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Theoretical Aspects of Heterosis

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Abstract—The phenomenon of heterosis, known as the superior performance of hybrid organisms over their parents, has been exploited by agricultural practices in the production of various crops since the beginning of the last century; however, its genetic basis has remained obscure. With the experimental data obtained from the study of maize hybrids and mathematical calculations, some genetic models have been proposed to explain heterosis in terms of various types of gene interaction, such as dominance, overdominance, and epistasis. However, each of the proposed concepts has weak points, which impose limitations on the possibility of the overall interpretation of the heterotic response in F_1. This review provides a critical assessment of the theoretical concepts of heterosis from the perspective of the currently accumulated data of genetics and molecular biology, which are focused on specific mechanisms acting for specific traits. In particular, the role of lethal and semi-lethal mutations in the formation of a heterotic phenotype in plants is shown. The issues of the interpretation of genetic effects in case of gene linkage, which are referred to as pseudo-overdominance, are considered. Particular attention is paid to nonallelic interactions of genes, which add new nuances when discussing the effects of dominance and overdominance. Information on combining ability and its practical use in the context of the concept of heterotic groups is presented. Some aspects of the genotype–environment interaction are shown. The analysis of the theoretical concepts of heterosis from the perspective of modern genetic data testifies to the important role of various types of gene action in the formation of an outstanding phenotype and confirms the need for a systematic approach to this complex and unique phenomenon.

Keywords: heterosis, gene interaction, dominance, overdominance, epistasis
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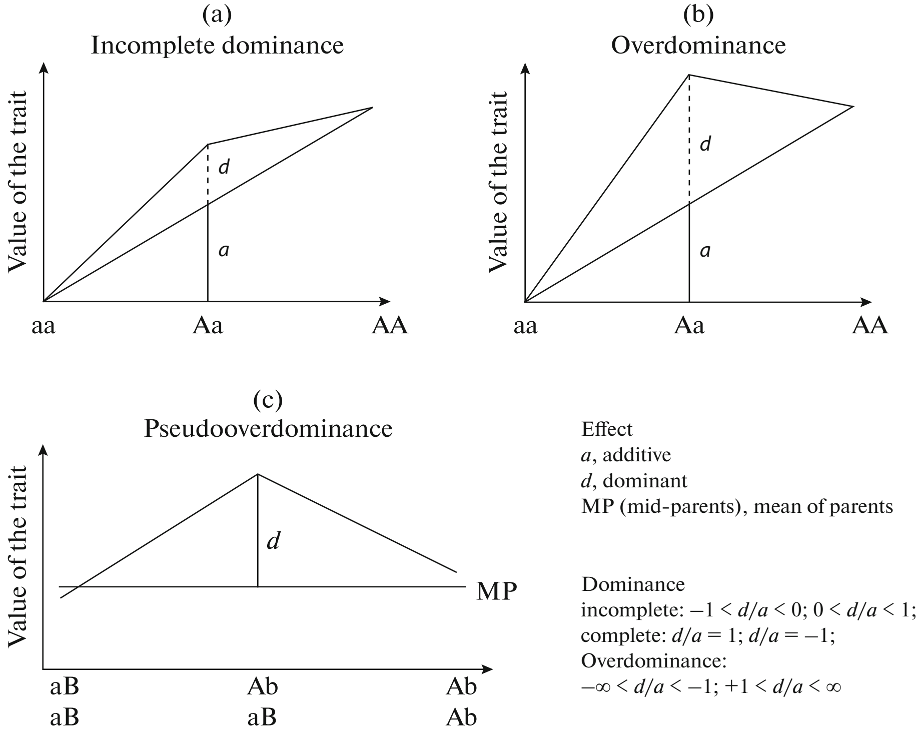
Heterosis is one of the most significant phenomena in biology. Its commercial use has significantly increased gross output in both crop and livestock production (Duvick, 2001; Fu et al., 2014). Published more than 100 years ago, the first publications on this problem (Shull, 1908, 1914) laid the basis for modern hybrid breeding not only in maize but also other economically valuable crops. Such high significance of heterosis served as an impulse to study the genetic mechanisms of this unique phenomenon and the development of theoretical models (Shull, 1908, 1952; Bruce, 1910; East and Hayes, 1912; Jones, 1917; Charlesworth and Willis, 2009).

