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TRANSCRIPTION FACTORS OF THE MADS FAMILY IN PLANTS: RELATIONSHIP WITH DOMESTICATION TRAITS AND PROSPECTS FOR BREEDING

(review)

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Abstract

The traits of domestication, which are subdivided into three groups (productivity, adaptability, and reproduction) and together make up a domesticated syndrome that brings together taxonomically distant domesticated forms, remain economically significant in modern cultivated crops as well. A significant part of the genes that control domestication traits in plants are represented by the genes of transcription factors, in particular, those belonging to the MADS-domain family. MADS-domain proteins are key regulators of almost all aspects of plant reproductive development, including the determination of the flowering time, the inflorescence structure, the flower organ identity, the development of roots, fruits, and seeds, as well as the adaptive and stress response to adverse environmental conditions. The presented review describes the possible involvement of MADS-box genes in plant domestication and breeding. We discuss the role of MADS-box genes in the regulation of vernalization (plant response to prolonged cold treatment), bud physiological dormancy, inflorescence and flower structure, plant fertility and fruit qualitative traits (ripening characteristics, synthesis of carotenoids and anthocyanins, the number of seeds, fruit shuttering, fruit shelf life), as well as plant stress response (salinity, drought, temperature changes). The phenomenon of MADS-box gene functional pleiotropy and redundancy (due to the existence of paralogs) is considered. It has been supposed that MADS-box genes high structural and functional conservatism may indicate their high potential as tools for predictable fine tuning of crop phenotypes by combining (including dose-dependent) different alleles and paralogs of MADS-box genes. Another possible method is the separation of the pleiotropic functions of the MADS-box gene by introducing mutations in its coding or *cis*-regulatory sequence to alter specific protein-protein or protein-DNA interactions, as well as the pattern and/or level of expression, including in response to various external and internal signals. It is concluded that fundamental and applied studies of MADS-box genes in various plant species (both wild and cultivated) will not only lead to a deeper understanding of the evolution and development of modern plants, but will also greatly contribute to the improvement of crops, including using CRISPR/Cas and other modern technologies.

Keywords: transcription regulation, transcription factors, MADS-box genes, conservatism, pleiotropy, domestication traits, productivity, adaptation, reproduction, economically valuable traits, target genes

Crops have emerged on the course of domestication, in which wild plant species have adapted to cultivation by humans in the process of co-evolution with them [1]. At the same time, the domesticated forms developed traits useful for volume, quality, harvest and storage time of the crop, as well as for adaptation to the influence of the environment [1-4]. Together, they constitute a domestication syndrome that brings together taxonomically distant domesticated forms, and are subdivided into three groups - productivity, adaptability and reproduction [5, 6],

which remain economically significant in modern cultivated crops. According to various estimates, there are currently known from 1000 to 2500 semi- and fully domesticated plant species from 120-160 families [2, 7]. Thanks to intensive genetics, genomics and archeology research, a view on how domestication took place is gradually being formed [2, 3, 8-10], which is of interest both for deepening the understanding of evolutionary events and for modern breeding programs based on the knowledge of the molecular genetic characteristics of the regulation of economically valuable traits. Moreover, it is assumed that understanding the evolutionary origin and regulation of key features of domestication can help not only in the improvement of existing and breeding new varieties, but even in the domestication of new plant species [10].

Observations based on archaeobotanical studies, population genomic analysis, and the study of ancient DNA have shown that formation of the phenotype of various cultures with the fixation of key features takes about 2-3 thousand years [3, 10-14]. The main reasons for such a long process are considered to be the flow of genes between populations of nascent domestic plants and their wild ancestors [15, 16], as well as the polygenic nature of many traits [17]. Besides, it is assumed that, although some characteristics (for example, color and taste) are most likely due to a conscious choice of a person, most of the signs of domestication (resistance to shattering of seeds, synchronous germination, etc.) were initially the result of unconscious selection occurring naturally [10, 17]. Introgressive hybridization between wild relatives is considered as a mechanism of plant domestication [18], due to which the diversification of crops [19], for instance, the banana *Musa* spp. [20], wheat *Triticum aestivum* [21], rice *Oryza sativa* [22], corn *Zea mays* [23], barley *Hordeum vulgare* [24], apple *Mlus domestica* [25], and other perennial fruit crops [26] is happening today.

Interestingly, the genes underlying the traits of domestication and diversification in different plant species are in many cases the same or closely related [4, 5, 9, 27]. It forms the basis for the use of evolutionary homology in order to transfer the desired traits to many species, of which by using new technologies (for example, CRISPR / Cas) that make it possible to repeat the genetic stages of domestication [28-30].

A significant part of the identified genes associated with the traits of domestication are transcription regulator genes. Although they account for only about 5% of protein-coding genes in the plant genome, changes in them can affect a whole set of properties in a relatively short time [31-33].

