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**SÃO PAULO STATE UNIVERSITY
SCHOOL OF AGRICULTURAL AND VETERINARIAN SCIENCES**

SELECTION SIGNATURES IN DAIRY CATTLE

Larissa Graciano Braga

Veterinary medicine
MsC. in Genetics and Animal Breeding

2025

SÃO PAULO STATE UNIVERSITY
SCHOOL OF AGRICULTURAL AND VETERINARIAN SCIENCES

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Thesis presented to the São Paulo State University - School of Agricultural and Veterinary Sciences, Campus of Jaboticabal, in partial fulfillment of requirements for the degree of Ph.D. in Animal Science

2025

B813s Braga, Larissa Graciano
Selection signatures in dairy cattle / Larissa Graciano Braga. --
Jaboticabal, 2025
116 p.

Tese (doutorado) - Universidade Estadual Paulista (UNESP),
Faculdade de Ciências Agrárias e Veterinárias, Jaboticabal
Orientador: Danísio Prado Munari
Coorientador: Marcos Vinicius Gualberto Barbosa Silva

1. Animais melhoramento genético. 2. Genética animal. 3.
Genômica. I. Título.

CERTIFICADO DE APROVAÇÃO

TÍTULO DA TESE: SELECTION SIGNATURES IN DAIRY CATTLE

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Jaboticabal, 12 de setembro de 2025

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Larissa Graciano Braga was born in Porto Velho, Rondônia, on May 29, 1996. She is the daughter of Bárbara Braga Graciano and Sebastião Graciano de Souza. She earned her degree in Veterinary Medicine from the Federal University of Goiás - School of Veterinary and Animal Science (EVZ/ UFG), in 2019. From 2016 to 2017, she served as a volunteer research assistant (PIVIC) in the Undergraduate Research Program (PIP/UFG), under the supervision of Prof. Dr. Paulo Henrique Jorge da Cunha. In 2016, she was Director of Projects at CONPAVet Jr., a junior enterprise based at EVZ/UFG. In 2017, she was awarded a scholarship through the MARCA/MERCOSUR academic mobility program and completed an exchange semester at the Facultad de Ciencias Veterinarias of the Universidad Nacional del Litoral in Esperanza, Santa Fé Province, Argentina. From August 2019 to July 2021, she pursued her Master's degree in Animal Breeding and Genetics at the School of Agricultural and Veterinary Sciences of São Paulo State University "Júlio de Mesquita Filho" (FCAV/UNESP), Jaboticabal Campus, under the supervision of Prof. Dr. Danísio Prado Munari and co-supervision of Dr. Tatiane Cristina Seleguim Chud and Dr. Marcos Vinicius Gualberto Barbosa da Silva. In August 2021, she began her Ph.D. in Animal Science at the same institution, under the same supervisor and co-supervisors. In June 2023, she started a 12-month doctoral research internship at the University of Guelph, in Guelph, Ontario, Canada, under the supervision of Prof. Dr. Flávio Schramm Schenkel. In February 2025, she began working as a Sessional Professor affiliated with the Department of Exact Sciences at FCAV, teaching courses related to Statistics and Informatics.

“The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows the great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat.”

Man in the Arena, 1910, Theodore Roosevelt

ACKNOWLEDGEMENTS

Gostaria de agradecer a Deus por ter me permitido realizar grandes sonhos, agraciando-me com saúde e por ter me guiado durante toda a caminhada. À mãe Maria, que sempre passou na frente dos meus medos, dificuldades e desafios.

Agradeço aos meus pais, Sebastião e Bárbara, por serem minha fortaleza e por me amarem incondicionalmente. Sempre me deram força e acolhimento nos momentos mais difíceis e sempre acreditaram no meu potencial. Vocês fizeram o que podiam para que eu tivesse uma excelente educação e me ensinaram o significado de responsabilidade e honestidade. A distância tem sido muito pesada, mas, mesmo assim, vocês sempre me apoiaram.

À Lucas Gazolla Rodrigues Soares, por vibrar a cada conquista minha, acreditar em mim (por muitas vezes mais do que eu mesma) e me incentivar. O seu apoio e suporte tem sido um acalento, especialmente nos dias mais tempestuosos. À Alzira e Sidney Rodrigues Soares, por todo cuidado, apoio, torcida e carinho que vocês têm comigo.