For the first time, the use of heterosis in agricultural practice was carried out on maize (*Zea mays*), then on beetroot (*Beta vulgaris*), sorghum (*Sorghum bicolor*), onion (*Allium cepa*), eggplant (*Solanum melongena*), tomato (*Lycopersicum esculentum*), pepper (*Capsicum*), rice (*Oryza sativa*), cotton (*Gossypium hirsutum*), sunflower (*Helianthus annuus*), and rape (*Brassica napus*) (Melchinger and Gumber, 1998). The beginning of hybrid breeding is considered to be 1920 (Crow, 1998). In 1924, the first few bushels of hybrid corn seeds (Crabb, 1947) were sold and a rapid transition from freely pollinated cultivars to hybrids began with its production. In Iowa, the share of hybrids in production crops increased from less than 10% in 1935 to over 90% in the next four years. By 1950, most of the maize seeds sown in the United States were hybrid (Crow, 1998). Due to the use of hybrids of this crop in agricultural practice, it was possible to increase grain yield by 15% compared to the best free-pollinated cultivar. By the end of the twentieth century, F_1 maize crops accounted for about 65% of the total area of its cultivation, which quadrupled its annual production (Duvick, 1999). Widely cultivated in Asia, hybrid rice gave an advantage of 20–30% compared to the best inbred cultivars, contributing to an increase in production efficiency by 44% (Cheng et al., 2007). In China, as one of the world's largest producers of rapeseed, its hybrids occupy at least 75% of the total acreage (Fu, 2009). In such an important cereal crop of the world as wheat (*Triticum aestivum*), hybrids provide a superiority of 10–25% (Hoisington et al., 1999). Despite the difficulties of producing *T. aestivum* hybrid seeds, in 2012 wheat F_1 crops in Europe reached 250000 hectares, with the predominant share of France, the main monopolist in the production of gametocides (http://www.hybridwheat.net). For sorghum, almost half of the world's crops are represented



Effect
a, additive
d, dominant
MP (mid-parents), mean of parents

Dominance
incomplete: $-1 < d/a < 0$; $0 < d/a < 1$;
complete: $d/a = 1$; $d/a = -1$;
Overdominance:
$-\infty < d/a < -1$; $+1 < d/a < \infty$

Fig. 1. Genetic models of heterosis: dominance (a) and overdominance (b), which correspond to the single-locus model; pseudooverdominance (c), which occurs when two loci with opposite additive effects are closely linked, according to (Goff and Zhang, 2013).

by hybrids with an economic effect of 35–40% (Duvick, 1999). The progress of using heterosis in practice stimulated the interest of genetic scientists in the study of this unique phenomenon and contributed to the emergence of theoretical concepts that underwent various modifications and interpretations with the development of analytical methods and on obtaining new data. In their classic version, they defined the directions of research for many years ahead.

Genetic Models of Heterosis

Basic ideas about the mechanisms of two functionally opposing phenomena (inbreeding and heterosis) are reffered to single- and multilocus models (Fig. 1). The single-locus model assumes (1) dominance, in which the action of deleterious recessives is suppressed by a dominant homolog (Davenport, 1908; Jones, 1917), and (2) overdominance, which is also due to the interaction between members of the same pair of alleles (Shull, 1908; East and Hayes, 1912). The genetic explanation of heterosis and inbreeding depression in the case of a single-locus model is associated with dominant allele levels. In the first case, the advantage of heterozygotes is assumed; in the second case, the effect of partially or completely recessive mutant alleles, leading to a decrease in the viability of homozygotes. The multilocus model considers heterosis from the position of the nonallelic interactions of the genes or epistasis.

In the context of the dominance theory (Davenport, 1908; Bruce, 1910; Keeble and Pellew, 1910; Jones, 1917; Collins, 1921), the superiority of F_1 hybrids is due to the accumulation of favorable dominant genes in the hybrid and the dominant complementation of deleterious recessives. Obviously, there is an interaction of allelic factors. The importance of dominance for explaining degeneration through inbreeding and a favorable effect of crossing was first noted by C.B. Davenport (1908), who suggested that the trait is affected by a small number of factors with a well-defined individual effect.

Can mutations explain the observed degree of depression in inbreeding and its removal in outbreeding? Certainly, detrimental mutations are presented in natural populations and occurrence of both semilethals and lethals does not in any way diminish their important role in maintaining a high level of biological adaptation. There is every reason to believe that unfavorable and even lethal in homozygous state alleles are necessary parts of the genotypes of a well-adapted population. Thus they are supported by natural selection at the appropriate frequency.

Studies carried out on *Drosophila melanogaster* have shown that about 30% of the second and third wild-type chromosomes isolated in the male are lethal in the homozygous state (Crow, 1993). Heterozygotes on lethal alleles are almost always viable, which confirms the recessive nature of these mutations. Various wild-type lethal chromosomes carry different lethal mutations. If the selection is aimed at the advantage of heterozygotes, the frequencies of alleles that decrease the viability of homozygotes should be intermediate (average) and distributed among different genotypes. Experiments on the analysis of mutations in *D. melanogaster* have shown that the frequencies of lethal mutations are maintained at a low level, and homozygosity reduces the fitness of flies during the life cycle to an average of 84% (Sved, 1971; Latter et al., 1998).

For most species of plants and animals, it has not been established to what extent inbreeding depression is associated with lethal mutations, since homozygous embryos die at the earliest stages of their development. However, in separate studies the frequencies of lethal mutations similar to *D. melanogaster* were shown in populations of mangrove trees and herbaceous plants *Mimulus guttatus*, as well as some fish species (Ohnishi, 1982, 1985; McCune et al., 2002).

