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LARGE-SCALE BIOLOGY ARTICLE

Decreased Nucleotide and Expression Diversity and Modified Coexpression Patterns Characterize Domestication in the Common Bean[W][OPEN]

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Using RNA sequencing technology and de novo transcriptome assembly, we compared representative sets of wild and domesticated accessions of common bean (*Phaseolus vulgaris*) from Mesoamerica. RNA was extracted at the first true-leaf stage, and de novo assembly was used to develop a reference transcriptome; the final data set consists of ~190,000 single nucleotide polymorphisms from 27,243 contigs in expressed genomic regions. A drastic reduction in nucleotide diversity (~60%) is evident for the domesticated form, compared with the wild form, and almost 50% of the contigs that are polymorphic were brought to fixation by domestication. In parallel, the effects of domestication decreased the diversity of gene expression (18%). While the coexpression networks for the wild and domesticated accessions demonstrate similar seminal network properties, they show distinct community structures that are enriched for different molecular functions. After simulating the demographic dynamics during domestication, we found that 9% of the genes were actively selected during domestication. We also show that selection induced a further reduction in the diversity of gene expression (26%) and was associated with 5-fold enrichment of differentially expressed genes. While there is substantial evidence of positive selection associated with domestication, in a few cases, this selection has increased the nucleotide diversity in the domesticated pool at target loci associated with abiotic stress responses, flowering time, and morphology.

INTRODUCTION

Plant domestication has long stimulated scientific interest. As stated by Charles Darwin, domestication can be considered a giant evolutionary experiment (Darwin, 1875), while from a plant-breeding perspective, understanding domestication is key to the development of breeding strategies and the identification of useful genetic variants.

Selection related to domestication has modified a number of traits that now distinguish the modern crops from their wild forms. These common features of many crop species contribute collectively to the "domestication syndrome" (Gepts and Papa, 2002), and they include the size, shape, and color of the plant organs used by humans (e.g., of seeds, fruit, and leaves) and seed dispersal (e.g., shattering, dormancy). Indeed, while increased seed and fruit size has been the most impressive change from the wild to the domesticated forms, the loss of seed dispersal mechanisms represents a major factor that has reduced the fitness of domesticated plants in the wild environment and has thus prevented these plants from reproducing outside the agro-ecosystem.

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The population genetics model of domestication predicts a reduction in diversity and increased divergence between wild and domesticated populations due to demographic factors affecting the whole genome and selection at target loci (Glémin and Bataillon, 2009). Allogamous species, such as maize (*Zea mays*), are generally characterized by a lower genetic bottleneck effect compared with autogamous species like the common bean (*Phaseolus vulgaris*) (Bitocchi et al., 2013). In particular, resequencing data have confirmed that in autogamous species, such as soybean (*Glycine max*) and rice (*Oryza sativa* ssp *japonica*) (Lam et al., 2010; Xu et al., 2012), a reduction in diversity has arisen as an effect of domestication, as also reported for the silkworm (*Bombyx*) and for mammalian species (Xia et al., 2009; Vonholdt et al., 2010; Lippold et al., 2011).

Signatures of selection during domestication have been reported for 2 to 4% of genes expressed in maize (Wright et al., 2005) and for 7.6% of the maize genome (Hufford et al., 2012). This finding suggests a prominent role for the combined effects of selection, drift, and reduction of effective recombination at loci linked to the selection targets. A strong hitchhiking effect (Smith and Haigh, 1974) has also been suggested for rice (Lu et al., 2006) and common bean (Papa et al., 2007), which supports the concept that domestication has had larger effects compared with those that can be explained solely by effects of selection.

Techniques such as next-generation sequencing offer a unique opportunity to scan the genome not only to obtain genotypic information, but also to analyze the molecular phenotype of the whole genome through the analysis of the transcriptome, the metabolome, and the proteome. Recent studies have reported major changes in the maize transcriptome expression, but without any reduction in the expression diversity of genes (Hufford et al., 2012; Swanson-Wagner et al., 2012). There is a need to extend these studies to other crop species to better establish the genome-wide consequences of domestication.

Here, we focused on the domestication process of the common bean in Mesoamerica, with the main aims of (1) describing the genome-wide molecular changes due to domestication using RNA sequencing (RNA-seq) technology and (2) identifying the molecular variants that are responsible for the phenotypic variations that constitute the basis of the domestication process within the common bean genome.

For *P. vulgaris* (2n=2x=22), at least two domestication events have occurred, in Mesoamerica and in the Andes (reviewed in Bitocchi et al., 2013). The two parallel domestications and the domestication of an additional four closely related *Phaseolus* species render the common bean a unique system in which to study domestication and crop evolution.

RESULTS

Transcriptome Sequencing and Assembly

To capture most of the allelic diversity observed for molecular markers in a cohort made up of 10 Mesoamerican wild (MW) genotypes and eight Mesoamerican domesticated (MD) genotypes, with one wild and two domesticated Andean genotypes as controls, we choose to use an approach based on de novo assembly of transcriptome from RNA-seq data. To maximize the information content provided by the data set, a reference transcriptome was built from a hypercore collection of the four most divergent wild genotypes in our cohort (three from Mesoamerica and one from the Andes). This approach was preferred over a reference-based/hybrid method as, given the well-established genetic divergence of the Andean and Mesoamerican gene pool, the use of the *P. vulgaris* reference genome derived from an Andean genotype (G19833) might lead to a loss of informative markers.

To minimize expression differences due to sampling errors, RNAs were extracted from the first trifoliate leaf, fully expanded and at stationary phase. On average, 38×10^6 paired-end reads (100 bp $\times$2) per sample were generated (Supplemental Table 1).

The transcriptome of each of the four members of the hypercore collection was assembled de novo using Trinity (Grabherr et al., 2011). Overall, each sample yielded from 55,069 to 70,826 clusters of contigs, as defined by the Chrysalis module of Trinity, with each cluster ideally representing a single gene. The longest contig out of each cluster was chosen as representative sequence, and redundancies among the four genotypes were collapsed with CD-HIT-EST (Li and Godzik, 2006; Supplemental Table 1). The set of resulting 124,166 sequences, comprising genes shared across all four members of the hypercore collection and genotype-specific genes, was thus used as the reference transcriptome for all subsequent analyses.

Comparing the sequences of each genotype with the reference transcriptome, we identified 284,812 high-quality homozygous single nucleotide polymorphisms (SNPs) on 43,789 contigs (see Methods). Contigs with only heterozygous SNPs or indels were not further considered. Excluding positions missing in more than three Mesoamerican genotypes (see Methods) and filtering for homozygous biallelic SNPs only, the final data set was further reduced to 188,107 SNPs on 27,243 contigs. When considering only the Mesoamerican accessions, the polymorphic contigs decreased to 26,141. Twenty-five of these contigs were fixed for alternative allelic states in the MW and MD populations (Table 1).

Population Structure, and Diversity and Expression Analysis

Multidimensional scaling analysis (Figure 1) reproduced the known genetic structure of the common bean populations: The

Table 1. Number of SNPs and Contigs Identified in This Study

Total number of biallelic SNPs	188,107
Total number of contigs	27,243
Total number of monomorphic contigs in Mesoamerican sample	1,102
Total number of polymorphic contigs in Mesoamerican sample	26,141
Number of contigs monomorphic in both MW and MD populations, except for alternative alleles	25
Shared polymorphic contigs between MW and MD	13,411
Number of contigs monomorphic in MD, but polymorphic in MW	12,014
Number of contigs monomorphic in MW, but polymorphic in MD	691

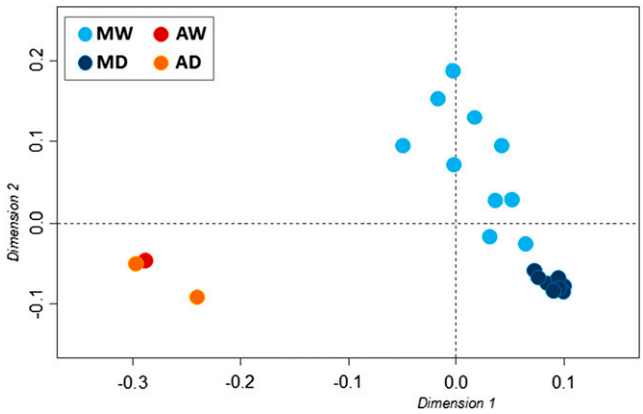

Figure 1. Multidimensional Scaling Analysis Representing the Genetic Relationships among the 21 Common Bean Genotypes.

Mesoamerican and Andean pools were separated, as were the MW and MD forms. The analysis also revealed that compared with MD, MW is characterized by a higher diversity. This agrees with all of the estimated statistics (e.g., S, nH, π, θ, and He) (Table 2; Supplemental Figure 1), with ~60% loss of diversity in the MD population (Table 2). Moreover, almost half of the contigs that were polymorphic in Mesoamerica (46%) were monomorphic in MD (Table 1; Supplemental Figure 1). The difference between the genetic variation within MW and MD was highly significant for all of the indices (Wilcoxon test, $P \leq 2.2 \times 10^{-16}$; Figure 2).

We tested the differential expression of MW versus MD considering the different individual genotypes within groups as replicates. Out of 27,243 contigs, 198 (0.7%) were differentially expressed when comparing MW and MD (Supplemental Data Set 1A), and 146 of them (74%) were downregulated in MD. Moreover, the $\log_2$ fold change in the level of transcription shifted significantly toward negative values (mean, −0.09; median, −0.02; skewness of distribution, −3.49), which indicates an abundance of downregulation in MD, with the mean $\log_2$ fold change significantly smaller than 0 (Wilcoxon two-sided test: $P \leq 2e^{-16}$). The coefficient of variation (CV) of gene expression was higher in MW (0.57) than in MD (0.47), with an 18% loss of expression diversity (Figure 3A, Table 3).

Gene Coexpression Networks

A total of 10,616 contigs were selected for the network-based analysis (Supplemental Figure 2 and Supplemental Methods 1). The selection avoided potentially noisy or invariant gene expression profiles, which would lead to the inclusion of spurious edges in the extracted networks. The introduction of systematic bias due to this selection strategy was examined, and no bias associated with the contig variations in gene expression was found (Supplemental Figure 3).

The correlations among gene expression profiles were based on the Pearson correlation coefficients (PCCs), which were similar for MW and MD, with both resembling normal distributions. In MD, the distribution was wider than in MW, with variance of 0.16 and 0.12, respectively (one-sided F-test, $P < 2.2e^{-16}$) (Figure 4). This implied that there was a higher number of stronger correlations in MD than in MW.

Coexpression of the 10,616 contigs in MW and MD was also considered using network analysis: extraction of proximity networks and generation of relevance networks. These two networks gave very similar results (Supplemental Methods 1); here, we describe in detail only those from the proximity networks.

The seminal properties (Newman, 2003, 2012) of the proximity networks appeared similar in MW and MD. Indeed, only slight differences were observed for the density (0.0012 and 0.0013) and transitivity (0.12 and 0.14) of the MW and MD networks (respectively). The MW network contained seven communities that correspond to groups of genes with mutually correlated expression (Figure 5A), while the MD network contains five communities (Figure 5B). Comparing the MW and MD networks using an adjusted Rand index, it appeared that although they had relatively similar properties, their community structures were divergent. This was supported by the consideration of the Jaccard similarity coefficient (Supplemental Table 2).

