Investigation of genes related with polledness in Nelore beef cattle by genome-wide association

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Introduction

- The first polled Nelore was first observed in Brazil in 1957
  - intensively used in matings, which quickly propagated this trait
- Inheritance of horns was one of the first Mendelian traits reported in cattle, although it later became evident that the inheritance pattern is more complex than a single gene mutation initially reported.
- The most commonly accepted bi-allelic model for inheritance of horns describes three loci (Polled, Scurs, and African). Nevertheless, no experiment has been able to fully elucidate the mechanism of inheritance of horns in cattle.
- The objective of this study was to perform a WssGWAS to identify the genomic region, potential candidate genes and their biological mechanisms underlying polledness in Nelore beef cattle.

Material and Methods

Data

- National Association of Farmers and Researchers (ANCP);
- 202,717 pedigreed animals, from 18 herds;
- 107,294 phenotypes (92,625 horned and 14,669 polled);
- After SNP QC, 461,865 SNPs available for 2,328 animals (777k Illumina), which of 1,721 had phenotypes record.

Threshold model

$$\mathbf{l} = \mathbf{1}\mu + \mathbf{Xa} + \mathbf{e}$$

l is the vector of underlying distribution of polledness;
μ is the general mean;
a is the vector of additive direct genetic effects;
1 is a vector of ones; and
X is the incidence matrix that relates animals with phenotypes.

Weighted single-step GWAS

1) Set $\mathbf{D}_t = \mathbf{I}$ and $\mathbf{G}_t = \frac{\mathbf{ZDZ'}}{2\sum p_i(1-p_i)}$
2) Compute GEBV using ssGBLUP approach
3) Compute SNP effects as $\hat{\mathbf{u}}_i = \lambda \mathbf{D}\,\mathbf{Z'G^{-1}}\widehat{\mathbf{GEBV}}$
4) Calculate SNP weight as $d_{i\,(t+1)} = \hat{\mathbf{u}}_i^2$ or $\hat{\mathbf{u}}_i^2\, 2p_i(1-p_i)$
5) Normalize $\mathbf{D}_{(t+1)}$
6) $\mathbf{G}_{(t+1)} = \frac{\mathbf{ZD}_{(t+1)}\mathbf{Z'}}{2\sum p_i(1-p_i)}$
7) Iterate from step 2

Results were presented for 1 Mb sliding SNP-windows.

Genes identification and Runs of Homozygosity (ROH)

- UMD_3.1 genome assembly, the classification of genes regarding their KEGG pathways ($p<0.05$) was performed by DAVID v6.8 tool.
- PLINK v1.07 was used to identify ROH as described by Peripolli et al. (2018).

Results and Discussion

- 3 adjacent windows are associated with the polled trait, located in a centromeric region on BTA1 with 3.11 Mb size (Fig. 1).
- 28 protein-coding genes and the taurine Polled locus are mapped in these windows that explained together, 65.54 % of this trait in Nelore breed (Tab. 1). The taurine Polled locus present two alleles described in taurine breeds: a duplication of 212 bp (BTA1: 1,705,834-1,706,045 bp) in place of a 10-bp deletion (BTA1: 1,706,051–1,706,060 bp) called Celtic allele and an 80,128 bp duplication (BTA1: 1,909,352–1,989,480 bp) named Friesian allele.

