



Kent Academic Repository

Marzanova, Saida N., Devrishov, Davud A., Turbina, Irina S., Marzanov, Nurbiy S., Griffin, Darren K. and Romanov, Michael N. (2023) *Genetic load of mutations causing inherited diseases and its classification in dairy cattle bred in the Russian Federation*. In: Chen, Zhi and Li, Cong, eds. *Breeding, Genetics and Safety Production of Dairy Cattle*. MDPI, Basel, Switzerland, pp. 143-158. ISBN 978-3-0365-8246-7.

Downloaded from

<https://kar.kent.ac.uk/102400/> The University of Kent's Academic Repository KAR

The version of record is available from

<https://doi.org/10.3390/books978-3-0365-8247-4>

This document version

Publisher pdf

DOI for this version

Licence for this version

CC BY-NC-ND (Attribution-NonCommercial-NoDerivatives)

Additional information

This is a reprint of articles from the Special Issue published online in the open access journal *Agriculture* (ISSN 2077-0472) (available at: https://www.mdpi.com/journal/agriculture/special_issues/Genetics_Dairy_Cattle). For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Versions of research works

Versions of Record

If this version is the version of record, it is the same as the published version available on the publisher's web site. Cite as the published version.

Author Accepted Manuscripts

If this document is identified as the Author Accepted Manuscript it is the version after peer review but before type setting, copy editing or publisher branding. Cite as Surname, Initial. (Year) 'Title of article'. To be published in ***Title of Journal***, Volume and issue numbers [peer-reviewed accepted version]. Available at: DOI or URL (Accessed: date).

Enquiries

If you have questions about this document contact ResearchSupport@kent.ac.uk. Please include the URL of the record in KAR. If you believe that your, or a third party's rights have been compromised through this document please see our [Take Down policy](https://www.kent.ac.uk/guides/kar-the-kent-academic-repository#policies) (available from <https://www.kent.ac.uk/guides/kar-the-kent-academic-repository#policies>).



agriculture

Special Issue Reprint

Breeding, Genetics and Safety Production of Dairy Cattle

Edited by
Zhi Chen and Cong Li

www.mdpi.com/journal/agriculture



Breeding, Genetics and Safety Production of Dairy Cattle

Breeding, Genetics and Safety Production of Dairy Cattle

Editors

Zhi Chen

Cong Li

MDPI • Basel • Beijing • Wuhan • Barcelona • Belgrade • Manchester • Tokyo • Cluj • Tianjin



Editors

Zhi Chen
Yangzhou University
Yangzhou, China

Cong Li
Northwest A&F University
Yangling, China

Editorial Office

MDPI
St. Alban-Anlage 66
4052 Basel, Switzerland

This is a reprint of articles from the Special Issue published online in the open access journal *Agriculture* (ISSN 2077-0472) (available at: https://www.mdpi.com/journal/agriculture/special_issues/Genetics_Dairy_Cattle).

For citation purposes, cite each article independently as indicated on the article page online and as indicated below:

LastName, A.A.; LastName, B.B.; LastName, C.C. Article Title. <i>Journal Name</i> Year , <i>Volume Number</i> , Page Range.
--

ISBN 978-3-0365-8246-7 (Hbk)

ISBN 978-3-0365-8247-4 (PDF)

© 2023 by the authors. Articles in this book are Open Access and distributed under the Creative Commons Attribution (CC BY) license, which allows users to download, copy and build upon published articles, as long as the author and publisher are properly credited, which ensures maximum dissemination and a wider impact of our publications.

The book as a whole is distributed by MDPI under the terms and conditions of the Creative Commons license CC BY-NC-ND.

Contents

About the Editors	vii
Sitian Yang, Xiang Cao, Yu Wang, Cong Li and Zhi Chen Genetics and Production of Safe, High-Quality Milk by Dairy Cattle Reprinted from: <i>Agriculture</i> 2023 , <i>13</i> , 1348, doi:10.3390/agriculture13071348	1
Xiaogang Cui, Tianqi Yuan, Zhengyu Fang, Jiao Feng and Changxin Wu Bta-miR-125a Regulates Milk-Fat Synthesis by Targeting <i>SAA1</i> mRNA in Bovine Mammary Epithelial Cells Reprinted from: <i>Agriculture</i> 2022 , <i>12</i> , 344, doi:10.3390/agriculture12030344	5
Run Liu, Hao Zhu, Jingwen Zhao, Xinyue Wu, Xubin Lu, Tianle Xu and Zhangping Yang <i>Lycium barbarum</i> Polysaccharide Inhibits <i>E. coli</i> -Induced Inflammation and Oxidative Stress in Mammary Epithelial Cells of Dairy Cows via SOCS3 Activation and MAPK Suppression Reprinted from: <i>Agriculture</i> 2022 , <i>12</i> , 598, doi:10.3390/agriculture12050598	19
Yujia Sun, Yaoyao Ma, Xinyi Wu, Tianqi Zhao, Lu Lu and Zhangping Yang Functional and Comparative Analysis of Two Subtypes of Cofilin Family on Cattle Myoblasts Differentiation Reprinted from: <i>Agriculture</i> 2022 , <i>12</i> , 1420, doi:10.3390/agriculture12091420	33
Tianle Xu, Wendi Cao, Yicai Huang, Jingwen Zhao, Xinyue Wu and Zhangping Yang The Prevalence of <i>Escherichia coli</i> Derived from Bovine Clinical Mastitis and Distribution of Resistance to Antimicrobials in Part of Jiangsu Province, China Reprinted from: <i>Agriculture</i> 2023 , <i>13</i> , 90, doi:10.3390/agriculture13010090	47
Xiaogang Cui, Changqing Li, Zhangqi Wei, Hangting Meng, Fengfeng Zhang, Yue Liu, et al. <i>DDIT3</i> Governs Milk Production Traits by Targeting IL-6 to Induce Apoptosis in Dairy Cattle Reprinted from: <i>Agriculture</i> 2023 , <i>13</i> , 117, doi:10.3390/agriculture13010117	57
Hailiang Zhang, Abdul Sammad, Rui Shi, Yixin Dong, Shanjiang Zhao, Lin Liu, et al. Genetic Polymorphism and mRNA Expression Studies Reveal <i>IL6R</i> and <i>LEPR</i> Gene Associations with Reproductive Traits in Chinese Holsteins Reprinted from: <i>Agriculture</i> 2023 , <i>13</i> , 321, doi:10.3390/agriculture13020321	69
Xin Zhao, Jun Li, Shuying Zhao, Lili Chen, Man Zhang, Yi Ma and Dawei Yao Regulation of bta-miRNA29d-3p on Lipid Accumulation via <i>GPAM</i> in Bovine Mammary Epithelial Cells Reprinted from: <i>Agriculture</i> 2023 , <i>13</i> , 501, doi:10.3390/agriculture13020501	83
Michał Trela, Dominika Domańska and Olga Witkowska-Piłaszewicz Diagnostic Use of Serum Amyloid A in Dairy Cattle Reprinted from: <i>Agriculture</i> 2022 , <i>12</i> , 459, doi:10.3390/agriculture12040459	93
Qinyue Lu, Weicheng Zong, Mingyixing Zhang, Zhi Chen and Zhangping Yang The Overlooked Transformation Mechanisms of VLCFAs: Peroxisomal β -Oxidation Reprinted from: <i>Agriculture</i> 2022 , <i>12</i> , 947, doi:10.3390/agriculture12070947	103
Zimeng Xin, Tianying Zhang, Qinyue Lu, Zhangping Yang and Zhi Chen Progress of m ⁶ A Methylation in Lipid Metabolism in Humans and Animals Reprinted from: <i>Agriculture</i> 2022 , <i>12</i> , 1683, doi:10.3390/agriculture12101683	125
Saida N. Marzanova, Davud A. Devrishov, Irina S. Turbina, Nurbiy S. Marzanov, Darren K. Griffin and Michael N. Romanov Genetic Load of Mutations Causing Inherited Diseases and Its Classification in Dairy Cattle Bred in the Russian Federation Reprinted from: <i>Agriculture</i> 2023 , <i>13</i> , 299, doi:10.3390/agriculture13020299	143

About the Editors

Zhi Chen

Zhi Chen, Ph.D., is an Associate Professor at the College of Animal Science and Technology of Yangzhou University, Yangzhou City, Jiangsu Province, China. From October 2021 to the present, Dr. Chen has served as Associate Professor in the College of Animal Science and Technology, Yangzhou University, and from September 2017 to October 2021, he served as a Lecturer in the College of Animal Science and Technology, Yangzhou University. He obtained a doctorate degree from Northwest A&F University, Shaanxi Provincial Key Laboratory of Molecular Biology for Agriculture, from September 2013 to June 2017, obtained a master's degree from the College of Animal Science, Guizhou University, from September 2010 to June 2013, and obtained a bachelor's degree from the College of Animal Science and Technology, Yangzhou University, from September 2006 to June 2010. He is active in many fields of milk fat traits, gene regulation network construction, gene expression, epigenetics, circRNA, lincRNA, miRNA, and mRNA.

Cong Li

Cong Li, Ph.D., is an Associate Professor at the College of Animal Science and Technology (Northwest A&F University, Yangling, 712100, China). He obtained a doctorate in Animal Genetics, Breeding and Reproduction from China Agricultural University from September 2010 to June 2016, and joined a joint training of functional genomics at the University of Illinois at Urbana–Champaign from February 2014 to February 2015; Dr. Li obtained a Bachelor's degree of Animal Science from Inner Mongolia University for Nationalities from September 2006 to June 2010. He is active in many fields of gene regulation, functional genomics, genetic polymorphisms, genetic heritability, gwas, bioinformatics, milk component, fatty acids, and proteins.



Review

Genetic Load of Mutations Causing Inherited Diseases and Its Classification in Dairy Cattle Bred in the Russian Federation

Saida N. Marzanova ¹, Davud A. Devrishov ¹, Irina S. Turbina ², Nurbiy S. Marzanov ³, Darren K. Griffin ⁴ and Michael N. Romanov ^{4,*}

¹ K.I. Skryabin Moscow State Academy of Veterinary Medicine and Biotechnology, 109472 Moscow, Russia

² Head Center for the Reproduction of Farm Animals, 142143 Bykovo, Moscow Oblast, Russia

³ L.K. Ernst Federal Research Center for Animal Husbandry, 142132 Dubrovitsy, Moscow Oblast, Russia

⁴ School of Biosciences, University of Kent, Canterbury CT2 7NJ, UK

* Correspondence: m.romanov@kent.ac.uk

Abstract: This review addresses the concept of genetic load from the point of view of molecular genetics, development and efforts in selective breeding. As typical examples, the assessment of animals in the Holstein breed and its high-blooded crossbreeds is considered for mutations that cause three inherited diseases: bovine leukocyte adhesion deficiency (*CD18* locus), complex vertebral malformation (*SLC35A3* locus), and brachyspina (*FANCI* locus). The reasons for their occurrence and accumulation in the breeding herds of the black-pied genealogical root are discussed. These include an intense artificial-selection of bulls and cows in highly productive herds and the intensive sale (within and between countries) of breeding material (animals, semen, embryos) from a small population of sires from countries with a high level of dairy-cattle breeding development. There is a founder effect when the source of mutant-allele spread is a prominent sire. For example, the greatest contribution to the spread of mutant alleles *CD18^G*, *SLC35A3^T* and *FANCI^{BY}* was made by the descendants of three closely related bulls. A genogeographic generalization of the mutation occurrence in the world and Russia is provided for these hereditary-disease loci and, includes a total of 31 countries where these mutations were detected. The genetic-load classification for these and other mutations is given. The mutations are inherited both recessively (*CD18^G*, *SLC35A3^T*, *FANCI^{BY}*) and codominantly (*CSN3^A*, *CSN3^C*, *CSN3^E*, *CSN2^{A1}*, *CSN2^B*). Genetic load is classified into the following types: mutational, segregation, substitutional, and immigration. For each of these, examples are given that explain their occurrence. Overall, it can be concluded that the phenomenon of genetic load in industrial herds of dairy cattle requires special attention when creating healthy livestock and obtaining high-quality dairy products.