À Faculdade de Ciências Agrárias e Veterinárias da Universidade Estadual Paulista (FCAV/UNESP) e à University of Guelph, por ser minha segunda casa e pela excelência em pesquisa e ensino. Aos professores e funcionários por darem o melhor de si para minha formação acadêmico-profissional. Agradeço ao Programa de Pós-Graduação em Ciência Animal e à CAPES (001 e 88887.802720/2023-00) pelo financiamento da minha bolsa de pesquisa e de sanduíche. Especialmente agradeço:

Ao meu orientador, Prof. Dr. Danísio Prado Munari, aos meus coorientadores Dr. Marcos Vinicius Gualberto da Silva e Dr.^a Tatiane Cristina Seleguim Chud, e ao meu supervisor durante estágio sanduíche, Prof. Dr. Flávio Schenkel. Eu sempre achei a frase “se pude ver mais longe é porque estava em ombros de gigantes” um clichê, mas não há melhor maneira de descrever o que foram esses anos de doutorado. Vocês sempre foram pacientes e solícitos comigo, agradeço por todas as oportunidades, críticas, discussões científicas, ensinamentos acadêmicos e de vida, e pela confiança depositada em mim. Vocês foram fundamentais na minha formação e continuam a me inspirar a ser uma pesquisadora melhor.

Aos membros da banca do exame geral de qualificação, Prof. Dr. Marcos Buzankas e Prof.^a Dr.^a Amanda Maiorano, e aos membros da banca de defesa da dissertação, Dra. Lenira El Faro, Prof.^a Dr.^a Priscila Bernardes, Prof.^a Dr.^a Amanda Maiorano e Prof. Dr. Salvador Ramos, e pelas críticas, reflexões e sugestões a este trabalho.

Agradeço à Embrapa (SEG 02.13.05.011.00.00), CNPq (310199/2015-8 e 431629/2016-1) e FAPEMIG (CVZ PPM 00606/16 e APQ-02750-23) pelo financiamento das amostras utilizadas neste trabalho. Agradeço também a Associação de Criadores de Gir Leiteiro (ABCGIL), Embrapa Gado de Leite e 1000 Bulls Project Consortium pelos dados cedidos e ao Laboratório Multiusuário de Bioinformática da Embrapa Informática Agropecuária e Centre for Genetic Improvement of Livestock (CGIL) pela infraestrutura computacional e recurso de TI.

Aos companheiros de pós-graduação e do Estatística Aplicada a Genética e Melhoramento Animal (EAGMA) pelo apoio durante toda a trajetória. Com vocês compartilhei muitas dúvidas, momentos de estudo, alegria e confraternização que fizeram meus dias mais leves e felizes. Em especial agradeço a Amanda Baldi, Ana Carolina de Jesus, Ana Carolina Paz, Bruna Salatta, Camilla Arantes, Edimar Gabiati, Gabriel Gubiani, Ivan Filho, Júlia Rodrigues, Júlia Valente, Larissa Temp, Rafael Watanabe, Tádía Stivanin, Roney Teixeira, Thomaz Sena e Viviane Ligori.

À Adriana e Shirley, funcionárias do departamento de Engenharia e Ciências Exatas, por toda atenção e disposição em me auxiliar.

I thank the CGIL group, especially Alice Vanzin, Bruno Galindo, Chiara Gini, Colin Lynch, Emanuelli Da Silva, Gabriella Dodd, Isis Hermisdorff, Ivan Campos, Krishani Sinhalage, Kristin Lee, Lucas Lopes, Ricarda Jahnel, Samla Cunha, Sirlene Lazzaro, and Stephanie Lam, for the amazing coffees, interactions in lab meetings, and for making the period abroad more fun. I also thank Dr. Filippo Miglior and Dr. Christine Baes for the scientific discussions and support.

To my friends in Canada. Melissa Nagy (*in memoriam*), who became one of my greatest friends. Thanks for making my life cozier and reminding me that some things “look like a tomorrow problem” and that we don’t need to take life so seriously. To Barbara Mann and Digant Purandare, with whom I shared great adventures and learned more about life and kindness. To Mélanie Gagné, Magalie, Mélianne,

Médéric, and Martin Gregoire for opening their home, farm, and hearts to me. At Triple G Farm, I learned so much about dairy farming and the beauty of Canadian endangered breeds.

Agradeço aos demais que, de alguma forma, contribuíram com a minha formação e com a realização deste trabalho, mas que não foram citados nominalmente.

Também agradeço pelas oportunidades, direitos não universalizados e privilégios que me foram concedidos ao longo de toda minha vida acadêmica. Aos meus objetivos, erros e acertos que me ensinaram muito.

