNP	Chr.	Position (bp)	Coefficients	
			Longevity	Fertility
ARS-BFGL-NGS-34586	8	31439257	- 0.00003	- 0.02074
UA-IFASA-6003	19	49523704	0.00084	0.00214
BTB-01524822	20	20128763	0.00041	0.01119

**Table 2** Number of associated SNPs in both single- and multiple-SNP analyses.

Trait	Single-SNP analysis		Multiple-SNP analysis	
	Original p-values (p-value ≤ 0.05)*	Bonferroni correction (p-value $\leq 1.22 \times 10^{-06}$)*	False discovery rate (FDR) (q-value ≤ 0.05)*	Elastic net ($\alpha = 0.05$)
Longevity	5467	4	270	143
Fertility	6304	19	726	183
Cystic Ovaries	2149	-	-	-

* Threshold of significant associations

Table 3 Number of associated SNPs for longevity and fertility on respective chromosome.

Longevity

BTA	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	X	Y
BON	-	-	-	-	-	-	1	-	-	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FDR	19	9	8	9	16	8	16	14	5	16	15	9	5	11	24	10	5	1	10	4	5	2	6	4	4	5	6	16	1	5	1
EN	12	7	5	5	6	4	6	8	5	5	9	4	3	6	10	4	3	1	10	3	1	2	2	3	4	3	3	7	1	1	-

Fertility

BTA	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	X	Y
BON	3	-	5	1	4	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	2	-	1	-	-	-	-	-	-	-
FDR	40	24	64	69	30	29	52	36	19	23	34	13	23	33	17	13	16	10	29	11	7	20	10	36	16	13	4	13	9	13	-
EN	8	4	17	19	9	3	15	7	6	8	14	3	2	7	2	4	4	2	11	2	-	1	3	13	4	3	-	7	1	4	-

BTA= *Bos taurus* autosomes; BON = Bonferroni correction; FDR = False discovery rate; EN = Elastic net ($\alpha = 0.05$)