The enrichment gene function analysis ($\alpha = 0.01$) indicated that eight of the 12 communities in the MW and MD networks were enriched for at least one gene function, with a mean of four and a maximum of seven gene functions over the communities (Supplemental Table 3 and Supplemental Data Sets 1B and 1C). Aside from having pronounced structural differences, these communities were also modular structures of largely different functions. For example, while there were communities in the MW and MD networks that were enriched for RNA regulation of transcription, the first and second MD communities were

Table 2. Diversity Estimates in the MW and MD Accessions Computed Considering the Polymorphic Contigs in the Entire Mesoamerican Sample (26,141 Contigs) and Loss of Nucleotide Diversity Estimates

Diversity Estimate	MW		MD
N	10		8
S	153,971		56,053
S^1	5.9		2.1
He	0.57		0.25
nH	3.5		1.8
π	2.11		0.85
θ	2.08		0.83
ΔH		0.56	
ΔH^1		0.56	
L_π		0.60	
L_π^1		0.58	
L_θ		0.60	
L_θ^1		0.58	
ϕ_{ST}		0.15	

N, sample size; S, total number of segregating sites; S^1, mean number of segregating sites per contig; He, average expected heterozygosity (Nei, 1978); nH, mean number of haplotypes per contig; π, θ, averaged estimates of nucleotide diversity (Tajima, 1983; Watterson, 1975; respectively); ΔH, L_π, and L_θ, loss of nucleotide diversity, from averaged He, π, and θ, for (MW – MD) comparison; ΔH^1, L_π^1, and $L_{\theta 1}$, loss of nucleotide diversity, from averaged ΔH, L_π, and L_θ of each contig, for (MW – MD) comparison; averaged ϕ_{ST}.

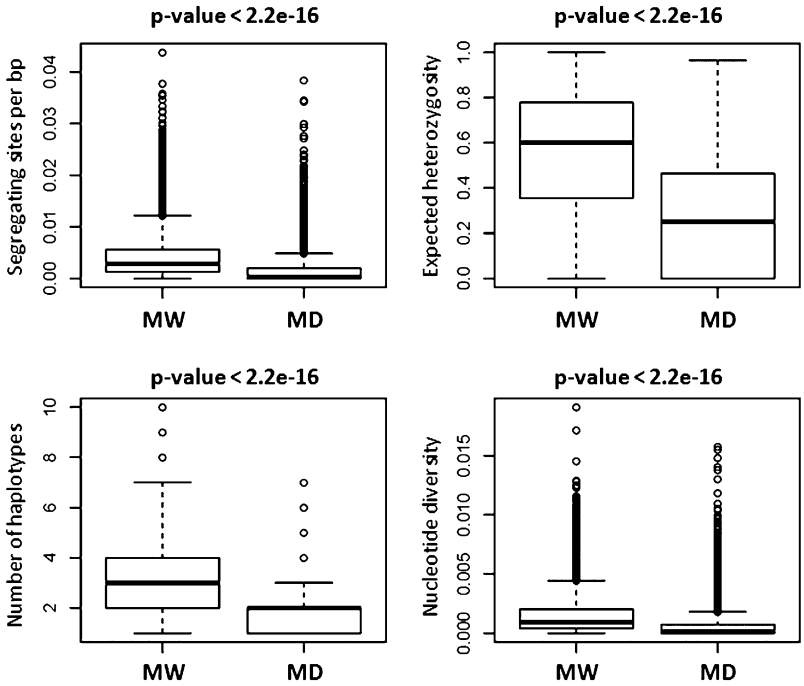

Figure 2. Within-Population Genetic Diversity Comparison between MW and MD Populations.

Box plots of the number of segregating sites (per base pair), the expected heterozygosity, the number of haplotypes, and the nucleotide diversity in the MW versus the MD population, evaluated over all of the contigs. The statistical significance was computed with the Wilcoxon signed rank test for paired data (P value: above each box plot).

enriched in specific transcription factor families that are involved in floral development (e.g., MADS box), abiotic stress responses (e.g., b-ZIP), and several biological functions related to domestication (Supplemental Methods 2).

We next determined the intersection network, with the expectation that the two networks would share only a few edges (otherwise, their community structures would have shown greater similarities); indeed, these edges were incident on only 857 nodes.

Selection

A total of 2364 contigs (9% of those polymorphic) were identified as putatively under selection (PS) during domestication. This was

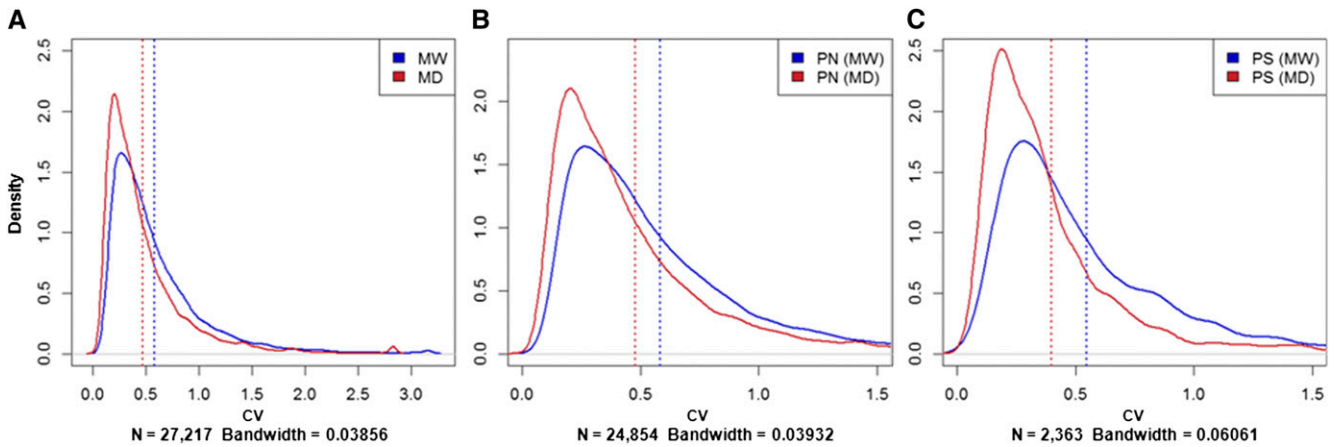

Figure 3. Estimated Density Functions for the Coefficients of Variation in MD and MW as a Reference.

Comparison of the density functions of the CVs considering: all contigs (n = 27,217 CVs of finite value in MW; 27,114 CVs of finite value in MD) **(A)**, subdivision in PN contigs (n = 24,854 CVs of finite value in MW; 24,759 CVs of finite value in MD) **(B)**, and PS contigs (n = 2363 CVs of finite value in MW; 2355 CVs of finite value in MD) **(C)**, where N denotes the number of contigs with CVs of finite values in MW as a reference.

Table 3. Coefficients of Variation of *P. vulgaris* Expression for the MW and MD Forms

Loci	CV_{MW}	CV_{MD}	L_{CV}	L'_{CV}
PN	0.58	0.48	0.17	0.16
PS	0.54	0.40	0.26	0.21
Total	0.57	0.47	0.18	0.16

L_{CV}, loss of expression diversity, calculated as $L_{CV} = 1 - (CV_{MD}/CV_{MW})$; L'_{CV}, loss of expression diversity, calculated as the mean of the single contig L_{CV}.

revealed by simulation of the evolutionary dynamics of Mesoamerican and Andean wild beans with the assumption of absence of selection during domestication, considering the demographic details available from previous studies (Mamidi et al., 2011, 2013). These simulations reconstructed the distribution across the genome of summary statistics that describe processes of differential selection. The comparison between these distributions with those of real contigs (controlling for false positives) identified those contigs that were most likely affected by selection during domestication (directly, or due to hitchhiking). Most of the PS contigs (82%) were fixed in MD and polymorphic in MW, with 14.2% showing shared polymorphism between MD and MW. A small fraction (2.8%) was fixed in MW and polymorphic in MD. Finally, ~1% was fixed both in MD and MW for alternative allelic states.

Contigs differentially expressed in MW compared with MD were highly enriched (about 5-fold) in PS compared with the putatively neutral (PN) contigs (2.75% versus 0.53%; Table 4), suggesting that selection was active for the expression pattern at already the first true leaf stage. In parallel, the loss of expression diversity due to domestication appeared significantly higher ($P < 0.0001$; χ^2 test) for PS (26%; Table 3, Figure 3C) than PN (17%; Table 3, Figure 3B); this effect may be the outcome of direct selection or hitchhiking in regulatory regions (within or outside the exome).

The gene set enrichment analysis (GSEA) is presented in Supplemental Data Set 1D. Single enriched MapMan bins are not common to PS and PN sets, which further indicates that the two sets have the tendency to participate in different metabolic pathways or have different functions. Briefly, when ordered according to 5% statistical significance of the GSEA, the genes that have been annotated in *Arabidopsis thaliana* as involved in regulation of RNA transcription, synthesis of ribosomal proteins, RNA processing and regulation, and DNA repair are overrepresented in the PS contigs. By contrast, PN had a lower number of significantly overrepresented MapMan bins, which encoded proteins involved in, among other things, cofactor and vitamin metabolism and nucleotide metabolism.

We observed that there was no shift of the CV toward higher/lower values for the PS contigs retained and those not included in the network analysis (Supplemental Figure 4). With respect to the position in the proximity networks, the PS contigs were underrepresented in the intersection network. We next tested if there was difference in the average centrality measures of PS and PN contigs, assessing their global position in the networks. We did not identify any statistically significant differences with respect to the average centrality measures of PS and PN contigs in both the MW and MD networks; however, a small, but statistically significant, difference was seen for the closeness centrality (Supplemental Table 4). At a local level, i.e., by focusing only on the immediate coexpressing partners of the PS contigs, we also found that the PS contigs showed significant, although small, assortativity in the MD network, which was not the case in the MW network (Supplemental Table 5). Qualitatively similar findings were obtained when the selection index was used instead of the partition of the contigs into the PS and PN classes. These data indicate that while the global position of the PS contigs in the coexpression network on average did not show differences with respect to the PN contigs, there were small local changes of coexpression patterns, as quantified by the assortativity, that might lead to tighter coexpression of the PS contigs in MD compared with MW. Associations between PS contigs and features of the expression network, like centrality indices and assortativity, were largely not significant. This might be due to our experimental system that is based on a specific developmental stage of the plant, which supports the view that only a fraction of the genes under selection had phenotypic effects associated to a differential fitness at this stage. Moreover, PS genes might be indirectly affected by selection due to hitchhiking. In addition, if domestication is considered a multitrait selection process, we have no reason to assume specific and common roles for all of the selected genes in the determination of the structure of the expression network.

Furthermore, function information allowed the investigation of whether a subset of contigs identified as PS is associated to the domestication process in other species. We focused on the 380 contigs with the highest selection index, including also the 23 PS contigs with an alternative allelic state between MW and MD as well as the 67 PS contigs monomorphic in MW and polymorphic in MD. Functional evaluation of these PS contigs is comprehensively discussed in Supplemental Methods 2.

The analysis revealed that several PS contigs are homologous to genes implicated in the process of domestication in other species or have functions associated with domestication, like light responses, signaling, plant development, and biotic and abiotic stress. For instance, the annotated PS contigs that

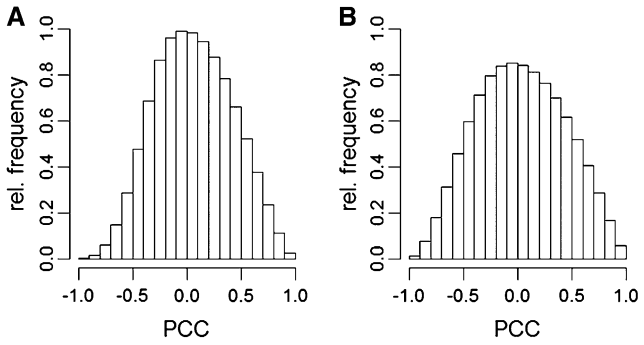

Figure 4. Distributions of the Pearson Correlation Coefficients Obtained from the Expression Profiles in the MW and MD Populations.

Distributions of the MW **(A)** and MD **(B)** populations resemble normal distributions, with the PCCs in MD showing greater values than those in MW.