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

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ASSINATURAS DE SELEÇÃO EM BOVINOS DE LEITE

RESUMO – Tanto a seleção natural como a seleção artificial deixam marcas no genoma, conhecidas como assinaturas de seleção, que podem revelar regiões relacionadas a características adaptativas e economicamente importantes para a produção de leite. Além disso, a seleção pode alterar a diversidade genética de uma população. Elevada intensidade de seleção e uso recorrente de um número reduzido de reprodutores podem diminuir a diversidade genética, com possíveis impactos negativos em programas de melhoramento a longo prazo. Como exemplo de população leiteira, a raça Holandesa tem sido fortemente selecionada para alta produtividade no Canadá e nos Estados Unidos, enquanto a raça Gir desempenha papel relevante na produção de leite em regiões tropicais, como Índia e América Latina. No Brasil, o gado Gir foi introduzido entre os séculos XIX e XX e, desde 1985, é selecionado para produção de leite. O objetivo desta tese foi caracterizar assinaturas de seleção em populações de bovinos leiteiros. O capítulo 2 teve como objetivo avaliar a diversidade genética e identificar assinaturas de seleção em bovinos Holandeses da América do Norte (HOL), Gir da Índia (GIR_IN) e Gir Leiteiro (GIR_BR). A diversidade genética foi medida por meio da nucleotide diversity, densidade de variantes de nucleotídeo único, frequência do alelo menor, heterozigosidade observada e esperada, e coeficiente de endogamia. As assinaturas de seleção foram detectadas utilizando Tajima's D, iHS (integrated haplotype score), F_{ST} (fixation index) e XP-EHH (cross-population extended haplotype homozygosity) nos cromossomos autossomos, além de Tajima's D e iHS no cromossomo X. A população HOL apresentou menor diversidade, enquanto GIR_IN e GIR_BR apresentaram maior variabilidade genética. Genes previamente associados a características de importância econômica, incluindo crescimento, reprodução, mastite, produção de leite, tolerância ao calor, saúde e adaptação, foram identificados em regiões sob seleção. No capítulo 3, uma revisão sistemática sobre assinaturas de seleção em bovinos leiteiros é apresentada. O total de 21 estudos em 19 raças (taurinas, zebuínas e compostas) foram selecionados, com assinaturas de seleção que sobrepujaram 5.099 genes. Genes sob seleção relacionados a características como fertilidade, saúde, produção e composição do leite, adaptação ambiental, padrões de pelagem e genes com possível pleiotropia, foram discutidos. Genes foram relatados recorrentemente nos estudos de assinaturas de seleção, como *PLAG1* e *HMG2*. Embora *DGAT1* seja um gene importante para características do leite, não apresentou evidências de seleção na literatura revisada. A revisão também discutiu perspectivas futuras envolvendo ferramentas moleculares e abordagens integrativas. Como uma conclusão geral, a seleção em bovinos leiteiros é moldada não somente por características econômicas, mas também por pressões ecológicas e adaptativas. Em ambos os capítulos 2 e 3, os genes sob seleção foram relacionados a diversas características de importância econômica. Por fim, o estudo de assinaturas de seleção fornece informações valiosas para o melhoramento genético e a sustentabilidade da pecuária leiteira.

Palavras-chave: assinatura de seleção, bovinos de leite, diversidade genética, genes