From the point of view of population genetics, open-pollinated populations tend to achieve an equilibrium with the frequency of recessive mutations. Therefore the number of unfavorable recessives added by the mutation process is balanced by the number of similar recessives which is eliminated by natural selection. If a deleterious mutation is completely recessive, selection only acts on the homozygote; the higher the frequency of recessive alleles in the population the higher the probability of the appearance of recessive homozygotes and the more such homozygotes are eliminated. The appearance of recessive homozygotes reduces the average viability of the population. Knowing the rate of mutation and the total number of loci that are capable of mutation, for a particular species of a freely pollinated population, it is possible to define the maximum value of the theoretically possible heterotic effect caused by the action of this reason. The corresponding calculation of J.F. Crow (1952) for corn showed that such an effect in interlinear hybrids is no more than 5%, while in reality the best interlinear hybrids surpass the yields of freely pollinated cultivars by at least 30%. Conceptually, the amount of heterosis should decrease whereas the pure lines accumulate strong alleles and are cleansed of deleterious recessives. Consequently the lines themselves should reach the level of yield of the best hybrids (Duvick, 2001). A retrospective analysis of the maize breeding showed no significant decrease in the F1 heterosis level as a result of improvement the inbred lines during the breeding, which should be present if the theory is correct. Meanwhile, the yields of hybrids increased in proportion to the yield of the best inbred lines (Fig. 2) (Duvick, 1999, 2001; Troyer and Wellin, 2009), that is, the elimination of deleterious recessives through inbreeding did not change the relative advantage of F_1 hybrids. J.A. Bercler et al. (2003) suggested that a constant increase in the F_1 yield and a significant heterotic effect over many years are due to the selection of alleles in the "favorable" set of loci that create the best cross combinations. Earlier, E.T. Bingham (1998) came to a similar conclusion, explaining the observed tendency by accumulation of favorable genes in chromosomal blocks and their associated interactions (cumulative effect), indicating the crucial importance of the presence of linkage disequilibrium. Theoretically, it is possible to assume the probability of obtaining powerful homozygous lines, but in practice this is impeded by the linkage of favorable dominant alleles to unfavorable recessives. G.N. Collins (1921) noted that at a significant number of factors influencing the vigor of hybrids, the possibility of obtaining an organism homozygous for all favorable dominant alleles is negligible ($1:4n$, where n is the number of pairs of factors controlling the trait). The most successful is the cleansing of mutations with significant effects. Consequently, both heterosis and inbreeding depression can be caused by the cumulative effect of many individual, rare, and partially deleterious mutations that are not the main target of selection and that can be eliminated only after hundreds or even thousands of generations (Charlesworth et al., 1990; Wang et al., 1999).

Frequent cases of linkage of favorable dominant factors with deleterious recessives and even lethal (in the homozygous state) alleles testify to the importance of these recessives for the genotype as a whole. Selective removal of major and minor mutations through inbreeding for several generations and subsequent crossing and analysis of outbred forms could clarify the contribution of mutations. A similar experiment on "cleansing" in the *Mimulus guttatus* plant only slightly reduced the inbreeding depression (Willis, 1999), whereas in the population of insects *Stator limbatus*, the contribution of mutations with significant effects was high and the decrease in inbreeding depression reached 35–73% (Fox et al., 2008). These results support the findings of D. Charlesworth and J. Willis (2009) who believe that "cleansing" through breeding can not completely eliminate the role of mutations, since the improved characteristics of the inbred lines may be due to the selection of alleles at loci not associated with heterosis, and high F_1 performance may be caused by numerous mutations with small effects that have not been removed by the selection of the best genotypes.

Another argument against the dominant model is progressive heterosis in polyploids, which is also difficult to explain from the dominance concept (Bingham et al., 1994). In this case, the amount of heterosis is maximized by the number of polyploid genomes, indicating that the dose effect may play a more important role than simple complementation or the interaction of alleles (Birchler and Veitia, 2010).

The third aspect, concerning polyploids and opposing the role of a mutation load in regulating the