Genes of transcription factors belonging to the MADS-domain family, which encode the conserved nucleotide sequence MADS-box (MADS-box genes), found in almost all eukaryotes are often considered the evolutionary targets. It is believed that duplication of precursors of MADS-box genes and subsequent diversification and neo- and subfunctionalization of duplicates played and play one of the key roles in the evolution and diversity of plants. [33-35]. While duplicates of most genes lose their functions, genes of transcription factors, including those that regulate transcription with the MADS domain, retain and renew their functions after duplication, which contributes to the expansion of genetic opportunities for the emergence of evolutionary innovations [36]. Moreover, analysis of the genomes of three pepper species - *C. baccatum*, *C. chinense*, and *C. annuum* showed that MADS-box genes are included in the top ten gene families with the largest mass duplication [37], which indicates the key positions occupied by these genes in evolution and diversification of plants. MADS-domain transcription factors are key regulators of almost all aspects of plant reproductive development, including the determination of the flowering time, the inflorescence and flower

structure, formation of pollen, seeds, fruits, as well as development of roots [38], and plant response to various stresses [39]. All this is another confirmation of the importance of MADS-box genes as objects of selection during the domestication of crops. Therefore, the data of the functional analysis of MADS-box genes in combination with the available biological resources can be used to improve various reproductive traits of crops using modern molecular breeding technologies.

This review is focused on the family of MADS transcription factors and their participation in the formation of characteristics of productivity, adaptability, and reproduction in plants.

Transcription factors of MADS-domain family. The abbreviation MADS comes from the names of the family founders: MINICHROMOSOME MAINTENANCE 1 (MCM1) (*Saccharomyces cerevisiae*), AGAMOUS (AG) (*Arabidopsis thaliana*), DEFICIENS (DEF) (*Antirrhinum majus*) and SERUM RESPONSE FACTOR (SRF) (*Homo sapiens*) (38). MADS-domain transcription factors are characterized by the presence of a highly conserved DNA-binding N-terminal MADS-domain [38].

In plants, MADS-domain transcription factors are represented by two structural types: type I — the protein including the MADS_SRF_like MADS-domain (NCBI: cd00266); type II, or MIKC, - the protein includes the MADS_MEF2_like MADS-domain (NCBI: cd00265), the interdomain I-site, the conservative keratin-like K-domain K-box (NCBI: pfam01486) and the variable C-region located sequentially (40). The first to isolate the MIKC genes, when knocked out, lead to a complete or partial homeotic transformation of some flower organs into others. Thus, the loss of the function of *DEF* or its ortholog *APETALA3 (AP3)* in *Arabidopsis* leads to the development of sepals instead of petals and carpels instead of stamens, and the *agamous-1* mutation causes the transformation of stamens into petals [41, 42].

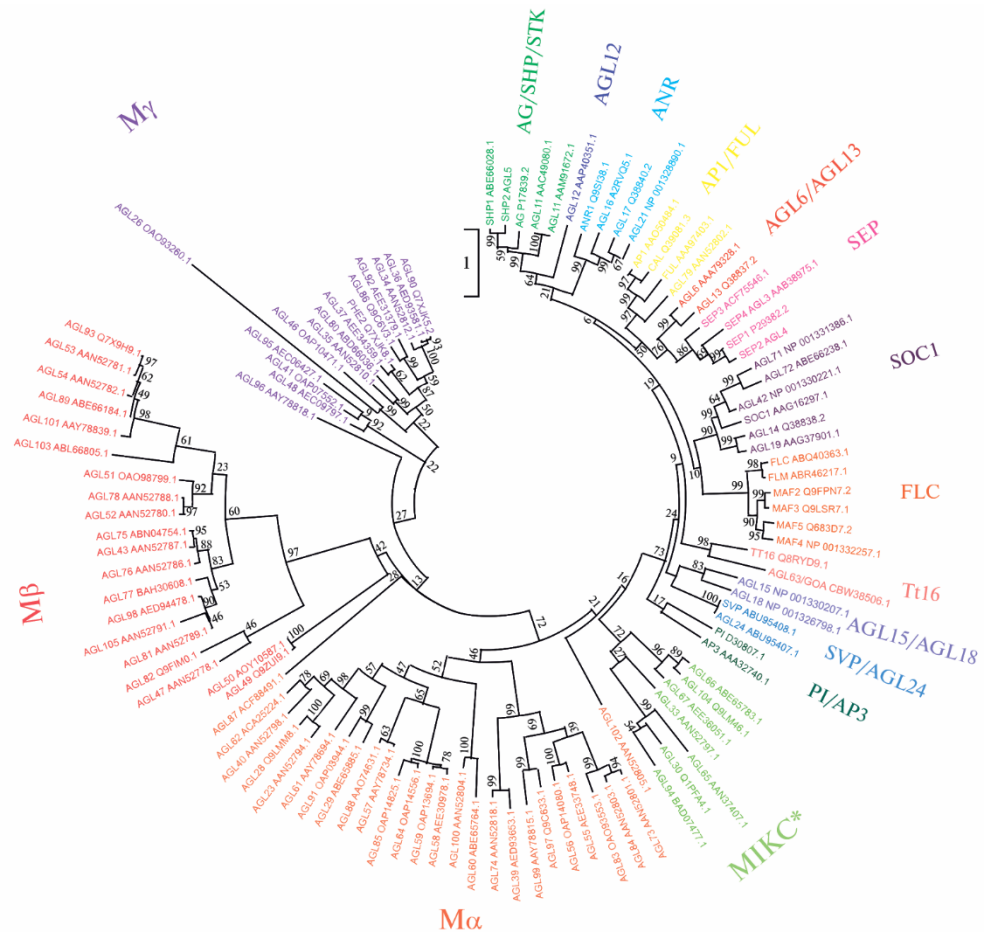
The number of MADS-box genes in the genomes of various plant species, including crops

