Elevated haplotypes frequencies reveal similarities for selection signatures in Western and Russian Simmental populations

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Abstract

This paper shows a straightforward, but surprisingly effective approach to detect genomic regions of importance, illustrated on two Simmental cattle populations. Medium density genomic data of 42 German/Austrian (denoted as “Western”) and 38 Russian Simmental cattle were used to identify the most frequent haplotypes within the two populations. The haplotypes were defined as non-overlapping segments of ten single nucleotide polymorphisms (SNP). The phasing was done with the SHAPEIT software, with a follow up analysis of haplotypes using the GHap package. Despite the low sample size a number of high frequency haplotypes could be identified across the whole genome. The identified genes residing directly in these high frequency haplotypes were extremely relevant for the dual purpose Simmental cattle. A large part of these genes influenced growth rate and carcass traits, others were relevant for the milk production. A smaller proportion was connected to the reproduction, immune system and cellular processes, with indirect influence on production traits.

Keywords: cattle, genome architecture, haplotype analysis, Simmental

Introduction

Haplotypes are chromosomal segments inherited from a single parent, as a result high genetic linkage that keeps the nucleotides within these segments tightly
together. Consequently, the haplotypes could be treated as a more complex form of genetic variant, but with similar utilization possibilities.

Haplotypes could be used, similarly to single nucleotide polymorphisms (SNP), to determine genetic distances between populations, draw associations between haplotypes and traits of interest, identify deleterious variants for disorders, enhancing inbreeding and admixture analyses. A more common use of haplotype based analyses is to detect selective sweeps to identify genomic regions and genes that are important to evolution of the respective species or breeds (Sabeti et al., 2002; Voight et al., 2006; Utsunomiya et al., 2013). Haplotypes with major beneficial effects could be also used to enhance the results of genomic selection.

One of the most popular dual-purpose cattle breed in Russia is the Simmental, with the second largest population after the Holstein cattle, with 96.5 thousand recorded cows in 271 herds and 31 regions (Dunin et al., 2017). The desire to improve the milk production properties in the Russian Simmental population led to imports of related breeds, with increased tendencies from the second half of the 19th century. The herd book of Simmental breed in Russia (USSR) was approved in 1926. From the 1950's for the next 30 years, there was a periodic sire’s delivery mainly from Austria, Switzerland, Germany and Hungary. Their offspring, according to the results of the sires' evaluation by the type traits (conformation traits) and the productivity trend, showed well-expressed meat qualities in comparison with milk features. A similar structure was observed between domestic and foreign Simmental populations in Russia. Since the late 1990s and the beginning of the 2000s, European (Western) Simmental livestock was imported, creating a large population of foreign origin in Russia (Sharkaeva, 2013). This required using of sires with the relevant genetic values. Use of the Holstein breed to improve the milk production traits also occurred in both populations.

Currently, the breeding purpose of Russian Simmental is the ratio 60/40 for milk and meat traits, while the German-Austrian population ratio is 38/16/46, respectively, for milk, meat and fitness. Regarding to this, the study for genetic determination of the Simmental population structure in Russia from the point of genomic data is important. The study of mutations caused by the selection pressure is a useful approach for determining the common breeding direction and adjusting the breeding objectives in Simmental breed on the continent. Determination of the genomic variants will make it possible to clarify the patterns associated with milk and meat production traits, which in turn will be taken into account in the development of the genomic evaluation program in Russian Simmental cattle.

Therefore, the aim of this study was to screen two populations of Simmental cattle in order to identify the genomic locations of the most prevalent haplotypes, including any functional genes residing in these regions that could be accounted in the breeding program in the future.

Materials and methods

For the purposes of this paper the Western Simmental cattle means animals with Austrian or German origin. The Russian Simmental population includes animals that have a common national breeding program and own genealogical structure from
1950s to present. The sperm samples from sires were provided by the AI stations located in European part of Russia.