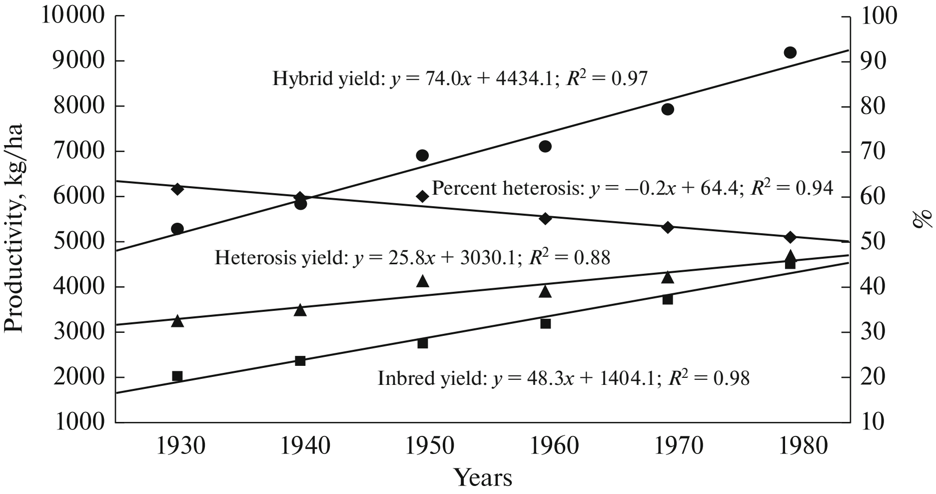


Fig. 2. Yield of simple hybrids (hybrid yield, ●), mean of their inbred parents (inbred yield, ■), relative heterosis (%, percent heterosis, ◆), and absolute heterosis (heterosis yield, ▲) of maize cultivated in the United States during 1916–1985 (Duvick, 1999; Troyer and Wellin, 2009).

heterotic effect, is the high comparability of the rate of inbreeding depression at the di- and tetraploid levels, although theoretically the loss of power at a higher level of ploidy should occur more slowly (Busbice and Wilsie, 1966; Dudley, 1974; Birchler et al., 2003).

Despite the controversial issues about the role of mutations in the manifestation of heterosis, the dominance theory is considered from a different point of view: from the position of the additive action of inherited factors. This changes the meaning of "dominance," when it is applicable to the case of interaction not between individual pairs of alleles, but between two parental sets of multiple factors that influence the expression of the traits in F_1 hybrids. Therefore, the maximum heterotic responce should be developed in cases where the hybrid has more loci with dominant, favorable alleles. The impact of possible effect achieved when suppressing the action of deleterious recessives by dominant analogs is limited.

To date, the concept of dominance occupies a leading position. Facts such as the absence of a decrease in the level of heterosis (Duvick, 2001), progressive heterosis in polyploids, and the rapid rate of inbreeding depression at the tetraploid level indicate the limited capabilities of this model (Birchler et al., 2003; Springer and Stupar, 2007). Nevertheless, it is widespread due to significance of both additive effects and the nonallelic interaction of genes that this theory is considering.

In the late 1940s, interest in the idea of heterozygosity as the main mechanism of heterosis increased due to the research of F. Hull (1952), who introduced the notion of overdominance, instead of superdominance proposed for this case by R.A. Fisher (1931). According to the theory of overdominance, the interaction of two members of the same pair of alleles can lead to the advantage of heterozygote *A1A2* over both homozygotes *A1A1* and *A2A2*. In this case, it is assumed that both alleles in the heterozygote perform somewhat different functions and mutually complement each other. Therefore, in a series of multiple alleles, the effect of overdominance can be manifested only by pairs of alleles that differ from each other. Thus, we are talking about a complementary effect in the interaction between alleles within a single locus. This hypothesis is a development of the ideas expressed by G.H. Shull (1952) and E.M. East and H.K. Hayes (1912) about the stimulating effect of heterozygosity, which are very close in meaning to the conclusions of Charles Darwin about the causes of the biologically beneficial effect of crossing.

An important argument in favor of the theory of overdominance was the heterosis of double interlinear maize hybrids, which are obtained by combining four unrelated lines. Heterosis of simple hybrids, which are the parental forms of a double hybrid, can be explained by the suppression of the effect of deleterious recessives by dominant alleles. However, when crossing simple hybrids, a greater number of deleterious homo- or heterozyotic recessives should be formed as a result of splitting and recombination. Consequently, in terms of the growth rates they should always be worse than simple hybrids. In fact, double interlinear maize hybrids are not inferior to the best simple ones, which is consistent with the theory of overdominance.

In the population, the overdominant alleles are maintained by selection at intermediate frequencies, even if one or both homozygotes have low viability. Sometimes chromosomal inversion polymorphism (Hoffmann and Rieseberg, 2008; Kirkpatrick, 2010) and polymorphism of large genomic regions with suppressed recombinations remain preserved (Dyer et al., 2007). The latter may accumulate various mutations that reduce viability in the homozygous state (overdominant regions) (Glemin et al., 2001). In addition, alleles with antagonistic pleiotropy may be maintained, for example, those having a negative effect on fitness and positive on other traits and ontogeny stages under certain environmental conditions (Charlesworth and Hughes, 1996).

Despite the fact that the overdominance have been confirmed experimentally, the dependence of hybrid vigor on the degree of heterozygosity is disputed by many authors. The main contradiction goes from the fact that this model implies interactions in one or a small number of loci, while the majority of agronomic traits are polygenic (Belyaev et al., 1968; Lippman and Zamir, 2007; Springer an Stupar, 2007). J.A. Birchler and R.A. Veitia (2010) suggested that in the case of monogenic heterosis there is an effect of action on regulatory networks that are not addressed by the concept of polygenic control. If changes in regulatory networks are associated with the manifestation of heterosis, the variation in individual or several genes for which there are differences among the parents will also affect the formation of the heterotic response in F_1.

