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Short Communication

Investigation on *BRCA1* SNPs and its effects on mastitis in Chinese commercial cattle

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ABSTRACT

The main objective of this study was to investigate whether the bovine breast cancer 1 (*BRCA1*) gene was associated with mastitis resistance in Chinese commercial cattle. A total of 51 SNPs were screened from public data resources and DNA sequencing. Three SNPs (c.5682 G>C,c.26198 C>T and c.46126 G>T) were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and created restriction site PCR (CRS-PCR) methods and 21 combinations of these SNPs were observed. The single SNP and their genetic effects on somatic cell score (SCS) were evaluated and a significant association with SCS was found in c.46126 G>T. The mean SCS of individuals with genotype KK was significantly lower than those of genotypes KL and LL. The results of combined genotypes analysis of three SNPs showed that HHLLNN genotype with the highest SCS was easily for the mastitis susceptibility, whereas GGKKMM genotype with the lowest SCS was favorable for the mastitis resistance. The information provided in the present study will be very useful for improving mastitis resistance in dairy cattle by marker-assisted selection (MAS).

1. Introduction

Mastitis is a very complex and common disease of dairy cattle, which causes a major economic losses to the dairy industry worldwide (Janzen, 1970; Lescourret and Coulon, 1994; Nash et al., 2003; Ruegg, 2003). Many factors, such as pathogens, genetic factors, poor management practices, and health of the dairy cattle cause mastitis (Zhang et al., 2009). Previous studies confirmed that somatic cell count (SCC) or somatic cell score (SCS) is the most suitable single trait for the reduction in the incidence of mastitis through the indirect selection, which indicated that the genetic evaluation and selection of sires for lower SCC or SCS may reduce the incidence of mastitis(Emanuelson et al., 1988; Schutz, 1994; Philipsson et al., 1995; Chu et al., 2012). Breast cancer 1 (*BRCA1*) was cloned as one of the genes that conferred genetic predisposition to early-onset breast cancer (Miki et al., 1994), which works in the process of DNA damage repair, cell cycle regulation, transcriptional regulation, other important pathway to inhibit tumor and make sure of the maintenance of genome stability (Xu et al., 2012). The bovine *BRCA1* gene has been mapped to chromosome 19 (BTA19) (Krum et al., 2003). This location place was within a region of similar gene order as the *BRCA1* locus in human (chromosome 17) and mouse (chromosome 11) (Miki et al., 1994; Lane et al., 1995; Yang and Womack, 1998; Krum et al., 2003). It was also located within or nearby the genomic region of SCS quantitative trait loci (QTL) (Bennewitz et al., 2003, 2004; Daetwyler et al., 2008) (http://www.genome.iastate.edu/cgi-bin/QTLdb/BT/draw_chromap?optqtl=SCS&chromos=19&orderqtl=QTL_symbol&scale=4&density=10&submit=GO). Many researches indicated that mutations in the gene encoding *BRCA1* were associated with a high risk of breast cancer, and related researches have been reported mainly in human and other model animals, but not well known in cattle mastitis (Narod et al., 1995; Struewing et al., 1997; Neuhausen, 1999; Rebbeck, 1999; Antoniou et al., 2000; Kennedy et al., 2002; Krum et al., 2003; Whitehouse et al., 2004; Mahfoudh et al., 2012; Wang et al., 2012; Xu et al., 2012; Yuan et al., 2012). Furthermore, Krum et al. reported that the bovine *BRCA1* sequence is a better predictor of disease alleles (versus polymorphisms) than either the murine or the canine sequences (Krum et al., 2003). Up to now, however, *BRCA1*gene polymorphisms associated with bovine mastitis in various cattle breeds have not been investigated except only the author firstly reported that the bovine *BRCA1* gene was a new candidate gene for bovine mastitis (Yuan et al., 2012); therefore, the purpose of this study was to further evaluate the bovine *BRCA1* as a candidate gene for association with milk SCS and mastitis in an attempt to identify SNP markers located

Abbreviations: BRCA1, Breast cancer 1 gene; PCR-RFLP, Polymerase chain reaction-restriction fragment length polymorphism; CRS-PCR, Created restriction site PCR; SNPs, Single nucleotide polymorphisms; SCC, Somatic cell count; SCS, Somatic cell score; QTL, Quantitative trait loci; ESTs, Expressed sequence tags; STSs, Sequence tagged sites; WGS, Whole genome shotgun; GSS, Genome survey sequences; HTGS, High throughput genome sequences; SAS, Statistical analysis system; Tyr, Tyrosine acid; Asp, Aspartic acid; MAS, Marker-assisted selection.