Taxonomic group	Species	Gene number	Reference
Moss	*Physcomitrella patens*	23	[43]
Glycophytes	*Selaginella moellendorffii*	40	[132]
Gymnospermae	*Picea abies*	278	[33]
	Pinus taeda	367	[133]
	Gnetum gnemon	41	[133]
Angiosperm monocotyledons	Model plant for grain crops species *Brachypodium distachyon*	75	[33]
	Rice *Oryza sativa*	75	[33]
	Wheat *Triticum aestivum*	180	[134]
Angiosperm dicotyledons	Model species *Arabidopsis thaliana*	107	[40]
	Basal group of flowering plants *Amborella trichopoda*	33	[132]
	Brassica rapa	160	[135]
	Glycine max	106	[136]
	Malus domestica	146	[137]
	Citrullus lanatus	39	[138]
	Lactuca sativa	82	[139]
	Vitis vinifera	90	[140]
	Solanum tuberosum	167	[33]
	Solanum lycopersicum	131	[33]

In total, the genome of the *A. thaliana* model plant contains 107 MADS-box genes (40); genomes of other plant species, including crops, include from 23 to 367 of them (table). The MADS-box family is divided into subfamilies, most of which are preserved throughout the evolution of seed plants (see Fig.), and the functions of genes within each subfamily in different plant species are often homologous [40, 43]. For example, the genome of all flowering plant species contains

orthologs of the *AP3 / DEF* and *AGAMOUS (AG)* genes involved in the development of reproductive organs [35, 40, 43], as well as the flowering time gene *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1 (SOC1,* or *AGL20)* [44].

The presence in the plant genome of duplicates of MADS-box genes that have undergone subfunctionalization leads to redundancy of function [45]. Thus, *AG* is involved in the reproductive development of a flower, while its paralogs *SHATTERPROOF1 (SHP1)* and *SHP2* are involved in the development of ovules [46]. This is due to differences in the expression patterns of these genes, since overexpression of *SHP1* and *SHP2* in *Arabidopsis* plants with the *ag* mutation is able to restore the development of stamens and carpels [46].



Phylogeny of MADS-domain transcription factors in *Arabidopsis thaliana*. Subfamilies are highlighted in different colors. The Mα, Mβ and Mγ subfamilies include type I MADS-domain proteins, the rest of the subfamilies are MIKC type II MADS-domain proteins. Next to the name of each protein is its identification number in the NCBI database (https://www.ncbi.nlm.nih.gov/). Bootstrap values are indicated at the base of the branches. The dendrogram was built using the MEGA 7.0 program (https://www.megasoftware.net/) using the maximum likelihood method.

Two genes involved in the control of the identity of the flowering meristem, *APETALA1 (AP1)* and *CAULIFLOWER (CAL)*, on the contrary, have similar expression patterns, but differ in functionally, partially duplicating each other [47]. While plants with the *ap1* mutation show strong defects in the identity of the flowering meristem and flower organs, the *cal* phenotype is similar to the wild type, while the *ap1 cal* double mutation has the cauliflower phenotype [47, 48]. It has been shown that the functional difference between CAL and AP1 is partly due

to several substitutions of amino acid residues that alter the pattern of protein-protein interactions [49].

The results of intensive studies of the evolution of MADS-box genes and their contribution to the evolution and diversification of flowering plants allow us to make assumptions about the role of MADS-box genes in the domestication of flowering plants [33-35]. Next, we will consider the economically valuable traits of modern cultures and their relationship with the MADS-box genes.

Flowering time of plants. Vernalization. With the transition of a plant from vegetative growth to reproductive development, the apical meristem of the shoot becomes an inflorescence meristem, on the periphery of which flowering meristems are formed. Control of this process is one of the targets of adaptation mechanisms [50]. Analysis of natural variations, mutations, and transgenic *A. thaliana* plants that bloom later or earlier than the wild type revealed gene loci involved in the regulation of flowering time [50].

Today, six main signaling pathways are known, under the influence of which the transition to flowering occurs. Of these, three (the autonomous pathway, the age pathway, and the pathway mediated by gibberellins) are largely independent of external signals, and the fourth (the photoperiod pathway) starts or stops flowering in response to changes in day length. The remaining two paths are temperature-dependent. Together, signaling pathways control the main regulators of flowering time - the MADS-box genes *FLOWERING LOCUS T (FT), FLOWERING LOCUS D (FD),* and *SOC1*, whose products activate the transcription of genes for the identity of the inflorescence and flower meristems [44, 51].

The temperature-dependent signaling pathway of vernalization, reflecting the plant's susceptibility to prolonged exposure to cold, effectively uses the MADS-box genes [51-54]. The vernalization syndrome in plants probably arose as an adaptation to seasonal cold and local climatic conditions [52] and is important for growing crops: spring varieties insensitive to vernalization are sown in spring, while sensitive winter varieties - in autumn [55]. Thus, vernalization, obviously, was the goal of artificial selection during domestication of monocotyledonous and dicotyledonous crops, and the key targets in this case were the MADS-box genes.