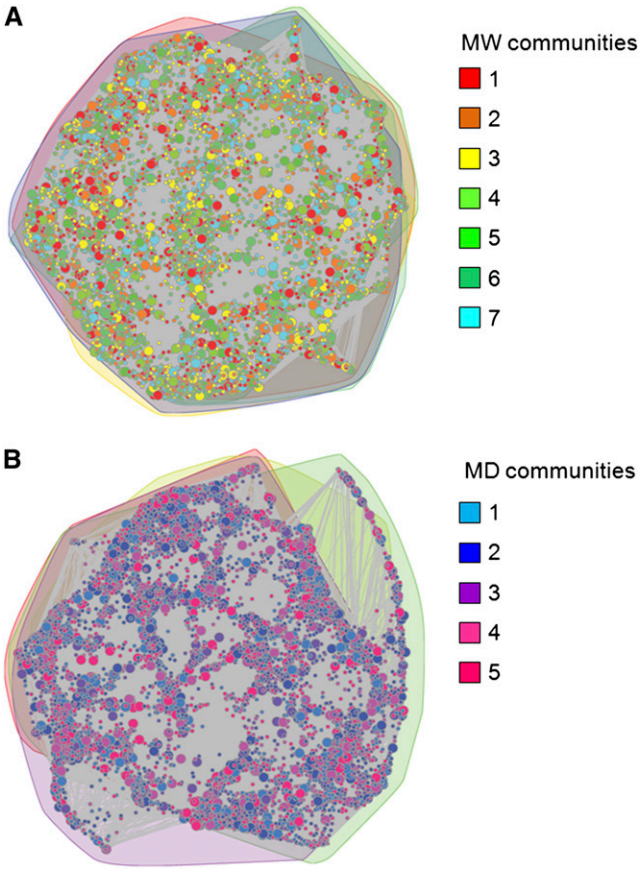

Figure 5. Proximity Networks of MW and MD and Their Community Structure.

Nodes are color-coded according to their participation in one of the seven and five communities in the MW **(A)** and MD **(B)** proximity networks, respectively, containing a single connected component. Nodes of bigger size correspond to contigs under selective pressure.

showed greater genetic diversity in MW compared with MD included a sequence homolog to *GIGANTEA* (*GI*), which has a pivotal role in the photoperiodic response, as it regulates flowering in a circadian clock–controlled manner. In *Arabidopsis*, under long days, *GI* acts earlier in the pathway than *CONSTANS* (*CO*) and *FLOWERING TIME* (*FT*), by increasing the *CO* and *FT* mRNA abundance. *CO* and *FT* were targets of selection during domestication of crops such as rice (Takahashi and Shimamoto, 2011; Wu et al., 2013) and sunflower (*Helianthus annuus*; Blackman et al., 2011). In pea (*Pisum sativum*), Hecht et al. (2007) identified *LATE BLOOMER1* (*LATE1*) as the pea ortholog of *Arabidopsis GI* and showed that *LATE1* is necessary for the promotion of flowering, the production of a mobile flowering stimulus, and the induction of an *FT* homolog under long-day conditions. Another interesting example among the PS contigs with two alternative allelic states is the homolog of *YABBY5* (*YAB5*), a transcription factor that is implicated in the regulation of seed shattering in cereal species, including sorghum (*Sorghum bicolor*), rice, and maize (Lin et al., 2012). A YAB-like transcription factor (*FASCIATED*) has also been shown to influence carpel number during flower and/or fruit development in tomato (*Solanum lycopersicum*; Cong et al., 2008).

Among the 67 PS contigs that show an increase in variability in MD is a homolog of K^+ *uptake transporter6* (*KUP6*). Osakabe et al. (2013) demonstrated that the KUP potassium transporter family has important roles in water stress responses and growth; moreover, KUP-type K^+ transporters are induced by various stresses that have an osmotic component, and they specifically inhibit cell expansion, while enhancing drought tolerance.

DISCUSSION

This report describes the profound effect that domestication has imposed on the genome variation and gene expression patterns of common bean. About one out of 10 contigs was likely to have been affected by selection during domestication: Directional selection was the rule, but diversifying selection was also probably active, with contigs of the domesticated gene pool frequently having different levels of expression and different patterns of coexpression compared with the wild relatives. The practical implication for future crop improvement is that lot of variation at DNA sequences and regulatory regions is still available in the wild bean for crop breeding, but that to fully exploit the diversity of wild germplasm a substantial effort is needed to understand the complex relationship between the genotypic and phenotypic diversity in plant populations.

As highlighted in this study, in common bean, expressed genomic regions lost half of the wild bean nucleotide diversity during domestication in Mesoamerica. Compared with common bean, in maize, there was a smaller reduction in diversity at the nucleotide level (Hufford et al., 2012), which suggests that there was a smaller effect of domestication on the maize genetic diversity. The different mating systems between these two crops might help to explain these results. In autogamous species like common bean, self-fertilization is expected to reduce the effective population size, which will enhance the effects of genetic drift and increase the extent of linkage disequilibrium, leading to large genomic windows affected by genetic sweep (Glémin and Bataillon, 2009; Bitocchi et al., 2013) as also confirmed by the resequencing results in the autogamous soybean and rice (*O. sativa*, variety *japonica*) (Lam et al., 2010; Xu et al., 2012).

Our study also demonstrated that there was a drastic change because of domestication in the pattern and structure of gene

Table 4. Enrichment of Differentially Expressed Contigs in the PS Contig Group

	PN	PS	Total
DE	$133_{(0.53\%)}$	$65_{(2.75\%)}$	198
NDE	24,730	2,298	27,028
Total	24,879[a]	2,364[a]	27,243[a]

DE, loci differentially expressed between MW and MD; NDE, not differentially expressed loci. In parentheses: percentages of DE contigs based on total number of PN and PS contigs.
[a]Data not available for 17 contigs (1 PS; 16 PNs).

expression over the entire set of genes. This was also found in maize, albeit with reduced intensity (Swanson-Wagner et al., 2012). Moreover, in common bean, we found that the reduction in sequence diversity also affects DNA regions implicated in the regulation of transcription, where ~20% reduction in gene expression levels has been associated with domestication. In other words, here, we demonstrate that the loss of genetic variation has direct genome-wide phenotypic consequences on transcriptome diversity. These findings differ from the case of maize and its wild progenitor teosinte, where no reduction in the variation of gene expression was observed (Swanson-Wagner et al., 2012). It is particularly relevant that such different expression levels and patterns are observed at a developmental stage that is considered relatively important for domestication, even if the presence of larger leaves and seedlings is a hallmark trait of domestication (Gepts, 2002).

The occurrence in domesticated bean of mostly down-regulated transcripts among those differentially expressed (74%) points to loss-of-function mutations, which are relatively frequent compared with gain-of-function changes, as a largely available source of variation that supports selection during rapid environmental changes (Olson, 1999). Such was the case of the transition from the wild to cultivated agro-ecosystems. In support of this, as first noted by Darwin (1859), in domesticated plants, the domestication traits have a recessive genetic nature (Lester, 1989). Moreover, a lower genome-wide gene expression level was found for domesticated compared with wild transcripts as if slightly deleterious mutations due to hitchhiking (mostly loss-of-function or with reduced expression) have been accumulated in the domesticated pool. This can be considered as the "cost of domestication." The accumulation of loss-of-function (or reduced expression) mutations might also have been due to reduced effective recombination, which would have increased the frequency of deleterious mutations in the domesticated pool, with a negative influence on fitness, as suggested in rice (Lu et al., 2006).

About 10% of the contigs were affected by selection during domestication or were physically linked to the selected genes. This supports again the view that domestication had a relevant influence on the common bean genome. In the allogamous species maize, ~2 to 4% of genes and ~7.6% of the whole genome (Wright et al., 2005; Hufford et al., 2012, respectively) were detected as affected by selection during domestication. Similarly, in sunflower, which is also predominantly allogamous, ~7.3% of genes show signatures of selection due to domestication (Chapman et al., 2008). These differences may be determined by a more relevant role of genetic hitchhiking in producing the observed results in *P. vulgaris* due to its autogamous mating system.

Most of the contigs affected by selection during domestication show reduced diversity in MD compared with MW, as would be expected following positive selection due to domestication. However, in a few cases, the opposite was observed: For instance, for 2.8% of the PS contigs, there was no diversity in MW, while there was diversity in MD. This can be taken as being due to diversifying selection in MD, with domestication increasing the level of functional diversity. The functional analysis of the drought-related *KUP6* gene shows that it is significantly overexpressed in MD compared with MW, as if domestication has also increased the functional diversity of selected genes and not just increased the nucleotide diversity. Our data therefore indicate that in parallel with an overall reduction in diversity, domestication increased the functional diversity at target loci. This can be imputed to novel mutations (or those that exist at low frequencies) that were selected because of the crop expansion into new environments with unexpected biotic and abiotic stress or because of selection for traits that improved the use of the plant organs by humans (de Alencar Figueiredo et al., 2008). As such, the data contribute to resolving the Darwin paradox (Darwin, 1878; Glémin and Bataillon, 2009): Domestication is associated with an increased phenotypic diversity at target traits and a reduction of nucleotide variation.

Our work presents relevant implications for the development of prebreeding strategies. Similarly to other studies, our findings support the need for wild germplasm for further crop improvements and calls for careful conservation of the wild populations. However, we also showed that the effect of domestication is pervasive throughout the genome in terms of expression patterns and diversity, probably because of the combination of linkage and pleiotropy. However, complex interactions within and among genes and their expression levels played an important role during the domestication of this species, suggesting that further genetic amelioration strongly requires new tools for genomics, molecular phenotyping, and phenomics. Moreover, our results suggest that the diversity in the domesticated pool (e.g., traditional landraces) that was originated by the fixation of useful mutations after domestication needs increased consideration as source of novel genetic variation for crop improvement.

METHODS

Sampling

On the basis of the molecular characterization of a wide and representative collection of *Phaseolus vulgaris* genotypes (Rossi et al., 2009; Nanni et al., 2011; Bitocchi et al., 2012, 2013; Desiderio et al., 2013) and with a focus on the Mesoamerican gene pool, 21 inbred genotypes (two cycles of single seed descent) were selected as the core collection to maximize the genetic diversity. The core included 10 MW genotypes, eight MD genotypes, and as controls, two domesticated and one wild Andean genotypes. With the aim also being to capture most of the allelic diversity observed for molecular markers, a further hypercore collection of four wild genotypes was built (three from Mesoamerica and one from the Andes). A complete list of the accessions used is reported in Supplemental Table 6.

The 21 individual genotypes were grown under greenhouse-controlled conditions (relative humidity, ~70%; average night/day temperature, 25°C). To minimize expression differences that might be attributed to developmental disparity between individuals, the fully expanded first trifoliate leaf at stationary phase was collected and frozen for all genotypes.

RNA Extraction

Frozen plant tissues were ground in liquid nitrogen, and 100 mg ground tissue was used for RNA isolation using Spectrum Total RNA kits (Sigma-Aldrich). The RNA was then treated with RNase-Free DNase using the On-Column DNase I Digestion Set (Sigma-Aldrich). Qualitative and quantitative control was performed with a Nanodrop 2000 spectrophotometer (Thermo Scientific) and an RNA 7500 series II chip bioanalyzer (Agilent). Only RNA samples with an RNA integrity number >8.0 were used.

Library Preparation and Sequencing

For each of the 21 RNA samples, 3 μg was used for the construction of a nondirectional Illumina RNA-seq library, using TruSeq RNA sample preparation kits, v2 (Illumina), following the manufacturer's instructions. Libraries were quantified using quantitative PCR, and quality control was performed with the DNA 1000 series II chip bioanalyzer (Agilent).

RNA-seq was performed with an Illumina HiSequation 1000 Sequencer using TruSeq SBS v3-HS kits (200 cycles) and TruSeq PE Cluster v3-cBot-HS kits (Illumina) generating 100-bp paired-end reads.

De Novo Transcriptome Assembly

Reads obtained from the sequencing of the four hypercore collection genotypes (Supplemental Table 1) were assembled de novo to obtain a common reference transcriptome. Each sample was assembled separately using Trinity version R2011-11-2 (Grabherr et al., 2011) using default parameters. To minimize the redundancy due to different transcript isoforms belonging to the same gene, a custom script was used to retain only the longest contig out of each trinity cluster as a representative of the cluster. The filtered contigs from the four assemblies were pooled together and redundancy among data sets was removed using CD-HIT-EST (Li and Godzik, 2006), with a 90% threshold on the contig identity. The contigs were compared with the sequences in the TAIR 10 protein database of *Arabidopsis thaliana* using BLASTX (Altschul et al., 1997), with an E-value $<10E^{-2}$.