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in this gene with predictive merit for improving mastitis resistance in dairy cattle.

2. Materials and methods

2.1. Animals and measure of SCC and SCS

Using standard methodology (Mullenbach et al., 1989), DNA was isolated from blood of three cattle breeds, Holstein (Caotan Dairy Farm, Xi'an, Shaanxi Province, $n=107$), Sanhe (Xiertala Breeding Farm, Hailar, Inner Mongolia Autonomous Region, $n=201$) and Simmental cows (Gaolintun Breeding Farm, Tongliao, Inner Mongolia Autonomous Region, $n=96$). The milk samples, including an antiseptic, were collected and sent to Beijing Dairy Cattle Centre for SCC detection and converted into SCS (SCS = $\log_2$[SCC/100] + 3, the unit of SCC is 1,000 cells/ml) (Rupp and Boichard, 1999). All experimental protocols and care of the animals were performed according to authorization granted by the Chinese Ministry of Agriculture.

2.2. Detection of candidate SNPs for bovine BRCA1 gene, primer design and PCR amplification

The retrieved bovine *BRCA1* gene sequences, including nucleic acid sequences, expressed sequence tags (ESTs), sequence tagged sites (STSs), whole genome shotgun (WGS), genome survey sequences (GSS), high throughput genome sequences (HTGS) and the genome sequences were downloaded to a local computer from the NCBI website. The redundant and non-homologous sequences were deleted. The dbSNP database of bovine *BRCA1* gene was also investigated in this study (http://www.ncbi.nlm.nih.gov/SNP/). The resulting sequences were assembled by DNAStar software to screen candidate SNPs. The experimental methods, including DNA sequencing, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and created restriction site PCR (CRS-PCR), were used to verify the candidate SNPs. Based on the mRNA sequences (GenBank ID: NM_178573.1) and DNA sequences (GenBank ID: NC_007317.4) of the bovine *BRCA1* gene, specific PCR primers were designed using Primer Premier 5.0 software to amplify and verify these candidate SNPs. Primers, annealing temperature, region, fragment sizes and selected restriction enzymes (MBI Fermentas, St. Leon-Rot, Germany) were given in Table 2. The PCR was carried out in a total volume of 20 μl solution containing 50 ng template DNA, 1 × buffer (Tris–HCl 100 mmol/L, pH 8.3; KCl 500 mmol/l), 0.25 μmol/l primers, 2.0 mmol/l $MgCl_2$, 0.25 mmol/l dNTPs, and 0.5 U Taq DNA polymerase (Promega, Madison, WI, USA). The PCR protocol was 94 °C for 5 min, followed by 35 cycles of 94 °C for 30 s, annealing at the corresponding temperature (shown in Table 2) for 30 s and 72 °C for 30 s, and a final extension at 72 °C for 8 min. The PCR products were separated on 1.5% agarose gel (Promega) including 0.5 μg/ml of ethidium bromide, photographed under UV light. The PCR amplified products from 45 samples (15 individuals were selected randomly from Holstein, Sanhe and Simmenta, respectively) were purified using a Wizard Prep PCR purification kit and sent to the TaKaRa Biotechnology Co. Ltd. (Dalian, China) for sequencing in both directions.

2.3. Genotyping tests

The c.26198 C>T and c.46126 G>T SNPs were genotyped by PCR-RFLP. The c.5682 G>C was genotyped by employing CRS-PCR method with one of the primers containing a nucleotide mismatch, which enables the use of restriction enzymes for discriminating sequence variations (Zhao et al., 2003). Aliquots of 5 μl PCR amplified products were digested with 2 U restriction enzyme at 37 °C for 10 h following the supplier's manual. The digested products were detected by electrophoresis for 1 h within 100 v in 2.5% agarose gel stained with ethidium bromide in 1×TAE buffer. The genotype results of allelic variation were based on the electrophoretic pattern of the restriction enzyme-treated PCR products.