One of them is the flowering repressor *FLOWERING LOCUS C (FLC*, or *FLF): in Arabidopsis*, the FLC factor suppresses the transcription of genes for the central flowering stimulators *SOC1, FT*, and *FD* [44, 51, 53]. Prolonged cold (vernalization) interferes with the expression of *FLC*, including epigenetic mechanisms, in particular, the modification of histones at the *FLC* locus, which, in turn, allows the activation of genes promoting flowering [54]. The genetic variability of *FLC*, which determines the amount and activity of the synthesized protein, can alter the need for vernalization in different *Arabidopsis* ecotypes [54]. Therefore, variations in *FLC* orthologues could play an important role in the adaptation of crops to different climatic conditions [56].

A striking example of the importance of the *FLC* genes is the species of the genus *Brassica L.* (*Brassicaceae* family) [57]. Thus, early flowering in Chinese cabbage *Brassica rapa* ssp. *pekinensis* (leafy vegetables) reduces the quality of the crop. Oilseeds (oilseed rape *Brassica napus* and field mustard *Brassica rapa* ssp. *oleifera*) have winter and spring varieties suitable for adapting reproductive development to various environmental conditions. Root vegetables (turnip *Brassica rapa* ssp. *rapa*) and, finally, cabbage (*Brassica oleracea*, varieties - cabbage var. *oleracea*, broccoli var. *italica*, cauliflower var. *botrytis*) are also subject to temperature-dependent regulation of flowering time.

Four *FLC* orthologs (*BrFLC1, BrFLC2, BrFLC3*, and *BrFLC5*) have been identified in the *Brassica* genome, variations of which determine the differences

in the flowering time of turnip cultivars [56, 58-60]. The *BrFLC1* gene is associated with late flowering of Chinese cabbage [58], and a mutation in the *BrFLC2* sequence is associated with accelerated flowering of rapeseed [61]. Variations in the *FLC* gene are responsible for differences between spring and winter rapeseed varieties [56] and changes in flowering time in broccoli [62]. Note that in the genome of *B. napus* resulting from the alloploidy between the paleopolyploid ancestors of *B. rapa* and *B. oleracea*, the flowering time genes are excessively represented; in particular, the *FLC* has nine identifiable copies [57]. Obviously, during the formation of *Brassica* species and their domestication, a number of molecular changes in the *FLC* orthologues and the presence of several *FLC* paralogs contributed to the differences in the sensitivity to vernalization and flowering time.

FLC orthologues have also been identified in cereals - barley (*H. vulgare*), wheat (*T. aestivum*), rice (*O. sativum*), and corn (*Z. mays*) [63]. Within the clade FLC of monocots, there are subclades *OsMADS51* and *OsMADS37*; the *OsMADS51* subclade is divided into two groups - *ODDSOC1* and *ODDSOC2* [63]. In wheat, the homologues of *ODDSOC2, TaAGL42* and *TaAGL33*, are characterized by different expression profiles in spring and winter varieties [63, 64]. This suggests that members of the *ODDSOC2* group were part of an adaptive mechanism through which different populations of cereals acquired different needs for vernalization [63, 64].

The *A. thaliana* genome contains five *FLC* paralogs: *MADS AFFECTING FLOWERING2 (MAF2*, or *AGL31), MAF3 (AGL70), MAF4 (AGL69), MAF5*, and *FLOWERING LOCUS M (FLM,* or *MAF1, AGL27*) [63]. The study of different populations of *A. thaliana*, representing the genetic diversity of the species, confirmed that the quantitative trait loci (QTL) of flowering include all three types of *FLC*-like genes (*FLC, FLM*, and *MAF2-5*) [65]. In addition, the MADS-box genes of the *StMADS11* clade, which in *A. thaliana* is represented by genes *AGAMOUS-like* 24 (*AGL24*) and *SHORT VEGATATIVE PHASE (SVP)*, are actively involved in the temperature-dependent regulation of flowering [34, 44].

Depending on the temperature, the *FLM* gene has different forms of splicing, two of which generate two different proteins, FLM-β and FLM-δ [34]. FLM-β is considered to be the main functional form of FLM responsible for temperature response [34]. It is assumed that the SVP/FLM-β complex binds to the promoters of target genes, such as the flowering inducer SOC1, repressing flowering, while the SVP/FLM-β complex cannot bind to DNA and, competing with SVP / FLM-β, acts as an indirect flowering inductor [34]. The amount of FLM-β increases at low temperatures, and elevated temperatures destabilizes the SVP protein, which implies that higher temperatures favor flowering due to a decrease in the formation of the SVP/FLM-β complex [34].

The tandem *MAF2-5* genes serve as flowering repressors [34]. The *MAF2* gene prevents early flowering in response to short periods of cold, thus avoiding the induction of flowering in the warm autumn period before the winter cold [66]. Like *FLM, MAF2* and *MAF3* are characterized by temperature-dependent alternative splicing [67, 68]. The low-temperature form of *MAF2* encodes a protein that interacts with *SVP* to inhibit flowering; at elevated temperatures, splicing shifts towards a variant that encodes a protein that does not interact with *SVP*; thus, at lower temperatures, *MAF2* and *SVP* suppress flowering simultaneously with *FLM* and *SVP* [68]. This may also be true for other *MAF* genes; however, the activity of *MAF* genes is not excessive, which is confirmed by the analysis of mutant phenotypes for individual genes [68]. Tandem genes are especially susceptible to sequence rearrangements during non-allelic homologous recombination [69]. Similar structural deviations in the *MAF2-5* cluster could serve as a tool for adaptation

of species to different climatic conditions.