Longevity

Fertility

11
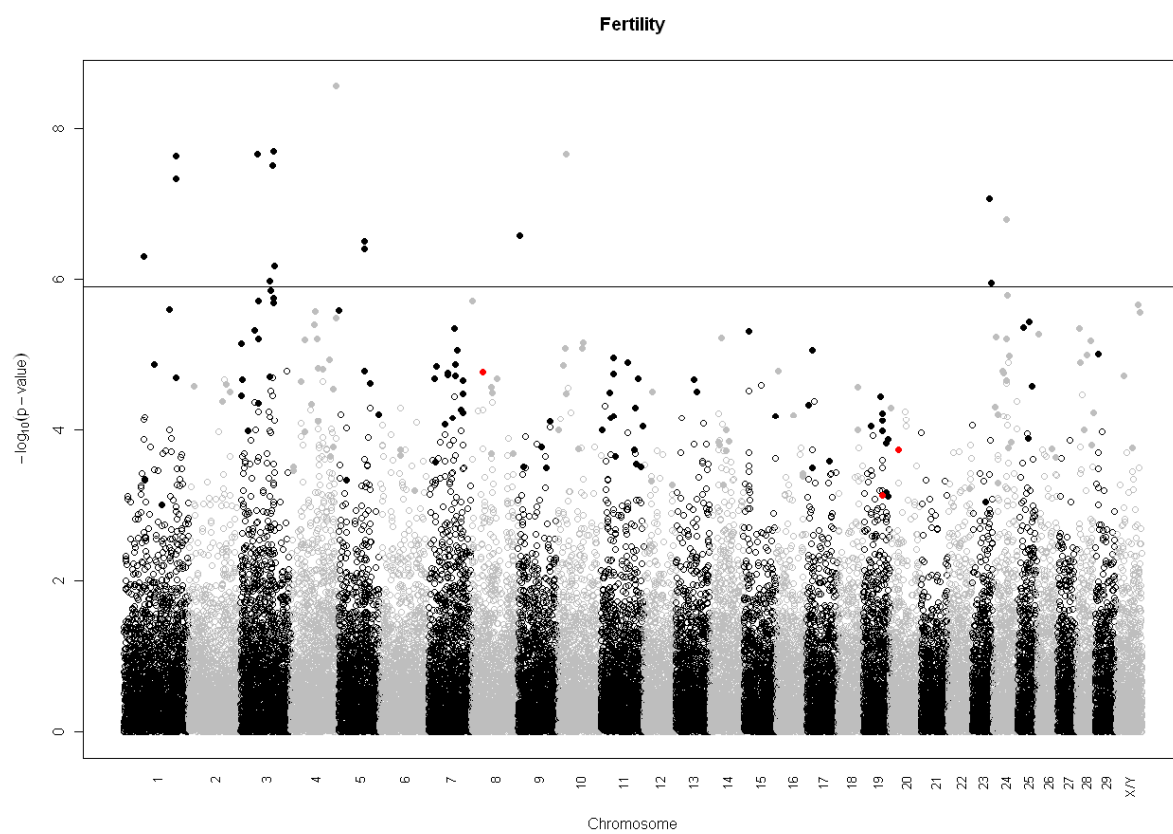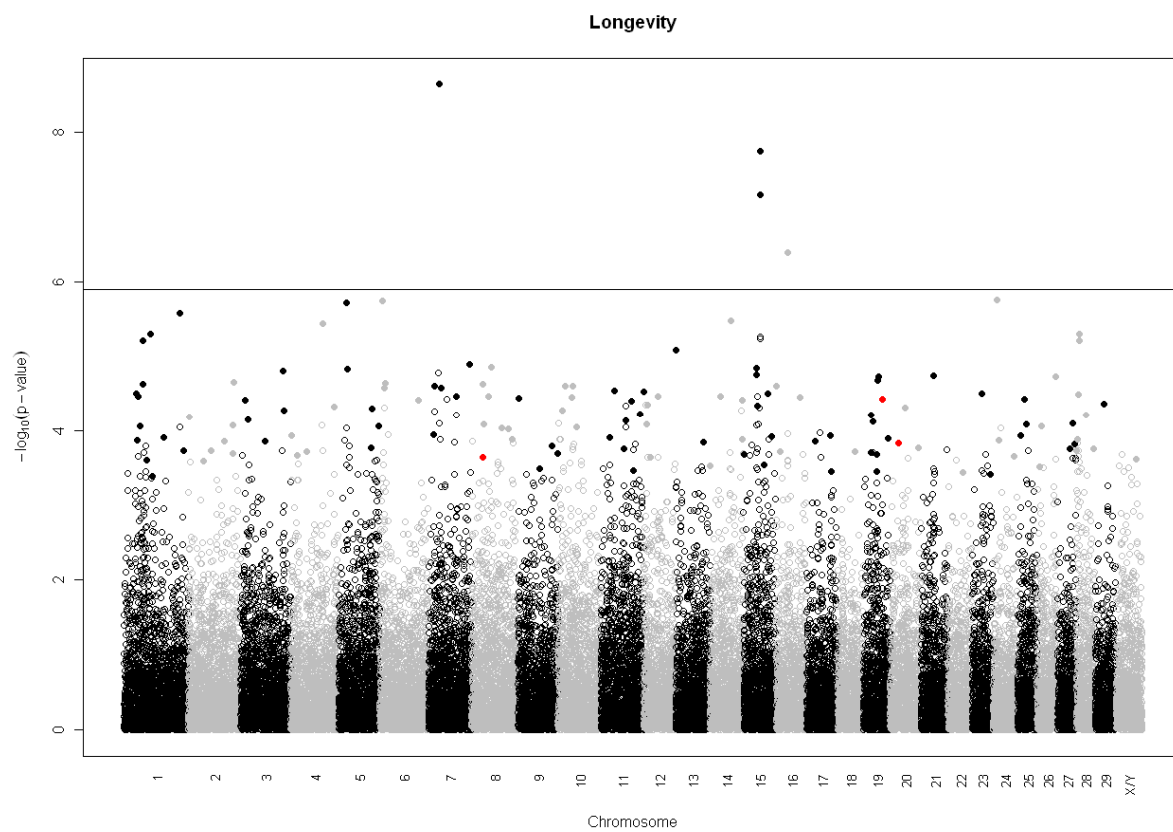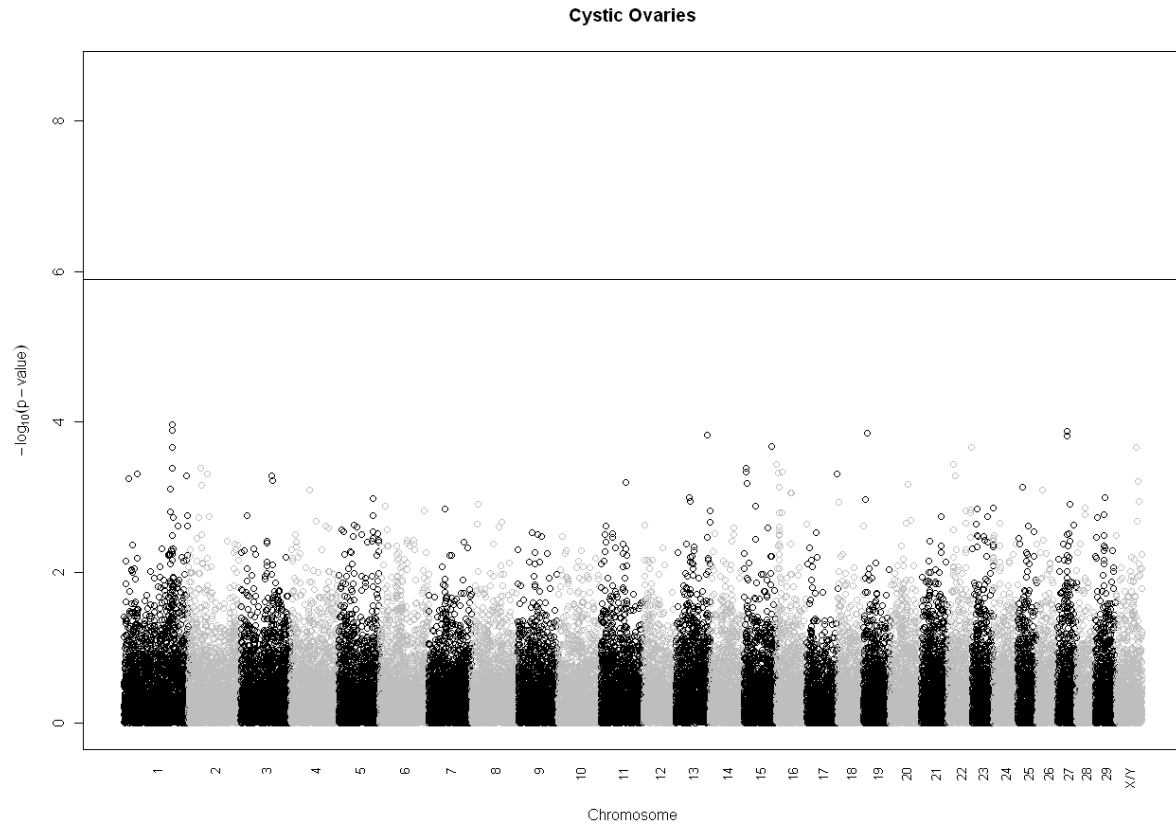
Cystic Ovaries