Keywords: hereditary diseases; breeds; dairy cattle; mutations; alleles; genetic-load classification

Citation: Marzanova, S.N.; Devrishov, D.A.; Turbina, I.S.; Marzanov, N.S.; Griffin, D.K.; Romanov, M.N. Genetic Load of Mutations Causing Inherited Diseases and Its Classification in Dairy Cattle Bred in the Russian Federation. *Agriculture* **2023**, *13*, 299. <https://doi.org/10.3390/agriculture13020299>

Academic Editors: Zhi Chen and Cong Li

Received: 23 December 2022

Revised: 19 January 2023

Accepted: 23 January 2023

Published: 26 January 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Genetic load is a term used to refer to the sum of unfavorable lethal and sublethal mutations in the genome of individuals within a population that reduces their viability or increases the risk of death. The concept was first proposed by the English population geneticist J.B.S. Haldane [1].

Geneticists who proposed the genetic-load theory expanded on the concept of an ideal genotype that conforms to ideal fitness. Currently, a drawback of this approach is apparent. That is, it is somewhat meaningless to proceed from such an assumption when referring to various types of farm animals, where we deal with extremely high requirements for adaptive plasticity. Nevertheless, the term “genetic load” here may be convenient for designating the burden of the gene pool due to a rather poor-quality heredity. Its artificial accumulation in the gene pool reduces the overall fitness of a particular species or leads to a low quality in the products obtained from it [2,3]. In this regard, it is important to study

the prevalence (i.e., genogeography) of mutations that cause certain diseases and disorders in animals.

The purpose of this review is to summarize the data on the distribution of mutations associated with a number of inherited diseases and classify the genetic load, mainly in populations of dairy cattle. As representative examples of hereditary diseases, we have focused in this review on bovine leukocyte adhesion deficiency (BLAD; *CD18^G* mutation), complex vertebral malformation (CVM; *SLC35A3^T* mutation), and brachyspina or short spine lethal syndrome (BY; *FANCI^{BY}* mutation), as well as abnormalities associated with mutations of beta- and kappa-caseins (*CSN2* and *CSN3* loci, respectively). These genetic syndromes are diagnosed on the basis of certain developed methods, according to which many patents have also been obtained (e.g., [4–8]). The method for diagnosing four alleles of beta-casein (*CSN2^{A1}*, *CSN2^{A2}*, *CSN2^{A3}*, *CSN2^B*) has come into practice thanks to the respective developments by Lien et al. [9] and Dinç [10], with subsequent modifications. An understanding of the distribution of the three mutations (*CD18^G*, *SLC35A3^T* and *FANCI^{BY}*) diagnosed in Holstein cattle can be obtained from the analysis of various literature sources, as will be discussed in this review below.

2. What Does Genetic Load Mean?

As summarized by Bertorelle et al. [11], the genetic load is part of the hereditary variability of a population that occurs as a result of natural or artificial selection and determines the appearance of less adapted individuals that undergo selective death. Along with diminishing a population's biodiversity, the genetic load is linked to a decline in the selection value of individuals. A population's incapacity to adjust to a given set of environmental factors is measured by the genetic load. The term "genetic load" refers to the accumulation of lethal and sublethal harmful mutations that significantly reduce an individual's viability or result in their death when the mutation enters a homozygous state. Thus, in a stricter sense, the genetic load is accepted in population genetics as an expression of a lowering of the selective value of a population compared to that which the population had in the past [12,13]. In dairy cattle, mutations causing hereditary diseases are often breed-specific, since they were introduced worldwide from a limited number of genealogical roots, e.g., through bulls that were the founders of the Holstein breed. Mutant alleles and genotypes at the casein loci can also be breed-specific (e.g., [14]).

3. Mutations Leading to Disorders in Cattle Breeds

Over 559 genetically determined morphological and functional disorders have been identified in cattle [15]. In Russia, among the six dairy breeds that are exploited in many regions, the largest number of such inherited deviations was recorded in Holstein cattle followed by the Friesian, Black Pied, Simmental, Brown Swiss and Ayrshire breeds (Figure 1).

The difference between the Holstein breed and others is associated with the peculiarities of its breeding and reproduction. Holstein cattle are known to have a limited number of sire lines and related groups (e.g., Osbornedale Ivanhoe, A.B.C. Reflection Sovereign, Montwick Chieftain, etc.). In addition, the formation of Holstein populations in the United States occurred with the intensive use of a small number of bulls. Therefore, in the pedigrees of almost all animals of the Holstein breed in the 7th–10th lines of ancestors, there are genes of at least one of the 20 founding bulls. Thus, in formal outbreeding, it is actually difficult to avoid the selection of pairs in the pedigrees of which there is no "blood" of these founders or their descendants. On the one hand, such a breeding system with intensive selection contributes to the consolidation of the breed, but on the other hand, it increases the likelihood of accumulation and transition to the homozygous state of a complex of mutant genes that cause various disorders [3,16].

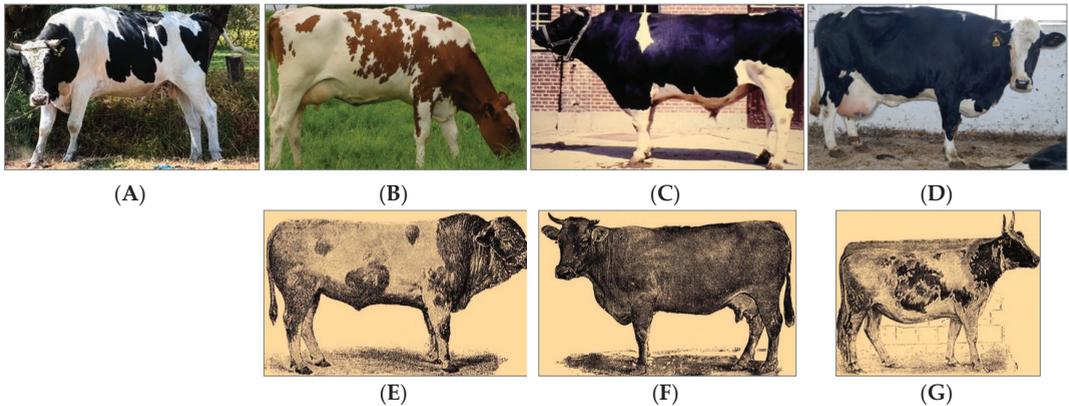


Figure 1. Some notable dairy cattle breeds that can be carriers of deleterious mutations. (A), Holstein Friesian bull with the black-pied coat color; (B), Holstein Friesian heifer with the red-pied coat color; (C), German Black Pied bull; (D), Russian Black Pied cow; (E), Simmental cow; (F), Brown Swiss cow; (G), Ayrshire cattle (Image sources: (A), https://commons.wikimedia.org/wiki/File:Tethered_bull_Holstein_Mexico_p1.jpg (accessed on 19 January 2022), by Cvmontuy, 2020, Creative Commons Attribution-Share Alike 4.0 International license, Category: Holstein Friesian cattle, cropped; (B), https://commons.wikimedia.org/wiki/File:Red_Holstein.jpg (accessed on 19 January 2022), by MGA73bot2, 2011, Creative Commons Attribution-Share Alike 3.0 Unported license, Category: Red Holstein, cropped; (C), [https://commons.wikimedia.org/wiki/File:%20Schwarzbunte_%3D_%E4%B8%96%E7%95%8C%E3%81%AE%E7%89%9B_%E3%83%89%E3%82%A4%E3%83%84%E9%BB%92%E7%99%BD%E6%96%91%E7%89%9B%EF%BC%88%E9%9B%84%EF%BC%89_\(36567900171\).jpg](https://commons.wikimedia.org/wiki/File:%20Schwarzbunte_%3D_%E4%B8%96%E7%95%8C%E3%81%AE%E7%89%9B_%E3%83%89%E3%82%A4%E3%83%84%E9%BB%92%E7%99%BD%E6%96%91%E7%89%9B%EF%BC%88%E9%9B%84%EF%BC%89_(36567900171).jpg) (accessed on 19 January 2022), by Tomasina, 2019, Creative Commons Attribution 2.0 Generic license, Category: Deutsches Schwarzbuntes Niederungsirind, cropped; (D), https://ru.wikipedia.org/wiki/%D0%9A%D0%BE%D1%80%D0%BE%D0%B2%D0%B0_%D1%87%D1%91%D1%80%D0%BD%D0%BE-%D0%BF%D1%91%D1%81%D1%82%D1%80%D0%BE%D0%B9_%D0%BF%D0%BE%D1%80%D0%BE%D0%B4%D1%8B.jpg (accessed on 19 January 2022), by Nicolas-a, 2018, Creative Commons Attribution 3.0 license, cropped; (E), https://commons.wikimedia.org/wiki/File:Brockhaus_and_Efron_Encyclopedic_Dictionary_b59_264-2.jpg (accessed on 19 January 2022), by ButkoBot, 2009, public domain, Category: Mammals illustrations from Brockhaus and Efron Encyclopedic Dictionary, cropped; (F), https://commons.wikimedia.org/wiki/File:Brockhaus_and_Efron_Encyclopedic_Dictionary_b59_264-1.jpg (accessed on 19 January 2022), by ButkoBot, 2009, public domain, Category: Mammals illustrations from Brockhaus and Efron Encyclopedic Dictionary, cropped; (G), https://commons.wikimedia.org/wiki/File:Brockhaus_and_Efron_Encyclopedic_Dictionary_b59_264-1.jpg (accessed on 19 January 2022), by ButkoBot, 2009, public domain, Category: Mammals illustrations from Brockhaus and Efron Encyclopedic Dictionary, cropped).

The described disorders are an example of the direct transfer of mutant genes from one breed or from one country to another. Recently, however, the opposite situation has developed: when using Holstein bulls to “improve” populations of black-pied cattle, recessive mutations causing BLAD, CVM and BY were transferred to their gene pool, along with the introduction of beneficial traits [17–19].

Many of the above mutations, which represent a genetic load that is characteristic only for the Holstein breed of black-pied and red-pied varieties and their crosses, probably arose recently and in a particular breed, while some other mutations are of an earlier origin. First of all, this concerns the BLAD, CVM and BY diseases that have become widespread in populations of the Holstein cattle, due to the intensive use of the descendants of the Osbornedale Ivanhoe 1189870 bull, including his son Penstate Ivanhoe Star 1441440 and especially his grandson Carlin-M Ivanhoe Bell 1667366, in reproduction [20,21].

As a result of the culling of bulls carrying inherited-disorder mutations in the 1990s and 2000s, numbers have been reduced to a minimum or have been eradicated. In recent years, the emergence of carrier bulls has been associated with the transmission of mutations from non-certified bull-breeding mothers [22].

4. Mutation Occurrence in the World and Russia

Genogeographic analysis of the distribution of the most well-known mutations (*CD18^G*, *SLC35A3^T*, *FANCI^{BY}*, *CSN3^A*, *CSN3^C*, *CSN3^E*, *CSN2^{A1}*, *CSN2^B*) was carried out broadly in the Holstein breed of both black-pied and red-pied types [4,21–26]. It was reported that the average frequency of heterozygous *CD18^{A/G}* carriers in the early studies on Holsteins in the USA and other countries was approximately 20% [27].

According to our generalization (Table 1), the mutant alleles *CD18^G*, *SLC35A3^T* and *FANCI^{BY}* were identified in most of the 31 countries where the Holstein breed or its high-blooded crosses were bred. As for the *SLC35A3^T* allele, it was discovered in a smaller number of countries, due to the past long-term lack of access to diagnostic methods. Even fewer studies have been conducted on the *FANCI^{BY}* allele, for the same reason [19]. In Table 1, some of the main world regions and countries are listed for which the occurrence of the alleles *CD18^G*, *SLC35A3^T* and *FANCI^{BY}* has been reported.

Table 1. Geography of dispersion of mutant alleles *CD18^G*, *SLC35A3^T* and *FANCI^{BY}*.