Genomic DNA was extracted using the Nexttec™ isolation kit (Nexttec Biotechnology GmbH, Germany). The original data consisted of 42 Simmental bulls of Western and 38 bulls of Russian origin, genotyped with the Illumina BovineSNP50 v2 chip. A follow up quality control was performed removing animals with SNP missingness more than 10%, as well as SNPs with missingness of more than 10% or minor allele frequency less than 1%. After the filtering process 41 animals and 40,525 SNPs remained in the Western Simmental, and 36 animals and 41,594 SNPs in the Russian Simmental population.

The PLINK 1.9 software (Chang et al., 2015) was used for data processing and quality control. The initial haplotypes were generated with the SHAPEIT software (O'Connell et al., 2014) using default settings. The haplotypes were further dissected to non-overlapping windows of 10 SNPs using the GHap package (Utsunomiya et al., 2016) in R programming language.

The haplotype frequencies were plotted against the starting position for both populations and compared visually. The highest haplotype frequencies at each chromosome without an explicit threshold were examined in detail using the NCBI database using the UMD 3.1.1 reference assembly. Special attention was given to the genomic regions showing elevated frequencies for the same haplotypes in the Simmental cattle of both Western and Russian origin.

Results and discussion

The average size of explored regions was 0.245 Mb with standard deviation of 0.209 Mb. In case there was more than one haplotype with elevated frequency directly connected to each other, these were examined as one region. This was especially the case of BTA27, where multiple haplotype blocks identified a region of 1.6 Mb. In other chromosomes, even the longest connected haplotype blocks were up to 0.527 Mb.

In general, the identified haplotypes showed remarkable affinity to identify regions with protein coding genes. The identified regions, their frequencies in the respective population and the full list of protein coding genes are shown in Table 1. The most relevant findings are highlighted in the further discussion. In case there was no haplotype of outstanding frequency on a particular chromosome, this chromosome was omitted from the list.

On BTA1 the haplotype in the same region was found for both populations, containing the SOX14 gene that regulates embryonic development (Arsic et al., 1998). A gene of the same family, SOX17 on BTA14, was identified to affect growth and calving ease (Pausch et al., 2011).

On BTA2 both TRIM63, SLC30A2 are involved in the metabolism of zinc in the body. Notably SLC30A2, also known as Zinc Transporter 2 (ZNT2) plays a role in secreting zinc into milk (Chowanadisai et al., 2006), which in turn affects the cow performance and health (Cope et al., 2009).
On BTA3 the KCNA10 gene is related to potassium metabolism (Lang et al., 2000), involved in a wide range of functional and structural functions.

The genomic region on BTA5 around 56-60 Mb shows elevated haplotype frequencies for both Western and Russian Simmental cattle. The highest frequency in this gene rich region was observed to be 0.83 at the 56.6 Mb in the Russian Simmental. At the edge of the most frequent haplotype is the STAT6 gene, previously associated with carcass and weight traits in cattle (Rincon et al., 2009). The other gene in the haplotype is LRP1, controlling biosynthetic and endocytic trafficking of neuronal prion proteins (Parkyn et al., 2008), including cellular signaling and lipid homeostasis.

On BTA6, the only gene residing in the most frequent haplotype was COX7B2, previously connected to reproductive traits (Randhawa et al., 2014). Further, the COX7B2 is paralog (i.e. a homologous gene that is a result of duplication event before speciation) to the COX7B, involved in the mitochondrial respiratory chain.

An another outstanding haplotype only in the Western Simmental population was in the 39 Mb region of BTA6, including the DCAF16 and LCORL genes, associated with growth and carcass traits (Takasuga, 2016; Zhang et al., 2016; Han et al., 2017).

On BTA10 in both the Western and Russian Simmental cattle there was a major haplotype within the MCC gene, but this gene is without an apparent importance in cattle.