Figure 2 Genome-wide associations for longevity, fertility and cystic ovaries: - $\log_{10}$ (p-value) from single-SNP analyses are plotted respective to chromosomes. The solid line is the Bonferroni threshold of - $\log_{10}$ (p-value) = 5.90. The filled black and grey dots are SNPs that also were detected with the elastic net. The red dots are SNPs found significant associations in both longevity and fertility.
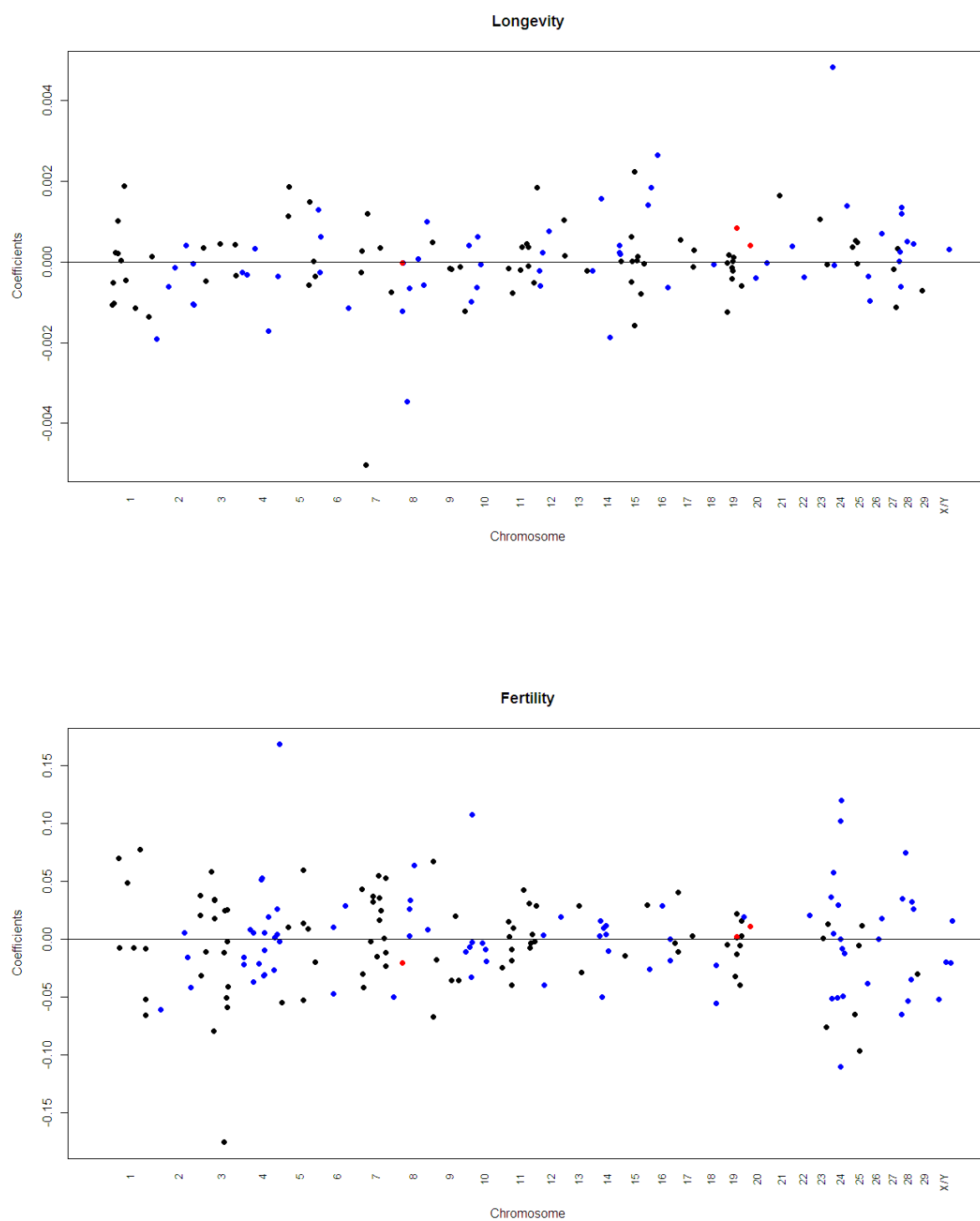
Figure 3 SNPs detected by the elastic net (penalty weight $\alpha = 0.5$) for longevity and fertility. The red dots are SNPs found significant associations in both longevity and fertility.

Discussion

Linkage disequilibrium

In a recent simulation study that investigated the performance of dense SNPs to detect quantitative trait loci (QTLs), it was shown that the QTL variance contributing 5% on the phenotypic variance could not be detected ($p < 0.001$) unless r^2 between QTL and SNP was 0.2 (MacLeod et al. 2010). According to this result, it could be difficult with the observed r^2 value of 0.18 to detect all QTLs of small effects that influence longevity, fertility and cystic ovaries in this study. However, some improvements can be attained by reducing the significance level. As shown in Table 2, a higher number of SNPs was detected when applying FDR instead of the Bonferroni threshold which is considered to be a conservative method (Pearson & Manolio 2008). One of the problems with GWAS is that it requires high LD between SNPs and QTLs, but often relies on statistical methods that assume no LD between SNPs. Goddard & Hayes (2009) suggested that the LD often observed at large distance (> 1 cM) makes precise QTL mapping difficult because SNP associations with QTLs will be observed in a very large interval and a very dense SNP panel does not result in any remarkable advantage in mapping precision, but improvements can be achieved by using multiple breeds because long-distance LD is only consistent within breed. However, the observed LD and the number of chosen SNPs in the present study seem to be sufficient to map QTL within a reasonable range. Besides, more phenotypic records could additionally enhance the power to detect SNP associations, and consequently locate QTL more precisely.

The Bonferroni correction vs. false discovery rate (FDR) for single-SNP analyses

The Bonferroni correction is considered to be a simple way to identify a significance level that adjusts for testing many hypotheses. However, the Bonferroni correction assumes independence of hypothesis testing so it can be very conservative when correlations between SNPs are observed (Sahana at el. 2010). In Fig. 2, only few SNPs were detected above the threshold of the Bonferroni correction which support the conclusion that this method is too conservative. The Bonferroni correction is a method

which controls Type I errors, or false positives. The higher the significance level, the less number of SNPs can be detected significantly, the higher possibility that positive results are true (MacLeod at el. 2010). A problem when implementing the strict significance level to reduce Type I errors is an increase of Type II errors, or false negatives, especially for the low heritable traits. It is difficult to find associations because the effect of the QTL is small. Despite that some SNPs actually contain an effect on a trait, they will be considered as insignificant because of their weak signal. Thus, it is preferable to relax the significance threshold to some level where it is acceptable in order to reduce Type II errors and gain higher power to detect associations. The false discovery rate has been introduced to provide a more preferable control of Type I errors when testing many hypotheses. The power of FDR was confirmed by a simulation study which compared the FDR and the conventional Bonferroni correction. The study concluded that FDR yielded slightly higher power compared to that of the Bonferroni correction when low LD between markers was observed (Yang et al. 2005). The similar case was observed in the present study where LD between adjacent SNP was relatively low (Table 3.). Hence, the FDR method seems to have higher power to detect SNP associations than the Bonferroni method, but it also appears to have higher degree of Type I errors. It is difficult to find the right trade-off between Type I and Type II errors in GWAS, and more effort ought to be devoted to this problem (Rice et al. 2008).

Single-SNP vs. multiple-SNP analyses

The number of SNPs detected with the elastic net method was one half (longevity) and one fourth (fertility) of the SNPs found with the FDR adjustment. On the other hand, the number of significant SNPs was much lower for the Bonferroni method than for the elastic net. Correlations between regression coefficients of significant SNPs detected in both single-SNP and multiple-SNP analyses were not so high; 0.78 (longevity) and 0.79 (fertility). Single-SNP analyses consider SNP-effects separately and ignore correlations (LD) between SNPs. Subsequently, highly correlated SNPs can be detected as significant with single SNP analysis, but their effects will most likely be overestimated

since they are regressed separately. Such a situation can result in a higher number of false significant SNPs in single-SNP than in multiple-SNP analyses.