2.4. Statistical analyses

Differences in genotype and allelic frequencies at bovine *BRCA1* gene among three populations were calculated. Analysis of associations between the genotypes of SNPs and SCS which reflects mastitis traits was carried out with the GLM procedure, using SAS software (Statistical Analysis System 9.1, SAS Institute Inc.) by the following formula: $y_{ijklmno}=\mu+b_i+f_j+a_k+p_l+g_m+h_n+s_o+e_{ijklmno}$, where $y_{ijklmno}$ = lactation average SCS, μ = global mean, b_i = breed effect, f_j = calving number effect, a_k = age effect, p_l = lactation month effect, g_m = genotype effect, h_n = farm effect, s_o = season effect, $e_{ijklmno}$ = residual effect.

Table 1
SNPs identified within the bovine *BRCA1* gene.

No.	Putative location	Position[1]	Amino acid change
M1	Intron1	c.731 C>G	
M2	Intron1	c.816 A>T	
M3	Intron1	c.2347 A>T	
M4	Intron1	c.2576 C>T	
M5	Intron2	c.5668 A>G	
M6	Intron2	c.5682 G>C	
M7	Intron2	c.8856 A>G	
M8	Intron2	c.8906 A>T	
M9	Intron2	c.11161 C>T	
M10	Intron2	c.11233 C>T	
M11	Intron4	c.15739 A>G	
M12	Intron4	c.15749 C>T	
M13	Intron4	c.15779 A>C	
M14	Intron4	c.15855 A>G	
M15	Intron4	c.15948 A>G	
M16	Intron6	c.21089 C>T	
M17	Intron6	c.21780 C>G	
M18	Intron6	c.22090 C>T	
M19	Intron6	c.22231 G>T	
M20	Exon9	c.24976 T>C	Phe→Ser
M21	Exon9	c.25025 T>A	Synonymous
M22	Exon9	c.25440 A>C	Cys→Arg
M23	Exon9	c.26198 C>T	Synonymous
M24	Exon9	c.27229 A>T	Ile→Lys
M25	Exon9	c.27234 A>G	Glu→Lys
M26	Exon10	c.28300 C>A	Thr→Pro
M27	Intron10	c.32166 C>T	
M28	Intron10	c.32208 A>C	
M29	Intron10	c.35469 C>T	
M30	Intron10	c.35635 C>T	
M31	Intron10	c.36054 G>A	
M32	Intron10	c.37158 C>T	
M33	Intron10	c.37323 C>T	
M34	Intron11	c.42022 C>T	
M35	Intron11	c.42246 A>T	
M36	Intron11	c.42284 A>C	
M37	Intron11	c.42550 C>T	
M38	Intron12	c.45220 A>C	
M39	Intron12	c.45251 A>G	
M40	Exon13	c.46126 G>T	Tyr→Asp
M41	Intron13	c.47790 G>T	
M42	Intron13	c.47986 A>C	
M43	Intron17	c.56217 A>C	
M44	Intron17	c.56297 A>T	
M45	Intron18	c.62143 A>G	
M46	Intron18	c.62267 C>T	
M47	Intron18	c.62678 A>G	
M48	Intron19	c.66502 C>T	
M49	Intron19	c.66669 A>G	
M50	Intron20	c.67411 C>G	
M51	Intron20	c.67419 C>T	

[1] Position is relative to reference sequence NC_007317.4.

Table 2
PCR, PCR-RFLP and CRS-PCR analysis used for genotyping SNPs detected in the bovine *BRCA1* gene.

SNPs	Primer sequences	AT (°C)	SAF (bp)	Region	RE	RES, genotype/bp
c.5682 G>C	5′- GTGGCTTTTCTTGTTTTGGAT-3′ 5′-CCTACCAAACTTTTCTGAAATT-3′	56.4	215	Intron 2	*Mbo* I	GG:197,18 GH:215,197,18 HH:215
c.26198 C>T	5′-GAGAGTACCAATATTTCCTTGG-3′ 5′-AATGTCATGTCCCAGTAGATCC-3′	55.5	219	Exon 9	*Fin* I	KK:219 KL:219,172,47 LL:172,47
c.46126 G>T	5′- GTGTGATTAGTCCTTTCACAAGC-3′ 5′-TCTCCACCAGAGCAGATGAAAT-3′	58.8	272	Exon 13	*Hpy188* I	MM:272 MN:272,184,88 NN:184,88

Note: SNPs means single nucleotide polymorphisms; AT means annealing temperature; SAF means size of amplification fragment; RE means restriction enzyme; RES means size of fragments at the indicated allele after digestion of the PCR product using the respective restriction enzyme. Underlined nucleotides mark nucleotide mismatches enabling the use of the selected restriction enzymes for discriminating sequence variations.