On BTA11 the 3 Mb region in Russian Simmental holds a frequent haplotype containing a large number of genes. In cattle, the most important seems to be the ANKRD23, which was differentially expressed in cows with lower fertility (Moore et al., 2016) and COX5B, also involved in mitochondrial respiratory chain (similarly to genes detected on BTA6), which is connected among others to APT supply to the muscle (Lehnert et al., 2007).

On BTA12 the most frequent haplotype in Western Simmental cattle, with only a low frequency in the Russian population, contained five genes with different functions. From the production perspective, PARP4 influenced carcass weight in Hanwoo cattle (Edea et al., 2018), but also contributed to the environmental adaptation via DNA repair mechanisms (Edea et al., 2014). RNF17 was associated with fatty acid composition in Nelore cattle (Lemos et al., 2016), growth traits in Hanwoo cattle (Edea et al., 2018) and pigs (Puig-Oliveras et al., 2014). MPHOSPH8 was up regulated in atretic follicles in cattle (Hatzizopoulos et al., 2014). ATP12A was connected to APT mechanisms and high altitude adaptation in goats (Wang et al., 2016).

On BTA13, only a single haplotype was over 50% frequency in the Western Simmental cattle, highlighting a gene rich region. Among the listed genes, the most relevant was DLGAP4, influencing processed ham quality in Italian pig populations (Fontanesi et al., 2017), MYL9 involved in the muscle development, tenderness and texture (Cui et al., 2012), positively selected in Angus cattle (Pérez O’Brien et al., 2014), NDRG3 connected to marbling score (Seong et al., 2016) and SAMHD1 involved in immune response.
Table 1. The list of genomic regions and protein coding genes within the most frequent haplotypes in the Western and Russian Simmental cattle

<table>
<thead>
<tr>
<th>BTA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Start position&lt;sup&gt;b&lt;/sup&gt;</th>
<th>End position&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Frequency Western Simmental&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Frequency Russian Simmental&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132.37</td>
<td>132.618</td>
<td>0.512</td>
<td>0.597</td>
<td>SOX14</td>
</tr>
<tr>
<td>2</td>
<td>127.626</td>
<td>127.655</td>
<td>0.512</td>
<td>0.666</td>
<td>TRIM63, SLC30A2</td>
</tr>
<tr>
<td>3</td>
<td>32.989</td>
<td>33.018</td>
<td>0.426</td>
<td>0.687</td>
<td>KCNA10</td>
</tr>
<tr>
<td>5</td>
<td>56.625</td>
<td>56.699</td>
<td>0.457</td>
<td>0.722</td>
<td>STAT6, LRP1</td>
</tr>
<tr>
<td>6</td>
<td>66.897</td>
<td>67.17</td>
<td>0.817</td>
<td>0.653</td>
<td>COX7B2</td>
</tr>
<tr>
<td>6</td>
<td>38.689</td>
<td>39.216</td>
<td>0.744</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>DCAF16, LCORL</td>
</tr>
<tr>
<td>10</td>
<td>0.496</td>
<td>0.52</td>
<td>0.854</td>
<td>0.708</td>
<td>MCC</td>
</tr>
<tr>
<td>11</td>
<td>2.691</td>
<td>3.14</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.625</td>
<td>CNNM4, ANKRBD23, SEMA4C, FAM178B, COX5B, ACTR1B, ZAP70</td>
</tr>
<tr>
<td>12</td>
<td>36.599</td>
<td>37.11</td>
<td>0.549</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>MPHOSPH8, PARP4, CENPJ, RNF17, ATP12A</td>
</tr>
<tr>
<td>13</td>
<td>66.179</td>
<td>66.66</td>
<td>0.51</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>DLGAP4, MYL9, TGF2, SLA2, NDRG3, TLDC2, SAMHD1, RBL1</td>
</tr>
<tr>
<td>14</td>
<td>29.444</td>
<td>29.894</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.528</td>
<td>NKAIN3, GGH, TTPA, YTHDF3</td>
</tr>
<tr>
<td>15</td>
<td>24.14</td>
<td>24.177</td>
<td>0.598</td>
<td>0.525</td>
<td>NCAM1</td>
</tr>
<tr>
<td>17</td>
<td>35.494</td>
<td>35.601</td>
<td>0.762</td>
<td>0.708</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>56.541</td>
<td>56.594</td>
<td>0.585</td>
<td>0.361</td>
<td>SAP30BP, RECQL5, SMIM5, SMIM6, MYO15B</td>
</tr>
<tr>
<td>20</td>
<td>22.195</td>
<td>22.293</td>
<td>0.829</td>
<td>0.742</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>57.723</td>
<td>57.765</td>
<td>0.64</td>
<td>0.701</td>
<td>SLC24A4</td>
</tr>
<tr>
<td>27</td>
<td>4.948</td>
<td>6.592</td>
<td>0.548</td>
<td>0.333</td>
<td>DEFB variants, GPM6A</td>
</tr>
</tbody>
</table>