Region	Country	References
North America	US USA	[24,28–36] *
	CA Canada	[37,38] *
Latin America and Caribbean	AR Argentina	[39]
	BR Brazil	[40]
Europe	AT Austria	[41]
	BE Belgium	[37,42,43] *
	GB United Kingdom	[44]
	HU Hungary	[45,46]
	DK Denmark	[47–54] *
	IT Italy	[55,56] *
	ES Spain	[57]
	MK North Macedonia	[58]
	NL The Netherlands	[53,59–61] *
	PL Poland	[62–64] *
	RU Russia	[19,20,27,65–69] *
	RO Romania	[70]
	FR France	[23,71–73] *
	DE Germany	[74–82] *
	UA Ukraine	[83–85]
CH Switzerland	[86]	
Southeast Asia and the Pacific Basin	CZ Czech Republic	[87]
	CN China	[88–92] *
	TW Taiwan	[22] *
Middle East	JP Japan	[93–96]
	NZ New Zealand	[97]
	AU Australia	
South Asia	IR Iran	[98–100]
	TR Turkey	[101]
Africa	IN India	[102,103]
	PK Pakistan	[104]
	ZA South Africa	[105]

* Reports of the diagnosed *FANCI^{BY}* allele in breeding animals. Otherwise, references for reports of the established mutant alleles *CD18^G* and *SLC35A3^T* are provided.

Since the Holstein breed is widely spread worldwide in over 150 countries [106], the range of mutations is most likely much broader. Based on the data obtained, it should be noted that the mutant alleles came to certain countries through the purchase of breeding material from the United States, Canada, and some European countries (Denmark, Germany, the Netherlands, France, etc.), i.e., through the acquisition of sires, semen and embryos from these countries. In this regard, the livestock-breeding communities of the USA, Canada, Germany, Belgium, the Netherlands, Russian Federation and other countries with the developed dairy-cattle breeding decided to implement the mandatory tests of breeding material for the presence of mutant alleles [107]. The imported materials are entered into the catalogs of Holstein bulls and their high-blooded crosses, along with recently discovered haplotypes. The mutant alleles $CD18^G$, $SLC35A3^T$ and $FANCI^{BY}$ are also considered to be breed-specific traits for the Holstein cattle. One of the reasons for this situation is the strict selection of sires that are carriers of genes for extraordinary milk production, while the occurrence of the $CD18^G$, $SLC35A3^T$ and $FANCI^{BY}$ alleles are a side effect of high milk-yield, fertility or milk quality [22,34,108].

Thus, based on the above observations, it can be stated that the struggle to cleanse the breeding stock from mutations has been undertaken in those countries where elite animals of the Holstein breed or synthetic populations produced by its crossing with local cattle breeds are used [69].

In the Russian Federation, an assessment based on genetic studies was made with respect to dispersion of the $CD18^G$, $SLC35A3^T$ and $FANCI^{BY}$ mutations. Since detailed results of the occurrence of $CD18^G$ and $SLC35A3^T$ alleles in Russia were reported in our own previous works (e.g., [4]), here, we can limit ourselves to a general characterization of the state of the $FANCI^{BY}$ mutation spread in the regions of the Russian Federation, covered by the respective studies. These latter involved animals from the Bryansk Oblast, Ivanovo Oblast, Lipetsk Oblast, Moscow Oblast and the Republic of Karelia. In particular, the $FANCI^{BY}$ allele was found in fifteen breeding sires and five breeding cows of the Holstein breed maintained by the joint-stock company "Head Center for Animal Reproduction" (JSC GTsV). The $FANCI^{BY}$ allele carriers were the following bulls of the Holstein breed, both black-pied and red-pied: Avanti 76845, Barkhat 38, Braslet 106759921, Garus 10917481, Kankan 11033687, Kapral 1400, Laur 10990032, Leroy 10990031, Opal 11007858, Pikul 106894920, Ramos 96286, Flint 1223, Floks 1448, Shtabel' 1780, and Etiket 7754. They were culled from the JSC GTsV breeding stock. Currently, there are no carriers of the $CD18^G$, $SLC35A3^T$ and $FANCI^{BY}$ alleles in this breeding center [19]. It should be noted that sires carrying the three alleles were purchased by the JSC GTsV before the development of methods for diagnosing these mutations in animals.

In the course of our investigations [19,21], it was found that the main way for a mutant allele to enter the Russian Federation is the acquisition of breeding material without checking for the carriage of mutations. Obviously, the Holstein breed had a hidden segregation load of mutations from the Dutch cattle from which it originated. Indeed, a number of anomalies are found both in the Dutch Black Pied, Friesian, and Holstein cattle [16,27,109].

5. Classification of Genetic Load

Each type of genetic load in farm animals correlates with a certain type of natural or artificial selection in them [110]. In animal husbandry, four types of genetic load are generally distinguished: mutation, immigration, segregation, and substitution (Figure 2).

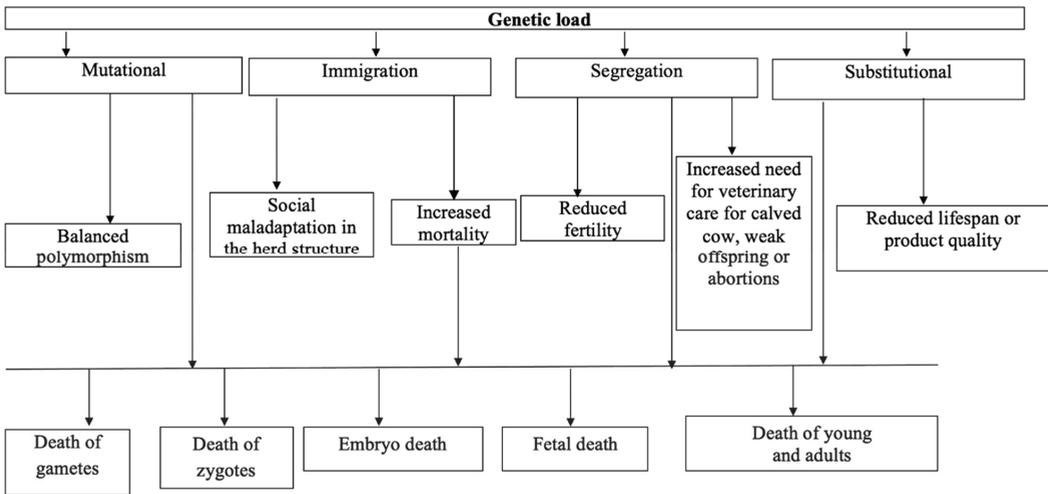


Figure 2. Classification of genetic load in dairy cattle and forms of its manifestation.

5.1. Mutational Genetic-Load

Most often, this type of genetic load includes autosomal-recessive mutations. A side effect of a mutation is the weakening of a population, due to the accumulation of various forms of unwanted alleles. Stabilizing natural selection either removes deleterious mutations from a population or, conversely, preserves them. In the process of artificial selection, which is widely used in breeding dairy cattle, when screening sires for mutant alleles such as *CD18^G*, *SLC35A3^T* and *FANCI^{BY}* causing BLAD, CVM and BY, respectively, and as well as reducing the cheese suitability of milk (*CSN3^C*, *CSN3^E*) or milk quality (*CSN2^{A1}*, *CSN2^B*) in daughters, most often such sires are culled from the user part of the breeders. Often, they are used under strict control, due to their high prepotency, selecting female non-carriers of one or another mutation for mating. This scheme is implemented by a breeder when a bull-reproducing group of cows is created and there is a need to obtain bulls desirable for reproduction. It also happens, on the contrary, that mutations are preserved due to associations with certain economically important traits (milk yield, high fat-content in milk or high fertility), most often in a heterozygous state and due to the impossibility of their presence in a homozygote. Thus, the mutation in this case is a trail of an important economic or biological trait. At the same time, there are more cows than sires in herds, so they are a kind of biological reserve, i.e., hidden carriers of the above mutant alleles. Marzanova [18] reported that, when creating a bull-reproducing group at one breeder site, a genetic test of the selected cows was performed for carriers of unwanted mutations. Of the 34 selected cows, 17 turned out to be carriers of the *SLC35A3^T* allele causing CVM; they turned out to be the daughters of two bulls carrying this mutation. It was also noted that under environmental conditions, natural selection removes carriers of harmful mutations from the animal population, since they are weaker than healthy animals [18].

5.2. Immigration Genetic-Load

One more genetic-load type is immigration load when, due to the influx of genes from other populations or breeds, an improved breed is saturated with mutations, along with useful gene variants. The immigration load is created by the inclusion of alien alleles in a given gene pool, which in the new genotypic environment lead to lower fitness. Striking examples of this phenomenon are missense mutations (*CD18^G* and *SLC35A3^T*) and deletions (*FANCI^{BY}*) in the Holstein breed, which cause the respective hereditary disorders in representatives of the black-pied genealogical root. They were introduced into the

Holstein breed from the aforementioned three famous sires [4]. There is another type of mutation: a missense mutation or deletion, which simultaneously have a codominant type of inheritance. Here, it is also necessary to undertake the entire course of genetic sanitation proposed for the purification of breeding herds in dairy breeds from recessive mutations. These mutations include abnormal allele variants of the beta-casein locus belonging to the A1 family [111], and there are only five alleles of this type: $CSN2^{A1}$, $CSN2^B$, $CSN2^C$, $CSN2^F$, and $CSN2^G$. However, the most remarkable representatives of this family are the $CSN2^{A1}$ and $CSN2^B$ alleles, which are most often discovered in herds. When a population finds itself in an extreme situation, it reacts in its own way through a change in the allelotype, first in individual animals and then in the entire population or breed which are dependent on their outstanding representatives used by humans, i.e., there is a founder effect in this case [4,111].

5.3. Segregation Genetic-Load

Another type of genetic load is characteristic of populations that take advantage of heterozygotes. In this case, less-adapted homozygous individuals resulted from mating two heterozygotes are removed from a herd. By purposeful selection of heterozygous animals, researchers from the Veterinary Institute of Hannover (Germany) [17] obtained 50 homozygous calves for the BLAD syndrome [75,76]. Homozygous calves ($CD18^{G/G}$) with BLAD-syndrome fell ill in the first months after birth, and died within 2 months (50%) and 12 months (100%) of life. It was also reported that the frequency of the $CD18^G$ allele causing BLAD was as high as 24% in 2000, and the mutation rate of $SLC35A3^T$, the trigger of CVM, ranged from 9 to 16% between 2001 and 2007 in the German Holstein population [17]. The course of BLAD disease in calves was chronic. Animals significantly lagged behind in growth and development, lost weight, despite having a good appetite, and were very susceptible to various infections. Lichen was often observed in calves. At the same time, there were fever attacks, and constant disturbances in the gastrointestinal-tract functioning, as well as signs of the respiratory-tract inflammation. In most cases, the surface of the oral cavity was inflamed due to gingivitis, in calves. The treatment attempt was unsatisfactory, time consuming and ultimately unsuccessful. A similar case in relation to CVM was examined by Danish scientists [52]. They showed that in the homozygous form, a fetus for the mutant allele $SLC35A3^T$ was aborted or a stillborn calf was born; accordingly, the calving cow fell ill for a long time [52]. BY syndrome has long been confused with the course of CVM disease. With BY, we also deal only with a recessive homozygote ($FANCI^{BY/BY}$), as in the case of BLAD ($CD18^{G/G}$) and CVM ($SLC35A3^{T/T}$). However, the mutant allele in the homozygotes causes fetal death in the womb, abortion before day 40 or, rarely, stillbirth. Both of the latter pathological features are special characteristics in BY [19,50,52].

