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Overdominance in livestock breeding: examples and current status

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Abstract

Recent data have revealed that genetic variation could be attributed to overdominance, or heterozygote advantage. However, genomic survey showed that only a small number of genes that have polymorphisms maintained by overdominance which is consistent with many published papers. Google Web, Google scholar, NCBI Databases and OMIC Tools were used to obtain data for this review paper. Different key words were used to retrieve the required research articles and bioinformatics-based information, such as "overdominance'' and "overdominance in animals''. Research papers used for this review were published over the last 10 to 15 years and information regarding overdominance in livestock was considered for current review. It is hoped that in the future, more loci with overdominance will be discovered. In this review, we will illustrate eight examples of overdominance in livestock. We also want to emphasize that given a low number of reported cases in overdominance, it does not reflect the unimportance of heterozygote advantage in adaptive functions.

Introduction

Overdominance is defined as heterozygotic individuals has higher fitness over both homozygotes in a locus with two alleles. Overdominance, which is often interchangeably used with the term heterozygote advantage, has been used to provides a plausible explanation to genetic polymorphism in a particular population during natural or artificial selection [1]. Since it first documentation in 1922 [2], there is only a small number of cases that can be classified as overdominance which are often associated with disease resistance [3]. In the Table 1., we presented a comprehensive, but not exhaustive, summary of overdominance examples collected from literature searches from human (Homo sapiens), brown rat (Rattus norvegicus), rock dove (*Columba livia)* and common house mosquito (*Culex pipiens*).

However, in these examples, the fitness of genotypes and their association to the infectious disease are not clearly elucidated. Moreover, some of the examples illustrated two directions of selection pressure. For instance, a classical textbook for overdominance is sickle-cell variations including malaria favoring heterozygotes and sickle cell anaemia favoring normal homozygotes. This polymorphism is not considered as overdominance since (i) heterozygotes should have the superior fitness over homozygotes, (ii) both malaria and sickle- cell anaemia affect survival and (iii) the fitness of heterozygotes is environment-dependent and present only when malaria is present [3].

As a result, in order to fully portray overdominance in the current generation, the following indicators must be known (i) the DNA sequence of the gene and its mutant alleles under selection must be pre-determined; (ii) the relative fitness of each genotype must be measured (with heterozygotes exhibiting greatest relative fitness); (iii) the mechanism of selection must be understood i.e., the reason why heterozygotes are fitter than homozygotes [4].

When applying these criteria, it appears that there are not as many examples of overdominance as expected. Nevertheless, some persuasive examples have been collected from many studies in livestock. Here we will illustrate and discuss these examples to portray genetic variations in the population by the maintenance of heterozygotic individuals despite the lethality of the mutant alleles in homozygotes.

Methods

Literature search and selection criteria

Google Web, Google scholar, NCBI Databases and OMIC Tools were used to obtain data for this review paper. Different key words were used to retrieve the required research articles and bioinformatics-based information, such as "overdominance" and "overdominance in animals". Research papers used for this review were those published over last 10 to 15 years and information regarding overdominance in animal was considered for current review.

Discussion

Examples in livestock selection

Numerous mutants in livestock recently identified by implementing molecular biology approaches appear to exhibit overdominance. Since the application of artificial insemination in breeding, the frequency of mutant alleles increases because of the superiority of the heterozygotes over mutant homozygotes and wild type homozygotes. Below we will address 8 examples of overdominance mutants in livestock including 3 cases in cattle, 4 cases in pigs, and 1 case in poultry. The general information of these cases is presented in Table 2.

Milk yield

In cow, genetic correlation illustrates that milk yield and composition are negatively correlated with fertility. It is widely assumed that because of the negative energy balance during lactation of high-producing cows, their fertility is reduced [28]. In 2014, a fine mapping study conducted by Khadri et al. in Nordic Red cattle has discovered a 600kb deletion that cause embryonically lethal mutation [29]. This deletion encompasses four genes including RNASEH2B (ribonuclease H2, subunit B). RNASEH2B gene encodes for the non-catalytic subunit of RNase H2, an endonuclease that specifically degrades the RNA of RNA: DNA hybrids and participates in DNA replication. RNASEH2B loss-of-function mutations are documented to cause embryonic death in mice [30,31] and Aicardi-Goutières syndrome type 2 in humans (AGS2, OMIM 610181). Nevertheless, it is also revealed that the deletion had positive effects on milk yield and composition in heterozygotic form. Upon the genetic survey, the presence of the heterozygote for this mutant in the Danish, Swedish and Finnish Red Cattle was 13%, 23% and 32%, respectively. Due to the high existence of high lethal allele in sampled population, it is hypothesized that conflicting characteristics of the mutant allele in fertility and milk yield and composition have led to the reduction of fertility in dairy cattle in recent years.