<sup>a</sup>BTA - *Bos Taurus* autosome; <sup>b</sup>Positions in mega bases; <sup>c</sup>If there was more than one haplotype in the same region, this is their average frequency; <sup>d</sup>Haplotype frequency low, thus it does not stand out within the population.
On BTA14 the genomic region around 29 Mb contained a frequent haplotype in the Russian population. The entire genomic region is of immense interest to growth related traits (Bolormaa et al., 2011). Also, NKAIN3, TTPA from this high frequency haplotype were associated to carcass and meat quality traits in cattle (Ramayo-Caldas et al., 2014; Sharma et al., 2014).

On BTA17, there were no genes found the highest frequency haplotype around 35 Mb at BTA17 of both breeds. Interestingly, the haplotypes region was flanked by IL2 and IL21, with a potential role in bovine tuberculosis prevention (Endsley et al., 2009). The 49 Mb region contained a region with increased haplotype frequency specific for the Russian population, with the TMEM132D gene connected to milk composition (Poulsen et al., 2015).

On BTA19, the region with highest haplotype frequency in Western Simmental cattle was around 57 Mb, overlapping with a QTL region related to udder health (Wu et al., 2015). The same haplotype region had an elevated frequency also in the Russian Simmental cattle, although the frequency was only about 36% compared to 58% in the Western population.

On BTA20 in both Western and Russian Simmental cattle there were haplotypes with elevated frequencies around 22.2 Mb. Interestingly, there was no gene present in this region. A haplotype with 66% frequency was detected, however, in the Russian population just upstream at 23.3 Mb, containing the MIER3 gene, connected to cattle fertility (Nayeri and Stothard, 2016) and survival (Raven et al., 2014).

On BTA21 the most prominent haplotype in both populations contained the SLC24A4 gene, which was connected to pigmentation related traits (Sulem et al., 2007), but also fertility in cattle (Nayeri et al., 2016).

The most frequent haplotypes on BTA27 overlap only partially in the Western and Russian Simmental population. This region contains surprisingly high number of uncharacterized genes, some of which are denoted as protein coding. In addition, there are a large number of genes from the Defensin (DEFB) family, related to immunity and regulation of inflammation. The GPM6A is also within these haplotypes, connected to udder health (Goldammer et al., 2004), with the whole region appears to be relevant to mastitis resistance in cattle.

Conclusions

Genomic regions with high frequencies of identical haplotypes were identified in Western and Russian Simmental populations. The high haplotype frequencies suggest that selection is acting in these regions. Even when the identified haplotype regions were narrow, they contained genes with remarkable relevance to the Simmental population, confirming the general suitability of the approach.

The functions of identified genes within the regions affect cellular regulation, milk production, but predominantly carcass and weight traits, which is well in line with the breeding goal of the dual purpose Simmental cattle.
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References


