Classification of Genetic Load

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

Keywords: breeds ; dairy cattle ; mutations ; alleles ; genetic-load

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 [1] 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 [1].

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 [2]. 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 [3], 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 [2][3].

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) [4] obtained 50 homozygous calves for the BLAD syndrome [5][6]. 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 [4]. 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 [7]. 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 [7]. 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 [7][8][9].

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 [10]. **Table 1** 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 1**, 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 [11][12][13].

Table 1. Polymorphism of the beta-casein locus in four different Russian dairy-cattle breeds (n = 177) [11][12][13].

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	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 [11][12][13]. 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 [14][15].

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