The penalized multiple regression implemented with the elastic net provides a tool to optimize between Type I and Type II errors in GWAS. In order to find optimal performance, the method has been investigated on simulated data where variables were correlated and had known effects. It was found that the elastic net performed better than the related lasso and ridge regression (Zou & Hastie 2005; Tutz & Ulbricht 2009; Waldmann et al. in prep). In the present study, most of the observed LD was not so strong, however, some SNP pairs display considerable LD. Hence, the multiple-SNP analyses in form of the elastic net should be interpreted as the most reliable method. Nevertheless, the single-SNP analysis is computationally less demanding when applied to the large dataset and therefore can serve as a compliment to multiple-SNP analysis (Balding 2006). Fortunately, in the present study, the number of bulls was not very high and the computational support efficiently provided, so the elastic net analyses only took a few hours.

Detected associations

There were 4 SNPs that showed highly significant signals on BTA7 and BTA16 for longevity and on BTA4 and BTA10 for fertility. These SNPs had high base 10 logarithm *p*-values over the stringent level of the Bonferroni threshold and therefore show strong evidence of association. Despite that four SNPs were detected in both single-SNP analyses with FDR and multiple-SNP analyses, the main proportion of significant SNPs were found in between the significance threshold of the Bonferroni correction and FDR. Ashwell et al. (2004) found a significant association on BTA7, however, only one significant marker effect was detected and it was suspected to be a false positive association. The very highly significant SNPs identified in the present study, however, have to be repeatedly found in other independent studies before a conclusion about causative QTLs can be drawn (Cantor et al. 2010).

QTLs affecting longevity have previously been reported on BTA2, BTA4, BTA17, BTA18 and BTA21 (Heyen et al. 1999; Van Tassell et al. 2000; Kuhn et al. 2003), similar to the SNP

associations detected in this study with the single-SNP analyses with FDR and the elastic net However, those putative QTLs of longevity were implied from one significant maker per chromosome. In present study, the number of QTLs affecting longevity was much higher due to the higher density of SNPs. Previous results were obtained from microsatellites distributed with large intervals resulting in much less accuracy. It seems to be advantageous for low heritable traits to use SNPs in association studies because SNPs are positioned more accurately on the chromosomes and are available with much smaller intervals. It allows small effects of SNPs to be observed while only the QTLs influencing the major proportion of phenotypic variance can be detected with microsatellites.

Kuhn et al. (2003) reported QTLs affecting fertility on BTA10 and BTA18, similar to some SNPs observed in this study. However, the phenotypic traits of fertility were different in the previous study (non-return rate: NR) and the present study (interval from first to last insemination: FLI). Even though a negative genetic correlation between NR and FLI has been reported in previous studies of Fuerst & Gredler (2009) and Koeck et al. (2010), the findings about the QTLs should be interpreted in light of the different trait definitions. Other putative QTLs were reported by Sahana et al. (2010) on BTA1, BTA 3, BTA4, BTA5, BTA7, BTA9, BTA10, BTA20 and BTA24. These results could be considered as a confirmation of potential QTL locations for the present study where significant SNPs were similarly detected on previously suggested chromosomes. The difference in number of significant SNPs and positions on chromosomes may be due to the genetic difference between breeds. The variation between positions and frequencies in recombination along the population history in each breed can be the cause of changes in position.

No associations between SNPs and cystic ovaries were detected in any of the analyses. One possible reason could be that daughter yield deviations of cystic ovaries have just been recently recorded, so the available number of daughters who provides the phenotypes per bull was lower than that of longevity and fertility (personal communication). Thus, in further studies when phenotypes become increasingly available, significant SNP associations with cystic ovaries could possibly be detected.

A negative genetic correlation between longevity and fertility has been reported in for example VanRaden et al. (2002). The regression coefficients of the three selected SNPs that influence both longevity and fertility ought to have different signs between the traits to explain the observed negative genetic correlation (Appendix). However, as this isn't the case, there must be some other process than simple pleiotropy that explains this phenomenon. In terms of management, longevity and fertility are also related since productive cows will have a higher chance to stay longer in a herd (higher longevity) than cows that are less productive. However, these cows will have undesirable fertility because of the unfavourable genetic correlation between production and fertility.

Conclusion

In the present study, SNP associations with longevity and fertility corresponded to previous results reported in other cattle breeds. However, the number of identified SNPs has to be further confirmed in independent populations. No significant SNP was found for cystic ovaries, but SNP associations can possibly be observed when more phenotypes are provided. We know from extensive analyses of simulated data that the elastic net method with $\alpha = 0.05$ has an almost optimal trade-off between Type I and Type II error rates in GWA studies where SNPs have moderate to high levels of linkage disequilibrium between each other. Therefore, it seems reasonable to draw the conclusion that single SNP analyses produce unreliable results, and that longevity and fertility in Fleckvieh are characters that probably is influenced by many genes.

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Appendix

I SNPs detected significant associations with longevity in multiple-SNP analyses.