5.4. Substitutional Genetic-Load

This type is manifested when the old allele is replaced by a new one. It conforms to the driving form of natural selection and transitional polymorphism. A distinct example is the substitution of the $CSN2^{A2}$ allele for $CSN2^{A1}$ and $CSN2^{A1}$ for $CSN2^B$ at the beta-casein locus during the evolution of cattle domestication. It is believed that the emergence of mutant alleles of the A1 family is more associated with domestication processes and the creation of high-milk cattle breeds [112]. Table 2 presents the data obtained for the diagnosed genotypes and alleles at the beta-casein locus in four dairy-cattle breeds of the Russian Federation. A comparative analysis of these data demonstrated a difference in the occurrence of three genotypes and two alleles in representatives of dairy breeds. In particular, the heterozygous genotype ($CSN2^{A1/A2}$) was most often detected in the Black Pied, Holstein and Yaroslavl breeds, while the Bestuzhev breed was homozygous for the $CSN2^{A1}$ mutant allele. This breed also had a high incidence of the heterozygous genotype ($n = 24$). It was also found that the most common mutant $CSN2^{A1}$ allele occurred in the Bestuzhev breed (0.67), with a lower frequency in the Black Pied (0.56) and Yaroslavl (0.52) breeds. As can be seen from Table 2, the mutant allele was least detected in the Holstein

breed, although its frequency of occurrence was also high (0.42). Disturbance of the genetic equilibrium at the beta-casein locus was not found in any of the studied breeds of dairy cattle [3,113,114].

Table 2. Polymorphism of the beta-casein locus in four different Russian dairy-cattle breeds ($n = 177$) [3,113,114].

Breed	<i>n</i>	Gt	Genotype Frequency			Allele Frequency		χ^2	df	<i>p</i>
			CSN2 ^{A1/A1}	CSN2 ^{A1/A2}	CSN2 ^{A2/A2}	CSN2 ^{A1}	CSN2 ^{A2}			
Russian Black Pied	50	O	15	26	9	0.56	0.44	0.145	1	>0.05
		E	15.68	24.64	9.68					
Holstein Friesian	30	O	4	17	9	0.42	0.58	0.82	1	>0.05
		E	5.21	14.58	10.21					
Yaroslavl	30	O	9	13	8	0.52	0.48	0.53	1	>0.05
		E	8.0093	14.9833	7.0074					
Bestuzhev	67	O	35	24	8	0.67	0.33	0.98	1	>0.05
		E	39	21	7					

Abbreviations: *n*, number of animals examined; Gt, genotype; O, observed number of genotypes; E, expected number of genotypes; χ^2 , chi-squared test statistic; df, number of degrees of freedom; $p > 0.05$, genetic equilibrium in breeds is not disturbed.

It was also established that the formation of the allelotype in herds of cows for the CSN2^{A1} and CSN2^{A2} alleles was influenced by such factors as the genetic genealogy of a sire, the founder effect, and the drift of the mutant allele. Moreover, the drift of the mutant CSN2^{A1} allele, both within one country and between countries, was due to artificial selection [3,113,114]. The main reason for this phenomenon is strict selection and widespread use of a small number of elite bulls, artificial insemination of a large number of cows, and multiple ovulation and embryo transfer (MOET). The dispersion of the mutant CSN2^{A1} allele in Russia occurs through the purchase of breeding material (animals, semen, and embryos). The CSN2^{A1} allele was found to be common where carrier bulls were used. Cows can also be suppliers of the mutant allele, but to a lesser extent. They serve more as a reserve, being homozygotes (CSN2^{A1}/CSN2^{A1}) or heterozygotes (CSN2^{A1}/CSN2^{A2}) in herds. The mutant CSN2^{A1} allele is the codominant factor, and it should be noted that this is a new phenomenon in the diagnosis of abnormal alleles in cattle breeding. Previously identified mutant-alleles were found only as recessive factors [115,116].

6. Integrating Genomic Approaches to Improve Dairy Cattle

Over the last few decades, dairy-cattle breeding has been transformed by the implementation of genomic technologies [117]. High contributions from foreign sires (potentially with deleterious mutations) are almost always found in contemporary dairy-breeding programs. While lowering the projected returns from investment to increase the accuracy of genomic prediction in a home country, having a foreign supply of genetic material with a high rate of genetic advance significantly contributes to the advantages of domestic genetic-progress [118].

Genomic evaluations are recognized by producers as reliable predictors of a bull's ultimate daughter-based appraisal. The traditional evaluation approach has been improved by the incorporation of genomics and DNA-marker technology. This has resulted in a reduction in generation gaps, an improvement in selection accuracy, a drop in progeny-testing expenses, and the detection of recessive lethal and semi-lethal mutations [117]. Crossing between inbred lines significantly enhanced homozygosis, which contributed to the cumulative negative impacts of inbreeding, such as a loss in reproductive efficiency. Therefore, there is a higher risk of suboptimal outcomes from errors in the selection of candidates with high genetic-merit based only on low-heritability phenotypic features for empirical-conventional models of dairy-production systems. Due to the drastic drop in

genetic gains, this lengthens generational intervals and raises costs. The recent significant advancement in genomic prediction increases the precision in choosing the best candidates [119]. Progeny testing of the top young males has been crucial to breeding programs' success, since it allows researchers to correctly determine each individual's genetic values and, consequently, breeding potential. Gains in the accuracy of projecting breeding-values for young animals without their own performance have been made possible by the incorporation of extensive genomic information into statistical algorithms used to make selection decisions, known as genomic selection [120].

Genome-wide approaches and tools will play an increasing role in the creation of a dairy sector that is strong, long-lasting, sustainable, and that prioritizes animal welfare (meeting the basic needs regarding animal health and promoting positive welfare and environmental efficiency in animal production) and productive effectiveness [120,121]. Precision management on contemporary dairy farms is facilitated by genomic selection-derived outcomes, and emerging genome-editing technologies will open up new perspectives on the future of dairy-cattle breeding [119]. Genomic applications relevant to Russian dairy-cattle breeding have also been implemented, and include genomic selection [122,123], genomic evaluation of the breeding value [124,125], identification of selection signatures [126], and genome editing [127].

7. Concluding Remarks

The genetic load is considered as part of the inherited variation of a population, which determines the appearance of less-adapted individuals that undergo selective death as a result of natural selection. In the 20th century, the intensive use of the world's breed gene-pool and reproduction biotechnologies (artificial insemination, embryo transplantation, cloning) facilitated the significant increase in the genetic potential of animal milk production by obtaining highly productive offspring, i.e., true-breed leaders [128].

At the same time, commercial breed-stocks are increasingly showing signs of genetic erosion, i.e., the accumulation of a harmful recessive-mutation load. Hereby, the reproductive ability and fertility, the viability of newborns and young animals, and the duration of the economic use of animals decrease, which negatively affects the profitability of production [129–132]. However, recently, the situation has changed in the reverse direction: while using Holstein bulls to “upgrade” populations of black-pied cattle, recessive genes producing BLAD, CVM, and BY were introduced to their gene pool along with the transfer of advantageous traits [4,17,133].

Many of the detected mutations which represent a genetic-load characteristic only of Holsteins, probably arose recently and in this breed alone. This applies to mutations that cause the BLAD, CVM and BY syndromes. They have become widespread in a number of countries of the world, including Russia, where populations of Holstein cattle are intensively used in the reproduction of the offspring of single bulls [109,134,135]. This has stimulated a further genogeographic analysis of the spread of known mutations ($CD18^G$, $SLC35A3^T$ and $FANCI^{BY}$) in the Holstein breed of both black-pied and red-pied varieties [3,4,23,25,26].

Because of the intensive use of the global gene-pool, as well as artificial insemination, embryo transplantation and cloning, it has become feasible to significantly increase the genetic potential of animal productivity by obtaining offspring of sires that are leaders of their breed. On the other hand, due to the fact that populations are increasingly showing signs of genetic erosion [3,25,45,136], social maladaptation of an animal in the herd exists, and manifests itself in a violation of the interaction of the individual with the external environment. This is characterized by the inability of such an individual to exercise a positive role in specific microsocio-conditions corresponding to the animal's capabilities. In this case, it manifests itself in the animal in the form of a reduced live-weight, frequent illnesses, decreased reproductive-ability, fertility, viability of newborns and young animals, declined resistance, and lower duration of economic use of animals, which ultimately negatively affects the profitability of livestock production.

Currently, if the *CD18^G*, *SLC35A3^T* and *FANCI^{BY}* mutations are detected, it is most often in cows that serve as a kind of reserve, since they often represent a source of inheritance of various mutations. Therefore, when conducting a genetic and genealogical analysis, it is often impossible to determine how a given cow received a mutant allele. As the data of various studies and pedigrees of Holstein bulls or high-blooded Holsteinized carriers show, the analysis of the occurrence of mutant alleles *CD18^G*, *SLC35A3^T* and *FANCI^{BY}* in the world continues to be relevant for developing healthy livestock intended for producing high-quality dairy products. Modern genomic technologies, including genomic selection and gene editing, will be instrumental for further genetic-progress and animal welfare in the dairy-breeding and production sectors.

Author Contributions: Conceptualization, S.N.M., D.A.D., I.S.T. and N.S.M.; resources, I.S.T.; writing—original draft preparation, S.N.M., D.A.D., I.S.T. and N.S.M.; writing—review and editing, N.S.M., D.K.G. and M.N.R.; visualization, N.S.M. and M.N.R.; supervision, N.S.M.; project administration, N.S.M. All authors have read and agreed to the published version of the manuscript.

Funding: This review received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Haldane, J.B.S. The cost of natural selection. *J. Genet.* **1957**, *55*, 511–524. [[CrossRef](#)]
- Marzanov, N.S.; Devrishov, D.A.; Marzanova, S.N. Genetic Burden of Mutations in Cattle Breeds. In *Materials of the International Scientific and Practical Conference on Molecular Genetic Technologies for Analysis of Gene Expression Related to Animal Productivity and Disease Resistance, Moscow, Russia, 21–22 November 2019*; Kochish, I.I., Romanov, M.N., Surai, P.F., Nikonov, I.N., Selina, M.V., Eds.; Sel'skokhozyaistvennyye tekhnologii: Moscow, Russia, 2019; pp. 124–130. Available online: <https://elibrary.ru/item.asp?id=41444945> (accessed on 19 January 2022).
- Marzanov, N.S.; Devrishov, D.A.; Abylkasymov, D.A.; Marzanova, S.N.; Konovalova, N.V.; Libet, I.S.; Novikova, L.F.; Popov, A.N.; Turbina, I.S.; Marzanova, L.K. Occurrence of β -CN^{A2} and β -CN^{A1} Alleles at the Beta-casein Locus in Cattle. In *Increasing the Competitiveness of Animal Husbandry and Staffing Tasks, Proceedings of the 25th International Scientific and Practical Conference, Podolsk, Bykovo, Moscow Oblast, Russia, 24–25 June 2019*; Pyzhov, A.P., Zhukov, V.F., Ponomarev, N.V., Pyzhova, E.A., Eds.; Russian Academy of Livestock Management: Podolsk, Moscow Oblast, Russia, 2019; pp. 134–143. Available online: <https://elibrary.ru/item.asp?id=38589459> (accessed on 19 January 2022).
- Marzanova, S.N.; Nagorniy, V.A.; Devrishov, D.A.; Alekseev, Y.I.; Konovalova, N.V.; Tokhov, M.K.; Eskin, G.V.; Turbina, I.S.; Lukashina, A.A.; Marzanov, N.S. Founder effect and geneogeography of CV and BL mutations in Black and White cattle. *Russ. Agric. Sci.* **2016**, *42*, 90–93. [[CrossRef](#)]
- Marzanova, S.N.; Devrishov, D.A.; Alekseev, Y.I.; Konovalova, N.V.; Marzanov, N.S. Set of Sequence of Primers and Allele-specific Probes for Simultaneous Gene Diagnostics of Two Mutant Alleles Causing CVM and BLAD in Cattle. Proprietor: LLC “Agrovet”. Patent for Invention RU 2 577 990 C1. Federal Service for Intellectual Property, Moscow, Russia. Applied 11 February 2015. Published 20.03.2016b. Bull. No. 8. Available online: <https://patents.google.com/patent/RU2577990C1/en> (accessed on 19 January 2022).
- Marzanova, S.N.; Devrishov, D.A.; Alekseev, Y.I.; Konovalova, N.V.; Marzanov, N.S. Set of Primers Sequence and Allele-Specific Probes for Simultaneous Four Mutant Kappa-Casein Alleles Gene Diagnostics in Bovine Cattle. Proprietor: LLC “Agrovet”. Patent for Invention RU 2 646 140 C1. Federal Service for Intellectual Property, Moscow, Russia. Applied 24 March 2017. Published 01.03.2018a. Bull. No. 7. Available online: <https://patents.google.com/patent/RU2646140C1/en> (accessed on 19 January 2022).
- Marzanova, S.N.; Devrishov, D.A.; Alekseev, Y.I.; Konovalova, N.V.; Marzanov, N.S. Method for Genetic Diagnosis of Mutant Allele That Causes Short Spine Syndrome or Brachyspine Syndrome in Cattle and a Test System for Implementation Thereof. Proprietor: LLC “Agrovet”. Patent for Invention RU 2 664 454 C2. Federal Service for Intellectual Property, Moscow, Russia. Applied 4 April 2016. Published 17.08.2018b. Bull. No. 23. Available online: <https://patents.google.com/patent/RU2664454C2/en> (accessed on 19 January 2022).
- Marzanova, S.N.; Devrishov, D.A.; Alekseev, Y.I.; Konovalova, N.V.; Marzanov, N.S. Method for Simultaneous Genodiagnostic of Four Mutant Alleles of Kappa-Casein in Cattle and Test System for Implementation Thereof. Proprietor: LLC “Agrovet”. Patent for Invention RU 2 691 995 C2. Federal Service for Intellectual Property, Moscow, Russia. Applied 2 March 2017. Published 19.06.2019. Bull. No. 17. Available online: <https://patents.google.com/patent/RU2691995C2/en> (accessed on 19 January 2022).
- Lien, S.; Aleström, P.; Klungland, H.; Rogne, S. Detection of multiple β -casein (CASB) alleles by amplification created restriction sites (ACRS). *Anim. Genet.* **1992**, *23*, 333–338. [[CrossRef](#)] [[PubMed](#)]
- Dinç, H. Genotyping of Beta-casein, Kappa-casein and Beta-lactoglobulin Genes in Turkish Native Cattle Breeds and Efforts to Delineate BCM-7 on Human PBMC. Ph.D. Thesis, Graduate School of Natural and Applied Sciences, Middle East Technical University, Ankara, Turkey. Available online: <https://open.metu.edu.tr/handle/11511/18963> (accessed on 19 January 2022).

