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ANIMAL

The SNP of WBP1 is associated with heifer reproductive performance in the Korean native cattle Hanwoo

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Abstract

It is well documented that intensive selection in dairy cattle for economic value such as increased milk yield led to a decline in reproductive performance. Recent studies using genome-wide association studies (GWASs) discovered candidate genes involved in the lower fertility including embryo development and conception rates. However, the information, which showed a lower reproductive performance, is limited to dairy cattle, especially Holstein, and the candidate genes were not examined in the Korean native cattle Hanwoo which has been intensively selected and bred for meat in the last few decades. We selected the candidate genes WBP1 and PARM1 reported to be associated with cow and/or heifer conception in dairy cattle and analyzed the genotype because those genes have non-synonymous single nucleotide polymorphisms (SNPs). To determine the single base change, we used the high resolution melting (HRM) assay which is rapid and cost-effective for a small number of genes. We found that most heifers with higher conception (1: service per conception) have the AA genotype coding Threonine rather than Proline in the WBP1 gene. We did not detect an association for a SNP in PARM1 in our analysis. In conclusion, the genetic variation of WBP1 can be used as a selective marker gene to improve reproductive performance, and HRM assay can be used to identify common SNP genotypes rapidly and cost effectively.

Keywords: conception, heifer, high resolution melting (HRM), single nucleotide polymorphism (SNP), WBP1

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Introduction

It is well documented that intensive selection for increased milk yield led to decline in the reproductive efficiency of dairy cattle, and genome-wide association study (GWAS) identified single nucleotide polymorphisms (SNPs) in candidate genes associated with reproductive performance including bull fertility, fertilization, preimplantation embryo development (Penagaricano and Khatib, 2012; Penagaricano et al., 2012; Cochran et al., 2013a; Cochran et al., 2013b; Penagaricano et al., 2013). Particularly, Cochran et al. (2013a) reported SNPs associated with daughter pregnancy rate,

heifer conception rate, cow conception rate, productive life, milk yield in Holstein cattle. However, GWAS studies of reproduction traits were mainly performed in dairy cattle because of economic impact of reproductive performance and breeding strategies (De Vries, 2006; Galvão et al., 2013; Azizian et al., 2016) rather than in beef cattle. Recently, we reported that Korean native cattle, Hanwoo showed lower reproductive performance, for example calving interval was increased 4.3% and pregnancy rate was decreased about up-to 2.8% year-on-year (Cho et al., 2016; Choi and Cho, 2016).

Here, we postulated that the decline in the reproductive performance in Hanwoo is due to intensive breeding programs using artificial insemination (AI) for economic purpose (Lim et al., 2016). In this context, we carried out *in silico* studies to select candidate genes associated with heifer pregnancy rate in Korean native cattle based on previous findings in dairy cattle (Cochran et al., 2013a; Ortega et al., 2017) and selected genes (WBP1 and PARM1) containing non-synonymous (missense) SNPs because the amino acid substitutions may have more functional impact on reproductive trait. In this study, we employed a new approach based on high resolution melting (HRM) that is a rapid, reliable and robust method (Garritano et al., 2009; Kysel'ová et al., 2012).

Materials and Methods

Genomic DNA isolation and HRM reaction

To develop the HRM method, we analysed a total of 29 Korean native cattle, Hanwoo from a university farm (Chungyang, Korea). DNA was extracted from whole blood samples using standard protocols for DNA Blood & Tissue kit (Qiagen, Germany). High-resolution melting analysis primer WBP 1 F (5′-ccagcctatgaggatgtggt-3′), WBP1 R (5′-acgtcttccacgtttgttcc-3′), PARM 1 F (5′- cacactcacctcccctcaag -3′), PARM1 R (5′- agatggaacctcaggtggtg -3′) were designed from the bovine genomic sequence and dbSNP (WBP1 rs134282828; PARM1 rs111027720) using the program Beacon Designer (PREMIER Biosoft International, CA, USA). Reactions were run in a volume of 25 μL using Qiagen Type-it® HRM™ PCR mix (Qiagen, Germany). Each reaction contained final concentrations of 1x HRM Type-it™ mix (Qiagen, UK) and 0.7 μM forward and reverse primer (for each target). Each sample was tested in duplicate. Reactions were run on a Qiagen Rotorgene-Q 5-plex machine (Qiagen, Germany) with temperature cycling parameters for the amplification stage being on hold at 95℃ for 5 minutes, followed by 40 cycles of 95℃ for 10 seconds, 55℃ for 30 seconds, and 72℃ for 20 seconds. For the HRM stage, fluorescence recordings were made over the range of 65 - 95℃ by increments of 0.1℃ for 2 seconds. A normalised graph was generated using normalisation regions of 73 - 75℃ and 86 - 88℃.