SNP	Chr.	Position (bp)	P-value	Coefficient (s)
BTB-00902072	1	34054462	3.13E-05	-0.00107
ARS-BFGL-BAC-12481	1	35238664	1.34E-04	-0.00052
Hapmap50634-BTA-26738	1	37438184	3.45E-05	-0.00102
BTB-01848824	1	42763138	8.72E-05	0.00023
ARS-BFGL-BAC-24524	1	48191477	2.37E-05	0.00022
BTB-02090792	1	48248143	6.18E-06	0.00101
ARS-BFGL-NGS-16908	1	59853273	2.52E-04	0.00004
ARS-BFGL-BAC-19439	1	66706736	5.03E-06	0.00187
Hapmap53495-rs29015962	1	71919664	4.09E-04	-0.00046
BTA-45180-no-rs	1	102153160	1.24E-04	-0.00115
ARS-BFGL-NGS-31728	1	144559050	2.61E-06	-0.00137
ARS-BFGL-NGS-39807	1	152125152	1.87E-04	0.00013
ARS-BFGL-NGS-27330	2	1439831	6.61E-05	-0.00190
Hapmap41880-BTA-47153	2	33655649	2.55E-04	-0.00061
BTB-01391891	2	56878350	1.87E-04	-0.00015
BTA-48480-no-rs	2	99766433	1.41E-04	0.00041
ARS-BFGL-NGS-25658	2	122338917	2.05E-04	-0.00005
ARS-BFGL-NGS-108811	2	123033891	8.53E-05	-0.00105
ARS-BFGL-NGS-83173	2	124329979	2.25E-05	-0.00106
ARS-BFGL-NGS-103120	3	14284629	3.87E-05	0.00034
Hapmap33860-BES7_Contig442_1439	3	24395609	7.19E-05	-0.00047
BTB-01635474	3	73072226	1.41E-04	0.00045
BTB-00148908	3	112789957	1.55E-05	0.00043
ARS-BFGL-NGS-38199	3	113335451	5.38E-05	-0.00034
ARS-BFGL-NGS-57926	4	3345193	1.15E-04	-0.00026
BTA-68470-no-rs	4	18426215	2.17E-04	-0.00033
ARS-BFGL-NGS-100360	4	42800178	1.91E-04	0.00032
BTB-01687779	4	82759658	3.63E-06	-0.00172
BTB-01367046	4	115298321	4.80E-05	-0.00037
Hapmap42303-BTA-72846	5	22049267	1.90E-06	0.00113
ARS-BFGL-NGS-93953	5	25369821	1.47E-05	0.00185
Hapmap28380-BTA-74649	5	103598357	1.70E-04	-0.00058
ARS-BFGL-NGS-118033	5	108461317	4.98E-05	0.00148
ARS-BFGL-NGS-102035	5	119223665	4.90E-04	0.00001
ARS-BFGL-NGS-66396	5	122778434	8.75E-05	-0.00037
ARS-BFGL-NGS-104900	6	6995395	1.79E-06	0.00129
BTA-88441-no-rs	6	10929392	2.62E-05	-0.00027
BTB-00244545	6	13047089	2.26E-05	0.00062
BTB-01096020	6	101535245	3.91E-05	-0.00115
ARS-BFGL-NGS-115326	7	13953341	1.14E-04	-0.00027
ARS-BFGL-NGS-108609	7	16744243	2.53E-05	0.00027
BTB-01074531	7	25930940	2.30E-09	-0.00504
BTB-00549286	7	30248328	2.68E-05	0.00119
BTA-113124-no-rs	7	71000776	3.47E-05	0.00036
ARS-BFGL-NGS-118583	7	107129422	1.27E-05	-0.00075

SNP	Chr.	Position (bp)	P-value	Coefficient (s)
Hapmap35664-SCAFFOLD116678_816	8	31322025	2.38E-05	-0.00123
ARS-BFGL-NGS-34586	8	31439257	2.27E-04	-0.00003
Hapmap33212-BTA-145669	8	32875216	8.20E-05	-0.00003
Hapmap33488-BTA-145765	8	46360789	3.46E-05	-0.00345
BTB-01713349	8	53599973	1.39E-05	-0.00066
ARS-BFGL-NGS-112998	8	78011419	9.17E-05	0.00007
Hapmap33490-BTA-146089	8	93945193	9.57E-05	-0.00058
BTB-00370321	8	104804278	1.31E-04	0.00100
BTB-01752812	9	1203863	3.60E-05	0.00048
ARS-BFGL-NGS-14862	9	59792267	3.24E-04	-0.00017
ARS-BFGL-NGS-34075	9	62427473	4.81E-04	-0.00019
BTA-07298-no-rs	9	94222826	1.62E-04	-0.00011
Hapmap33058-BTA-158159	9	106108337	2.03E-04	-0.00122
Hapmap54740-rs29013264	10	12484781	5.31E-05	0.00040
ARS-BFGL-NGS-116044	10	16761174	2.52E-05	-0.00099
ARS-BFGL-NGS-41641	10	35690157	3.50E-05	-0.00064
ARS-BFGL-BAC-12255	10	36532186	2.49E-05	0.00061
ARS-BFGL-NGS-60054	10	46854373	9.00E-05	-0.00006
Hapmap30865-BTA-157248	11	18824844	1.22E-04	-0.00016
ARS-BFGL-NGS-75483	11	29494439	2.89E-05	-0.00078
BTA-88741-no-rs	11	51927012	1.77E-04	-0.00020
Hapmap59053-rs29015825	11	61852402	7.42E-05	0.00036
Hapmap35883-POMC_121F2-SNP1	11	76264190	3.96E-05	0.00045
Hapmap39216-BTA-107320	11	82317187	3.41E-04	0.00036
BTA-107309-no-rs	11	82339003	5.20E-04	-0.00010
ARS-BFGL-NGS-100840	11	102123682	5.90E-05	-0.00052
ARS-BFGL-NGS-37958	11	110015338	2.94E-05	0.00183
ARS-BFGL-NGS-25155	12	8427467	8.23E-05	-0.00022
BTA-120902-no-rs	12	10523482	4.50E-05	-0.00059
ARS-BFGL-NGS-108858	12	17419046	2.31E-04	0.00024
ARS-BFGL-NGS-114010	12	43636515	3.41E-05	0.00076
Hapmap48962-BTA-96730	13	989485	8.14E-06	0.00104
ARS-BFGL-NGS-103379	13	3766392	4.90E-04	0.00015
ARS-BFGL-NGS-14434	13	72031068	1.44E-04	-0.00023
ARS-BFGL-NGS-34135	14	260341	2.97E-04	-0.00023
ARS-BFGL-NGS-112623	14	18683217	3.42E-05	0.00156
Hapmap39451-BTA-89611	14	47793525	3.34E-06	-0.00187
ARS-BFGL-BAC-18907	14	78370249	3.89E-05	0.00041
ARS-BFGL-NGS-104251	14	78428895	1.32E-04	0.00022
Hapmap34730-BES8_Contig464_1373	14	80458251	2.05E-04	0.00018
ARS-BFGL-NGS-95231	15	209270	2.12E-04	0.00001
ARS-BFGL-NGS-118826	15	33186638	1.77E-05	0.00061
ARS-BFGL-NGS-21358	15	33361753	1.44E-05	-0.00051
ARS-BFGL-NGS-96067	15	34384053	4.54E-05	0.00001
BTA-36844-no-rs	15	41250286	6.79E-08	-0.00157
ARS-BFGL-NGS-41288	15	41305003	1.81E-08	0.00224
BTA-37062-no-rs	15	50121949	5.05E-04	0.00003
ARS-BFGL-NGS-110365	15	52334932	2.86E-04	0.00013
ARS-BFGL-NGS-112293	15	61746413	3.15E-05	-0.00078

