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Ancestral Haplotypes, Quantal Genomics and Healthy Beef

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ABSTRACT: Identifying bovine haplotypes associated with healthy beef is our goal. We developed haplospecific markers spanning 14Mb-16Mb on Bota Chromosome 19 known to influence fat metabolism and muscle growth. Haplotypes, assigned by segregation over 3-generation pedigrees, can be identified in different cattle breeds and are therefore species ancestral haplotypes, while other ancestral haplotypes are breed-specific. Previous work on the human major histocompatibility complex (MHC) established the relevant unit of inheritance is not the allele but the ancestral haplotype inherited faithfully from remote ancestors. Comparing haplotype frequencies between Simmental, Angus and Wagyu reveals breed-specific ancestral haplotypes distinguishing most Wagyu from Angus. Ancestral haplotypes are associated with traits characteristic of the breed and can be used for marker-assisted selection of favourable breed-specific characteristics or blend desired traits of different breeds. We offer our conclusions for selective breeding strategies as recommendations based on the new "quantal genomics" paradigm.
Keywords: Ancestral haplotypes; Healthy beef; Genetics Marker assisted selection

Introduction

Genetic selection for tender, tasty, healthy beef (low melting point fat) is an important goal of cattle breeding. However we recognize the selection for such complex traits requires a different concept on the way the genome is structured and has evolved. Our approach is based on our previous work on the human MHC where we and others have established that the human and higher mammalian genome has a "quantal" ancestral haplotype structure (Dawkins et al. 1999; McClure et al. 2013). Recently we extended this work to the MRIP region on Bota Chromosome 19 documenting numerous ancestral haplotypes in various cattle breeds spanning a region of 14 Mb -16 Mb (Williamson et al. (2011). The blending strategy outlined here based on ancestral haplotypes depends upon identifying the most informative breed markers.

Materials and Methods

Region of interest. The MRIP region of Bota chromosome 19 was chosen because it contains several genes relevant to muscle growth and lipid metabolism. (Williamson *et al.,* 2011). In the region from SREB1 through to FASN there are perhaps 100-200 protein coding genes and their regulatory regions.

Samples. DNA was extracted from blood, hair, semen or ear tissues using standard salting out methods. The cattle sampled for study were Angus (n=65), Simmental (n~=316) and Wagyu (n=188) either full bloods registered with breed societies in Australia or confirmed pedigrees tracing back to registered animals.

PCR markers. PCR methods followed those described in Williamson et al (2011) for five haplotype markers in Chr 19 : SREB1, NT5M, MRIP, TCAP, and GH. Recently we have developed an additional marker near SECTM to extend the haplotype 2.2 Mb past the GH marker towards FASN the fatty acid synthesis locus. The forward and reverse primers for this region are : CAGACTGATAAGGGGGGCAAAG and CTATAGAGTGCAGAAGGGGTGT

Haplotypes. Haplotypes were identified and assigned by segregation of these markers through at least 3-generation family pedigrees or by homozygosity. The breed haplotype frequencies are shown in Figure 1.Animals for which insufficient information was available to determine haplotypes were excluded from haplotype frequency counts

Results and Discussion

Haplotype frequency distributions between breeds These data are shown in the "W" plots in Fig 1 Comparing MRIP haplotype frequencies in Wagyu versus Simmental (top panel) and Wagyu versus Angus (bottom panel). Haplotypes C1-C8 were found in all three breeds. W1-W8 haplotypes were found in Wagyu but not in Simmental or Angus. A1 and A2 haplotypes were found in Angus but not in Wagyu or Simmental. S1 was found in Simmental but not in Angus or Wagyu and AS1-AS6 were found in Angus and Simmental but not Wagyu. WS1-WS4 haplotypes were found in Wagyu and Simmental but not Angus. Haplotype WA1 was found in Wagyu and Angus but not Simmental.

Breed specific and common ancestral haplotypes. We are using the haplotype approach to blend the healthy beef characteristics of the various breeds. A given full length haplotype reflects the activities of 100-200 genes. The W plots in Figure 1 are informative. Wagyu, Angus and Simmental all have their breed specific haplotypes yet carry within each breed common haplotypes

shared across all breeds tested. These we identify as common "ancestral haplotypes" and must offer a survival benefit by their transmission and conservation over thousands of generations.