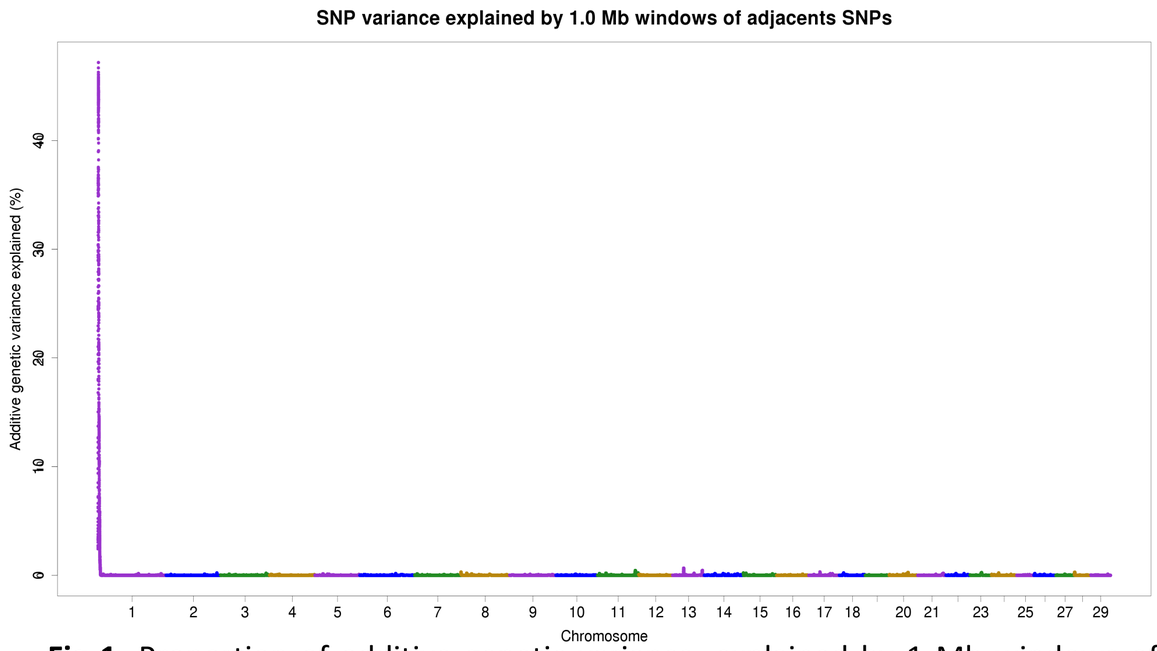

Fig 1. Proportion of additive genetic variance, explained by 1 Mb windows of adjacent SNPs, for the polled trait in Nelore cattle.

Tab 1. Genes on BTA1 based on the additive genetic variance explained by 1Mb windows of adjacent SNPs of the polled trait.

Position (BTA1)	Genes	Variance
0,87-1,87 Mb	*ATP5O, ITSN1, CRYZL1, DONSON, SON, GART, DNAJC28, TMEM50B, IFNGR2, IFNAR1, IL10RB, IFNAR2, LOC526226, OLIG1, OLIG2*	47.18%
1,98-2,98 Mb	*C1H21orf62, PAXBP1, SYNJ1, C1H21orf59, EVA1C, URB1, MRAP, MIS18A, HUNK*	14.66%
2,98-3,98 Mb	*SCAF4, SOD1, TIAM1, KRTAP11-1*	3.70%

- A total of 5 ROH islands on BTA1, which of one island (located at 0.27-2.70Mb) matched with that 3.11 Mb region identified by WssGWAS (Tab. 1), providing a consensus region for hornless trait in Nelore with 1.86 Mb size.
- Gene annotation enrichment analysis identified 3 significant ($p<0.05$) KEGG pathways:

(bta04380) osteoclast differentiation: development and homeostasis of the skeletal system depend on a critical balance between bone formation and resorption. Osteoclasts are multinucleated cells which are responsible for bone resorption, playing a central role in the formation of the skeleton and regulation of bone mass.

(bta04060) cytokine-cytokine receptor interaction: cytokines regulate inflammatory host defenses, angiogenesis, cell growth, differentiation, and cell death. Mediate hematopoiesis and immune response activating JAK-STAT signaling pathway and regulate the osteoclast formation/function through modulating the RANKL gene expression by osteoblasts/stromal cells.

(bta04630) JAK-STAT signaling: important role in the growth and differentiation of several cell types. Evidences suggests that this pathway may be involved in bone development, metabolism and homeostasis.

Conclusion

- Polledness in Nelore cattle is associated with one region in the genome with 3.1 Mb size in BTA1. Several genes are mapped in this region, and they may act together in the determination of the polled phenotype. Considering that the causal mutation responsible for polledness in Nelore emerged in Brazil, this study offers a path to fine map the polled locus and to identify the molecular mechanism regulating the growth of horns in Nelore beef cattle.