11. Bertorelle, G.; Raffini, F.; Bosse, M.; Bortoluzzi, C.; Iannucci, A.; Trucchi, E.; Morales, H.E.; van Oosterhout, C. Genetic load: Genomic estimates and applications in non-model animals. *Nat. Rev. Genet.* **2022**, *23*, 492–503. [[CrossRef](#)] [[PubMed](#)]
12. Altukhov, Y.P. *Genetic Processes in Populations*, 3rd ed.; Akademkniga: Moscow, Russia, 2003; ISBN 5-94628-083-X. Available online: <https://search.rsl.ru/en/search#q=ISBN%205-94628-083-X> (accessed on 19 January 2022).
13. Mutovin, G.R. *Clinical Genetics. Genomics and Proteomics of Hereditary Pathology: Textbook*, 3rd ed.; GEOTAR-Media: Moscow, Russia, 2010; ISBN 978-5-9704-1152-0. Available online: <https://search.rsl.ru/en/search#q=ISBN%20978-5-9704-1152-0> (accessed on 19 January 2022).
14. Farrell, H.M., Jr.; Jimenez-Flores, R.; Bleck, G.T.; Brown, E.M.; Butler, J.E.; Creamer, L.K.; Hicks, C.L.; Hollar, C.M.; Ng-Kwai-Hang, K.F.; Swaisgood, H.E. Nomenclature of the proteins of cows' milk—Sixth revision. *J. Dairy Sci.* **2004**, *87*, 1641–1674. [[CrossRef](#)] [[PubMed](#)]
15. Online Mendelian Inheritance in Animals—OMIA. Sydney School of Veterinary Science. Available online: <https://omia.org/> (accessed on 19 January 2022).
16. Zhigachev, A.I.; Ernst, L.K.; Bogachev, A.S. About accumulation of mutation weight in the cattle breeds as result of intensive reproduction technology and improvement on target determinants. *Sel'skokhozyaistvennaya Biol. (Agr. Biol.)* **2008**, *43*, 25–32. Available online: <https://www.elibrary.ru/item.asp?id=11709790> (accessed on 19 January 2022).
17. Schütz, E.; Scharfenstein, M.; Brenig, B. Implication of complex vertebral malformation and bovine leukocyte adhesion deficiency DNA-based testing on disease frequency in the Holstein population. *J. Dairy Sci.* **2008**, *91*, 4854–4859. [[CrossRef](#)]
18. Marzanova, S.N. Development of Gene Diagnostics of the Complex of Spinal Anomalies [CVM] and Immunodeficiency [BLAD] in Black-and-White Holstein Cattle. Ph.D. Thesis, K.I. Skryabin Moscow State Academy of Veterinary Medicine and Biotechnology, Moscow, Russia, 2012. Available online: <https://search.rsl.ru/ru/record/01005529649> (accessed on 19 January 2022).
19. Marzanova, S.N.; Devrishov, D.A.; Turbina, I.S.; Alekseev, Y.I.; Konovalova, N.V.; Marzanov, N.S. Genetic diagnostics of FANCI^{BY} mutation in representatives of the Holstein breed and its crosses. *Biotekhnologiya* **2021**, *37*, 16–25. [[CrossRef](#)]
20. Turbina, I.S. Characterization of Sires by Various Genetic Markers. Ph.D. Thesis, Russian Academy of Livestock Management, Moscow, Russia, 2006.
21. Marzanova, S.N.; Devrishov, D.A.; Turbina, I.S.; Marzanov, N.S. DNA Technology and estimation of drift of mutant alleles in populations of the Holstein breed and its crosses. *Russ. J. Genet.* **2022**, *58*, 876–879. [[CrossRef](#)]
22. Chun, H.C.; Yi, M.C.; Kuo, H.L. Genotype screening of bovine brachyspina in Taiwan Holstein cows. *Am. J. Anim. Vet. Sci.* **2020**, *15*, 206–210. [[CrossRef](#)]
23. Boichard, D.; Amigues, Y. Investigation on possible linkage between the BLAD gene and a QTL for production or type traits in Holstein cattle. In *Book of Abstracts, Proceedings of the 46th Annual Meeting of the European Association for Animal Production (EAAP), Prague, Czech Republic, 4–7 September 1995*; van Arendonk, J.A.M., Ed.; Wageningen Pers.: Wageningen, The Netherlands, 1995; p. 27. Available online: <https://hal.inrae.fr/hal-02772606> (accessed on 19 January 2022).
24. Casas, E.; Kehrl, M.E., Jr. A review of selected genes with known effects on performance and health of cattle. *Front. Vet. Sci.* **2016**, *3*, 113. [[CrossRef](#)] [[PubMed](#)]
25. Eshpishko, O.A.; Pestis, B.K.; Tanana, L.A.; Kuzmina, T.I.; Cheburanova, E.S.; Shevchenko, M.Y.; Petrova, A.P.; Glinskaya, H.A.; Trahimchik, R.V. Definition of recessive mutations of BLAD, CVM and BS in population of cattle of the lactic direction of Republic of Belarus. In *Agriculture—Problems and Prospects: Collection of Scientific Papers—Zootekhnika*; Pestis, V.K., Ed.; Grodno State Agrarian University: Grodno, Belarus, 2017; Volume 37, pp. 44–51. Available online: <https://www.elibrary.ru/item.asp?id=32443408> (accessed on 19 January 2022) ISBN 978-985-537-108-4.
26. Ivanov, V.A.; Marzanov, N.S.; Eliseeva, L.I.; Tadzhiyev, K.P.; Marzanova, S.N. Genotypes of cattle breeds and quality of milk. *Problemy Biologii Produktivnykh Zhivotnykh (Probl. Product. Anim. Biol.)* **2017**, *3*, 48–65. Available online: <https://www.elibrary.ru/item.asp?id=30058078> (accessed on 19 January 2022).
27. Ignatiev, V.M. Screening of the Leukocyte Adhesion Gene (BLAD-Syndrome) in Black-and-White Bovine Animals. Ph.D. Thesis, All-Russia Research Institute for Animal Husbandry, Dubrovitsy, Moscow Oblast, Russia, 1998. Available online: <https://elibrary.ru/item.asp?id=19145898> (accessed on 19 January 2022).
28. Hagemoser, W.A.; Roth, J.A.; Lofstedt, J.; Fagerland, J.A. Granulocytopenia in a Holstein heifer. *J. Am. Vet. Med. Assoc.* **1983**, *183*, 1093–1094. Available online: <https://pubmed.ncbi.nlm.nih.gov/6643217/> (accessed on 19 January 2022). [[PubMed](#)]
29. Kehrl, M.E., Jr.; Schmalstieg, F.C.; Anderson, D.C.; Van der Maaten, M.J.; Hughes, B.J.; Ackermann, M.R.; Wilhelmson, C.L.; Brown, G.B.; Stevens, M.G.; Whetstone, C.A. Molecular definition of the bovine granulocytopenia syndrome: Identification of deficiency of the Mac-1 (CD11b/CD18) glycoprotein. *Am. J. Vet. Res.* **1990**, *51*, 1826–1836. Available online: <https://pubmed.ncbi.nlm.nih.gov/1978618/> (accessed on 19 January 2022). [[PubMed](#)]
30. Kehrl, M.E., Jr.; Shuster, D.E.; Ackermann, M.R. Leukocyte adhesion deficiency among Holstein cattle. *Cornell Vet.* **1992**, *82*, 103–109. Available online: <https://pubmed.ncbi.nlm.nih.gov/1623723/> (accessed on 19 January 2022).
31. Ackermann, M.R.; Kehrl, M.E., Jr.; Morfitt, D.C. Ventral dermatitis and vasculitis in a calf with bovine leukocyte adhesion deficiency. *J. Am. Vet. Med. Assoc.* **1993**, *202*, 413–415. Available online: <https://pubmed.ncbi.nlm.nih.gov/8440633/> (accessed on 19 January 2022).
32. Gilbert, R.O.; Rebhun, W.C.; Kim, C.A.; Kehrl, M.E., Jr.; Shuster, D.E.; Ackermann, M.R. Clinical manifestations of leukocyte adhesion deficiency in cattle: 14 cases (1977–1991). *J. Am. Vet. Med. Assoc.* **1993**, *202*, 445–449. Available online: <https://pubmed.ncbi.nlm.nih.gov/8095042/> (accessed on 19 January 2022).