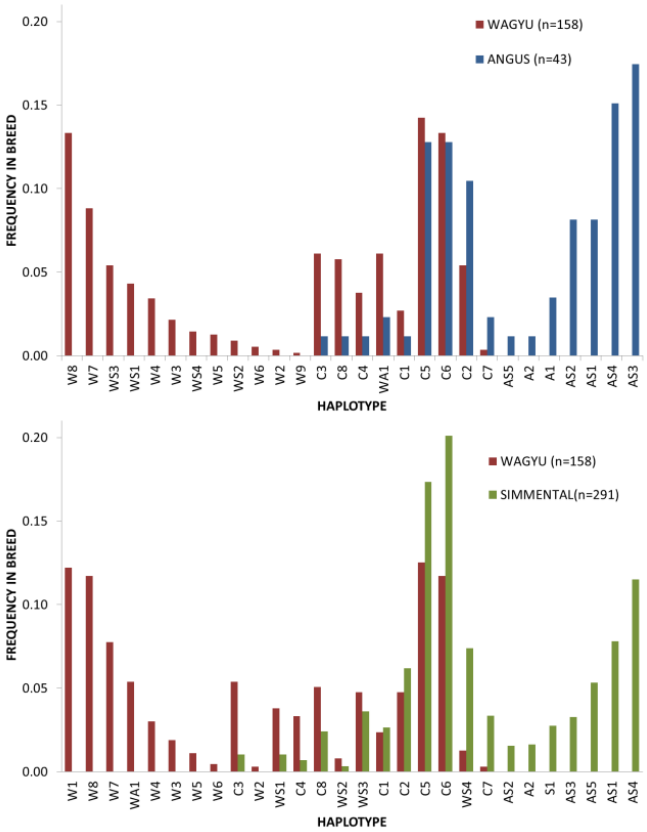

Figure 1. Frequencies of TCAP-SECTM haplotypes on Bota chromosome 19 between MRIP and FASN in different breeds. Haplotype names reflect the occurrence in the breeds (W=Wagyu; S=Simmental; A=Angus; C = present in all breeds; n=number of cattle).Taken from Dawkins RL et al "Experiments in Evolution" (In preparation, 2014)

Many genotypes within a breed are heterozygous for a breed-specific haplotype and a common haplotype. This is not a "50% split of genes" - it is a qualitative split based on long ≥14Mb haplotypes. The meat quality characteristics of common interbreed haplotypes are modified by breed specific haplotypes. We adjudge this approach to be superior to that of identifying single locus alleles or SNPs as QTL markers. The combined integrated affect of several hundred genes is more likely to lead to better breeding outcomes in selecting for desired traits such as low melting point fat or marbling. Such approaches are underway and will be the subject of future reports.

Conclusion

An alternative strategy for selective breeding. This new approach to higher vertebrate genetics, we term "quantal genomics", has been developed from over 35 years research in clinical and molecular immunology. This work has characterized the ancestral haplotypes (≥ 4 Mb) composed of strings of polymorphic frozen blocks (≥ 300-500Kb) within the MHC and other regions of the human genome. Such regions encompass numerous polymorphic protein coding genes and their regulatory sequences (n≥200). Each ancestral haplotype has its own unique set of variant gene sequence combinations and other DNA sequence polymorphisms (duplications, indels, gene copy number variations, retroviral and retroelement insertions). The deep insights and lessons from this approach can be applied to the selective breeding of beef cattle for complex desirable traits. In our view it is proving a far more useful strategy for selective livestock breeding than the usual prescriptions based on population genetics (SNP/LD and GWA studies for QTLs) and neo-Darwinian theoretical concepts. To be perfectly honest this is not surprising since the classical genetic paradigm of the past 100 years has been built on far simpler invertebrate genetic systems such as drosophila, earth worms, fungi and bacteria. We are applying this new strategy for the identification of haplotypic blocks associated with "healthy beef " traits in selective breeding.

The steps recommended in our strategy include:

1. Define polymorphic frozen blocks and their ancestral haplotypes in the region of interest.
2. Develop robust haplospecific markers.
3. Identify those haplotypes which are relatively frequent in breeds with desirable (or interesting) traits whilst excluding those which are common to multiple breeds.
4. Develop minimal requirements for reliable determination of breed and parentage.
5. Compare haplotype frequencies in elite versus poor performers within a breed, and in cross breeds, allowing for vagaries of penetrance.
6. Compare candidate haplotypes to determine whether these have arisen by ancestral recombination events which can help to localize the operative components.
7. Consider functional explanations for observed haplotype associations.
8. Test the hypotheses of specific haplotype associations and interactions using AI, ET and Cloning experiments.
9. Use Marker Assisted Selection to blend preferred haplotypes into already successful herds, or to increase the frequency of haplotypes already present.

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