Another counterargument comes from the fact of the existence of a linkage between genes, which has been confirmed by most contemporary research. Nevertheless, evidence has been presented that supports discussions about the importance of the overdominant action of alleles. Some studies demonstrate single-locus interactions in the manifestation of heterosis for different traits in a number of variety (Gustafson, 1946; Redei, 1962; Shumnyi et al., 1982; Dollinger, 1985; Semel et al., 2006; Krieger et al., 2010). D. Schwartz and W.J. Laughner (1969) studied the activity of the enzyme alcohol dehydrogenase last I (*adg*I), which is a heterodimer. The enzyme allele with high activity was combined with an allele causing tolerance to high temperatures. Further observations showed that the heteroallelic form of the enzyme is more active than the homoallelic one under specific stress conditions. An increased expression of the maize *Pl* gene in heterozygotes containing one copy of the epigenetically modified allele *Pl* is shown, which is expressed in the increase in pigmentation due to an increase in the level of anthocyanins (Hollick and Chandler, 1998). A recent study also describes a monogenic model of overdominance in tomato (Krieger et al., 2010). Heterozygosity for allele SFT (single flower trust) with a mutant copy, which controls the synthesis of the florigen hormone, leads to an increase in yield by more than 60%, confirming the leading role of overdominance. The observed reaction is associated with a shift in the development program of the SFT-heterozygous genotype toward an increase in the number of flowering inflorescences in comparison with wild-type homozygotes, which are characterized by a more powerful vegetative growth but which form a small number of inflorescences. Unlike the case with *adh*1, the overdominant effect of SFT is due to the effect of the dose on molecular expression, which leads to the balance of the gene product in the overdominant genotype. This example also highlights the potential for fine-tuning the development program of the organism. Another study carried out on tomato lines with introgressions of *Solanum pennellii* noted that F_1 heterosis for most reproductive traits, that is, those associated with yield and seed productivity, is caused by overdominance, whereas vegetative traits are more due to dominance and epistasis (Semel et al., 2006). One of the expressive examples of monogenic heterosis was demonstrated for the *tenera* hybrid (*dura* × *pisifera*) of oil palm, whose yields exceed 30% in production crops (Singh et al., 2013; Ong-Abdullah et al., 2015). The high yield level of *tenera*-F_1 is provided by the overdominance effect of the *SHELL* gene involved in fetal formation, one copy of which is represented by a wild type and the other is a normal highly productive one. It is this heterozygous combination of alleles (Aa > AA) that ensures a high yield of seed oil.

In assessing the effect of overdominance, there is one significant problem mentioned above, namely, the inability to separate overdominance from dominance. This is a situation that corresponds to the multilocus model of interactions in heterosis – pseudo-overdominance, which associated with linkage disequilibrium (repulsion phase linkage), also called linkage bias (Bingham, 1998). In this case, F_1 is characterized by complementation between closely linked dominant alleles and various deleterious recessives in the repulsion phase (Fig. 3) (Crow, 1952; Stuber et al., 1992; Graham et al., 1997). The linked loci will simulate a single-locus interaction, not allowing, therefore, to separate the true effects. The heterosis associated with pseudo-overdominance will not appear in the self-pollinated offspring (F_2), because genetic recombination will lead to the dissociation of alleles that were initially in the repulsion phase, which was confirmed by Y. Semel et al. (2006). Pseudo-overdominance can also occur through recombination-suppressed regions where favorable and unfavorable allele combinations are in the repulsion phase (Gore et al., 2009; Mcmullen et al., 2009).

The third model explains heterosis from nonallelic interactions, or epistasis, which adds new nuances to the discussion of the role of dominance and overdominance (Sprague et al., 1962; Phillips, 2008). It is this type of interaction that allows us not only to explain well the many facts related to heterosis but also to offer some specific methods of using hybrid vigor in agricultural practice. There are (i) genetic (physiological) epistasis, when the action of one locus is caused by another locus and a masking effect is observed, and (ii) statistical epistasis, which describes the deviation that occurs when the combined additive effect of at least two genes does not explain the observed phenotype. While physiological epistasis does not depend on

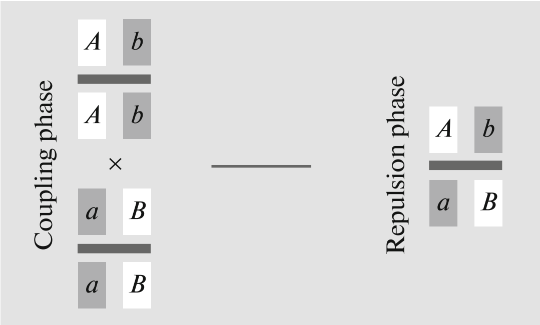


Fig. 3. The linked recessive semi-lethals (a, b) in the coupling and repulsion phases in the parent forms and the hybrid, according to (Charlesworth and Willis, 2009).

gene frequencies of the population and is a distinctive feature of the genotype, statistical epistasis characterizes the population and is dependent on the gene frequencies.