SNP	Chr.	Position (bp)	P-value	Coefficient (s)
BTA-117758-no-rs	15	71772710	1.19E-04	-0.00005
ARS-BFGL-NGS-6005	16	178911	2.47E-05	0.00141
BTB-01533537	16	9042653	1.90E-04	0.00183
Hapmap60111-rs29017285	16	30848373	4.10E-07	0.00264
ARS-BFGL-NGS-5658	16	64652341	3.50E-05	-0.00063
BTA-16055-no-rs	17	20526118	1.41E-04	0.00054
BTB-00682000	17	61731804	1.16E-04	-0.00012
Hapmap38836-BTA-41399	17	61825773	3.52E-04	0.00030
ARS-BFGL-NGS-103406	18	40776667	1.90E-04	-0.00007
Hapmap40539-BTA-44669	19	20230001	1.96E-04	-0.00002
Hapmap55122-rs29020857	19	21275791	6.25E-05	-0.00124
ARS-BFGL-NGS-110331	19	25110983	7.54E-05	0.00017
ARS-BFGL-NGS-93931	19	34566918	2.10E-04	-0.00015
ARS-BFGL-NGS-68563	19	35538971	3.54E-04	-0.00042
ARS-BFGL-NGS-42120	19	36189296	7.51E-04	0.00002
Hapmap42945-BTA-45128	19	36323785	2.11E-05	-0.00022
BTB-01941088	19	39320627	1.85E-05	0.00011
UA-IFASA-6003	19	49523704	3.80E-05	0.00084
UA-IFASA-5305	19	61120357	1.28E-04	-0.00059
BTB-01524822	20	20128763	1.48E-04	0.00041
BTA-50515-no-rs	20	39949594	4.83E-05	-0.00040
ARS-BFGL-NGS-22607	20	70432715	1.71E-04	-0.00003
ARS-BFGL-NGS-20345	21	30811150	1.81E-05	0.00165
ARS-BFGL-BAC-28083	22	2299767	5.60E-04	0.00039
ARS-BFGL-BAC-2599	22	39279847	3.67E-04	-0.00038
BTA-81631-no-rs	23	24620814	3.18E-05	0.00105
ARS-BFGL-NGS-39402	23	47944649	3.88E-04	-0.00006
BTB-02092251	24	8249290	1.77E-06	0.00482
ARS-BFGL-NGS-90674	24	12625164	1.37E-04	-0.00009
ARS-BFGL-NGS-62630	24	53079451	2.21E-04	0.00139
Hapmap26025-BTC-050671	25	6443233	1.19E-04	0.00037
ARS-BFGL-NGS-41995	25	15991777	3.70E-05	0.00053
ARS-BFGL-NGS-111246	25	21931845	4.58E-04	-0.00005
ARS-BFGL-NGS-42285	25	21972654	8.21E-05	0.00048
BTB-01957902	26	8201489	3.04E-04	-0.00037
Hapmap48022-BTA-62041	26	13461008	8.69E-05	-0.00096
BTA-88023-no-rs	26	46281134	1.87E-05	0.00070
Hapmap26091-BTA-109412	27	33755284	1.78E-04	-0.00018
ARS-BFGL-NGS-9378	27	38709510	7.98E-05	-0.00112
ARS-BFGL-NGS-37647	27	45253564	1.53E-04	0.00033
ARS-BFGL-NGS-2154	28	1108078	1.88E-04	0.00002
ARS-BFGL-NGS-72206	28	1970800	1.32E-04	0.00024
ARS-BFGL-NGS-81213	28	6152105	3.29E-05	-0.00061
BTB-00975169	28	6259059	6.15E-06	0.00120
ARS-BFGL-NGS-2530	28	6287621	4.98E-06	0.00136
Hapmap44654-BTA-63754	28	24327771	6.13E-05	0.00051
ARS-BFGL-NGS-105545	28	43627647	1.76E-04	0.00045
ARS-BFGL-NGS-32389	29	25977926	4.29E-05	-0.00071
BTB-01827114	X	0	2.44E-04	0.00030

II SNPs detected significant associations with fertility in multiple-SNP analyses.

SNP	Chr.	Position (bp)	P-value	Coefficient (s)
BTA-27925-no-rs	1	52328172	5.05E-07	0.06962
BTB-01605050	1	54065831	4.50E-04	-0.00728
ARS-BFGL-BAC-33415	1	80155226	1.32E-05	0.04844
ARS-BFGL-NGS-60021	1	98787466	9.90E-04	-0.00728
BTB-00050187	1	116476338	2.48E-06	0.07703
ARS-BFGL-NGS-104132	1	134258378	4.68E-08	-0.05187
ARS-BFGL-NGS-68753	1	134280052	2.31E-08	-0.06595
Hapmap45405-BTA-111896	1	134419504	2.01E-05	-0.00807
BTB-01085257	2	15217858	2.59E-05	-0.06087
Hapmap35020-BES8_Contig415_403	2	92309638	4.17E-05	0.00551
ARS-BFGL-NGS-113504	2	105865903	2.45E-05	-0.01566
BTA-34427-no-rs	2	115742595	3.12E-05	-0.04151
ARS-BFGL-NGS-27655	3	3683166	3.45E-05	0.03735
INRA-483	3	4064093	7.20E-06	0.02017
ARS-BFGL-NGS-118372	3	5763386	2.12E-05	-0.03182
ARS-BFGL-NGS-104522	3	23959922	1.03E-04	-0.01093
Hapmap43129-BTA-105623	3	43284600	4.80E-06	0.05802
ARS-USMARC-Parent-AY842474-rs29003226	3	50318221	2.17E-08	-0.07913
INRA-611	3	54677955	4.33E-05	0.01805
INRA-618	3	55234368	6.11E-06	0.03400
ARS-BFGL-NGS-35164	3	55278469	1.93E-06	0.03336
ARS-BFGL-NGS-67919	3	83751467	1.06E-06	-0.17550
BTB-01155362	3	84619370	1.95E-05	-0.01183
ARS-BFGL-NGS-112987	3	86973360	1.41E-06	0.02485
Hapmap43161-BTA-116272	3	92007242	3.14E-08	-0.05088
BTB-01240408	3	92027498	2.03E-08	-0.05912
BTB-01240396	3	92050074	1.80E-06	-0.00233
Hapmap58361-rs29011460	3	92528259	2.04E-06	0.02497
BTA-89470-no-rs	3	93984558	6.70E-07	-0.04110
ARS-BFGL-NGS-31713	4	7848817	3.16E-04	-0.02218
ARS-BFGL-NGS-82575	4	7886460	3.51E-04	-0.01556
BTB-01114756	4	28805507	2.27E-05	0.00813
Hapmap44201-BTA-114510	4	37991516	1.09E-04	0.00574
Hapmap61001-rs29016986	4	38894271	6.35E-06	-0.03690
ARS-BFGL-NGS-25383	4	54749801	4.51E-05	-0.02131
Hapmap49717-BTA-70840	4	62504574	3.99E-06	0.05102
BTB-00191792	4	63697915	2.65E-06	0.05254
ARS-BFGL-NGS-116611	4	69656392	6.10E-06	-0.03140
ARS-BFGL-NGS-116468	4	72831516	7.76E-05	-0.03115
Hapmap49439-BTA-109526	4	72939016	1.53E-05	0.00551
ARS-BFGL-NGS-36876	4	72988437	7.69E-05	-0.00946
BTB-01162643	4	83347929	1.55E-05	0.01891
Hapmap52502-rs29022385	4	99054354	1.17E-05	-0.02672
ARS-BFGL-NGS-15146	4	103370908	2.30E-04	0.00136
ARS-BFGL-NGS-35219	4	110022608	2.86E-05	0.00429
ARS-BFGL-NGS-30190	4	112181263	1.70E-04	0.02591
BTB-00213426	4	118208860	3.27E-06	-0.00235