Besides *FLC* orthologs and paralogs, wheat vernalization is largely regulated by three *VERNALIZATION (VRN)* genes, two of which, *VRN1* and *VRN3*, are MADS-box genes [63]. Vernalization leads to an increase in the expression of the flowering stimulator *VRN1* (ortholog *AP1*), the product of which suppresses the transcription of the flowering repressor gene *VRN2*, mitigating the repressive effect of this gene on the flowering stimulator *VRN3* (orthologue *FT*); *VRN3* then upregulates *VRN1* expression resulting in positive feedback and induces flowering [63]. Given that the *FLC* clade exists in monocots, it seems likely that both *FLC* and *AP1 / VRN1*-like genes were present in the genome of ancestral dicotyledonous and monocotyledonous species, and each group was replenished differently in development of susceptibility to vernalization [63]. A wide variety of responses to vernalization in wheat, barley, and ryegrass (*Lolium perenne*) samples is caused by various mutations in the regulatory regions of *VRN1* orthologs [70-72]. Interestingly, the wheat MADS-box *VRN4* gene, which appeared as a result of the *VRN1* gene duplication, is not present in all wheat samples; its activity reduces the need for vernalization, which can be used by breeders to modulate the vernalization response [73].

Physiological rest of buds. For agriculture, it is important to obtain fruit trees that are adapted to local climatic conditions in terms of the timing of recovery from dormancy. Induction of bud dormancy due to winter cold is an adaptive feature of perennial plants of a temperate climate, which provides optimal protection of vegetative and reproductive meristems from low temperatures [74].

Similar to the regulation of flowering by vernalization, the emergence of dormant buds of woody plants requires exposure to low temperatures during a certain period of time, and the *DORMANCY-ASSOCIATED MADS-BOX* genes (*DAM, SVP* and *AGL24* orthologs) are key regulators of this process [74, 75].

The genome of peach (*Prunus persica*) contains a cluster of six tandemly located *PpDAM1-PpDAM6* genes, which are considered one of the most important genetic elements underlying the response to vernalization [74, 75]. In apple (*Malus × domestica*) and pear (*Pyrus communis*), the main QTLs associated with the response to cold and dormancy in the buds are also associated with the *DAM* gene loci [75].

Thus, it is believed that the *DAM* genes played a key role in fine tuning the flowering time and adaptation to different climatic zones in cultivated plants. It was also shown that, in addition to the *DAM* genes, overexpression of the MADS-box gene *BpMADS4* (subfamily *FUL*) of birch (*Betula pendula*) in poplar plants (*Populus tremula*) leads to a delay in the winter transition of buds to the dormant state [76].

Inflorescence structure. Inflorescence structure was an important target trait for increasing yields during plant domestication [9].

The most vivid example is the head of cauliflower and broccoli, consisting of a dense mass of inflorescences with a delay in development, respectively, at a very early and later stage, as well as many varieties with an intermediate phenotype [77, 78]. The cauliflower phenotype in mutant *Arabidopsis* plants is explained by the *ap1 cal* double mutation [47]. Similarly, in cauliflower and broccoli cultivars, the structure and function of the MADS-box genes *BoCAL* and *BoAP1* are disrupted [79]. This indicates the selection of certain *BoCAL* and *BoAP1* alleles, as a result of which plants with modified inflorescences were obtained [78]. At the same time, the existence of several *AP1* paralogs in the *B. oleracea* genome can determine the differences between different phenotypes by inflorescences [78, 79].

Another example is the branched inflorescences in tomato (*Solanum lyco-*

persicum), the formation of which is regulated by MADS-box genes of the *SEPALLATA1 (SEP1)* subfamily: *JOINTLESS2 (J2), ENHANCER OF JOINTLESS2 (EJ2)*, and *LONG INFLORESCENCE (LIN)* [80]. Branching of tomato inflorescences is usually accompanied by a high percentage of barren flowers, and combinations of different mutant alleles *J2, EJ2* and *LIN*, depending on the gene dose, can reduce branching and simultaneously increase the fruiting rate, which increases the yield [80].

Another important target trait is branching of shoots (tillering) [81]. It was shown that the MADS-box gene *OsMADS57* (subfamily *AGL17*) affects the tillering of *O. sativa* rice plants. The mutation of the transcription factor *OsMADS57*, associated with the absence of the C-terminal region, significantly increases tillering of the rice plant and, thus, increases the grain yield [82].

The *OsMADS1* gene (subfamily *SEP1*), the overexpression of which leads to dwarfism of rice plants [83], can be another target for altering the inflorescence structure.