3. Results and discussion

3.1. Identification of SNPs information

In this study, 51 SNPs in the bovine *BRCA1* gene were selected and identified from internet and public data resources by using bioinformatics methods (Table 1). Three SNPs (c.5682 G>C in intron 2, c.26198 C>T in exon 9 and c.46126 G>T in exon 13) of them were genotyped by PCR-RFLP, CRS-PCR and DNA sequencing methods, including C→G mutation at position 5682, T→C mutation at position 26198 and T→G mutation (resulting in Tyrosine(Tyr) to Aspartic acid(Asp) amino acid replacement) at position 46126 of the bovine *BRCA1* gene, respectively (Reference sequences GenBank ID: NC_007317.4, NM_178573.1 and NP_848668.1).

3.2. SNPs and genotyping

The PCR product of c.5682 G>C was digested with the *Mbo* I enzyme, and the three possible genotypes were defined by three distinct banding patterns: GG (197 bp and 18 bp), GH (215 bp, 197 bp and 18 bp), and HH (215 bp). The PCR product of c.26198 C>T was digested with the *Fin* I enzyme, the genotype KK represents the occurrence of one band of 219 bp, the genotype KL represents three restriction fragment bands of 219 bp, 172 bp and 47 bp, and the genotype LL represents two bands of 172 and 47 bp. The PCR product of c.46126 G>T was digested with *Hpy188* I enzyme and divided into three genotypes, MM (272 bp), MN (272 bp, 184 bp and 88 bp) and NN (184 bp and 88 bp) (Table 2). The genotype and allelic frequencies of these three SNPs in the different studied cattle herds were given in Table 3. Allele C, allele T and allele T were predominant alleles and the value of the genotype GH, KK and MM frequency were the maximum in the studied populations, respectively, in c.5682 G>C, c.26198 C>T and c.46126 G>T loci (Table 3). PCR-RFLP method was used to identify the mutation at c.26198 C>T and c.46126 G>T locus. However, no suitable endonuclease restriction sites were detected at c.5682 G>C locus. Fortunately, CRS-PCR approach based on mismatch bases technology, a simple and easy technology, was enabled to investigate these mutations, which produced a restriction site by PCR amplification and a suitable restriction enzyme was used to determine the genotype. Consequently, the CRS-PCR method is considered as a convenient way to identify genotype of monobasic mutation (Zhao et al., 2003).

3.3. Associations between single SNP, combined genotypes of SNPs and SCS

Yuan suggested that the study of association analysis of candidate gene is a useful step for the knowledge of the genetic basis of productive traits, and compared to other genomic approaches is potentially more easily and efficiently implemented in breeding program (Yuan et al., 2011). Therefore, the present study sought to identify genetic variants in the form of SNPs in candidate genes that may contribute to host susceptibility to mastitis in dairy cattle. The gene-specific SNP markers and their genetic effects on SCS were evaluated and shown in Table 3. The gene-specific SNP marker analysis showed a significant association of c.46126 G>T with SCS in these populations; individuals with the genotype MM were significantly lower than those of genotype MN and NN ($P<0.05$). The c.5682 G>C and c.26198 C>T polymorphism were not significantly associated with SCS (Table 3). As we know that the genotype effect of one SNP may be influenced by other SNPs and the genotype combination effect is a reflection of interactions of multiple SNPs (Zheng et al., 2011). Therefore, the analysis of genotype combination is superior to the analysis of one single SNP. This coincides with the conclusion of Fallin et al., who considered that the inheritance of genotype combinations was more effective than that of one single SNP (Fallin et al., 2001). In this work, 21 kinds of combined genotypes of three SNPs combination (c.5682 G>C, c.26198 C>T and c.46126 G>T) were observed in the studied cattle herds. There was significant association between the combined genotypes of three SNPs and SCS ($P<0.01$). Statistic results showed that the cows with the genotype HHLLNN had the highest SCS value, while cow with genotype GGKKMM with the lowest SCS value (Table 4). This would indicate that increasing the frequency of the GGKKMM combined genotype in a dairy herd

Table 3
Genotype and allelic frequencies of *BRCA1* SNPs and their association with SCS.