Classically, epistasis is defined as the interaction between genes in at least two loci that affect the phenotypic expression of the trait. Such an interaction can be observed between loci with different effects, including dominance, overdominance, and additivity. Proceeding from this, three main forms of epistatic interaction of genes are distinguished: additive-additive, additive-dominant, and dominant-dominant epistasis. C.J. Goodnight (1999) analyzed the role of epistasis in the manifestation of heterosis and showed that under additive-dominant and dominant-dominant epistasis the manifestation of heterosis in a separate locus changes, that is, intraloci heterosis is a function of the genetic background. Consequently, the genetic background and interactions there can influence the effects of individual loci, including in the formation of a heterotic response. Therefore, epistasis poses a serious obstacle to the mapping and study of complex traits whose phenotypic effects are masked by nonallelic interactions.

Some works (Wolf and Hallauer, 1997, Kusterer et al., 2007) demonstrated the presence of epistasis for a number of traits in individual heterotic combinations. Our works aimed at studying the association of heterosis with nonallelic gene interactions have made it possible to establish that although there is a correlation between these two phenomena, heterosis can exist in the absence of nonallelic interaction. This convincingly confirms the results of analyses of the components of heterosis for a number of quantitative traits in maize hybrids (Khotyleva and Tarutina, 1997). It was established that in cases where positive heterosis was manifested in the presence of a nonallelic interaction, it was of the duplicate type. The complementary type of epistasis was not found in any of the hybrids analyzed. Such regularities are extremely rare. While the literature notes an association between high and positive heterosis and nonallelic interaction, as a rule, this interaction is of a complementary type, which was confirmed by the study of diallelic hybrids F_1 of tomato and sweet pepper (Tarutina et al., 1996; Tarutina et al., 1999; Khotyleva et al., 2005). The genetic control of the traits determining the fruit yield included the epistasis of a complementary type, caused by one or several parental forms. However, the level of heterosis observed in different hybrids with the using of these forms is not always directly dependent on the epistasis.

Recent studies using molecular markers and modern statistical approaches have increased the accuracy of detecting epistatic interactions. Evidence of the role of epistasis in the formation of the F_1 heterotic response was presented by D.P. Wolf and A.R. Hallauer (1997), who carried out a triple testcross on corn. The epistatic interactions for several traits, including the yield, its main components, and different developmental stages were found in offspring the heterotic hybrid B73 × Mo17. Similar data were obtained for *Arabidopsis* (Kusterer et al., 2007; Melchinger et al., 2007a) and rice (Li et al., 2001; Hua et al., 2003). The important role of nonallelic interactions for the expression of quantitative traits is noted by A.E. Melchinger et al. (2007b). Based on analysis of QTLs with strong effects, theoretical models for the analysis of epistatic interactions have been developed (Melchinger et al., 2007b; Reif et al., 2009). When studying the role of epistasis in the manifestation of heterosis in *Arabidopsis*, the results substantiating the classical genetic theory that describes heterosis as a sum of individual QTL effects were obtained. Approaches have been developed to assess epistatic interactions of individual QTLs with an entire genetic background (QTL-by-background interactions). Thus, the concept of epistasis has been expanded from a digenic to a systemic level of interactions. If we consider *Arabidopsis* as a model object for autogamous species, then the relevance of the QTL epistatic interactions with the corresponding genetic background indicates the difficulties of marker-assisted selection (MAS), since the genetic value of the introgressed regions will depend on the set of factors of the genetic background of the recipient. For established digenic additive-additive interactions with an effect exceeding 75% of MAS, selection can be successful only in the case of the complementary transfer of the segments exhibiting the digenic epistasis (Reif et al., 2009).

All studies carried out to elucidate the role of epistasis in the determination of economically valuable quantitative traits confirm the statements of classical genetics that epistasis acts as one of the factors determining the heterosis in some specific combinations of crossing and indicate that nonallelic gene interactions serve as a source of bias for simplified theoretical models.

When studying the effects of gene interactions for a number of quantitative traits, it was shown that heterosis, as a rule, does not directly depend on the magnitude and type of the gene action. For example, higher extend of dominance, as well as the occurrence of nonallelic interaction, are not always accompanied by higher heterosis. Probably, all three types, additivity, dominance, and epistasis, act together when developing a heterotic response in F_1. Thus, heterosis cannot be explained by any single genetic reason or by any single type of gene interaction. This is the summary effect of the phenotypically similar action of heterogeneous genetic processes, and, apparently, different genetic causes lie at the basis of different forms of heterosis. This concept, explaining the complexity of the genetic mechanisms of heterosis, was expressed by K. Mather (1955) and later developed by N.V. Turbin (1961), proceeding from the assumption (Mather, 1942, 1943) that the normal development of the trait is the result of a certain equilibrium between the actions of various hereditary factors oppositely directed on this trait. Removing, changing, or replacing some of them will inevitably give preference to factors having the opposite effect, and in some cases this should lead to a change in the expression of certain traits in organisms with a biased genetic balance. Recently, studies have appeared that confirm at the molecular level the balance of action of various genetic factors in the formation of a superior phenotype (Birchler and Veitia, 2010; Birchler et al., 2016).