SELECTION SIGNATURES IN DAIRY CATTLE

ABSTRACT – Natural and artificial selection leave footprints on the genome, known as selection signatures, which can reveal regions related to adaptive and economically important traits for the dairy sector. Additionally, selection may also alter the genetic diversity of a population. Strong selection pressure and the recurrent use of a limited number of sires may decrease genetic diversity, with possible negative effects on long-term breeding programs. As an example of dairy cattle, the Holstein breed has been strongly selected for high productivity in Canada and the United States. In contrast, the Gir breed has an important role in milk production in tropical regions such as India and Latin America. In Brazil, Gir cattle were introduced during the 19th and 20th centuries and, since 1985, have been selected for milk production. This doctoral dissertation aimed to characterize selection signatures in dairy cattle populations. The second chapter aimed to assess genetic diversity and identify selection signatures in Holstein cattle from North America (HOL), Gir cattle from India (GIR_IN), and Dairy Gir cattle from Brazil (GIR_BR). Genetic diversity was measured using nucleotide diversity, single-nucleotide variant density, minor allele frequency, observed and expected heterozygosity, and the inbreeding coefficient. Selection signatures were detected using Tajima's D, integrated haplotype score (iHS), fixation index (FST), and cross-population extended haplotype homozygosity (XP-EHH) on autosomes, as well as Tajima's D and iHS on the X chromosome. The HOL population showed lower diversity, while GIR_IN and GIR_BR presented greater variability. Genes previously associated with traits of economic importance were identified, including traits related to growth, reproduction, mastitis, milk production, heat tolerance, health, and adaptation. In addition, in the third chapter, we systematically reviewed studies published from 2016 to 2023 on selection signatures in dairy cattle. A total of 21 studies in 19 breeds (taurine, indicine, and composite) identified selection signatures overlapping with 5,099 genes. We discussed genes under selection related to economically important traits, such as fertility, health, milk production and composition, environmental adaptation, color patterns, and potential pleiotropic genes. Several genes were reported in numerous selection signature studies, such as *PLAG1* and *HMGA2*. Although *DGAT1* is an important gene for milk production and composition, it did not show evidence of selection in recent literature. The systematic review also discussed future perspectives involving molecular tools and integrative approaches. As a general conclusion, dairy cattle selection is shaped not only by economic traits but also by ecological and adaptive pressures. In both chapters, the genes under selection were linked to several traits, including growth, reproduction, milk production and components, heat tolerance, health, and adaptation. The study of selection signatures provides valuable information for genetic improvement and sustainable breeding.

Keywords: dairy cattle, genes, genetic diversity, selection signatures

CHAPTER 01 – GENERAL CONSIDERATIONS

1 INTRODUCTION

The identification of regions under selection and their consequences on the modification of species is one of the interests of genetic and animal breeding area. The combination of geographic separation and natural and artificial selection has shaped the genomic architecture of cattle, leading to genetic differentiation among bovine breeds. Therefore, this differentiation can shape patterns of genetic variation of selected regions, leading to selection signatures that provide information on genome-changing mechanisms and can be used to identify loci subject to selection (Campos et al. 2017). The study of selection signatures and genetic diversity contributes to understanding processes related to genome evolution (Nielsen et al. 2005). Furthermore, it may help the identification of causal variants that control the economically important phenotypes in cattle, such as milk production, reproduction, body conformation, diseases and parasites resistance, and behavior.

In Brazil, the Dairy Gir cattle in the main dairy zebu breed, and Holstein is the primary dairy taurine breed. However, the genetic mechanism underlying selection signatures in these populations remains incompletely elucidated. Taurine cattle have higher performance but also larger environmental demands. Zebu cattle are better adapted to breeding conditions in the tropics. Taurine breeds have been selected for economic traits for a longer period and with greater intensity than zebu breeds, especially when referring to zebu populations from developed and sub-developed countries.

The strong selection pressure may be the reason for the higher linkage disequilibrium (LD) level observed in *Bos taurus* than in *Bos indicus* animals (Thévenon et al. 2007; O'Brien et al. 2014). The detection of selection signatures is based on the frequency of alleles that are under selection or in adjacent haplotypes. When the frequency is higher, it may generate segments of consecutive homozygous genotypes (Ghoreishifar et al. 2020b, a).

With the widespread use of reproductive technologies and increasing selection pressure, monitoring genetic diversity and selection signatures in dairy genetic resources is fundamental. This importance is recognized in Sustainable Development

Goal (SDG) 2.5, which aims to maintain genetic diversity. The aim of this thesis is to characterize selection signatures in dairy cattle populations. In Chapter 2 of this thesis, a study on selection signature and genetic diversity in Holstein and Dairy Gir cattle is presented. In Chapter 3, a systematic review of recent studies on selection signatures in dairy cattle is reported.

6 CONCLUSIONS

This review provided a comprehensive overview of the current scenario of selection signatures in dairy cattle studies, including the selection of the most relevant traits for milk production worldwide and specific adaptive and disease resilience traits of dairy breeds. We highlighted important genes found to be under selection in taurine, indicine, and composite dairy cattle breeds. However, there is a lack of functional validation of candidate genes; these studies will enhance understanding in multiple fields of animal breeding and genetics. An alternative that can provide more information is the integration of GWAS and selection signature studies, as this may lead to gains in marker-enhanced selection and functional understanding of complex traits.

Dairy cattle populations have not been selected only for traits that are present in the selection indices; rather, their genomes are also shaped by environmental pressures and the selection of desirable exterior traits, such as human preference regarding coat color. As selection indices evolve to incorporate sustainable traits such as feed efficiency and methane emission, the identification of selection signatures linked with these traits is encouraged in future generations.

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