Breed	Number	Frequency	c.5628 G>C			c.26198 C>T			c.46126 G>T		
			GG	GH	HH	KK	KL	LL	MM	MN	NN
Holstein	107	Genotype	0.3738(40)	0.4767(51)	0.1495(16)	0.4206(45)	0.3832(41)	0.1962(21)	0.5047(54)	0.2803(30)	0.2150(23)
		Allele	0.6121		0.3879	0.6121		0.3879	0.6449		0.3551
Sanhe	201	Genotype	0.3930(79)	0.4577(92)	0.1493(30)	0.4577(92)	0.4229(85)	0.1194(24)	0.5025(101)	0.3284(66)	0.1691(34)
		Allele	0.6219		0.3781	0.6692		0.3308	0.6667		0.3333
Simmental	96	Genotype	0.3438(33)	0.5208(50)	0.1354(13)	0.4167(40)	0.3958(38)	0.1875(18)	0.5938(57)	0.2500(24)	0.1562(15)
		Allele	0.6042		0.3958	0.6146		0.3854	0.7187		0.2813
Total	404	Genotype	0.3763(152)	0.4777(193)	0.1460(59)	0.4381(177)	0.4059(164)	0.156(63)	0.5248(212)	0.2970(120)	0.1782(72)
		Allele	0.6151		0.3849	0.6411		0.3589	0.6733		0.3267
SCS (LSM ± SE)			4.48 ± 0.32	4.82 ± 0.37	4.65 ± 0.28	3.85 ± 0.29	4.31 ± 0.22	4.49 ± 0.27	3.30 ± 0.14a	4.96 ± 0.49b	5.64 ± 0.38b

Note: The numbers in parentheses are the genotype individuals. Values with different letters (a, b) within the same line in the same locus denote significant difference ($P<0.05$).

Table 4
Effects of combinations of three SNPs (c.5628 G>C, c.26198 C>T and c.46126 G>T) on SCS ($n = 404$).

Genotype of combination	Number of combination	SCS* (mean ± SE or mean)
GGKKNN	28	4.54 ± 0.31
GGKKMN	13	4.16 ± 0.28
GGKKMM	42	3.58 ± 0.25
GGLLMM	15	5.01 ± 0.38
GGKLMM	16	4.41 ± 0.19
GGLLMN	14	4.62 ± 0.14
GGLLNN	21	4.42 ± 0.15
GHKKMM	15	4.26 ± 0.19
GHKKMN	14	4.21 ± 0.32
GHKKNN	18	4.81 ± 0.24
GHKLMM	26	4.39 ± 0.27
GHLLMN	16	4.91 ± 0.19
GHKLMN	19	4.26 ± 0.16
GHLLNN	18	4.91 ± 0.33
HHKKMM	21	4.38 ± 0.21
HHKKNN	20	5.12 ± 0.11
HHKLMN	17	4.35 ± 0.19
HHKLNN	12	4.39 ± 0.21
HHLLNN	26	5.88 ± 0.29
HHLLMN	13	4.78 ± 0.15
HHLLMM	20	5.31 ± 0.31

*$P < 0.01$.

while decreasing the frequency of HHLLNN may have a beneficial effect of lowering average SCS and productivity of dairy cattle. In general, the SCS of Holstein cows were higher than that of Sanhe and Simmental cows, and the SCS of Sanhe cows were higher than that of Simmental cows. Dairy cattle were less resistant to mastitis than dual-purpose breeds, Holstein cows were more easily having mastitis than Sanhe and Simmental cows (data not shown). Zhang et al. (2009) and Wang et al. (2007) had reported the similar results, respectively (Wang et al., 2007; Zhang et al., 2009). Similar researches have been reported in human and other model animals but only one paper shown in cattle (Yuan et al., 2012), and numerous papers indicated that mutations in the gene encoding *BRCA1* are associated with a high risk of breast cancer (Narod et al., 1995; Struewing et al., 1997; Neuhausen, 1999; Rebbeck, 1999; Annab et al., 2000; Antoniou et al., 2000; Ijichi et al., 2000; Dimitrov et al., 2001; Kennedy et al., 2002; Krum et al., 2003; Whitehouse et al., 2004; Mahfoudh et al., 2012; Wang et al., 2012; Xu et al., 2012; Yuan et al., 2012). Yuan et al. reported that the combined genotypes analysis of three SNPs (G22231T, T25025A and C28300A in bovine *BRCA1* gene) showed that BBDDFF genotype with the highest SCS was easily for the mastitis susceptibility, whereas AACCEE genotype with the lowest SCS was favorable for the mastitis resistance. This work is a further systematically study of the association analysis of the *BRCA1* gene in various cattle. Results from this study indicated that the *BRCA1* gene has potential effects on SCS and mastitis resistance.