Variant Identification

RNA-seq reads of each of the 21 genotypes were mapped on the reference transcriptome using BWA version 0.6.2-r126 (Li and Durbin, 2009) using default parameters and with a minimum mapping quality threshold of q = 30 to minimize false variant calls due to misalignments or reads mapping to multiple positions in the transcriptome. The variants in the transcriptome sequence were identified using Samtools 0.1.18 (Li et al., 2009) and Varscan v2.2.8 (Koboldt et al., 2012), with a maximum P value of 0.01 and a minimum read depth of three reads in order not to penalize transcripts that are present in low abundance in the samples. Only positions of the transcriptome covered by at least three reads in all the 18 Mesoamerican genotypes analyzed were considered for variant calling. For all of the positions for which a homozygous SNP (percentage of reads supporting the alternate allele ≥75%) was called in at least one sample, we analyzed the samples with no SNP call in the same position using the following criteria: (1) if read depth ≥3 and percentage of reads supporting the reference base >75%, the reference base was called; (2) if read depth ≥3 and percentage of reads supporting an alternate allele already called in other samples (P value <0.01) for that position >75%, the alternate base was called; (3) if read depth ≥3 and percentage of reads supporting an alternate allele already called in the other samples (P value < 0.01) was between 25 and 75%, a heterozygous call was recorded. The positions for which a genotype was not detected in at least 15 of the Mesoamerican genotypes were removed, allowing a maximum of three missing data for each called SNP. Only biallelic homozygous SNPs were retained for the analyses.

RNA-seq Expression Analysis

Gene expression levels were based on TopHat2 (Kim et al., 2013) and HTSeq (Anders, 2010), with the default parameters. Differentially expressed contigs between the wild and domesticated genotypes ($|\log FC| > 1$; FDR <5%) were identified using DESeq version 1.6.1 (Anders and Huber, 2010). The experimental design contrasted two groups of accessions, as MW versus MD, using individual genotypes as replicates. The CV was calculated as the ratio between the SD and the mean number of fragments mapping on each contig, for each genotype, in both the MW and MD populations.

Population Genetics Analysis

Exploratory analysis of the genetic relationships among individuals was based on a metric multidimensional scaling, using the *cmdscale* command in the R statistical environment (http://www.r-project.org/; R Development Core Team, 2013). Genetic distances were computed as one minus the average fraction of nonshared alleles.

The following diversity statistics were computed using *Arlequin 3.5* (Excoffier and Lischer, 2010): S, total and mean number of segregating sites; expected heterozygosity (He; Nei, 1978); nH, number of haplotypes; and π and $\ominus$, two measures of nucleotide diversity from Tajima (1983) and Watterson (1975), respectively, computed on SNPs within each contig. The divergence between the MW and MD forms was measured using Φ_{ST} (Excoffier et al., 1992).

To assess the reduction of diversity in MD versus MW, we used the statistical loss of diversity, as proposed by Vigouroux et al. (2002), and computed as $[1 - (x_{MD}/x_{MW})]$, where x_{MD} and x_{MW} are the diversities in the MD and MW populations, respectively, measured using three different statistics: He, π, and $\ominus$; the loss of diversity parameter ranges from zero to one, whereby zero indicates no loss of diversity and one indicates a total loss of diversity. The differences between the distributions of each genetic diversity statistic (S, He, nH, π, and $\ominus$) in MW and MD were statistically evaluated by the Wilcoxon signed ranked test for paired data.

Identification of Contigs Putatively under Selection

PS contigs in MD compared with MW were identified by computing two selection indices and testing their significance with a simulation approach. The selection indices were based on two between-groups and one within-groups genetic variation statistics, and their neutral distribution (assuming no selection) was based on coalescent simulations calibrated with previous demographic inferences on *P. vulgaris* divergence and domestication. Missing data were statistically imputed in the real data set before comparison to the simulated null distributions. All of these steps are individually described below.

Missing Data Imputation

A small fraction of the 188,107 SNPs had missing data. In particular, 2.73% of the total number of nucleotides was missing in the data set, with similar fractions in the different groups. We performed missing data imputation using the clustering algorithm implemented in *fastPhase1.4* (Scheet and Stephens, 2006). This method does not require pedigree information and takes the population information into account. Individuals were assigned to three groups, according to their sampling origin: MW, MD, and Andean (due to the low number of Andean genotypes, all three of the individuals belonging to this area were grouped). Haplotype reconstruction was switched off, and the missing genotypes were imputed independently for each contig, setting the number of the cluster from one to 15. The complete set of *fastPhase* parameters was -KL1 -KU15 -Ki2 -H-4 -n -B -u.

Coalescent Simulations of Domestication Models

Coalescent simulations were used to generate neutral distributions of summary statistics, assuming three likely domestication scenarios reconstructed in previous studies (Supplemental Figure 5). In particular, our models were based on the population histories and demographic parameters estimated by Mamidi et al. (2011, 2013).

In all of the models, the Mesoamerican and Andean gene pools originated from an ancestral population, and domestication then occurred independently in each group. Only in more recent times did the domesticated groups expand exponentially, and some hybridization between domesticated and wild forms took place. Models B1 and B2 included a bottleneck event in the Andean or in both groups, respectively.

For each parameter, we defined prior distributions (Supplemental Table 7) based on previous estimates of their uncertainty (Mamidi et al., 2011, 2013). For each model, 100,000 simulations were performed by sampling random parameter combinations from these distributions using the ABCsampler program from the ABCtoolbox package (Wegmann et al., 2010). In each simulation, we generated a sample for each population that was equal to the observed one (10 haploid individuals for MW, eight for MD, two for AD, and one for AW). The lengths of the DNA sequences were extracted from a distribution calibrated for the distribution of contig lengths in the real samples.

Selection Index

For each locus, we initially calculated three statistics that were likely to be affected by differential selection in MD compared with MW. First, the population differentiation statistic Φ_{ST} (Excoffier et al., 1992) between MW and MD was calculated, following the classical view that loci differently affected by natural selection in different populations can be detected as outliers in population comparisons (Lewontin and Krakauer, 1973). Second, we considered the locus-specific branch-length statistic (Shriver et al., 2004). This is based on the genetic distance between two populations, but it also includes a third reference group (Andean, in our case) to identify which of the two populations experienced the positive selective pressure.

Finally, we computed a third statistic as the ratio of $(S_{MW}-S_{MD})/(S_{MW}+S_{MD})$, where S_{MW} is the number of segregating sites in MW, and S_{MD} is the number of segregating sites in MD. This statistic measures the absolute value of the difference between the genetic variation in the MW and MD forms, as standardized by their sum; it is intended to capture the relative change in genetic diversity due to selection (Pritchard et al., 2010). All of these statistics tend to increase with increasing evidence of selection.

Φ_{ST} and the number of segregating sites were computed using the command-line version of *Arlequin 3.5* (Excoffier and Lischer, 2010). The statistics were normalized using the neutral distributions obtained by simulation.

The three statistics above were combined into two different indices. The first index was built as the sum of all of the above statistics, and it was computed for 26,116 contigs. Due to the different alleles fixed in the two groups, in 1127 contigs, the statistics based on the segregating sites were undetermined. For these contigs, we created a second index that was obtained by summing up only the standardized Φ_{ST} and the locus-specific branch length. The same procedure was followed in the simulated data to generate the distribution of both of these indices assuming that only the demographic processes, and not the selection processes, shaped the pattern of the genetic variation. P values for each contig were then computed as the fraction of the simulated indices larger that the real value, and corrected to account for false positives, following the approach of Benjamini and Hochberg (1995), implemented in the *p.adjust* function available in the R statistical environment. This approach was repeated for each of the three simulated models, and we obtained three different lists of corrected p values. We then identified positively selected contigs when the false discovery rate was <5%, in each of the three models.

Gene Annotation

A BLASTX (Altschul et al., 1997) analysis against protein databases of *Arabidopsis* TAIR 10 was performed for all of the transcripts. Moreover, for functional characterization of PS contigs or PN contigs, a MapMan GSEA was conducted. See Supplemental Methods 1 for further details.

Network Analysis of Gene Coexpression

We performed a network-based comparative analysis of the RNA-seq data in the MW and MD populations. The analysis was based on expression level estimates for the 27,243 contigs. First, the contigs were selected for subsequent network analyses to avoid inclusion of potentially noisy or invariant gene expression profiles. Altogether, we did not consider 581 contigs that showed zero expression levels in at least nine genotypes. For each of the remaining 26,662 contigs, two statistical tests were performed: the differences in the means and in the variance of expression levels between the MW and MD populations, based on ANOVA and on the F-test, respectively (Ho et al., 2008). A very loose level of significance ($\alpha = 0.1$) was considered for both of these tests. These allowed the selection of a subset of contigs to be used for the network analysis. The Wilcoxon rank sum test with continuity correction (Bauer, 1972) was applied to the CVs computed for MW and MD for each chosen contig. To this end, we tested whether the strategy applied for contig selection introduced any systematic bias with respect to favoring contigs that vary strongly in both MW and MD populations, in comparison to the entire set of contigs we considered. The possibility of introducing a shift in CVs toward higher/lower values for the PS contigs retained and those excluded from subsequent analysis was also tested.

Correlations of gene expression profiles were estimated using PCCs. The MW and MD expression profiles for the selected contigs were subjected to network-based analysis following two procedures: (1) extraction of proximity networks and (2) generation of relevance networks; both of these were based on PCCs (Klie et al., 2012; Kleessen et al., 2013). For details of these procedures, see Supplemental Methods 1. In contrast to relevance networks, the extraction of the proximity network took into consideration the observation that genes are often activated as modules of a program to fulfill a particular function (Quackenbush, 2003).

For the proximity networks, the following properties (reviewed in Newman, 2003, 2012) were analyzed: number of edges (proportional to the density), degree distribution (a degree of a node is the number of nodes with which it shares edges; hence, the degree distribution is given for the probability distribution of degrees in the network), distribution of connected components (defined as maximal subnetworks in which any two nodes are connected by a path), radius (the smallest of all of the node eccentricities), transitivity, and community structure (where a network community is a set of nodes that have more edges between each other than with the rest of the network and can be regarded as modules with particular functions). The adjusted R and index (Hubert and Arabie, 1985) and Jaccard index (Jaccard, 1912) were used for comparisons of the community structures (partitions of nodes) of the MW and MD networks.

To determine whether the network communities have a biological signal, the enriched gene functions for each of the determined communities were investigated (significance level, $\alpha = 0.01$). MapMan ontology and a test based on the hypergeometric function (Rivals et al., 2007) were used. Potential enrichment for PS contigs of each of the network communities identified was also investigated.

The intersection network composed of the edges shared between the MW and MD proximity networks was determined. Moreover, the potential overrepresentation or underrepresentation of PS contigs in the intersection network was investigated.

The position of PS contigs in the extracted proximity networks was determined by considering two attributes of the contigs: (1) as under selective pressure (both for binary attribution PS/PN, and for selection index); and (2) CV of their expression profiles. To test whether similar contigs tend to be neighbors with respect to these two attributes, we used the concept of weighted assortativity, which is equivalent to PCCs between the attributes of nodes and the attributes of all of their immediate neighbors (Newman,

2003). A value of 1 denotes a high degree of assortativity (i.e., similar is a neighbor of similar), 0 denotes no assortativity (i.e., complete dispersion), and −1 denotes dissortativity (i.e., similar is a neighbor of dissimilar).

We investigated whether the PS contigs tend to be more central than the rest of the contigs. To quantify the centrality of position in the network, we used several measures of node centrality in a network (Newman, 2003), including betweenness, closeness, degree, eigenvalue, page rank, eccentricity, Burt's constraint, and transitivity. We also used the latent centrality, which was obtained via principal component analysis and integrated the information from the eight centrality measures used. The correlation between the selection index and the node centrality measures was also investigated through PCC.

Finally, to examine the functional characterization of the PS contigs, GSEA (Rivals et al., 2007) based on MapMan ontology was conducted.

Accession Numbers

All data are available in the Sequence Reads Archive under accession number SRP028116. The Transcriptome Shotgun Assembly project has been deposited at DDBJ/EMBL/GenBank under accession number GAMK00000000. The version described in this article is the first version, GAMK01000000.