Some Physiological-Biochemical and Molecular Aspects of Heterosis

Studies carried out in different years have confirmed that all three types of gene action (additivity, dominance, and epistasis) mutually control the final manifestation of the heterotic effect and heterosis cannot be explained from the standpoint of any particular theoretical concept. Heterosis should be considered as the overall effect of the phenotypically similar action of heterogeneous genetic processes, and, apparently, various genetic causes underlie the manifestation of heterosis (Turbin, 1961; Tarutina et al., 1996; Hotyleva et al., 2005). At the same time, its consideration from the point of view of the hypothesis of genetic balance does not exclude the possibility of studying the role of certain types of interaction of hereditary factors as causes of heterosis under simplified theoretical models.

The study of the phenomenon of heterosis has been accompanied by the accumulation of information about the mechanisms of its manifestation at various levels: molecular, biochemical, physiological, cellular, and organismic. At the First International Conference on Heterosis in 1952 in Mexico, to explain the physiological causes of heterosis, A.J. Mangelsdorf (1952) put forward the concept of limiting factors, or physiological bottlenecks. To explain the effect of heterosis, R.H. Hageman et al. (1967) proposed a concept of metabolic balance, which is very close to the views of A.J. Mangelsdorf (1952). According to this concept, traits express as a result of biochemical reactions, each of which is controlled by one or more specific enzymes. The effect of heterosis is manifested in the coordination of all reactions and systems for effective growth in the medium. The concept of complementation of biochemical systems connects the hypotheses of dominance and overdominance because it is based on the interaction of multiple alleles and intergenic complementation, as a result of which biochemical processes are intensified.

Khotyleva et al. (1991) proposed a bioenergetic approach to the analysis of heterosis. V.V. Titok (2002) formulated the main issue of the bioenergy concept, according to which heterosis is caused by the bioenergetic balance arising in the heterozygous state when the genetic blockage is removed due to the compensatory action of genomes of the parents that carry the segregated loci of the bottlenecks of the energy metabolism. It is shown that the advantage of F_1 hybrids is due to the good balance of the activity of the main energy-producing systems: photophosphorylation, oxidative phosphorylation, glycolysis, pentose-phosphate pathway, tricarboxylic acid cycle, and growth processes during ontogenesis. A number of authors noted that heterosis hybrids differ from the original forms by mitotic (Essad and Maunory, 1979), photosynthesis (Loomis et al., 1971), mitochondria and plastid activity (Srivastava, 1974), and the content of endogenous growth regulators (Pashkar', 1974).

New perspectives in studying the effect of heterosis are revealed by the contemporary methods of molecular genetics, which make it possible to study the DNA variability and investigate the structural and nonstructural sequences of the genome. Variability at this level is many times higher than its phenotypic manifestation. In recent years, extensive research has been carried out to identify markers linked to heterosis (Wang et al., 2014; Feng et al., 2015). Promising results have been obtained on number of variety using different types of DNA markers (Springer and Stupar, 2007; Shapturenko et al., 2014, 2015).

The Concept of Combining Ability

The entire set of studies carried out over more than a century of researching the phenomenon of heterosis testifies to the important role of different types of gene actions, which give the key to understanding the causes of heterosis in hybrids with varying degrees of heterozygosity. Cases of favorable combinations of crossbreeding components demonstrate the maximum increase in the indices of traits in F_1 in comparison with the parental lines. At present, assessment of the combining ability has become an indispensable element of breeding for heterosis, especially at the initial stage, when the selection of source material is extremely important not only in terms of the significance of the economically valuable traits of the lines themselves but also in terms of their combining value.

G.F. Sprague and L.A. Tatum (1942) singled out the terms of general (GCA) and specific (SCA) combining ability, defining GCA as the average value of parental form in all hybrid combinations which were getting with its using, and SCA as a deviation of individual hybrid combinations from GCA of the parental forms under investigation (Turbin, 1961; Turbin et al., 1974; Khotyleva and Tarutina, 2008).

Based on theoretical studies, D. Matzinger and O. Kempthorne (1956) deduced the relation between the general and specific combinational ability and the additive, dominant, and epistatic effects of genes, describing it mathematically. Following their calculations, it can be concluded that GCA depends on the additive effect of genes in that part of the epistatic effect which is due to the interaction of genes with the additive effect, and SCA depends on the dominant and epistatic action of genes. The statistical apparatus for evaluating the effects and variances of GCA and SCA was developed and detailed by B. Griffing (Griffing, 1956; Griffing and Langridge, 1963).