Fecundity

Mutations on BMP15 or GDF9 genes have been revealed to affect female fecundity in domesticated sheep that display overdominance [32]. Both genes encode for proteins belong to transforming growth factor ß superfamily. BMP15 and GDF9 proteins

regulates ovarian function. Reduced expression of one of these genes may be associated with polycystic ovary syndrome. Heterozygotic mutants on one of these genes increases ovulation rates and fecundity, while homozygotes reduced oocyte development and maturation. The observed frequencies of mutant alleles appear high in some breeds [33]. In 2014, a survey showed that there were more than 33% mutant allele in Belclare breed for GDF9 gene.

Crooked tail

Loss of function mutation of mannose receptor MCR2 has been reported to cause crooked tail phenotype in Belgian Blue beef cattle. MCR2 is a constitutively recycling endocytic receptor belonging to the mannose receptor family and is found to bind and internalize both intact and degraded collagens and in turn take part in the turnover of collagens in both cytomembrane and extracellular matrix In heterozygotic individuals, this mutant phenotype is characterized by increase in muscle mass, leading to skeletal and muscular malformations [34]. Although this phenotype is not lethal, some cases have been documented that the heterozygote have retarded growth and poor meat quality. Thanks to the molecular biology approach, the mutant allele has been gradually eliminated from the population.

Embryonic lethality

The pig fetus is implanted by day 35 and born at day 114 of gestation. It may die at any time between those days for several reasons. Piglets which die and remain in the uterus undergo a series of standard changes. The skin loses its color, the eyes sink, and the placenta becomes darker. As water is removed, the fetus becomes drier and finally becomes dark brown, enveloped in its placenta. There has been a several reasons attributed to mummified piglets, one of which has been recently discovered in 2018 by Derk at al. BBS9 protein's function has not been identified in pigs although BBS9 mutants in mice showed embryonic lethality [35]. However, a 212-kb deletion has caused a truncated BBS9 protein, leading to a lower expression of BMPER gene in swine. The homozygotic mutants cause fetal death while heterozygotes increase growth rates [36].

Litter size

Immotile, short-tail sperm phenotype defect (ISTS) is a reproductive problem detected in Finnish Yorkshire population boars in 1990s. This phenotype is characterized by lowered sperm counts, short sperm tails and sperm structure abnormalities. In 2012, Sironen et al. (2012) have successfully identified an insertion in an intron region of SPEF2 (Sperm flagellar protein 2) to be the causal mutation for ISTS [37]. SPEF2 is required for correct axoneme development in spermatozoa. Surprisingly, the frequency of SPEF2 mutant carriers in pig population increases to 36% in 2001 has led to the speculation of overdominance. Observation subsequently showed that SPEF2 mutant carriers have significantly higher litter size in first parity (0.51 piglets higher) than females not having the insertion.

Porcine stress syndrome

Pigs with porcine stress syndrome can be fatal without intervention. Other symptoms include behavioral disturbances, discoloration of the skin, muscle rigidity. Homozygote for single nucleotide mutation in RYR1 (ryanodine receptor 1) gene is responsible for this syndrome [38]. RYR1 protein is part of a group of related proteins called ryanodine receptors, which form channels that, when turned on, release positively charged calcium atoms from storage within cells. RYR1 channels play a critical role in muscles used for movement. Heterozygotes for this mutant exhibit higher lean meat content and larger musculature due to the increase in muscle contraction resulting more burning fat and muscle growth [39]. A survey conducted by O'Brien et al. (1993) depicted the presence of the mutant allele with the highest frequency in Pietrain (51.7% heterozygotes and 44.8% homozygotes) and in Landrace (33.2% heterozygote, 2.1% homozygotes). After the introduction of DNA testing, the mutants can be molecular identified, and the mutant allele was able to be eliminated from these breeds.