SNP	Chr.	Position (bp)	P-value	Coefficient (s)
ARS-BFGL-NGS-119660	4	118348425	2.79E-09	0.16800
ARS-BFGL-NGS-26978	5	1166619	2.55E-06	-0.05509
BTA-74304-no-rs	5	20380400	4.70E-04	0.00999
Hapmap54557-rs29012924	5	82134398	3.91E-07	-0.05285
BTB-01738032	5	82164520	3.91E-07	-0.05241
Hapmap50896-BTA-122135	5	82220247	3.14E-07	0.05935
BTB-01908691	5	82278516	3.91E-07	-0.05285
BTA-104619-no-rs	5	83897767	1.66E-05	0.01338
BTA-94299-no-rs	5	100372425	2.40E-05	0.00885
ARS-BFGL-NGS-16699	5	123626392	6.13E-05	-0.01982
BTB-01553462	6	51567324	2.19E-04	-0.04712
BTA-103370-no-rs	6	51603450	1.87E-04	0.01035
Hapmap43045-BTA-76998	6	91961905	6.45E-04	0.02841
ARS-BFGL-NGS-12159	7	16540058	2.10E-05	0.04279
ARS-BFGL-NGS-17196	7	18833893	2.71E-04	-0.03002
ARS-BFGL-NGS-115712	7	19914481	1.41E-05	-0.04164
UA-IFASA-6047	7	40308074	8.55E-05	-0.00196
ARS-BFGL-NGS-103354	7	45779192	1.72E-05	0.03661
ARS-BFGL-NGS-15177	7	45822826	1.87E-05	0.03203
BTB-00314778	7	60727957	6.93E-05	-0.01483
BTB-00318021	7	64863946	4.43E-06	0.05486
ARS-BFGL-NGS-39099	7	68608337	1.88E-05	0.01612
ARS-BFGL-NGS-35004	7	68760341	1.33E-05	0.03540
BTB-00319402	7	71417757	8.82E-06	0.02468
BTB-01924842	7	81679040	5.31E-05	0.00072
Hapmap44668-BTA-119022	7	86376788	2.17E-05	-0.02327
BTA-94810-no-rs	7	86494535	3.33E-05	0.05291
BTB-00324772	7	86905200	5.87E-05	-0.01156
ARS-BFGL-NGS-113904	8	3520745	1.94E-06	-0.05011
ARS-BFGL-NGS-34586	8	31439257	1.71E-05	-0.02074
BTB-00348844	8	53942221	2.09E-04	0.00298
Hapmap57994-rs29022887	8	53991682	2.69E-05	0.02593
BTB-00348409	8	54348396	3.18E-05	0.03377
Hapmap57239-rs29018125	8	65595478	2.04E-05	0.06371
BTA-82556-no-rs	8	104971778	2.12E-04	0.00829
BTB-01800430	9	4905204	2.66E-07	0.06703
BTB-01800374	9	4927068	2.66E-07	-0.06696
BTB-00932823	9	15878710	3.12E-04	-0.01791
ARS-BFGL-NGS-60933	9	63830137	1.70E-04	-0.03554
BTA-84286-no-rs	9	76754516	3.24E-04	0.01982
BTA-84665-no-rs	9	89558591	7.79E-05	-0.03529
BTB-01855834	10	2818173	1.00E-04	-0.01066
BTB-00410198	10	14028461	1.39E-05	-0.00678
ARS-BFGL-NGS-22837	10	17583453	8.26E-06	-0.03273
ARS-BFGL-NGS-117076	10	18842692	3.28E-05	-0.00274
ARS-BFGL-NGS-22915	10	19876316	2.19E-08	0.10710
BTB-00427152	10	50562940	1.82E-04	-0.00376
Hapmap49031-BTA-114687	10	59934508	8.11E-06	-0.00885
BTA-72321-no-rs	10	60756095	6.97E-06	-0.01925