Flower structure. Sterility. According to the ABCDE model, the budding of flowering organs is determined by the combinatorial interaction of genes of five different classes of activity: the identity of sepals is determined by genes of classes A and E, petals - A, B, and E, stamens - B, C, and E, carpels - C and E, and ovules - C, E and D [35]. Almost all ABCDE genes encode MIKC-type transcription factors containing MADS domains. In *Arabidopsis*, this is *AP1* (class A); *AP3* and *PISTILLATA* (*PI*) (B); *AG, SHP1* and *SHP2* (C), *SEEDSTICK (STK)* (D); *SEP1, SEP2, SEP3* and *SEP4* (E) [35]. Loss of the function of these genes leads to homeotic transformations of the flower. For example, the *ag* mutation causes petals to replace stamens, and carpels to new flowers with the same developmental model [41]. Such phenotypes are attractive in view of breeding for ornamental plants. For example, *ag* mutations, including those in the cis-regulatory regions of the gene (changing the profile of its expression), cause double flowers to form in the ornamental varieties of Japanese cherry *Prunus lannesiana* and rose *Rosa* spp. [84, 85]. In the apple tree, suppression of the activity of *AG* orthologues (*MdMADS15* and *MdMADS22*) leads to the appearance of decoratively attractive flowering trees and a decrease in the number of seeds due to male sterility [86].

Seedlessness and male sterility of apple fruits are also observed in the case of knockout of the *PI, MdPI* orthologue, when flowers form sepals instead of petals and carpels instead of stamens [87].

Male sterility and prevention of outcrossing are desirable in many crops as these traits avoid gene flow between the cultivated plants and their wild relatives. A way to keep genes in check while maintaining male fertility is to prevent the flower from opening (cleistogamy). This is shown on the example of rice, flowers of which open under the influence of lodicules - organs homologous to petals. Mutant alleles of the rice *AP3* ortholog *SUPERWOMAN1 (SPW1,* or *OsMADS16*), depending on the allele strength, can cause a number of phenotypic changes, including male sterility and cleistogamy [88].

A number of studies have identified the key role of type I proteins containing MADS-domains in the regulation of plant reproduction (in particular, in determining the development of the female gametophyte, embryos, and endosperm) and their decisive importance for establishing reproductive boundaries between plant species [89].

Quality of fruits and seeds. Fruit quality is one of the main signs of plant domestication, including changes in the number and size of fruits, the number of seeds, the ability to crack, the rate of ripening, storage period and shelf

life, as well as the visual appeal and taste characteristics of the fruit. As the results of numerous studies show, the key regulatory role in the formation of these traits here also belongs to the MADS-box genes. Thus, in *Arabidopsis*, the *SHP1, SHP2*, and *STK* genes overemphasize the identity of the ovules; triple mutation *stk shp1 shp2* leads to abortion or lack of seeds [46].

Seedlessness refers to the desirable traits in the selective improvement of juicy fruits, when it helps to extend their shelf life, as well as the use for the production of juices. The reason for seedlessness in grape varieties (*Vitis vinifera*) is a decreased level of expression of the *STK* ortholog, *VviAGL11*, due to changes in its promoter, where the repeat length is inversely correlated with seed development [90]. The genetic characteristic of the *VviAGL11* locus allows winemakers and breeders to evaluate plants for the number of seeds in fruits before reaching the reproductive stage [91]. Expression levels of the *STK* ortholog in tomato - *SlyAGL11* positively correlate with the degree of seed development; knockout of *SlyAGL11* results in seedless fruit [92]. Suppression of the expression of *STK* orthologues in petunia (*Petunia* × *hybrida*) - *FBP7* and *FBP11* - led to the complete replacement of ovules by carpels-like structures [93]. Thus, *STK* orthologues in various plant species can be used in breeding in order to reduce the number of seeds.

Cracking of the fruit leads to problems in the harvest of grain and oilseeds. It is known that pod cracking in *Arabidopsis* is excessively regulated by *SHP1* and *SHP2* genes; in the case of a double mutation *shp1 shp2*, the ripe pod remains closed [46]. Possibly, *SHP* genes turned out to be a target in the selection of cereals for the sign of non-shedding grain. Knowledge of the function of these genes can be used to increase yields by reducing seed shedding. For example, suppression of the *SHP1* - *BnSHP1* ortholog in oilseed rape plants leads to an increase in pod resistance to cracking, thereby increasing crop yield [94].

The FUL transcription factor containing the MADS-domain is also involved in fetal development, which regulates the differentiation of fetal cells during development and serves as a negative regulator of *SHP1* and *SHP2* expression [95]. Overexpression of the *FUL* ortholog of mustard - *MADSB* in *B. napus* plants reduces pod cracking [96]. Interestingly, in the case of a juicy tomato fruit, suppression of the activity of two *FUL* orthologues, *FUL1* and *FUL2*, causes a strong delay in fetal maturation, presumably due to a decrease in the synthesis of ethylene and carotenoids [97].

Another important feature taken into account in tomato breeding is the absence of an articular area on the peduncle, which facilitates fetal shedding [98]. Several MADS-box genes are involved in the specification of the drop zone [98]. Among them, *J2* is considered the most suitable for plant breeding; the *j2* mutation is present in many tomato lines without an articular zone [80, 98]. A mutation in another MADS-box gene, *JOINTLESS1 (J1*, or *JOINTLESS*), which is homologous to the *SVP* flowering time gene, also leads to an arthritic phenotype [99]. However, its value for breeding is questionable, since *j1* inflorescences are prone to re-version to vegetative development after the formation of several flowers [80].