33. Duncan, R.B., Jr.; Carrig, C.B.; Agerholm, J.S.; Bendixen, C. Complex vertebral malformation in a Holstein calf: Report of a case in the USA. *J. Vet. Diagn. Investig.* **2001**, *13*, 333–336. [CrossRef]
34. VanRaden, P.M.; Olson, K.M.; Null, D.J.; Hutchison, J.L. Harmful recessive effects on fertility detected by absence of homozygous haplotypes. *J. Dairy Sci.* **2011**, *94*, 6153–6161. [CrossRef]
35. Holstein Association USA, Inc. Brattleboro, VT, USA. Available online: <https://www.holsteinusa.com/> (accessed on 19 January 2022).
36. Select Sires Inc. Plain City, OH, USA. Available online: <https://www.selectsires.com/> (accessed on 19 January 2022).
37. Anon. VDS-Beschluß zu BLAD. *Ostfr. Landvolk.* **1992**, *107*, 28.
38. Agerholm, J.S.; DeLay, J.; Hicks, B.; Fredholm, M. First confirmed case of the bovine brachyspina syndrome in Canada. *Can. Vet. J.* **2010**, *51*, 1349–1350. Available online: <https://pubmed.ncbi.nlm.nih.gov/21358926/> (accessed on 19 January 2022).
39. Poli, M.A.; Dewey, R.; Semorile, L.; Lozano, M.E.; Albariño, C.G.; Romanowski, V.; Grau, O. PCR screening for carriers of bovine leukocyte adhesion deficiency (BLAD) and uridine monophosphate synthase (DUMPS) in Argentine Holstein cattle. *J. Vet. Med. Ser. A* **1996**, *43*, 163–168. [CrossRef] [PubMed]
40. Ribeiro, L.A.; Baron, E.E.; Martinez, M.L.; Coutinho, L.L. PCR screening and allele frequency estimation of bovine leukocyte adhesion deficiency in Holstein and Gir cattle in Brazil. *Genet. Mol. Biol.* **2000**, *23*, 831–834. [CrossRef]
41. Schilcher, F.; Hotter, H.; Tammen, I.; Schuh, M. Occurrence of bovine leukocyte adhesion deficiency (BLAD) of Holstein Friesian in Austria. *Wien. Tierarztl. Monatsschr.* **1995**, *82*, 207–212. Available online: <http://a.xueshu.baidu.com/usercenter/paper/show?paperid=52ca18b04dbff9c033612a462f966bfd> (accessed on 19 January 2022).
42. Cox, E.; Kuczka, A.; Tammen, I.; Schwenger, B. Leukocyten adhesien deficientie bij rund en hond: Een erfelijke stoornis van het immuunstelsel. *Vlaams Diergeneesk. Tijdschr.* **1993**, *62*, 71–79. Available online: <https://library.wur.nl/WebQuery/titel/830081> (accessed on 19 January 2022).
43. Georges, M.; Coppieters, W.; Charlier, C.; Agerholm, J.S.; Fredholm, M. A Genetic Marker Test for Brachyspina and Fertility in Cattle. Patent for Invention EP2310528B1. International Patent Publ. No. WO2010/012690, 20 November 2013. Available online: <https://patents.google.com/patent/EP2310528B1/en> (accessed on 19 January 2022).
44. Andrews, A.H.; Fishwick, J.; Waters, R.J. Bovine leukocyte adhesion deficiency (BLAD) in a one year old Holstein Friesian bull—The first report in the United Kingdom. *Br. Vet. J.* **1996**, *152*, 347–351. [CrossRef]
45. Zsolnai, A.; Fésüs, L. Simultaneous analysis of bovine κ -casein and BLAD alleles by multiplex PCR followed by parallel digestion with two restriction enzymes. *Anim. Genet.* **1996**, *27*, 207–209. [CrossRef]
46. Fésüs, L.; Zsolnai, A.; Anton, I.; Bárány, I.; Bozós, S. BLAD genotypes and cow production traits in Hungarian Holsteins. *J. Anim. Breed. Genet.* **1999**, *116*, 169–174. [CrossRef]
47. Agerholm, J.S.; Houe, H.; Jørgensen, C.B.; Basse, A. Bovine leukocyte adhesion deficiency in Danish Holstein-Friesian cattle. II. Patho-anatomical description of affected calves. *Acta Vet. Scand.* **1993**, *34*, 237–243. [CrossRef]
48. Agerholm, J.S.; Basse, A.; Christensen, K. Investigations on the occurrence of hereditary diseases in the Danish cattle population 1989–1991. *Acta Vet. Scand.* **1993**, *34*, 245–253. [CrossRef]
49. Jørgensen, C.B.; Agerholm, J.S.; Pedersen, J.; Thomsen, P.D. Bovine leukocyte adhesion deficiency in Danish Holstein-Friesian cattle. I. PCR screening and allele frequency estimation. *Acta Vet. Scand.* **1993**, *34*, 231–236. [CrossRef]
50. Agerholm, J.S.; Bendixen, C.; Andersen, O.; Arnbjerg, J. Complex vertebral malformation in Holstein calves. *J. Vet. Diagn. Investig.* **2001**, *13*, 283–289. [CrossRef]
51. Agerholm, J.S.; Andersen, O.; Almskou, M.B.; Bendixen, C.; Arnbjerg, J.; Aamand, G.P.; Nielsen, U.S.; Panitz, F.; Petersen, A.H. Evaluation of the inheritance of the complex vertebral malformation syndrome by breeding studies. *Acta Vet. Scand.* **2004**, *45*, 133–137. [CrossRef]
52. Agerholm, J.S.; McEvoy, F.; Arnbjerg, J. Brachyspina syndrome in a Holstein calf. *J. Vet. Diagn. Investig.* **2006**, *18*, 418–422. [CrossRef] [PubMed]
53. Agerholm, J.S.; Peperkamp, K. Familial occurrence of Danish and Dutch cases of the bovine brachyspina syndrome. *BMC Vet. Res.* **2007**, *3*, 8. [CrossRef] [PubMed]
54. Charlier, C.; Agerholm, J.S.; Coppieters, W.; Karlskov-Mortensen, P.; Li, W.; de Jong, G.; Fasquelle, C.; Karim, L.; Cirera, S.; Cambisano, N.; et al. A deletion in the bovine FANCI gene compromises fertility by causing fetal death and brachyspina. *PLoS ONE* **2012**, *7*, e43085. [CrossRef] [PubMed]
55. Stöber, M.; Pohlenz, J.; Leibold, W.; Simon, D.; Kuczka, A.; Schwenger, B.; Kuhlmann, E.; Tammen, L.; Piturru, P. Deficienza di adesione dei leucociti nei bovini (BLAD) un difetto ereditario da porre sotto vigilanza. *Prax. Vet.* **1992**, *8*, 5–7.
56. Testoni, S.; Diana, A.; Olzi, E.; Gentile, A. Brachyspina syndrome in two Holstein calves. *Vet. J.* **2008**, *177*, 144–146. [CrossRef]
57. Viana, J.L.; Fernández, A.; Iglesias, A.; Pernas, G.S. Diagnóstico y control de las principales enfermedades genéticas (citrulinemia, DUMPS y BLAD) descritas en ganado Holstein-Frisón. *Med. Vet.* **1998**, *15*, 538–544. Available online: <https://dialnet.unirioja.es/servlet/articulo?codigo=4410498> (accessed on 19 January 2022).
58. Adamov, N.; Mitrov, D.; Esmerov, I.; Dovc, P. Detection of recessive mutations (BLAD and CVM) in Holstein-Friesian cattle population in Republic of Macedonia. *Maced. Vet. Rev.* **2014**, *37*, 61–68. [CrossRef]
59. Müller, K.; Bernadina, W.E.; Kalsbeek, H.C.; Wensing, T.; Elving, L.; Verbeek, B.; Wentink, G.H. BLAD: Bovine leukocyte adhesion deficiency. *Tijdschr. Diergeneesk.* **1993**, *118*, 183–184. Available online: <https://pubmed.ncbi.nlm.nih.gov/8096659/> (accessed on 19 January 2022).

60. Mirck, M.H.; Von Bannisseht-Wijsmuller, T.; Timmermans-Besselink, W.J.; Van Luijk, J.H.; Buntjer, J.B.; Lenstra, J.A. Optimization of the PCR test for the mutation causing bovine leukocyte adhesion deficiency. *Cell. Mol. Biol.* **1995**, *41*, 695–698. Available online: <https://pubmed.ncbi.nlm.nih.gov/7580848/> (accessed on 19 January 2022). [PubMed]
61. Arrayat, J.L.; Oberbauer, A.M.; Famula, T.R.; Garnett, I.; Oltjen, J.W.; Imhoof, J.; Kehrl, M.E., Jr.; Graham, T.W. Growth of Holstein calves from birth to 90 days: The influence of dietary zinc and BLAD status. *J. Anim. Sci.* **2002**, *80*, 545–552. [CrossRef] [PubMed]
62. Lubieniecki, K.; Grzybowski, G. Diagnostyka molekularna wrodzonego niedoboru leukocytarnych czasteczek adhezyjnych [BLAD] u bydla. *Med. Weter.* **1997**, *53*, 214–217. Available online: <http://agro.icm.edu.pl/agro/element/bwmeta1.element.agro-article-b700eed0-54f0-4e01-9630-f8a5be251758> (accessed on 19 January 2022).
63. Ruś, A.; Kamiński, S. Prevalence of complex vertebral malformation carriers among Polish Holstein-Friesian bulls. *J. Appl. Genet.* **2007**, *48*, 247–252. [CrossRef] [PubMed]
64. Ruś, A.; Kamiński, S. Detection of Brachyspina carriers within Polish Holstein-Friesian bulls. *Pol. J. Vet. Sci.* **2015**, *18*, 453–454. [CrossRef]
65. Marzanov, N.S.; Popov, A.N.; Zinovieva, N.A.; Polezhaeva, V.A.; Ignatiev, V.M.; Brem, G. Screening of the BLAD syndrome gene in Black-and-white root animals. *Vestnik Rossiyskoy Akademii Sel'skokhozyaystvennykh Nauk (Her. Russ. Acad. Sci.)* **1997**, *4*, 59–61. Available online: <https://elibrary.ru/item.asp?id=21635211> (accessed on 19 January 2022).
66. Marzanov, N.S.; Eskin, G.V.; Turbina, I.S.; Devrshov, D.A.; Tokhov, M.K.; Marzanova, S.N. *Gene Diagnostics and Distribution of the Immunodeficiency Allele, or BLAD Syndrome, in Black-and-White Cattle*; Rosinformagrotech: Moscow, Russia, 2013. Available online: <https://elibrary.ru/item.asp?id=21055161> (accessed on 19 January 2022).
67. Kalashnikova, L.A.; Dunin, I.M.; Glazko, V.I.; Glazko, G.V.; Ryzhova, N.V.; Golubina, E.P. *DNA Technologies in the Evaluation of Farm Animals*; All-Russian Research Institute of Animal Breeding: Lesnye Polyany, Moscow Oblast, Russia, 1999. Available online: <https://www.elibrary.ru/item.asp?id=25478053> (accessed on 19 January 2022).
68. Turbina, I.S.; Fedorova, E.V.; Kertieva, N.M.; Yeskin, G.V.; Turbina, G.S.; Marzanov, N.S. Genealogy and some biological features in BLAD carrier and non-carrier bulls. In *Selektsiya, kormleniye, sodержaniye sel'skokhozyaystvennykh zhivotnykh i tekhnologiya proizvodstva produktov zhivotnovodstva: Trudy VNIIPlem (Breeding, Feeding, Keeping Farm Animals and Technology for the Production of Livestock Products: Proceedings of VNIIPlem)*; All-Russian Research Institute of Animal Breeding: Lesnye Polyany, Moscow Oblast, Russia, 2004; pp. 3–7.
69. Kalashnikova, L.A.; Khabibrakhmanova, Y.A.; Prozherin, V.P.; Yaluga, V.L. Genotyping of brachyspina anomaly in Holsteinized cattle of the Kholmogory breed. In *Molecular Diagnostics 2021—Section 21: Technologies for the Detection of Infectious and Hereditary Animal Diseases, Proceedings of the 10th Anniversary International Scientific and Practical Conference, Moscow, Russia, 9–11 November 2021*; Center for Strategic Planning and Management of Biomedical Health Risks: Moscow, Russia, 2021; Volume 2, pp. 186–188.
70. Vătăşescu-Balcan, R.A.; Manea, M.A.; Georgescu, S.E.; Dinischiotu, A.; Tesio, C.D.; Costache, M. Evidence of single point mutation inducing BLAD disease in Romanian Holstein-derived cattle breed. *Biotechnol. Anim. Husb.* **2007**, *23*, 375–381. [CrossRef]
71. Grobet, L.; Charlier, C.; Hanset, R. Diagnosis of bovine leukocyte adhesion deficiency (BLAD) at the DNA level. *Ann. Med. Vet.* **1993**, *137*, 27–31. Available online: <https://agris.fao.org/agris-search/search.do?recordID=BE9300687> (accessed on 19 January 2022).
72. Eggen, A.; Duchesne, A.; Laurent, P.; Grohs, C.; Denis, C.; Gautier, M.; Boichard, D.; Ducos, A. Controlling genetic disorders in the French dairy cattle population. In *Proceedings of the 29th International Conference on Animal Genetics, Tokyo, Japan, 11–16 September 2004*; International Society for Animal Genetics (ISAG), INT: Tokyo, Japan, 2004; p. 35. Available online: https://hal.inrae.fr/hal-02762175/file/ISAG_Proceedings_2004_1.pdf (accessed on 19 January 2022).
73. Valour, D.; Michot, P.; Eozenou, C.; Lefebvre, R.; Bonnet, A.; Capitan, A.; Uzbekova, S.; Sellem, E.; Ponsart, C.; Schibler, L. Dairy cattle reproduction is a tightly regulated genetic process: Highlights on genes, pathways, and biological processes. *Anim. Front.* **2015**, *5*, 32–41. [CrossRef]
74. Anon. Erbfehler—Was ist Blad? *Hann. Land. Forstwirtschaft. Ztg.* **1991**, *11*, 91.
75. Kuczka, A.; Schwenger, B. BLAD im Griff [The right feeling for BLAD [bovine leukocyte adhesion deficiency]]. *Tierzüchter* **1993**, *45*, 32–35. Available online: <https://agris.fao.org/agris-search/search.do?recordID=DE19930058362> (accessed on 19 January 2022).
76. Lienau, A.; Stöber, M.; Kehrl, M.E.; Tammen, I.; Schwenger, B.; Kuczka, A.; Pohlenz, J. Bovine Leukozyten-Adhäsions-Defizienz: Klinisches Bild und Differential-Diagnostik (Bovine leukocyte adhesion deficiency: Clinical picture and differential diagnosis). *Dtsch. Tierärztl. Wochenschr.* **1994**, *101*, 405–406. Available online: <https://pubmed.ncbi.nlm.nih.gov/7851303/> (accessed on 19 January 2022).
77. Tammen, I. Weiterentwicklung des DNA-Tests auf BLAD (Bovine Leukozyten-Adhäsions-Defizienz) für den Einsatz in Rinderzucht und Klinischer Diagnostik. Ph.D. Thesis, Tierärztliche Hochschule Hannover, Hannover, Germany, 1994. Available online: <https://agris.fao.org/agris-search/search.do?recordID=US201300291400> (accessed on 19 January 2022).
78. Duesmann, K.; Schmidt, W.; Görlach, A. Die PCR als Methode zur Gendiagnostik im Routinebetrieb einer Besamungsstation am Beispiel der Bovinen Leukozyten-Adhäsions-Defizienz (BLAD). *Reprod. Domest. Anim.* **1994**, *29*, 193.
79. Engelhardt, I. Inzucht, Bedeutende Ahnen und Wahrscheinlichkeit für BLAD-Merkmalsträger in der Deutschen Schwarzbuntzucht. Ph.D. Thesis, Tierärztliche Hochschule Hannover, Hannover, Germany, 1996. Available online: <https://agris.fao.org/agris-search/search.do?recordID=US201300016803> (accessed on 19 January 2022).