Supplemental Data

The following materials are available in the online version of this article.

Supplemental Figure 1. Diversity Estimates in MW and MD Populations.

Supplemental Figure 2. Network-Based Analysis: Results of the Contig Selection Strategy.

Supplemental Figure 3. Network-Based Analysis: Selection Strategy and Bias of the CVs.

Supplemental Figure 4. Network-Based Analysis: Selection Strategy and Bias of CVs in the PS Contigs.

Supplemental Figure 5. Demographic Models for the Mesoamerican and the Andean Populations Used in This Study.

Supplemental Table 1. Transcriptome Assembly Statistics for the Four *P. vulgaris* Reference Genotypes and for the Final Nonredundant Data Set.

Supplemental Table 2. Jaccard Similarity of the Community Structure in the MW and MD Proximity Networks.

Supplemental Table 3. Community Gene Function Enrichment: List of Selected Enriched Gene Functions for Each of the Communities Determined for the MW and MD Networks.

Supplemental Table 4. Difference in Mean Node Centralities of Contigs under Selective Pressure and the Rest of the Nodes in the MW and MD Networks.

Supplemental Table 5. Difference in Assortativity, Both Nominal and Based on the "Selection Index," between the MW and MD Networks.

Supplemental Table 6. Accessions Used in This Study.

Supplemental Table 7. Demographic Parameters in the B0, B1, and B2 Models.

Supplemental Methods 1. Details on Network-Based Analysis and Gene-Set Enrichment Analysis Using MapMan.

Supplemental Methods 2. Details Regarding Gene Function Investigation.

Supplemental Data Set 1A. List of Contigs and Information about Results of Differential Expression and Selection Analyses.

Supplemental Data Set 1B. Community Gene Function Enrichment in MW: Full List of MapMan Bins Enriched in Each of the MW Communities at a Significance Level of $\alpha = 0.05$.

Supplemental Data Set 1C. Community Gene Function Enrichment in MD: Full List of MapMan Bins Enriched in Each of the MD Communities at a Significance Level of $\alpha = 0.05$.

Supplemental Data Set 1D. Gene function Enrichment of PS and PN Contigs: Overrepresentation of MapMan Bins in Both PS and PN Contigs by GSEA Analysis.

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AUTHOR CONTRIBUTIONS

E. Bellucci, E. Bitocchi, L.N., and R.P. designed the project. E. Bellucci, E. Bitocchi, E. Biagetti, L.N., and R.P. managed the project. E. Bellucci, E. Bitocchi, L.N., and R.P. wrote the article. E. Bellucci, E. Bitocchi, A.F., A.B., E. Biagetti, S.K., D.R., M.R., G.A., E.A., S.A.J., L.N., A.R.F., Z.N., G.B., and R.P. contributed to the drafting and writing of the article. E. Bellucci and E. Biagetti performed greenhouse experiments and RNA extraction. A.F. and E. Biagetti developed library preparation and managed sequencing. A.F. and M.D. directed RNA-seq and bioinformatic analysis and performed differential expression analysis. A.F., L.V., and M.D. performed de novo transcriptome assembly. A.M. performed variant identification. A.F., E. Biagetti, A.M., and M.D. performed annotation. E. Bellucci, E. Bitocchi, A.B., E. Biagetti, A.P., G.B., and R.P. conducted genetic diversity analysis. A.B. and G.B. performed coalescence simulations. A.B., A.P., G.B., and R.P. conducted selection detection and population genetics analysis. S.K. and Z.N. conducted network-based analysis and GSEA. D.R., M.R., G.A. E.A., A.R.F., E. Bitocchi, and E. Biagetti performed gene function investigation. E. Bellucci, E. Bitocchi, D.R., G.B., and R.P. edited the article. All authors read and approved the article.

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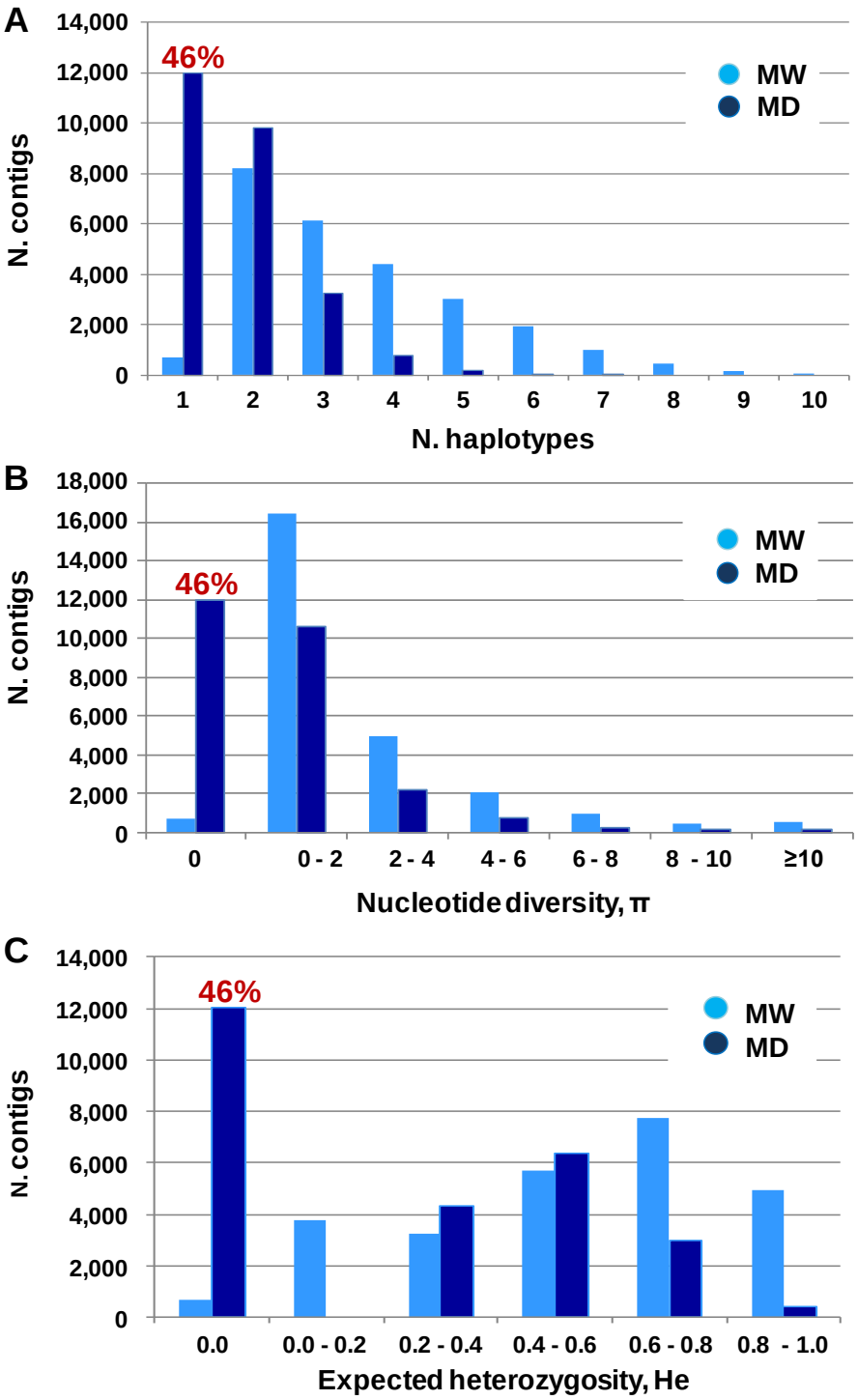


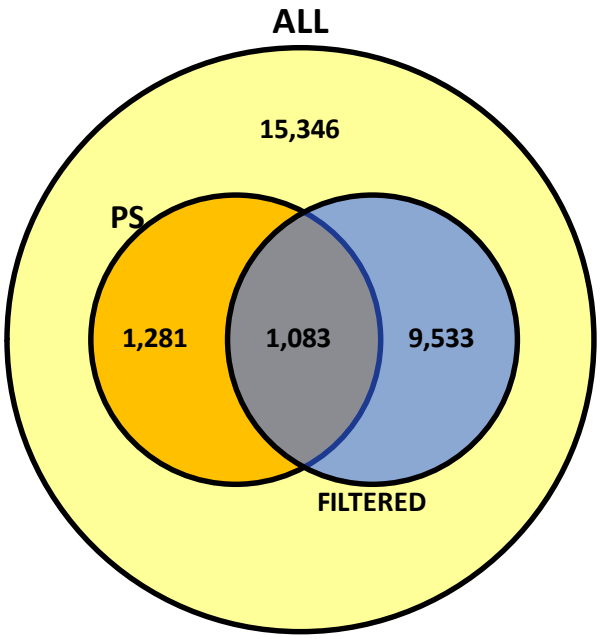
Supplemental Figure 1. Diversity estimates in MW and MD populations.

Number of contigs for the different classes.

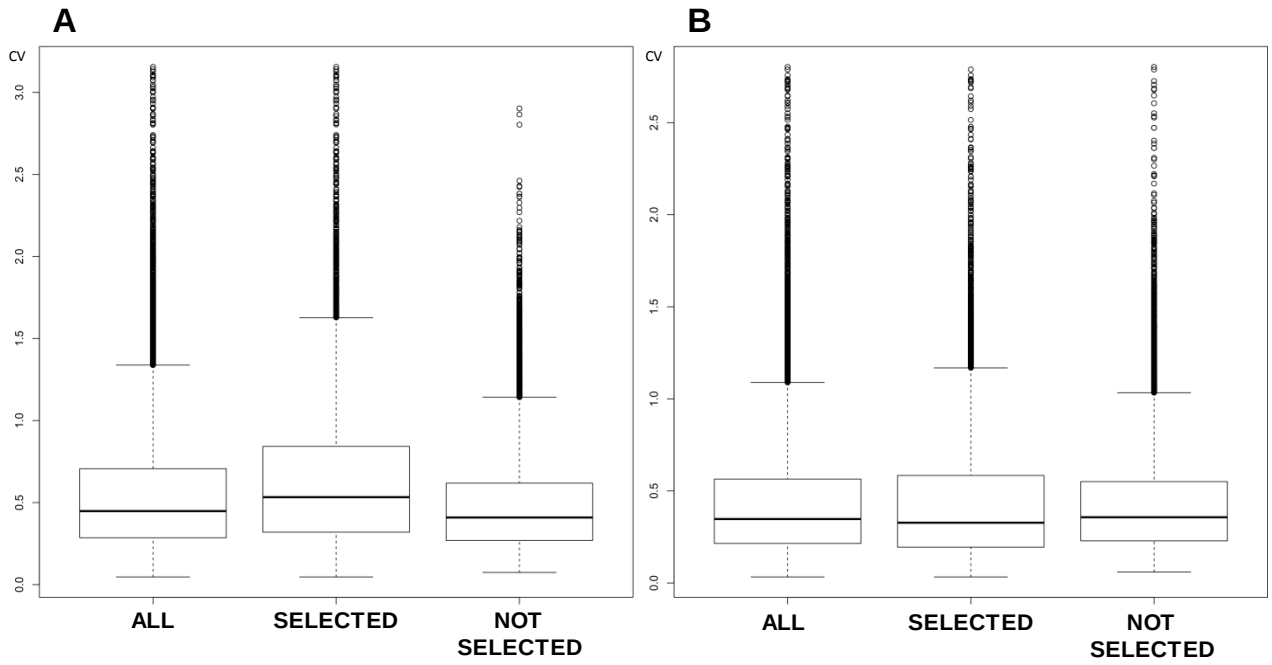
(A) Number of haplotypes (nH).

(B) Nucleotide diversity (π).