4. Conclusion

In conclusion, our research established a useful and economical method to screen and verify new candidate SNPs. We also demonstrated the feasibility of our research method, which screens candidate SNPs using various published sequence resources from public databases. The present study has firstly suggested that the possible associations of c.46126 G>T with mastitis resistance traits and the occurrence of preferable combined genotype GGKKMM within the *BRCA1* gene are interesting topics for future studies. Results from association analysis provided preliminary evidence that the bovine *BRCA1* gene could be used as a candidate gene or molecular marker for the improvement of bovine mastitis resistance traits in Chinese commercial cattle. Further studies will be very necessary to use these confirmed SNPs for marker-assisted selection (MAS) in larger populations and carried out to clarify the effects of these markers on bovine mastitis resistance traits.

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References

Annab, L.A., et al., 2000. Isolation of a functional copy of the human BRCA1 gene by transformation-associated recombination in yeast. Gene 250, 201–208.
Antoniou, A.C., Gayther, S.A., Stratton, J.F., Ponder, B.A., Easton, D.F., 2000. Risk models for familial ovarian and breast cancer. Genet. Epidemiol. 18, 173–190.
Bennewitz, J., et al., 2003. Combined analysis of data from two granddaughter designs: a simple strategy for QTL confirmation and increasing experimental power in dairy cattle. Genet. Sel. Evol. 35, 319–338.
Bennewitz, J., et al., 2004. Multiple quantitative trait loci mapping with cofactors and application of alternative variants of the false discovery rate in an enlarged granddaughter design. Genetics 168, 1019–1027.
Chu, M.X., et al., 2012. Polymorphism of exon 2 of BoLA-DRB3 gene and its relationship with somatic cell score in Beijing Holstein cows. Mol. Biol. Rep. 39, 2909–2914.
Daetwyler, H.D., Schenkel, F.S., Sargolzaei, M., Robinson, J.A., 2008. A genome scan to detect quantitative trait loci for economically important traits in Holstein cattle using two methods and a dense single nucleotide polymorphism map. J. Dairy Sci. 91, 3225–3236.
Dimitrov, S., Brennerova, M., Forejt, J., 2001. Expression profiles and intergenic structure of head-to-head oriented Brca1 and Nbr1 genes. Gene 262, 89–98.
Emanuelson, U., Danell, B., Philipsson, J., 1988. Genetic parameters for clinical mastitis, somatic cell counts, and milk production estimated by multiple-trait restricted maximum likelihood. J. Dairy Sci. 71, 467–476.
Fallin, D., et al., 2001. Genetic analysis of case/control data using estimated haplotype frequencies: application to APOE locus variation and Alzheimer's disease. Genome Res. 11, 143–151.
Ijichi, H., Tanaka, T., Nakamura, T., Yagi, H., Hakuba, A., Sato, M., 2000. Molecular cloning and characterization of a human homologue of TBPIP, a BRCA1 locus-related gene. Gene 248, 99–107.
Janzen, J.J., 1970. Economic losses resulting from mastitis. A review. J. Dairy Sci. 53, 1151–1161.
Kennedy, R.D., Quinn, J.E., Johnston, P.G., Harkin, D.P., 2002. BRCA1: mechanisms of inactivation and implications for management of patients. Lancet 360, 1007–1014.
Krum, S.A., Womack, J.E., Lane, T.F., 2003. Bovine BRCA1 shows classic responses to genotoxic stress but low in vitro transcriptional activation activity. Oncogene 22, 6032–6044.
Lane, T.F., Deng, C., Elson, A., Lyu, M.S., Kozak, C.A., Leder, P., 1995. Expression of Brca1 is associated with terminal differentiation of ectodermally and mesodermally derived tissues in mice. Genes Dev. 9, 2712–2722.
Lescourret, F., Coulon, J.B., 1994. Modeling the impact of mastitis on milk production by dairy cows. J. Dairy Sci. 77, 2289–2301.
Mahfoudh, W., et al., 2012. Hereditary breast cancer in Middle Eastern and North African (MENA) populations: identification of novel, recurrent and founder BRCA1 mutations in the Tunisian population. Mol. Biol. Rep. 39, 1037–1046.
Miki, Y., et al., 1994. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266, 66–71.
Mullenbach, R., Lagoda, P.J., Welter, C., 1989. An efficient salt-chloroform extraction of DNA from blood and tissues. Trends Genet. 5, 391.
Narod, S.A., et al., 1995. An evaluation of genetic heterogeneity in 145 breast-ovarian cancer families. Breast Cancer Linkage Consortium. Am. J. Hum. Genet. 56, 254–264.
Nash, D.L., Rogers, G.W., Cooper, J.B., Hargrove, G.L., Keown, J.F., 2003. Heritability of intramammary infections at first parturition and relationships with sire transmitting abilities for somatic cell score, udder type traits, productive life, and protein yield. J. Dairy Sci. 86, 2684–2695.
Neuhausen, S.L., 1999. Ethnic differences in cancer risk resulting from genetic variation. Cancer 86, 2575–2582.
Philipsson, J., Ral, G., Berglund, B., 1995. Somatic-cell count as a selection criterion for mastitis resistance in dairy-cattle. Livest Prod Sci 41, 195–200.
Rebbeck, T.R., 1999. Inherited genetic predisposition in breast cancer. A population-based perspective. Cancer 86, 2493–2501.
Ruegg, P.L., 2003. Investigation of mastitis problems on farms. Vet Clin N Am-Food A 19, 47–73.
Rupp, R., Boichard, D., 1999. Genetic parameters for clinical mastitis, somatic cell score, production, udder type traits, and milking ease in first lactation Holsteins. J. Dairy Sci. 82, 2198–2204.