SEP orthologs have been shown to be involved in the ripening of juicy fruits. Suppression of the activity of *SEP* homologues of banana and apple trees, *MaMADS1 / MaMADS2* and *MdMADS8 / MdMADS9*, respectively, inhibits the ripening of climacteric fruits and increases their shelf life [100, 101]. *SEP* orthologs are also involved in the development of non-climacteric (ethylene insensitive) fruits such as strawberries [102]. It points to *SEP* orthologs as a versatile target in optimizing fruit ripening.

The MADS-box gene *LeMADS-RIN* (*SEP* subfamily), a mutation in

which leads to fetal immature, is considered a key regulator of the ripening of the juicy tomato fruit, as well as an important gene involved in domestication [103]. Green and hard *rin* fruits are characterized by the absence of an increase in ethylene synthesis and accumulation of pigments and aromatic compounds [103]. In the heterozygous state, the *rin* mutation is widely used in the breeding of tomato varieties, since it prolongs the shelf life of fruits [104]. However, in this case, the nutritional and gustatory value of the fruit is disturbed (due to the low content of likopin and other compounds) [103]. Using the *CRISPR / Cas9* approach, a number of tomato lines with different *SNPs* (single nucleotide polymorphisms) and short indels in the coding sequence of the *RIN* gene were created, leading to different degrees of manifestation of the fetal immature phenotype [105]. These lines are considered as candidates for use in breeding varieties with an extended shelf life of fruits [105].

It is worth mentioning the MADS-box genes involved in the initiation of pathways for the biosynthesis of metabolites of the succulent fruit. Succulent plant fruits (such as tomato and pepper) contain two important types of secondary metabolites — anthocyanins and carotenoids, which not only color the fruit, but also act as antioxidants [106].

The *LeMADS-RIN* gene is one of the key factors in the regulation of carotenoid biosynthesis in tomato fruits [107]. In this case, the genes of the key enzymes of carotenoid biosynthesis, phytoinsynthase 1 (PSY1) and phytoindesaturase (PDS), serve as the target of the *LeMADS-RIN* product, while the homologues of AG, TOMATO AGAMOUS (TAG1) and TAG-LIKE1 (TAGL1), regulate the biosynthesis of carotenoids genes for lycopene-β-cyclase (CYC-β) and carotenoid isomerase (CRTISO) [108, 109]. The MADS-box gene *SlCMB1* (*SEP* subfamily) is also involved in the induction of expression of the *PSY1* and *PDS* genes and inhibition of the transcription of lycopene cyclase genes (*CYCB, LCYB*, and *LCYE*) [110].

A lot of evidence has been found for the effect of MADS-box genes on the biosynthesis of anthocyanins in juicy fruits. Thus, the expression of *MrMADS01* (*SEP* subfamily) in the berries of the red gumboil (*Myrica rubra*) significantly increases at the last stage of maturation, which allowed the authors to suggest the participation of this gene in the biosynthesis of anthocyanins [111]. Silencing of the *PaMADS7* gene in sweet cherry (*Prunus avium*) inhibited fruit ripening and influenced, among other things, the content of anthocyanins [112]. In red pear (*Pyrus*) fruits, the *PbrMADS11* and *PbrMADS12* genes are involved in the activation of the expression of structural genes of the anthocyanin pathway, as well as in the regulation of the anthocyanin synthesis reaction in response to light and temperature changes [113].

Evidence that MADS-box genes were the target of selection during domestication was also obtained in studies performed on maize [114]. For example, the gene *ZEA AGAMOUS-LIKE1 (ZAGL1*), which is a homologue of the flowering time gene *SOC1*, during the domestication stage, apparently, not only influenced the timing of flowering, but also contributed to the increase in the number of rows of corn on the cob, thereby increasing the size of the fruits and yield [114, 115].

Plant response to stress. The signs of plant domestication include the mechanisms of resistance and adaptation to unfavorable environmental factors. The participation of MADS-box genes in the regulation of plant resistance to various stresses, such as dehydration, salinity, low and high temperatures, as well as oxidative and biotic stresses, has been recently noticed by researchers [39].

For example, in rice, the *OsMADS26* gene (ortholog *AGL12*) is known as a regulator of responses associated with the response to drought and disease caused

by pathogens [116]. Another gene, *OsMADS57* (clade *AGL17*), functions as a stimulator of resistance to cold stress; in addition to cold, gene expression is induced by exposure to salinity, drought, and abscisic acid [117].

The *Arabidopsis SVP* MADS-box gene causes modifications in some developmental processes and gas exchange functions in response to dehydration: plants with the *svp* mutation exhibit increased moisture loss and maintain a significant rate of photosynthetic CO_2 assimilation throughout the dry period [118].

In tomato, salt stress, dehydration, and injury induce the expression of the *SlMBP11* gene (ortholog *AGL15*) [119]. At the same time, a close homologue of *SIMBP11*, the *SIMBP8* gene, has the opposite effect on the resistance of tomato plants to salinity [120]. The *TOMATO APETALA3 (TAP3*) gene is induced under cold stress conditions [121], while the expression of the *TAP3, TOMATO MADS BOX GENE6 (TM6*), and *LePISTILLATA (LePI*) genes is suppressed in the anthers under high temperature conditions [122].