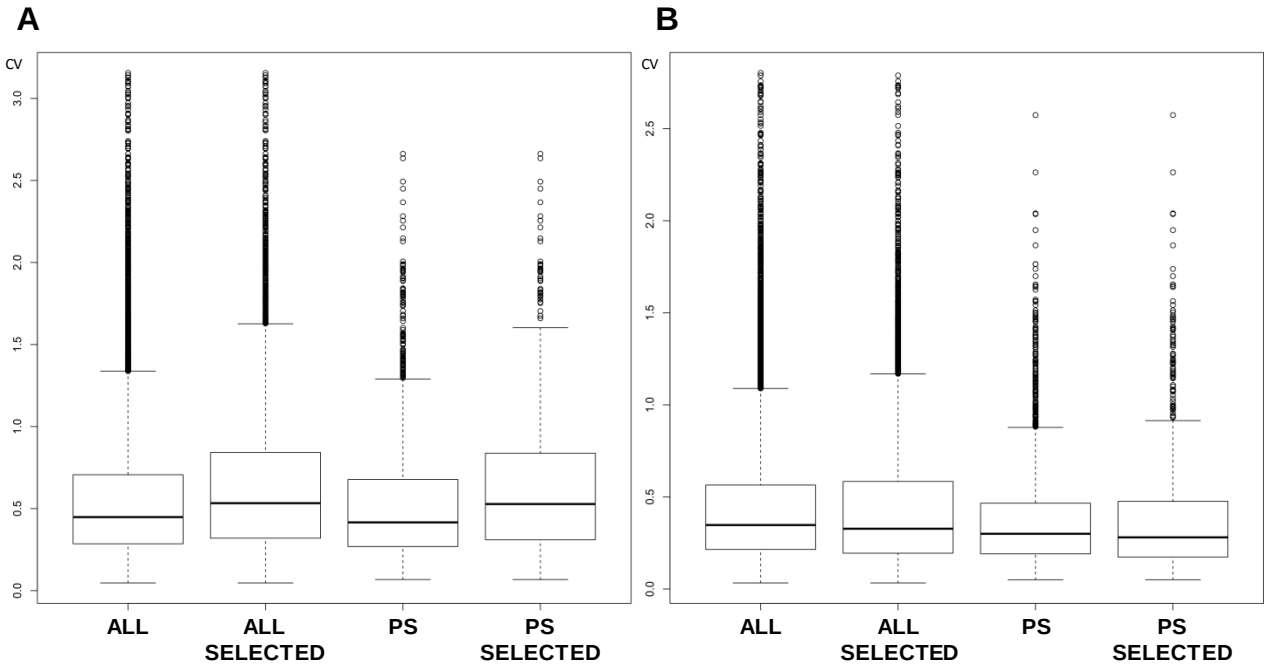
(C) Expected heterozygosity (He).



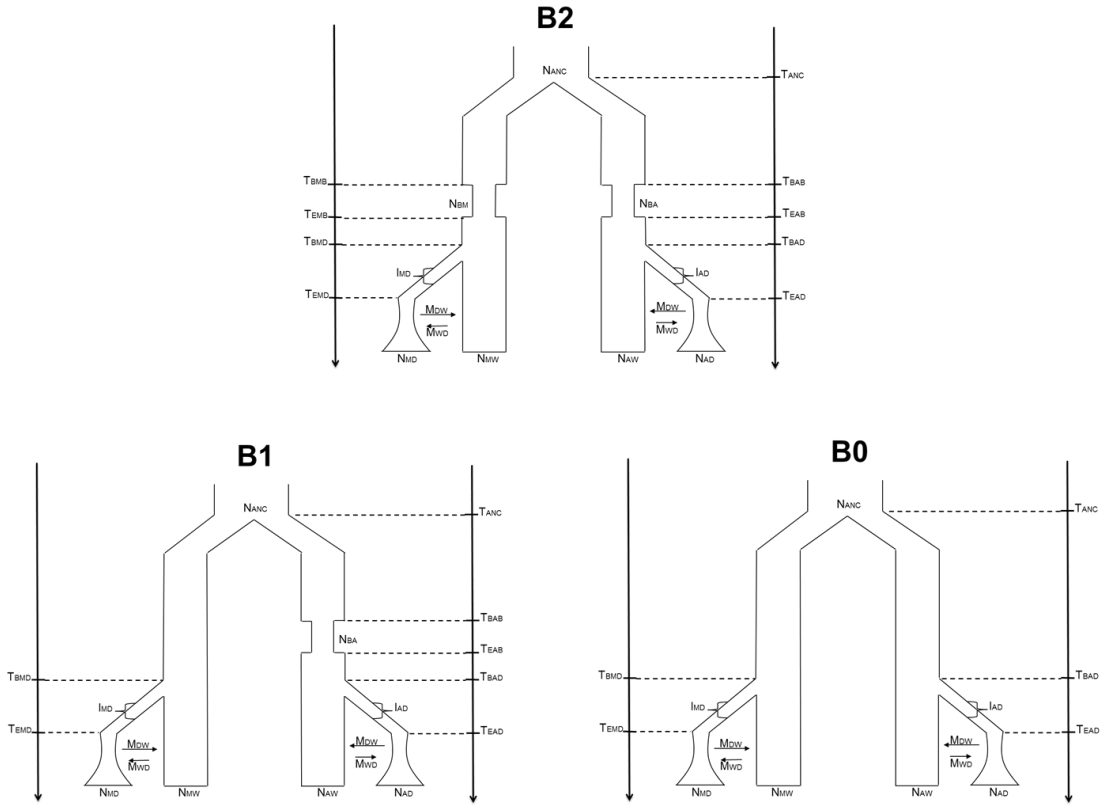
Supplemental Figure 2. Network-Based Analysis: Results of the selection strategy. The Venn diagram illustrates the overlap between the entire set of contigs (yellow), the putatively under selection (PS) contigs (orange), and the contigs selected using the outlined strategy for subsequent network-based analysis (blue). Altogether 1,083 of 2,364 PS contigs were retained for the network-based analysis.



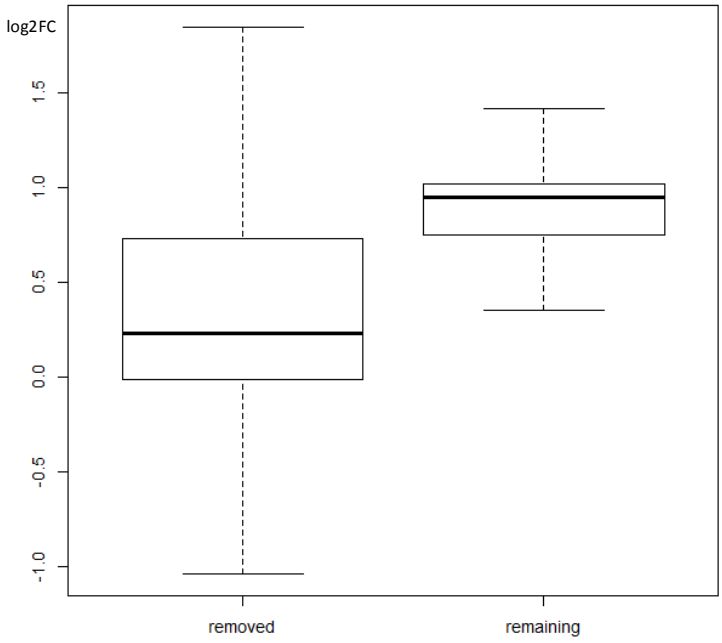
Supplemental Figure 3. Network-Based Analysis: Selection strategy and bias of the CVs. Boxplots of the CVs over all of the contigs (ALL), those selected for the subsequent network-based analysis (SELECTED), and those not selected by the strategy used (NOT SELECTED), for the MW **(A)** and MD **(B)** populations. The boxplots support the absence of systemic bias.



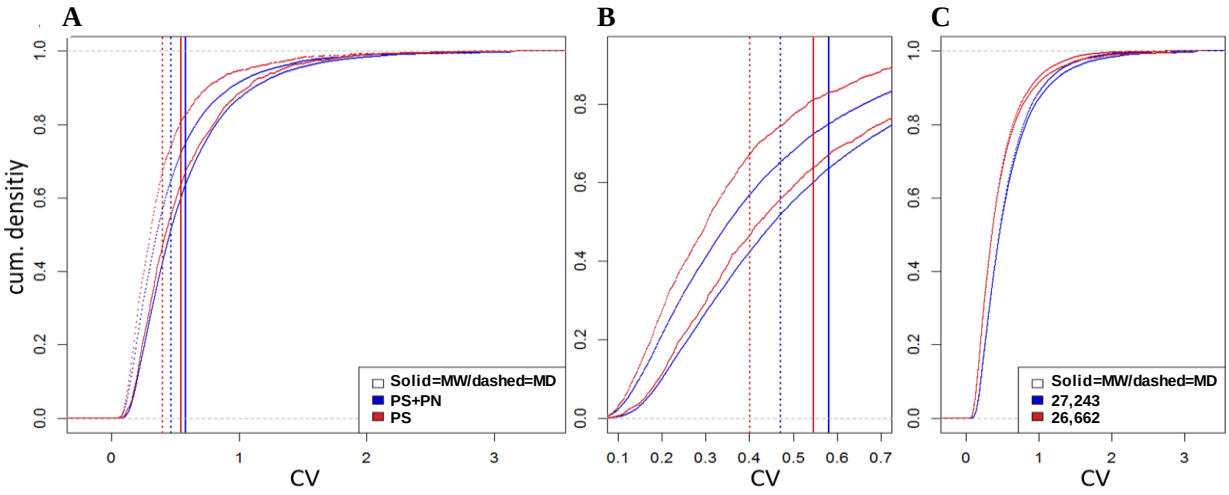
Supplemental Figure 4. Network-Based Analysis: Selection strategy and bias of CVs in the PS contigs. Boxplots of the CVs for all of the contigs (ALL), and those selected for the network-based analysis (ALL SELECTED), and of all the PS contigs (PS) and those retained (PS SELECTED) for the network-based analysis, in the MW **(A)** and MD **(B)** populations. The boxplots support the absence of systematic bias; i.e., no shifts towards higher/ lower values in the CVs for the PS contigs that were retained for further analysis.



Supplemental Figure 5. Demographic models used in this study. Demographic scenarios for the Mesoamerican and the Andean populations. See Supplemental Table 7 online for the details of the parameters.



Supplemental Figure 6. Boxplot illustrating the differences in the log2FC for the 581 removed contigs (removed) and the remaining 26,662 contigs (remaining). Note that negative values indicate higher expression levels in the MD forms.

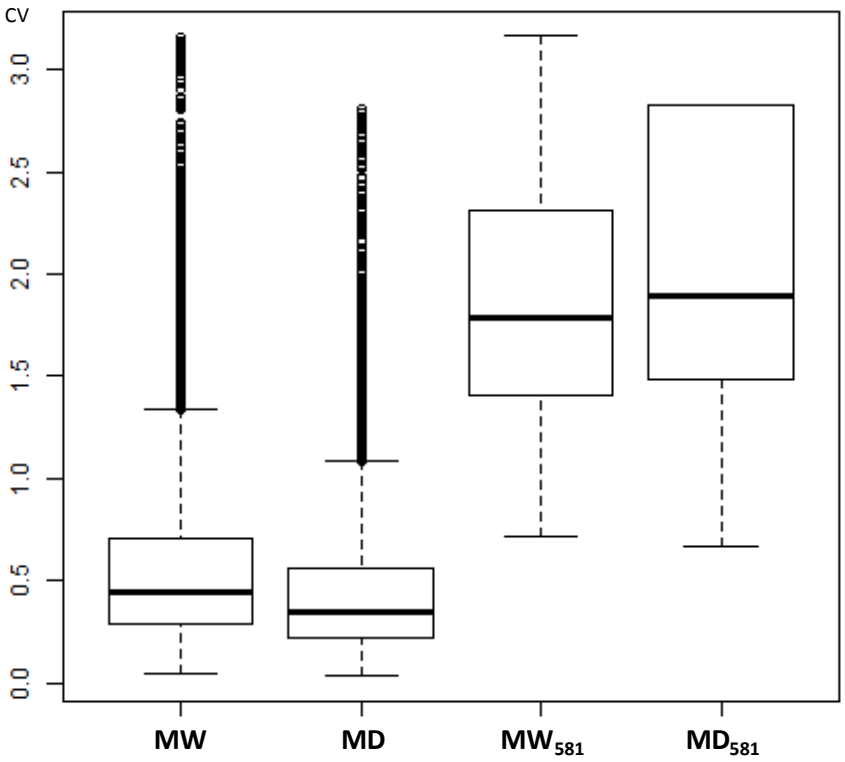


Supplemental Figure 7. Empirical cumulative density functions for the CVs considering all of the 27,243 contigs as reference.