80. Distl, O.T. The use of molecular genetics in eliminating of inherited anomalies in cattle. *Arch. Anim. Breed.* **2005**, *48*, 209–218. [CrossRef]
81. Buck, B.C.; Ulrich, R.; Wöhlke, A.; Kuiper, H.; Baumgaertner, W.; Distl, O. Missbildungen an der Wirbelsäule mit multiplen Organanomalien bei einem Kalb der Rasse Deutsche Holsteins (Vertebral and multiple organ malformations in a black and white German Holstein calf). *Berl. Munch. Tierarztl. Wochenschr.* **2010**, *123*, 251–255. [CrossRef] [PubMed]
82. Segelke, D.; Täubert, H.; Reinhardt, F.; Thaller, G. Considering genetic characteristics in German Holstein breeding programs. *J. Dairy Sci.* **2016**, *99*, 458–467. [CrossRef]
83. Glazko, V.I.; Lavrovsky, V.V.; Filenko, A.N.; Mariutsa, A.E. Intra-breed genetic differentiation and the presence of the BLAD mutation in Holstein. *Sel'skokhozyaistvennaya Biol. (Agr. Biol.)* **2000**, *4*, 45–47. Available online: <https://scholar.google.com/scholar?cluster=663656290483334721&hl=en&oi=scholar> (accessed on 19 January 2022).
84. Mariutsa, A.E. Population-Genetic Mechanisms of Adaptation and Spread of Semi-Lethal Recessive Mutations on the Example of BLAD in Cattle. Ph.D. Thesis, Institute of Agroecology and Environmental Management UAAS, Kyiv, Ukraine, 2005. Available online: <http://www.disslib.org/populjatsyonno-henetycheskye-mekhanizmy-adaptatsyy-y-rasprostraneny-poluletnykh.html> (accessed on 19 January 2022).
85. Birukova, O.D. The Population-Genetic Monitoring of Gene Pool Forming of the Ukrainian Black-and-White Dairy Breed. Ph.D. Thesis, Institute of Animal Breeding and Genetics UAAS, Chubinske, Kyiv Region, Ukraine, 2005. Available online: http://www.irbis-nbuv.gov.ua/cgi-bin/irbis_nbuv/cgiirbis_64.exe?C21COM=2&I21DBN=ARD&P21DBN=ARD&Z21ID=&Image_file_name=DOC/2005/05bodrmr.zip&IMAGE_FILE_DOWNLOAD=1 (accessed on 19 January 2022).
86. Meylan, M.; Abegg, R.; Sager, H.; Jungi, T.W.; Martig, J. Fallvorstellung: Bovine Leukozyten-Adhäsions-Defizienz (BLAD) in der Schweiz (Case presentation: Bovine leukocyte adhesion deficiency (BLAD) in Switzerland). *Schweiz. Arch. Tierheilkd.* **1997**, *139*, 277–281. Available online: <https://pubmed.ncbi.nlm.nih.gov/9411734/> (accessed on 19 January 2022). [PubMed]
87. Citek, J.; Rehout, V.; Hajkova, J.; Pavkova, J. Monitoring of the genetic health of cattle in the Czech Republic. *Vet. Med.* **2006**, *51*, 333–339. [CrossRef]
88. Li, Y.; Han, G.; Zhang, S.; Li, N.; Sun, F. Detection of bovine leukocyte adhesion deficiency (BLAD) and haplotype analysis. *Acta Vet. Zootech. Sin.* **2008**, *39*, 1285–1288. Available online: <http://www.xmsyxb.com/CN/Y2008/V39/19/1285> (accessed on 19 January 2022).
89. Chu, Q.; Sun, D.; Yu, Y.; Zhang, Y.; Zhang, Y. Identification of complex vertebral malformation carriers in Chinese Holstein. *J. Vet. Diagn. Investig.* **2008**, *20*, 228–230. [CrossRef] [PubMed]
90. Zhang, Y.; Fan, X.; Sun, D.; Wang, Y.; Yu, Y.; Xie, Y.; Zhang, S.; Zhang, Y. A novel method for rapid and reliable detection of complex vertebral malformation and bovine leukocyte adhesion deficiency in Holstein cattle. *J. Anim. Sci. Biotechnol.* **2012**, *3*, 24. [CrossRef] [PubMed]
91. Fang, L.; Li, Y.; Zhang, Y.; Sun, D.; Liu, L.; Zhang, Y.; Zhang, S. Identification of brachyspina syndrome carriers in Chinese Holstein cattle. *J. Vet. Diagn. Investig.* **2013**, *25*, 508–510. [CrossRef] [PubMed]
92. Li, Y.; Zhai, L.; Fang, L.; Zhang, S.; Liu, L.; Zhu, Y.; Xue, J.; Xiaoqing, L.; Qiao, L.; Sun, D. A novel multiplex polymerase chain reaction method for the identification of brachyspina syndrome carriers in Chinese Holstein cattle. *J. Vet. Sci. Med. Diagn.* **2016**, *5*. [CrossRef]
93. Takahashi, K.; Miyagawa, K.; Abe, S.; Kurosawa, T.; Sonoda, M.; Nakade, T.; Nagahata, H.; Noda, H.; Chihaya, Y.; Isogai, E. Bovine granulocytopenia syndrome of Holstein-Friesian calves and heifers. *Nihon Juigaku Zasshi* **1987**, *49*, 733–736. [CrossRef] [PubMed]
94. Tajima, M.; Irie, M.; Kirisawa, R.; Hagiwara, K.; Kurosawa, T.; Takahashi, K. The detection of a mutation of CD18 gene in bovine leukocyte adhesion deficiency (BLAD). *J. Vet. Med. Sci.* **1993**, *55*, 145–146. [CrossRef] [PubMed]
95. Nagahata, H.; Miura, T.; Tagaki, K.; Ohtake, M.; Noda, H.; Yasuda, T.; Nioka, K. Prevalence and allele frequency estimation of bovine leukocyte adhesion deficiency (BLAD) in Holstein-Friesian cattle in Japan. *J. Vet. Med. Sci.* **1997**, *59*, 233–238. [CrossRef] [PubMed]
96. Nagahata, H. Bovine leukocyte adhesion deficiency (BLAD): A review. *J. Vet. Med. Sci.* **2004**, *66*, 1475–1482. [CrossRef]
97. Healy, P.J. Bovine leukocyte adhesion deficiency (BLAD)—Another genetic defect of Holstein/Friesians. *Aust. Vet. J.* **1992**, *69*, 190. [CrossRef]
98. Norouzy, A.; Nassiry, M.R.; Eftekhari Shahrody, F.; Javadmanesh, A.; Mohammad Abadi, M.R.; Sulimova, G.E. Identification of bovine leukocyte adhesion deficiency (BLAD) carriers in Holstein and Brown Swiss AI bulls in Iran. *Russ. J. Genet.* **2005**, *41*, 1409–1413. [CrossRef]
99. Rezaee, A.R.; Nassiry, M.R.; Valizadeh, R.; Tahmoospour, M.; Javadmanesh, A.; Zarei, A.; Janati, H. Study of complex vertebral malformation disorder in Iranian Holstein bulls. *World J. Zool.* **2008**, *3*, 36–39. Available online: <https://profdoc.um.ac.ir/paper-abstract-1014702.html> (accessed on 19 January 2022).
100. Hemati, B.; Saberi, J.; Noshary, A.R. The study of complex vertebral malformation genetic defect in a population of Sistani cows. *J. Plant Anim. Environ. Sci.* **2014**, *4*, 485–487. Available online: <https://www.cabdirect.org/cabdirect/abstract/20143288422> (accessed on 19 January 2022).
101. Öner, Y.; Keskin, A.; Elmaci, C. Identification of BLAD, DUMPS, citrullinaemia and factor XI deficiency in Holstein cattle in Turkey. *Asian J. Anim. Vet. Adv.* **2010**, *5*, 60–65. [CrossRef]