In response to cold, drought, and salt stress, expression of the *CaMADS* gene (clade *SEP1*) [123] is induced in pepper plants (*Capsicum annuum*) [123], and in *Ginkgo biloba — GbMADS9* (clade B-sister) [124]. Transcription of *AGAMOUS LIKE21 (AGL21*) in *Arabidopsis* is induced by various stresses (including osmotic stress) and phytohormones, which suggests the involvement of the gene in the regulation of the plasticity of the root system (its ability to change the structure under the influence of environmental factors) and seed germination [125].

Another important stress for plants is soil depletion in minerals such as phosphorus. It has been shown that nine MADS-box genes are differentially regulated in wheat (*T. aestivum*) under P-deprivation [126]. A functional analysis of one of them, *TaMADS51*, showed that its overexpression under conditions of phosphorus deficiency improves plant growth, as well as increases biomass, phosphorus accumulation, and increases antioxidant enzymatic activity [126]. Another example is the *ARABIDOPSIS NITRATE REGULATED 1* gene (*ANR1*, or *AGL44*), a well-known positive regulator of root development in response to nitrate availability [127].

Pleiotropy and redundancy of MADS-box genes. The above examples show that MADS-box genes, whose functions are pleiotropic and often redundant, were involved in the processes of plant domestication. It is worth noting that, in many cases, the gene networks were not completely disrupted - more subtle variations were introduced, which made it possible to fine-tune the phenotype [128]. An example is *Brassica* and tomato, where variations in *FLC*- and *SEP*-like genes lead to modulation, respectively, of flowering time and inflorescence structure [62, 80]. In many cases, certain traits are over-regulated by several paralogs of the MADS-box genes, highlighting their potential for fine-tuning the phenotype. For example, several *FLC* paralogs are present in the *B. rapa* genome [58-62], and the combination of different allelic variants of these genes can make it possible to adapt the flowering time to a wide range of climatic conditions. In the same way, the combination of different alleles of *SEP*-like genes makes it possible to customize the structure of the tomato inflorescence [80]. However, the pleiotropic effects of many MADS-box genes can create problems: while mutations in *SEP* genes *J2* and *EJ2* of tomato separately have a beneficial effect, a double mutation due to the redundancy of the function of these genes turns out to be harmful: although *j2 ej2* plants show increased branching of inflorescences, at the same time the number of barren flowers increases [80]. However, in many cases, this and similar effects can be mitigated by careful selection of combinations of alleles that affect one, but not another trait [80]. In addition, one

should take into account the dose-dependent effect of many alleles of the MADS-box genes [129], as well as paralogs of the MADS-box genes, for instance, the *SEP* genes in *Arabidopsis* [130], and this adds opportunities for fine-tuning the phenotypic result.

According to the "quartet" model, transcription factors of the MADS family perform their functions as part of tetramers and can have many overlapping DNA targets, some of which are regulated in the opposite way using protein complexes of different compositions [35, 38, 131]. Therefore, in the absence of functional redundancy, the introduction of mutations into the coding sequence of MADS-box genes can change specific protein-protein or protein-DNA interactions and, as a consequence, separate the pleiotropic functions of one gene [131].

In conclusion, it is worth noting that the high functional conservatism of the MADS-box genes and the detailed characterization of their homologues in model and cultivated plants make these genes perfect candidates for predictable manipulation of phenotypes [80]. This can, in particular, be achieved by changing the cis-regulatory elements of the MADS-box genes and, as a consequence, the level of their spatio-temporal expression (during a specific phase of development, in a specific tissue), including in response to various signals [128]. Modifications in the coding region can also be used to fine-tune the phenotype, since the function of proteins of the MADS family is largely determined by protein-protein and protein-DNA interactions, and, by changing partners and targets, the same protein can participate in different developmental pathways (determination of the identity of organs and other parameters of plant growth and ontogenesis; response to stress; formation of various economically valuable traits) [131].

Thus, in plants MADS-box genes are considered one of the key targets that were involved in the formation of domestication traits influencing such properties as productivity, adaptability, and reproduction, that remain economically significant in modern cultivated crops. The variability of the MADS-box homologues of the *FLC, SOC1*, *SVP*, and *VRN* genes determines the differences in the time of flowering initiation, including in response to low temperatures. Changes in the process of physiological dormancy of the kidneys are associated with the homologues *SVP, AGL24*, and *FUL*. Morphological diversification of inflorescence and flower is associated with homologues *AP1 / CAL, SEP, AP3, PI, AG*, and *AGL17*, while sterility and the number of fruits and seeds are associated with *AG, SEP, FUL*, and *SVP*. Homologues of the MADS-box genes of *SVP, SEP, AP3, AGL12, AGL15, AGL17, AGL21*, and *AGL44* are associated with differences in plant stress response. Considering the amount of accumulated qualitative and quantitative data, the prediction of specific phenotypic consequences of changes in MADS-box genes is much more realistic than in the vast majority of genes from other families. Continued fundamental and applied research on MADS-box genes in a wide variety of species will not only lead to a deeper understanding of plant development and evolution, but will also greatly contribute to crop improvement.

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