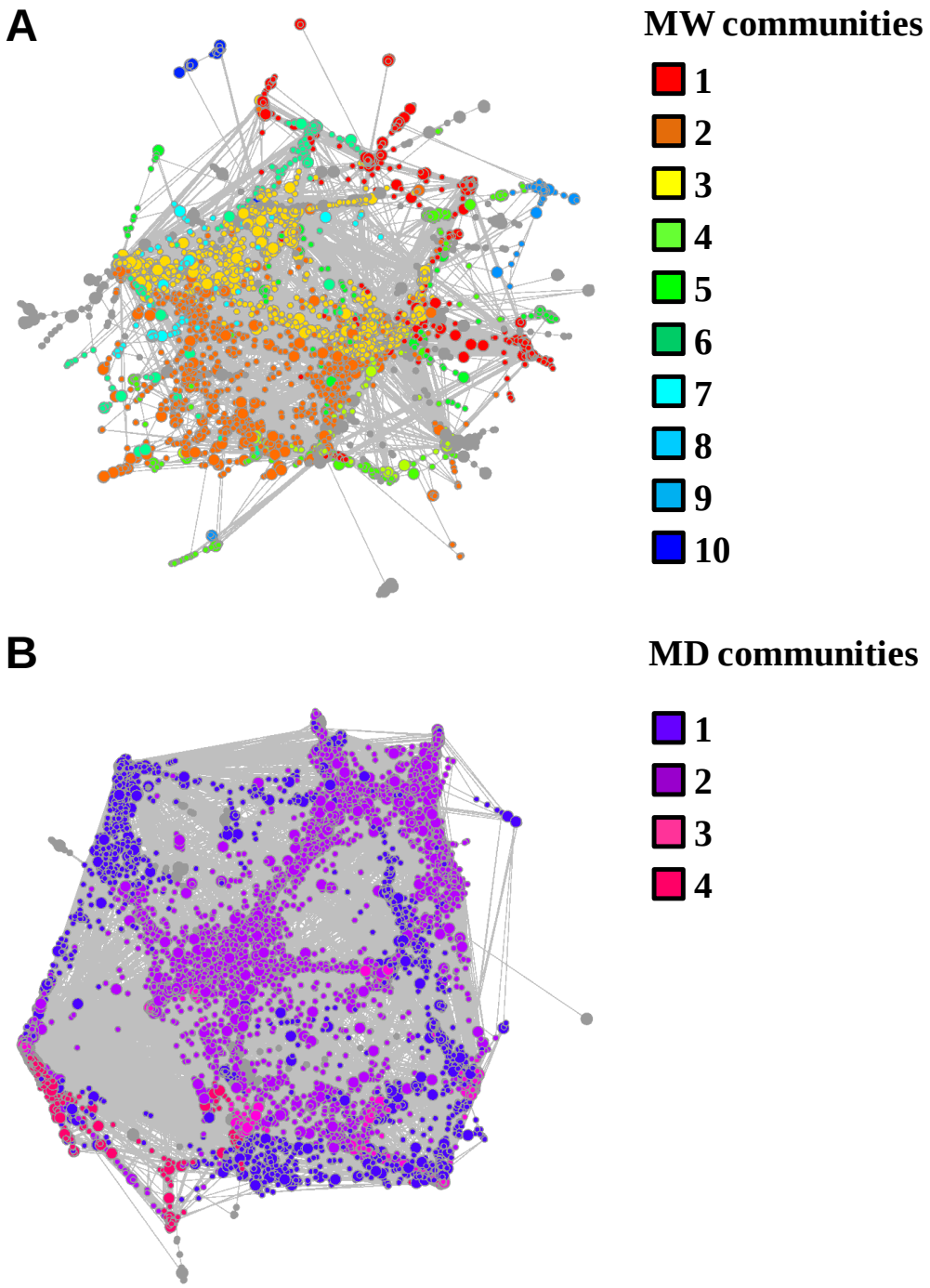
(A) Comparison of the empirical cumulative density functions of the CVs considering all of the contigs and PS.

(B) Detail of the panel in **(A)**, to show the range of the CVs between 0.1 and 0.7.

(C) Effect on the CVs with the removal of the 581 contigs containing more than nine individuals with zero expression levels.



Supplemental Figure 8. Boxplot illustrating the differences in the CVs for the 26,662 contigs (MW, MD) after the removal of the 581 contigs (MW_{581}, MD_{581}) in the MW and MD populations. Note: the majority of high CVs observed for the 581 contigs arise from the very small mean expression values.



Supplemental Figure 9. Relevance network from the MW (A) and MD (B) populations. The relevance network was extracted to match the density of the proximity networks. The different colors indicate the different communities of size ≥40 in the network; the nodes of larger sizes correspond to contigs under selective pressure; isolated nodes are not visualized.

SUPPLEMENTAL TABLES

Supplemental Table 1. Transcriptome assembly statistics. Assembly statistics for the four *P. vulgaris* reference genotypes and for the final nonredundant dataset.

	Assembly statistics			
	G24378	**W617475**	**G12873**	**G12979**
Number of sequences	55,069	65,273	70,826	61,141
Assembled bases	46,396,157	52,104,578	59,851,108	51,083,455
Average length	842.51	798.26	845.04	835.50
Median length	448	431	458	447
N50	1,515	1,393	1,486	1,491
	Nonredundant dataset statistics			
Number of sequences	124,166			
Assembled bases	104,901,858			
Maximum length	16,891			
Minimum length	201			
Average length	844.85			
Median length	428			
N50	1,595			

Supplemental Table 2. Jaccard similarity of the community structure in the MW and MD proximity networks. The Jaccard index was determined for each pair of communities for the extracted MW and MD proximity networks. The low similarity supports the comparison of the corresponding node partitions based on the adjusted Rand index.

		MD network				
		1	**2**	**3**	**4**	**5**
MW network	**1**	0.188	0.214	0.122	0.004	0.066
	2	0.202	0.245	0.133	0.003	0.042
	3	0.066	0.037	0.209	0.002	0.024
	4	0.133	0.052	0.092	0.004	0.054
	5	0.095	0.125	0.104	0.004	0.052
	6	0.001	0.001	0	0	0
	7	0.002	0	0.001	0	0

MW, Mesoamerican wild accessions; MD, Mesoamerican domesticated accessions.

Supplemental Table 3. Community gene function enrichment: List of selected enriched gene functions for each of the communities determined for the MW and MD networks (the full list of enriched terms and corresponding p-values is given in Supplemental Data Sets 1B and 1C online for MW and MD, respectively).

Network	Function
MW	
Community 1	Cell wall (hemicellulose synthesis, glucuronoxylan, cellulose synthesis)
	OPP oxidative PP.6-phosphogluconate dehydrogenase
	Amino acid metabolism (aromatic), hormone metabolism
	RNA regulation
Community 2	Protein synthesis (ribosomal proteins)
	RNA regulation and transcription (HSF, HAD, and AS2-lateral organ boundaries)
	Secondary metabolism (flavanoids and flavanols)
	N-metabolism (ammonia)
	Hormone metabolism (jasmonate and absisic acid synthesis-degradation)
	Signaling
Community 3	DNA synthesis (chromatin structure); lipid metabolism
Community 4	Hormone synthesis (jasmonate synthesis-degradation)
	PS lightreaction (photosystem II)
	Minor CHO metabolism
Community 5	Major CHO biosynthesis (starch)
	Redox (thioredoxin)
	Protein degradation (AAA type)
Community 6	Not enriched for any MapMan bins at significance level of α = 0.05
Community 7	Not enriched for any MapMan bins at significance level of α = 0.05
MD	
Community 1	PS lightreaction (photosystem II and other electron carrier)
	Cell wall (hemicellulose and cellulose synthesis, precursor synthesis (UXS), and glucuronoxylan)
	Minor CHO metabolism (raffinose family)
	RNA regulation of transcription (MYB domain and MADS box transcription factor family, Aux/IAA family, and Trihelix and Triple-Helix transcription factor family),
	N-metabolism (ammonia)
	Stress (abiotic)
	Hormone metabolism (slicylic and abscisic acid)
Community 2	Protein synthesis (ribosomal protein)
	Protein degradation (ubiquitin)
	Protein targeting (secretory pathway)
	Post-transcriptional modification (kinase)
	Signaling (receptor kinase)
	RNA regulation of transcription (bZIP and WRKY domain transcription factor family)
	Fermentation (aldehyde dehydrogenase)
Community 3	DNA synthesis (chromatin structure)
	RNA regulation of transcription (zf-HD)
	Cell wall degradation (mannan-xylose-arabinose-fucose)
Community 4	Not enriched for any MapMan bins at significance level of α = 0.05
Community 5	Not enriched for any MapMan bins at significance level of α = 0.05

MW, Mesoamerican wild accessions; MD, Mesoamerican domesticated accessions.

Supplemental Table 4. Difference in mean node centralities of contigs under selective pressure, and the rest of the nodes in the MW and MD networks. The centrality of each node was estimated for the MW and MD proximity networks. The differences in means between the contigs under selective pressure and the rest of the nodes in the networks were tested. Negligible, although statistically significant, differences were observed for closeness centrality in both the MW and MD proximity networks.

Difference factor	MW proximity network			MD proximity network		
	Mean value of contigs		p value	Mean value of contigs		p value
	Under selective pressure	Remaining		Under selective pressure	Remaining	
Betweenness	26,890	25,470	**0.0063**	28,220	27,920	0.6068
Closeness	1.632E-05	1.621E-05	**3.96E-05**	1.518E-05	1.511E-05	**0.0167**
Degree	12.69	12.88	0.1059	13.69	13.64	0.5963
Ev centr.	0.00217	0.002651	0.7984	0.001401	0.003122	0.025
Page rank	9.356E-05	9.427E-05	0.2401	9.44E-05	9.417E-05	0.6278
Eccentricity	9.208	9.258	0.0031	10.42	10.44	0.6459
Burt's constraint	0.1244	0.1245	0.9176	0.1204	0.1213	0.1221
Transitivity	0.2468	0.2533	0.033	0.2832	0.2886	0.01287

Supplemental Table 5. Difference in assortativity, both nominal and based on the 'selection index', between the MW and MD networks. Significance obtained with permutation tests (permutation of node labels) for the observed assortativity values for the MW and MD networks, and their difference.

Permutation test	**Network**	**Node (n = 10,000)**	
		Observed	**p value**
Assortativity (nominal)	MW	0.005828	0.0608
	MD	0.011888	9.00E-04
	MW-MD	-0.00606	0.1246667
Assortativity (S-Index)	MW	0.008214	0.0154
	MD	0.014609	1.00E-04
	MW-MD	-0.00639	0.1135

MW, Mesoamerican wild accessions; MD, Mesoamerican domesticated accessions.

Supplemental Table 6. Accessions used in this study.

