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Review

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

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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

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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].

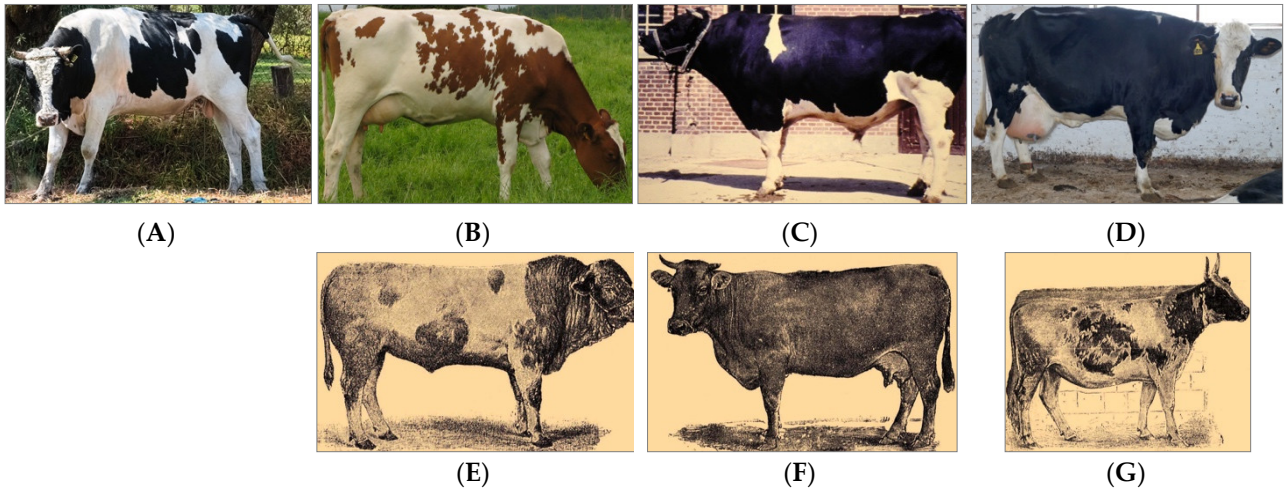

Figure 1. Some notable dairy cattle breeds that can be carriers of deleterious mutations. (**A**), Holstein Friesian bull with the black-pied coat color; (**B**), Holstein Friesian heifer with the red-pied coat color; (**C**), German Black Pied bull; (**D**), Russian Black Pied cow; (**E**), Simmental bull; (**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 (accessed on 19 January 2022), by Tomasina, 2019, Creative Commons Attribution 2.0 Generic license, Category: Deutsches Schwarzbuntes Niederungsrind, 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]
	CZ Czech Republic	[87]
Southeast Asia and the Pacific Basin	CN China	[88–92] *
	TW Taiwan	[22] *
	JP Japan	[93–96]
	NZ New Zealand AU Australia	[97]
Middle East	IR Iran	[98–100]
	TR Turkey	[101]
South Asia	IN India	[102,103]
	PK Pakistan	[104]
Africa	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).

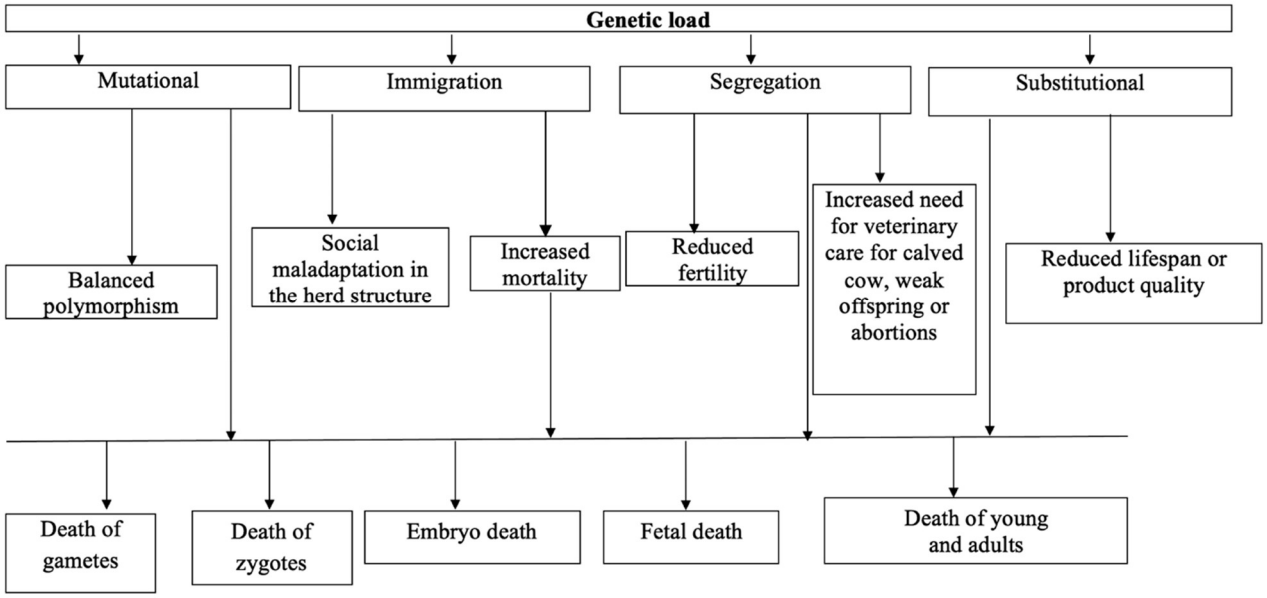

Figure 2. Classification of genetic load in dairy cattle and forms of its manifestation.

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

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 predicators 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 microsocial-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.

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