To obtain the necessary data on the combining ability, crossings are carried out with the subsequent testing of the hybrid progeny. The GCA can be estimated for various crossing systems (free pollination, poly- and topcross, and diallelic crosses). The SCA is evaluated only in diallel crosses and topcrosses, where in the latter case there are limitations imposed on testers: they should be either inbred lines or simple hybrids with a well-known genetic background. An approach to the choice of the tester largely determines the accuracy of the estimation of both the general and specific combining ability. However, the most complete information on the combining ability can be obtained only in the system of diallelic crosses (Griffing, 1956; Turbin et al., 1966). In this case, it is possible to determine the relative value of the forms analyzed and to indicate the ways in which a particular form can be used in specific crossing combinations. Various models used for diallelic analysis are described in detail by N.V. Turbin et al. (1974), L.V. Khotyleva, and L.A. Tarutina (2008).

To maximize the use of the overdominance effect in selection for heterosis, it is convenient to use the method of estimating the combining ability according to A.V. Kilchevsky (1982), which is based on the principle of reciprocity and ensures the selection of overdominant loci. The proposed scheme for heterosis selection is superior to the classical scheme of topcrosses with subsequent diallelic crossings in the selection for genes exhibiting the overdominance effect and is not inferior to it in the selection for additive and dominant genes.

Direct use of the data on combining ability is demonstrated by the concept of heterotic groups (Melchinger and Gumber, 1998; Akinwale et al., 2014). Each of them fixes different alleles, which in combination with alleles of another heterotic group make it possible to obtain a potentially high heterosis effect in F_1 due to the positive complementation of alleles, which causes a high expression of the trait in the hybrid (Schon et al., 2010). Carrying out reciprocal crosses between these groups will make it possible to establish the best cross-combination of parental forms (Melchinger and Gumber, 1998).

The acquisition and maintenance of various heterotic pools leads to a differentiation of the source material (lines) not related by origin: to an increase in allelic diversity among heterotic pools; to an increase in the degree of heterozygosity in F_1 and the potential level of heterosis; to a decrease in the specific combining ability and, correspondingly, the ratio of GCA to the SCA variance and ultimately to stable and efficient selection for heterosis (Melchinger, 1987; Melchinger and Gumber, 1998; Reif et al., 2005).

Genotype–Environment Interactions

Since heterosis is manifested in specific environmental conditions, it is important to take into account genotype–environment interactions. Under different exogenous factors, the type of inheritance in a particular hybrid combination can vary widely. Approaches of genetic analysis that are based on the testing of genotypes in various conditions are developed and make it possible to reveal the general and specific adaptive ability of genotypes, their stability, and breeding value and to select according to the adaptive capacity depending on a given breeding goal. Along with estimating the general and specific adaptive ability, such approaches make it possible to obtain information about the environment as backgrounds for selection (Zhuchenko, 1980; Kilchevsky and Khotyleva, 1985; Kilchevsky, 1986). In this case, the general adaptive ability (GAA) of the genotype characterizes the mean value of the trait under different environmental conditions, and the specific adaptive ability (SAA) characterizes the deviation from the GAA in a certain condition. The proposed technique is based on combining the linear and nonlinear part of the genotype response to the environment and thus differs from the method of K.W. Finlay and G.N. Wilkinson (1963), where the measure of stability is a linear reaction; G. Wricke's method (1962), where stability is assessed by a nonlinear reaction; and methods of S.A. Eberhart and W.A. Russell (1966) and G.C. Tai (1971), where the corresponding parameters of the linear and nonlinear reaction of the genotype are introduced.

Along with the above-mentioned works, a great contribution to the development of heterosis studies initiated by N.V. Turbin was made by scientists of the Institute of Genetics and Cytology of the National Academy of Sciences of Belarus, who developed not only genetics of the combinational ability property

(Turbin et al., 1974; *Geneticheskie osnovy...*, 2008), methodical problems of selection for heterosis and genotype–environment interactions (Kilchevsky and Khotyleva, 1985; Tarutina and Khotyleva, 1990), but also approaches to the use of reccurent selection (Kaminskaya, 1985), the study of mechanisms of cytoplasmic male sterility and its use in the production of hybrid seeds (Turbin and Palilova, 1975), and the study of genetics of polyploid plants in relation of using heterotic effect at the level of tri- and tetraploid hybrids in sugar beet (Bormotov and Turbin 1971; *Geneticheskie osnovy...*, 2008, 2014).

The data of numerous studies carried out over more than a century of studying heterosis show that this complex and intriguing phenomenon is the result of the action of the overall set of gene diversity, ways of interaction, and processes acting at different systemic levels and development stages of a organism. Certain studies, as a rule, concentrate on specific mechanisms in the context of specific features and operate within a limited variation of events and therefore are insufficient for a system interpretation of the mechanisms of this complex and unique phenomenon. The existing conceptual approaches of biology such as genomics, transcriptomics, metabolomics, etc., can facilitate the identification of underlying mechanisms and elements of the regulation of heterosis and clarify the prospects of their effective applying in agricultural practice.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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