Schutz, M.M., 1994. Genetic evaluation of somatic cell scores for United States dairy cattle. J. Dairy Sci. 77, 2113–2129.
Struewing, J.P., et al., 1997. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. New Engl J Med 336, 1401–1408.
Wang, X., Xu, S., Gao, X., Ren, H., Chen, J., 2007. Genetic polymorphism of TLR4 gene and correlation with mastitis in cattle. J. Genet. Genomics 34, 406–412.
Wang, F., Fang, Q., Ge, Z., Yu, N., Xu, S., Fan, X., 2012. Common BRCA1 and BRCA2 mutations in breast cancer families: a meta-analysis from systematic review. Mol. Biol. Rep. 39, 2109–2118.
Whitehouse, C., Chambers, J., Catteau, A., Solomon, E., 2004. Brca1 expression is regulated by a bidirectional promoter that is shared by the Nbr1 gene in mouse. Gene 326, 87–96.
Xu, J., Wang, B., Zhang, Y., Li, R., Wang, Y., Zhang, S., 2012. Clinical implications for BRCA gene mutation in breast cancer. Mol. Biol. Rep. 39, 3097–3102.
Yang, Y.P., Womack, J.E., 1998. Parallel radiation hybrid mapping: a powerful tool for high-resolution genomic comparison. Genome Res. 8, 731–736.
Yuan, Z.R., et al., 2011. Single nucleotide polymorphism of CACNA2D1 gene and its association with milk somatic cell score in cattle. Mol. Biol. Rep. 38, 5179–5183.
Yuan, Z., et al., 2012. BRCA1: a new candidate gene for bovine mastitis and its association analysis between single nucleotide polymorphisms and milk somatic cell score. Mol. Biol. Rep. http://dx.doi.org/10.1007/s11033-012-1467-5.
Zhang, L.P., et al., 2009. Toll-like receptor 2 gene polymorphism and its relationship with SCS in dairy cattle. Anim. Biotechnol. 20, 87–95.
Zhao, C.J., Li, N., Deng, X.M., 2003. The establishment of method for identifying SNP genotype by CRS-PCR. Yi Chuan 25, 327–329.
Zheng, X., et al., 2011. Single nucleotide polymorphisms, haplotypes and combined genotypes of LAP3 gene in bovine and their association with milk production traits. Mol. Biol. Rep. 38, 4053–4061.