Leg weakness syndrome

Leg weakness, or lameness is a serious problem in pig breeding due to its negative impacts on animal welfare and productivity. Several studies conducted in various breeds reported there is a significant association between lameness and heritability, especially in Landrace breeds. By using whole genome sequencing approaches, Matika et al. (2019) identified a mutation causing a premature stop codon in exon 3 of MSTN gene on chromosome 15. MSTN is a member of the transforming growth factor beta (TGF-β) superfamily, which is highly conserved across species, and is typically expressed in developing and mature skeletal muscle as a key regulator of muscle growth [40]. In the homozygotic form, piglets suffer the lameness syndrome and do not survive post 40 kg live weight. However, heterozygotes have higher muscle depth and lower fat depth compared to wild type, suggesting that the deleterious allele was maintained at moderate frequency due to overdominance.

Species	*Locus*	Evidence for overdominance		Citations
		Heterozygotes	Mutant homozygotes	
H. sapiens	*HBB*	increased resistance to malaria	sickle cell anaemia	[5]
	CFTR	increased resistance to cholera	cystic fibrosis	[6]
	HBA α-thalassemia	increased resistance to malaria	α-thalassemia	[7]
	HBB β-thalassemia	increased resistance to malaria	β-thalassemia	
	HLA (MHC)	increased resistance to infectious diseases and reproductive advantages		[8] [9].
	TDS	increased resistance to diseases, such as tuberculosis		[10]
	TDS and GD	fat (sphingolipid) storage processes		[11]
	G6PD	malaria resistant		[12,13]
	PRNP	increased resistance to kuru		[14,15]
	GJB2	increased cell survival and thicker epidermis, thereby increasing resistance to infection by pathogens	deafness	[16,17]
	GBA	Reproductive benefits	Gaucher disease	[18]
	MTHFR		neural tube defects	[19]
	PAH	resistant to ochratoxin A, a mycotoxin produced by aspergillus and penicillium species that infest grains	phenylketonuria (*PKU*)	[20]
	CCR5	slower progression to AIDS	cannot perceive bitter tastes	[21,22]
	PTC			[23]
	MEFV	reduced susceptibility to tuberculosis	Familial Mediterranean Fever (FMF).	[24]
Rattus norvegicus	*RW*	resistant to the pesticide, warfarin.	less viable	[25]
Columba livia	*TF*	lower microbial infection and higher egg hatching rates		[26]
Culex pipiens	*Ace.1 Ester*	resistant to pesticides		[27]

Table 1: Overdominance examples in various species.

Species	Trait	Mutated gene	Type of mutation	Heterozygote mutant phenotype	Homozygote mutant phenotype
Cattle	Milk yield	RNASEH2B	600-kb deletion	Increase milk yield	Embryonic lethal
Sheep	Fecundity	BMP15, GDP9	1-bp change	Increase female fecundity	Female infertility
Cattle	Crooked tail	MCR2	2-bp deletion	High muscle	Crooked tail
Pig	Litter size	SPEF2	9-kb insertion	Increase litter size	Male infertility
Pig	Halothane sensitivity	RYR1	1-bp change	Increase lean meat content	Porcine stress syndrome
Pig	Embryonic lethality				
Pig	Leg weakness syndrome	MSTN	1-bp change	Lower fat content, higher muscle depth	Lameness
Chicken	Rose-comb	MNR2	7.4-Mb inversion	Rose-comb	Male infertility

Table 2: Examples of 8 mutants in livestock with overdominance in heterozygotes.

Rose comb

Rose-comb is a been widely described monogenic trait that was first reported by William Bateson [41]. This trait has been documented in many breeds and are found in both heterozygotic and mutant homozygotic forms. The wild type chicken exhibits a single comb phenotype while the mutant chicken shows altered comb extensive phenotypic variability. As a result, the rose-comb phenotypes are influenced by several genes and represents an excellent model between gene interactions. The mutant phenotype is due to the inversion of 7.4Mb that relocate the gene homeodomain protein MNR2. Consequently, this leads to misexpression of MNR2 and disruption of the gene coiled-coil domain-containing protein 108 (CCDC108) causing the poor sperm mobility in homozygotes and male fertility. However, the female chicken shows normal phenotype in mutant homozygote [42].

Conclusion

Overdominance remains a popular and persuasive explanation for genetic variation in a specific herd. Since its definition first proposed almost 100 years ago, the number of mutant alleles maintained by overdominance is low. To date, genomic data only suggested only a small number of gene that can be categorized as overdominance. However, it does not reflect that overdominance is not important. In this review, we discuss 8 examples that can be readily available for adaptations to new environmental challenges. Perhaps further analysis is needed to identify more genes regulated by overdominance.

Author contributions

ABPN and TVN conceived the project. TVN conducted literature searching. All the authors read and provided the edits. ABPN approved the manuscript.

Competing Interest

The authors declare that there is no conflict of interest.

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