102. Patel, R.K.; Singh, K.M.; Soni, K.J.; Chauhan, J.B.; Sambasiva Rao, K.R. Low incidence of bovine leukocyte adhesion deficiency (BLAD) carriers in Indian cattle and buffalo breeds. *J. Appl. Genet.* **2007**, *48*, 153–155. [CrossRef]
103. Gholap, P.N.; Kale, D.S.; Sirothia, A.R. Genetic diseases in cattle: A review. *Res. J. Anim. Vet. Fish. Sci.* **2014**, *2*, 24–33. Available online: <http://www.isca.in/AVFS/Archive/v2/i2/5.ISCA-RJAVFS-2014-005.php> (accessed on 19 January 2022).
104. Nasreen, F.; Altaf Malik, N.; Naeem Riaz, M.; Anver Qureshi, J. Detection and screening of bovine leukocyte adhesion deficiency in Pakistan using molecular methods. *Hereditas* **2009**, *146*, 74–78. [CrossRef]
105. Stadler, P.; Van Amstel, S.R.; Van Rensburg, I.B.; Williams, M.C. Verdagte oorerflike granulosisopatie in vier Holstein frieskalwers (Suspected inherited granulocytopenia in four Holstein Friesian calves). *J. S. Afr. Vet. Assoc.* **1993**, *64*, 172–177. Available online: <https://pubmed.ncbi.nlm.nih.gov/8176699/> (accessed on 19 January 2022).
106. FAO. Gateway to Dairy Production and Products. Available online: <https://www.fao.org/dairy-production-products/en/> (accessed on 19 January 2022).
107. Kosyachenko, N.M.; Abramova, M.V.; Ilyina, A.V.; Zyryanova, S.V.; Konovalov, A.V.; Kosourova, T.N. *Holstein Breed in the Creation of Improved Genotypes and Intra-breed Types of Cattle*; Kantsler: Yaroslavl, Russia, 2020; ISBN 978-5-907417-06-9. Available online: <https://search.rsl.ru/ru/search?q=ISBN%20978-5-907417-06-9> (accessed on 19 January 2022).
108. Cole, J.B.; Null, D.J.; VanRaden, P.M. Phenotypic and genetic effects of recessive haplotypes on yield, longevity, and fertility. *J. Dairy Sci.* **2016**, *99*, 7274–7288. [CrossRef]
109. Marzanov, N.S.; Turbina, I.S.; Eskin, G.V.; Turbina, G.S.; Ignat'ev, V.M.; Popov, A.N.; Harlizius, B. Screening of the gene of the leukocytal adhesion deficiency in Black-and-white Holsteinized cattle. *Sel'skokhozyaistvennaya Biol. (Agr. Biol.)* **2003**, *38*, 23–30. Available online: <https://www.elibrary.ru/item.asp?id=18100805> (accessed on 19 January 2022).
110. Grant, V. *The Evolutionary Process: A Critical Study of Evolutionary Theory*; Columbia University Press: New York, NY, USA, 1991; ISBN 0-231-07324-0. Available online: https://www.google.com/books/edition/The_Evolutionary_Process/qAt_QgAACAAJ?hl=en (accessed on 19 January 2022).
111. Kaminski, S.; Cieslinska, A.; Kostyr, E. Polymorphism of bovine beta-casein and its potential effect on human health. *J. Appl. Genet.* **2007**, *48*, 189–198. [CrossRef]
112. Woodford, K.B. *Devil in the Milk: Illness, Health and Politics of A1 and A2 Milk*; Chelsea Green Publishing: White River Junction, VT, USA, 2009; ISBN 978-1-60358-102-8. Available online: https://www.google.com/books/edition/_/QqD6btySu7AC?hl=en (accessed on 19 January 2022).
113. Marzanov, N.S.; Devrishov, D.A.; Abylkasymov, D.A.; Marzanova, S.N.; Konovalova, N.V.; Libet, I.S. Characteristics of Russian dairy cattle by the occurrence of genotypes and alleles in the beta casein locus. *Veterinariya Zootekhniya i Biotechnologiya (Vet. Med. Zootech. Biotechnol.)*, 2020; *1*, 47–52. [CrossRef]
114. Marzanov, N.S.; Abylkasymov, D.A.; Devrishov, D.A.; Marzanova, S.N.; Libet, I.S. The characteristic of allelotype in cows of Black and multicolored breed of β - and k-casein locus and qualitative indicators of milk. In *Aktual'nyye Voprosy Molochnoy Promyshlennosti, Mezhotraslevyye Tekhnologii i Sistemy Upravleniya Kachestvom (Actual Issues of the Dairy Industry, Intersectoral Technologies and Quality Management Systems)*; All-Russian Dairy Research Institute: Moscow, Russia, 2020; pp. 368–376. [CrossRef]
115. Marzanova, S.N.; Alekseev, Y.I.; Konovalova, N.V.; Turbina, I.S.; Devrishov, D.A.; Sochivko, D.G.; Marzanov, N.S. Developing a method of diagnostics of complex vertebral malformation (CVM) by Real-Time PCR method in Black-and-white cattle. *Problemy Biologii Produktivnykh Zhivotnykh (Probl. Product. Anim. Biol.)* **2011**, *79*–82. Available online: <https://elibrary.ru/item.asp?id=17644709> (accessed on 19 January 2022).
116. Marzanov, N.S.; Devrishov, D.A.; Marzanova, S.N.; Getokov, O.O.; Abylkasymov, D.A.; Libet, I.S. DNA diagnostics of populations of the Black-and-white breed by the beta-casein locus. *Veterinariya Zootekhniya i Biotechnologiya (Vet. Med. Zootech. Biotechnol.)* **2021**, *3*, 78–84. [CrossRef]
117. Wiggins, G.R.; Cole, J.B.; Hubbard, S.M.; Sonstegard, T.S. Genomic Selection in Dairy Cattle: The USDA Experience. *Annu. Rev. Anim. Biosci.* **2017**, *5*, 309–327. [CrossRef]
118. Matthews, D.; Kearney, J.F.; Cromie, A.R.; Hely, F.S.; Amer, P.R. Genetic benefits of genomic selection breeding programmes considering foreign sire contributions. *Genet. Sel. Evol.* **2019**, *51*, 40. [CrossRef]
119. Gutierrez-Reinoso, M.A.; Aponte, P.M.; Garcia-Herreros, M. Genomic Analysis, Progress and Future Perspectives in Dairy Cattle Selection: A Review. *Animals* **2021**, *11*, 599. [CrossRef]
120. Bouquet, A.; Juga, J. Integrating genomic selection into dairy cattle breeding programmes: A review. *Animal* **2013**, *7*, 705–713. [CrossRef]
121. Brito, L.F.; Bedere, N.; Douhard, F.; Oliveira, H.R.; Arnal, M.; Peñagaricano, F.; Schinckel, A.P.; Baes, C.F.; Miglior, F. Review: Genetic selection of high-yielding dairy cattle toward sustainable farming systems in a rapidly changing world. *Animal* **2021**, *15* (Suppl. S1), 100292. [CrossRef]
122. Smaragdov, M.G. Genomic selection of milk cattle. The practical application over five years. *Russ. J. Genet.* **2013**, *49*, 1089–1097. [CrossRef]
123. Plemiyashov, K.V.; Smaragdov, M.G.; Romanov, M.N. Molecular Genetic Polymorphism in Animal Populations and Its Application in Intensive Breeding of Dairy Cattle—A Review. In *Materials of the 3rd International Scientific and Practical Conference on Molecular Genetic Technologies for Analysis of Gene Expression Related to Animal Productivity and Disease Resistance, Moscow, Russia, 30 September 2021*; Pozyabin, S.V., Kochish, I.I., Romanov, M.N., Eds.; Sel'skokhozyaistvennyye tekhnologii: Moscow, Russia, 2021; pp. 368–378. Available online: <https://elibrary.ru/item.asp?id=46668865> (accessed on 19 January 2022).

124. Plemiyashov, K.V.; Smaragdov, M.G.; Romanov, M.N. Genomic Assessment of Breeding Bulls. In *Materials of the 3rd International Scientific and Practical Conference on Molecular Genetic Technologies for Analysis of Gene Expression Related to Animal Productivity and Disease Resistance, Moscow, Russia, 30 September 2021*; Pozyabin, S.V., Kochish, I.I., Romanov, M.N., Eds.; Sel'skokhozyaistvennyye tekhnologii: Moscow, Russia, 2021; pp. 363–367. Available online: <https://elibrary.ru/item.asp?id=46668864> (accessed on 19 January 2022).
125. Sharko, F.S.; Khatib, A.; Prokhortchouk, E.B. Genomic estimated breeding value of milk performance and fertility traits in the Russian Black-and-white cattle population. *Acta Nat.* **2022**, *14*, 109–122. [[CrossRef](#)]
126. Zinovieva, N.A.; Dotsev, A.V.; Sermyagin, A.A.; Deniskova, T.E.; Abdelmanova, A.S.; Kharzinova, V.R.; Sölkner, J.; Reyer, H.; Wimmers, K.; Brem, G. Selection signatures in two oldest Russian native cattle breeds revealed using high-density single nucleotide polymorphism analysis. *PLoS ONE* **2020**, *15*, e0242200. [[CrossRef](#)]
127. Krivonogova, A.S.; Bruter, A.V.; Makutina, V.A.; Okulova, Y.D.; Ilchuk, L.A.; Kubekina, M.V.; Khamatova, A.Y.; Egorova, T.V.; Mymrin, V.S.; Silaeva, Y.Y.; et al. AAV infection of bovine embryos: Novel, simple and effective tool for genome editing. *Theriogenology* **2022**, *193*, 77–86. [[CrossRef](#)]
128. Cziszter, L.-T.; Ilie, D.-E.; Neamt, R.-I.; Neciu, F.-C.; Saplacan, S.-I.; Gavojdian, D. Comparative study on production, reproduction and functional traits between Fleckvieh and Braunvieh cattle. *Asian-Australas. J. Anim. Sci.* **2017**, *30*, 666–671. [[CrossRef](#)]
129. Ernst, L.K.; Zhigachev, A.I. *Monitoring of Animal Genetic Diseases in the System of Large-Scale Breeding*; Russian Agricultural Academy Publishing House: Moscow, Russia, 2006; ISBN 5-85941-250-9. Available online: <https://search.rsl.ru/ru/search#q=ISBN%205-85941-250-9> (accessed on 19 January 2022).
130. Marzanov, N.S.; Amerkhanov, H.; Yeskin, G.; Turbina, G.; Fedorova, E.; Turbina, I.; Samorukov, Y.; Kiyko, E.; Popov, N.; Shukurova, E.; et al. Genogeography of BLAD in populations of Black-and-white cattle in Russia and abroad. *Molochnoye i Myasnoye Skotovodstvo (Dairy Beef Cattle Breed.)* **2008**, *4*, 2–5. Available online: <https://www.elibrary.ru/item.asp?id=11149171> (accessed on 19 January 2022).
131. Ussenbekov, E.S.; Terletskiy, V.P. On the absence of genetic defects BLAD, CVM, DUMPS and BC in stud bulls of the local Alatau cattle breed. *Veterinariya (Vet. Med.)* **2016**, *6*, 49–51. Available online: <https://www.elibrary.ru/item.asp?id=26556053> (accessed on 19 January 2022).
132. Terletskiy, V.P.; Buralkhiyev, B.A.; Ussenbekov, Y.S.; Yelubayeva, M.; Tyshchenko, V.I.; Beyshova, I.S. Screening for mutations that determine the development of hereditary diseases in breeding cattle. *Aktual'nyye Voprosy Veterinarnoy Biologii (Actual Quest. Vet. Biol.)* **2016**, *3*, 3–6. Available online: <https://www.elibrary.ru/item.asp?id=26644420> (accessed on 19 January 2022).
133. Marron, B.M.; Robinson, J.L.; Gentry, P.A.; Beever, J.E. Identification of a mutation associated with factor XI deficiency in Holstein cattle. *Anim. Genet.* **2004**, *35*, 454–456. [[CrossRef](#)]
134. Kuznetsov, V.M. Statistical analysis of pedigrees. *Zootekhnika (Zootechnics)*. 1998, *2*, pp. 5–8. Available online: https://vm-kuznetsov.ru/files/book/Pap1998_2_pedig.pdf (accessed on 19 January 2022).
135. Zhigachev, A.I.; Suller, I.L. Hereditary anomalies and their control in cattle. *Praktik (Practitioner)*, 2002; 3–4, 46–53.
136. Zhigachev, A.I. Estimation of breeding male for invisible genetic defects. *Zootekhnika (Zootechnics)* **2001**, *2*, 10–12. Available online: <https://www.elibrary.ru/item.asp?id=9124606> (accessed on 19 January 2022).

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

MDPI
St. Alban-Anlage 66
4052 Basel
Switzerland
Tel. +41 61 683 77 34
Fax +41 61 302 89 18
www.mdpi.com

Agriculture Editorial Office
E-mail: agriculture@mdpi.com
www.mdpi.com/journal/agriculture





Academic Open
Access Publishing

www.mdpi.com

ISBN 978-3-0365-8247-4