Results and Discussion

We carried out HRM assay for genotype of WBP1 and PARM1. SNP of WBP is missense variant in which ACT is changed into CCT, consequently amino acid residue Threonine is changed into Proline. Interestingly, in the group of heifers that are pregnant after one AI service, a high proportion of heifers have AA while lower conception or failed heifers have hetero GA or GG (Table 1). However, we did not find relationship between PARM1 and conception rates of heifers. A recent study demonstrated depletion of WBP1 decreased the blastocyst development with a decrease number of trophectoderm cells in the bovine blastocyst (Ortega et al., 2017), suggesting that changes of protein folding pattern by an amino acid substitution (Thr-Pro) may affect protein-protein interaction during embryo development.

Table 1. Genotype of WBP1 and PARM1 using high resolution melting (HRM).

S/C	Heifer	Genotype	Confidence	Genotype	Confidence
1/1	1	WBP1_AA	98.63	PARM1_AA	100.00
1/1	2	WBP1_AA	90.59	PARM1_GA	100.00
1/1	3	WBP1_AA	89.54	PARM1_GA	62.35
1/1	4	WBP1_AA	96.69	PARM1_GA	74.47
1/1	5	WBP1_AA	99.02	PARM1_GA	75.42
1/1	6	WBP1_AA	98.74	PARM1_AA	99.23
1/1	7	WBP1_AA	99.77	PARM1_GA	80.13
1/1	8	WBP1_AA	96.06	PARM1_GA	74.98
1/1	9	WBP1_AA	99.68	PARM1_GA	96.70
1/1	10	WBP1_AA	96.60	PARM1_GA	44.41
1/1	11	WBP1_AA	100.00	PARM1_GA	94.21
1/1	12	WBP1_AA	97.58	PARM1_GA	43.28
1/1	13	WBP1_AA	96.75	PARM1_GA	52.90
1/1	14	WBP1_AA	99.89	PARM1_AA	45.39
1/1	15	WBP1_AA	95.69	PARM1_GA	90.97
1/1	16	WBP1_AA	94.21	PARM1_GA	90.62
1/1	17	WBP1_AA	89.05	PARM1_GA	82.64
1/1	18	WBP1_AA	85.72	PARM1_AA	75.22
5/1	19	WBP1_AA	78.46	PARM1_GA	78.13
4/1	20	WBP1_GA	86.86	PARM1_AA	60.28
4/0	21	WBP1_GA	93.68	PARM1_GA	55.76
4/1	22	WBP1_GA	95.31	PARM1_GA	83.04
4/1	23	WBP1_GA	100.00	PARM1_GG	63.06
5/1	24	WBP1_GA	90.86	PARM1_GA	87.46
7/0	25	WBP1_GG	95.88	PARM1_GG	58.03
6/1	26	WBP1_GG	99.57	PARM1_GG	64.43
5/0	27	WBP1_GG	100.00	PARM1_GA	91.53
6/0	28	WBP1_GA	62.36	PARM1_GG	100.00
4/0	29	WBP1_GG	52.15	PARM1_GG	77.75

S/C, service per conception.

Conclusion

In line with a loss of function study of WBP1 in dairy cattle, our HRM analysis demonstrated that WBP1 is closely related with conception and maintenance of pregnancy in Korean native beef cattle as well. In summary, our results indicated that genetic variation of WBP1 can be used as a selective marker gene for cattle breeding programs to improve reproductive performance and minimize cost of AI. In addition, HRM assay is able to clearly distinguish a single base variance and can be used for common SNP genotypes rapidly and cost effectively when the targets are selected.

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