SNP	Chr.	Position (bp)	P-value	Coefficient (s)
Hapmap36649-SCAFFOLD175947_14270	11	2603118	1.00E-04	-0.02438
Hapmap26417-BTA-147042	11	18174964	3.22E-05	0.01483
ARS-BFGL-NGS-54076	11	21289389	6.93E-05	0.00196
ARS-BFGL-NGS-12964	11	25878965	6.53E-05	-0.00908
ARS-BFGL-NGS-27885	11	26621223	1.80E-05	-0.01841
ARS-BFGL-BAC-5846	11	26644920	1.09E-05	-0.03977
ARS-BFGL-NGS-87426	11	30070766	2.26E-04	0.00952
Hapmap42754-BTA-99156	11	65298768	1.25E-05	0.04221
Hapmap46768-BTA-117394	11	84956219	1.86E-04	0.03040
ARS-BFGL-NGS-115717	11	88794226	5.05E-05	-0.00724
ARS-BFGL-NGS-22703	11	91050647	2.83E-04	-0.00381
ARS-BFGL-NGS-103958	11	96733243	2.06E-05	0.00431
ARS-BFGL-NGS-112243	11	104735294	3.17E-04	-0.00186
ARS-BFGL-NGS-81167	11	108735701	9.03E-05	0.02881
ARS-BFGL-NGS-34964	12	21668640	4.84E-04	0.00348
Hapmap58664-rs29014508	12	23425505	3.06E-05	-0.03964
ARS-BFGL-NGS-2850	12	75808867	5.49E-04	0.01919
BTA-111959-no-rs	13	47507513	2.12E-05	0.02888
ARS-BFGL-NGS-33859	13	55510255	3.13E-05	-0.02888
ARS-BFGL-NGS-549	14	14409359	1.49E-04	0.00250
UA-IFASA-6356	14	18376288	1.62E-04	0.01576
ARS-BFGL-NGS-15935	14	21767300	5.92E-06	-0.05026
Hapmap25002-BTC-073386	14	25964396	5.41E-04	0.00921
BTB-01119610	14	33219827	1.03E-04	0.00419
ARS-BFGL-BAC-22135	14	34569563	1.91E-04	0.01172
BTB-00567405	14	42562278	1.45E-04	-0.01006
ARS-BFGL-NGS-13356	15	17437755	4.85E-06	-0.01408
ARS-BFGL-NGS-26681	15	81819535	6.52E-05	0.02930
BTA-38126-no-rs	16	3144809	1.66E-05	-0.02630
BTA-109721-no-rs	16	46379875	6.31E-05	0.02896
BTA-108613-no-rs	16	69359947	3.87E-04	-0.01842
ARS-BFGL-NGS-36241	16	69412579	4.23E-04	-0.00037
UA-IFASA-5010	17	5068025	4.68E-05	-0.00380
ARS-BFGL-NGS-113821	17	11049453	3.24E-04	-0.01120
ARS-BFGL-NGS-112310	17	11426727	8.63E-06	0.04060
Hapmap43572-BTA-41227	17	57608128	2.65E-04	0.00264
ARS-BFGL-NGS-86321	18	48755332	2.66E-05	-0.05517
ARS-BFGL-NGS-51636	18	50622200	1.02E-04	-0.02232
ARS-BFGL-NGS-34770	19	20558561	9.10E-05	-0.00499
ARS-BFGL-NGS-1032	19	43194877	3.61E-05	-0.03192
ARS-BFGL-NGS-56312	19	48022449	1.06E-04	0.00129
ARS-BFGL-BAC-32504	19	48045874	7.52E-05	-0.01308
BTA-21339-no-rs	19	48185189	5.97E-05	0.02205
UA-IFASA-6003	19	49523704	7.37E-04	0.00214
ARS-BFGL-NGS-30781	19	56804496	6.74E-04	-0.00564
ARS-BFGL-BAC-32937	19	56908707	1.51E-04	-0.03960
ARS-BFGL-NGS-110875	19	56974654	6.79E-04	-0.00540
BTA-121196-no-rs	19	60771790	7.70E-04	0.00254
UA-IFASA-8495	19	61214504	1.34E-04	0.01542

SNP	Chr.	Position (bp)	P-value	Coefficient (s)
ARS-BFGL-NGS-110115	20	2684475	5.06E-05	0.01930
BTB-01524822	20	20128763	1.85E-04	0.01119
Hapmap47043-BTA-54956	22	55425156	6.03E-04	0.02075
ARS-BFGL-NGS-104089	23	35650338	9.15E-04	0.00052
ARS-BFGL-NGS-5653	23	46150649	8.45E-08	-0.07578
ARS-BFGL-NGS-28289	23	50282270	1.10E-06	0.01272
BTB-00877492	24	3487596	4.96E-05	0.03643
ARS-BFGL-NGS-32109	24	5196813	5.87E-06	-0.05111
BTB-00881336	24	11361601	6.19E-05	0.05769
ARS-BFGL-NGS-54408	24	12108239	5.10E-04	0.00459
ARS-BFGL-NGS-94607	24	24519728	1.66E-05	-0.05052
BTA-57747-no-rs	24	29302591	1.72E-05	0.02961
ARS-BFGL-NGS-72010	24	34294939	1.61E-07	0.10221
BTB-00158707	24	35115196	2.22E-05	0.00006
ARS-BFGL-NGS-33871	24	35150288	6.13E-06	-0.11011
BTB-00886858	24	35865190	1.62E-06	0.11990
BTB-01343672	24	37456528	1.77E-04	-0.00823
ARS-BFGL-NGS-90060	24	40401785	1.02E-05	-0.04903
ARS-BFGL-NGS-111021	24	46615489	1.48E-04	-0.01249
Hapmap26254-BTC-024038	25	12327472	4.36E-06	-0.06492
Hapmap40884-BTA-110443	25	26929196	1.32E-04	-0.00577
Hapmap39665-BTA-59836	25	27657824	3.67E-06	-0.09646
ARS-BFGL-NGS-73511	25	34258184	2.59E-05	0.01155
ARS-BFGL-NGS-26848	26	4643986	5.26E-06	-0.03815
ARS-BFGL-NGS-40727	26	37123806	1.82E-04	-0.00018
Hapmap35265-BES1_Contig647_1466	26	46456796	2.35E-04	0.01767
ARS-BFGL-NGS-36770	28	6700074	4.42E-06	-0.06487
ARS-BFGL-NGS-16093	28	11251657	1.25E-05	0.03476
BTA-65177-no-rs	28	18557592	1.03E-04	0.07433
ARS-BFGL-NGS-103901	28	26354615	1.02E-05	-0.05370
ARS-BFGL-NGS-33494	28	35633803	6.43E-06	-0.03512
ARS-BFGL-NGS-74050	28	40437690	1.60E-04	0.03215
ARS-BFGL-NGS-106657	28	43715255	5.86E-05	0.02622
ARS-BFGL-NGS-51329	29	10278512	9.74E-06	-0.02983
ARS-BFGL-NGS-35937	X	0	1.88E-05	-0.05235
BTB-01094119	X	0	1.78E-04	-0.01960
Hapmap25898-BTA-158488	X	0	2.20E-06	-0.02067
Hapmap43483-BTA-117844	X	0	2.75E-06	0.01589