	Accession number/name	Population code[1]	Source[2]	Country	Department, State or Province	Biological status	Altitude (m s.l.m.)	Latitude (°N)	Longitude (°E)
1	G12873*	MW	CIAT	Mexico	Morelos	Wild	1981	19.000	-99.250
2	G9989	MW	CIAT	Mexico	Jalisco	Wild	1400	20.500	-104.817
3	G11050	MW	CIAT	Mexico	Michoacan	Wild	2040	19.683	-101.267
4	G12979*	MW	CIAT	Mexico	Jalisco	Wild	/	20.117	-104.367
5	G22837	MW	CIAT	Mexico	Chihuahua	Wild	1750	26.933	-106.417
6	G24378*	MW	CIAT	Mexico	Oaxaca	Wild	1250	16.040	-97.083
7	PI325677	MW	USDA	Mexico	Morelos	Wild	1828	18.967	-99.100
8	PI417770	MW	USDA	Mexico	Nayarit	Wild	2000	20.667	-102.383
9	G20515	MW	CIAT	Mexico	Puebla	Wild	/	19.800	-97.783
10	G12922	MW	CIAT	Mexico	Jalisco	Wild	1829	20.700	-102.350
11	G5191	MD	CIAT	Venezuela	Distrito Federal	Landrace	/	10.500	-66.917
12	PI151017	MD	USDA	Chile	/	Landrace	660	-33.450	-70.667
13	PI201349	MD	USDA	Mexico	Puebla	Landrace	1000	20.183	-98.050
14	PI281981	MD	USDA	Mexico	Jalisco	Landrace	/	20.417	-103.667
15	PI300668	MD	USDA	Chile	/	Landrace	/	/	/
16	PI309831	MD	USDA	Costa Rica	Cartago	Landrace	1200	9.867	-83.783
17	PI310660	MD	USDA	Guatemala	Chimaltenango	Landrace	2000	14.667	-90.817
18	PI311794	MD	USDA	El Salvador	Santa Ana	Landrace	660	13.983	-89.567
19	W617475*	AW	USDA	Argentina	Salta	Wild	1470	-25.167	-65.617
20	Midas	AD	P.Gepts	Argentina	/	Cultivar	/	/	/
21	PI298109	AD	USDA	Brazil	/	Landrace	/	/	/

[1]MW, Mesoamerican wild; MD, Mesoamerican domesticated; AW, Andean wild; AD, Andean domesticated;
[2]CIAT, International Centre for Tropical Agriculture; USDA, United States Department of Agriculture. Seeds of Midas accession were kindly provided by Prof. Paul Gepts, Department of Plant Sciences, Section of Crop and Ecosystem Sciences, UC Davis, CA, USA.
*Accessions of the hyper-core collection used for the *de novo* assembly.

Supplemental Table 7. Demographic parameters in the B0, B1 and B2 models.

Model	Parameter	Description	Units	Distribution	Mean	S.D.	Min	Max
B0,B1,B2	T_{ANC}	Divergence time between Andean and Mesoamerican gene pools	Generations	Normal	111,000	40,000	67,330	192,835
B2	T_{BMB}	Time of the beginning of the Mesoamerican founder bottleneck	Generations	Normal	99,833	750	98,375	99,833
B1,B2	T_{BAB}	Time of the beginning of the Andean founder bottleneck	Generations	Normal	98,845	3,000	94,051	104,027
B2	T_{EMB}	Time of the ending of the Mesoamerican founder bottleneck	Generations	Normal	67,341	1,400	64,568	67,341
B1,B2	T_{EAB}	Time of the ending of the Andean founder bottleneck	Generations	Normal	67,858	1,500	64,655	70,865
B0,B1,B2	T_{BMD}	Time of the beginning of the Mesoamerican domestication	Generations	Normal	8,160	133	7,922	8,426
B0,B1,B2	T_{BAD}	Time of the beginning of the Andean domestication	Generations	Normal	8,500	8	8,495	8,517
B0,B1,B2	T_{EMD}	Time of the ending of the Mesoamerican domestication	Generations	Normal	6,260	150	5,971	6,567
B0,B1,B2	T_{EAD}	Time of the ending of the Andean domestication	Generations	Normal	7,012	35	6,945	7,075
B0,B1,B2	N_{ANC}	Ancestral effective population size	Haploid individuals	Normal	418,000	105,000	266,000	628,000
B2	N_{BM}	Mesoamerican effective population size during the founder bottleneck	Haploid individuals	Normal	168,000	7,500	153,000	170,000
B1,B2	N_{BA}	Andean effective population size during the founder bottleneck	Haploid individuals	Normal	105,000	20,000	65,000	142,000
B0,B1,B2	N_{MD}	Effective population size of the domesticated Mesoamerican population	Haploid individuals	Uniform			100,000	100,000
B0,B1,B2	N_{MW}	Effective population size of the wild Mesoamerican population	Haploid individuals	Normal	292,000	240,000	125,000	773,000
B0,B1,B2	N_{AW}	Effective population size of the wild Andean population	Haploid individuals	Normal	137,000	182,000	70,000	502,000
B0,B1,B2	N_{AD}	Effective population size of the domesticated Andean population	Haploid individuals	Uniform			100,000	100,000
B0,B1,B2	I_{MD}	Intensity of the domestication bottleneck in Mesoamerica	Ratio	Normal	47.65	3	41.66	52.13
B0,B1,B2	I_{AD}	Intensity of the domestication bottleneck in the Andes	Ratio	Normal	47.26	0.5	46.25	48.59
B0,B1,B2	M_{WD}	Migration rate from wild to domesticated population	Rate	Uniform			0.000001	0.00001
B0,B1,B2	XM	Asymmetric migration factor	Rate	Uniform			2	6
B0,B1,B2	M_{DW}	Migration rate from domesticated to wild population	Rate	XM*MWD				
B0,B1,B2	μ	Mutation rate (per site per generation)	Rate	Normal	$1E^{-9}$	$5E^{-9}$	$1E^{-10}$	$1E^{-8}$
B0,B1,B2	L	Length of the simulated sequences	Base pairs	Normal	1,300	1,500	250	5,000

Supplemental Table 8. Enriched MapMan bins for 581 (140 annotated) contigs removed prior to the network analysis. These 581 contigs were removed from the set of contigs subjected to the network-based analysis due to zero expression estimates in at least nine individuals. These contigs are enriched for the MapMan bins included in the first two columns at a significance level of 0.05.

MapMan bin	Description	p value
28.1.3.2	DNA.synthesis/chromatin structure.histone.core	1.94e-08
28.1.3	DNA.synthesis/chromatin structure.histone	5.01e-08
28.1.3.2.4	DNA.synthesis/chromatin structure.histone.core.H4	0.000118
30.8	Signaling.misc	0.000153
28.1.3.2.3	DNA.synthesis/chromatin structure.histone.core.H3	0.000294
28.1	DNA.synthesis/chromatin structure	0.000978
27.3.24	RNA.regulation of transcription.MADS box transcription factor family	0.002902
30.2.8.1	Signaling.receptor kinases.leucine rich repeat VIII.VIII-1	0.00347
10.2.1	Cell wall.cellulose synthesis.cellulose synthase	0.004913
33	Development	0.005296
28.1.3.2.1	DNA.synthesis/chromatin structure.histone.core.H2A	0.00622
33.99	Development.unspecified	0.006365
30	Signaling	0.01005
10.5.1	Cell wall.cell wall proteins.AGPs	0.01069
10.5.1.1	Cell wall.cell wall proteins.AGPs.AGP	0.01069
28	DNA	0.0132
10.2	Cell wall.cellulose synthesis	0.01921
10	Cell wall	0.02384
30.2.8	Signaling.receptor kinases.leucine rich repeat VIII	0.02721
24	Biodegradation of Xenobiotics	0.03194
27.3.67	RNA.regulation of transcription.putative transcription regulator	0.04299
10.5	Cell wall.cell wall proteins	0.04417
29.7	Protein.glycosylation	0.0499

GLOSSARY

MD: Mesoamerican domesticated accessions.

MW: Mesoamerican wild accessions.

S, ***nH***, ***π***, ***Θ***, ***He***: statistics for the estimation of the levels of molecular diversity.

L_{π}, L_{Θ}, L_{He}: loss in molecular diversity (in MD compared to MW).

Lcv: loss in gene expression diversity (in MD compared to MW).

Log2FC: when significantly shifted, indicates down-regulation or up-regulation of gene expression.

CV: coefficient of variation, estimated for gene expression.

Selection indices: based on two between-groups and one within-groups genetic variation statistics that were likely to have been affected by differential selection for MD compared to MW (see Online Methods for details). Used to identify PS contigs.

PS contigs: contigs putatively under selection in MD compared to MW, identified by computing two selection indices and testing their significance with a coalescent simulation (see Online Methods for details). The opposite is PN contigs (i.e., putatively neutral contigs).

Coalescent simulations of domestication models: used to identify PS contigs by computing two selection indices and testing their significance. Coalescent simulations are used to generate neutral distributions of summary statistics, assuming three likely domestication scenarios (models) that are reconstructed and based on the population histories and demographic parameters estimated in previous studies.

PCCs: Pearson correlation coefficients among gene expression profiles; a wider distribution of PCCs supports stronger correlations.

Network analysis (proximity networks, relevance networks): concerns gene co-expression. In a network, a community is a group of genes with correlated expression (see Online Methods for details).

Rank index, Jaccard similarity: allow the comparison of networks.

Enrichment gene-function analysis and gene-set enrichment analysis: comparative degree of enrichment in gene functions in a comparison among communities and/or groups (e.g., MW *versus* MD; PS *versus* PN), and used to determine biological signals (in the communities) or to examine the functional characterization (PS contigs).

MapMan ontology and test on hypergeometric function: allows the functional characterization of contigs, and to derive which MapMan bins are statistically significantly over-represented.

SUPPLEMENTAL METHODS 1

1. Network-based analysis

1.1 Contig selection strategy and investigation of bias

The contigs for the network analyses were selected to avoid the inclusion of potentially noisy or invariant gene expression profiles, which might lead to the inclusion of spurious edges in the extracted networks.

We removed 581 contigs that showed zero expression levels in at least nine genotypes from the analysis. Of these, 40 were determined to be under selective pressure (PS), with 17 of these contigs having expression values of zero in all of the investigated samples. The removal of these contigs from the total of 27,243 did not introduce bias with respect to the contigs that were determined as PS, as their proportion was within the expected range (binomial test, p-value >0.2). In addition, 140 of these 581 contigs were annotated by MapMan bins. The results of the enrichment analysis are presented in Supplemental Table 8 online.

The log2FC between the MW and MD populations for the 581 contigs show negative values due to the larger expression values in the MD samples (see Supplemental Figure 6 online). There is a shift towards smaller CVs between MD and MW (Supplemental Figures 7A and 7B online), and this also holds when focusing on the PS contigs. The effect of removing the 581 contigs on the distribution of CVs was not pronounced (Supplemental Figure 7C online). However, there were statistically significant differences between the CVs of the 26,662 contigs and the CVs for the 581 removed contigs; these are, however, artefacts due to the high CVs for the removed contigs as a result of their small mean expression levels; this is a common drawback of the CV statistic (Supplemental Figure 8 online).

To select a subset of contigs to use for the network analysis, two statistical tests were performed for each of the remaining 26,662 contigs: the differences in the means and variance of the expression levels between the MW and MD populations, based on ANOVA and on the F-test, respectively (Ho et al., 2008). A very loose level of significance ($\alpha = 0.1$) was considered for both of these tests. The Wilcoxon rank sum test with continuity correction (Hollander and Wolf, 1973) was applied to the CVs computed for MW and MD for each chosen contig, to determine whether the strategy applied for the contig selection had introduced any systematic bias with respect to favoring contigs that vary strongly in both the MW and MD populations, in comparison to the entire set of contigs that were considered. The possibility of a shift in the CV towards higher/ lower values for the PS contigs retained and those excluded from subsequent analysis was also tested.

These tests resulted in the selection of 10,616 contigs, the profiles of which were further subjected to network-based analysis (Supplemental Figure 2 online). There was no bias associated with the contigs variation of gene expression (as shown in Supplemental Figure 3 online). From the remaining 2,324 PS contigs, about 50% were included in the network analysis (Supplemental Figure 2 online). However, we derived two much larger networks using cut-offs of 0.2 and 0.3 for ANOVA and homogeneity of variance (the F-test). We found that the results remained qualitatively unchanged.

1.2 Proximity and relevance networks

The MW and MD expression profiles for the 10,616 contigs were subjected to network-based analysis following two procedures, both of which were based on the Pearson correlation coefficients (PCCs): (i) generation of relevance networks; and (ii) extraction of proximity networks (Klie et al., 2012; Klessen et al., 2013). With the first procedure, an edge is established between two nodes (which represent genes) if the PCC between the corresponding expression profiles is higher than a threshold τ that ensures a given level of statistical significance. According to the second procedure, for a fixed k, an edge is created between two nodes, *u* and *v*, if *u* appears in the list of the k genes with the highest PCC to *v*, and if *v* is in the list of the k genes with the highest PCC to *u*. As a result, the second procedure, which generates a proximity network, takes into consideration the observation that the genes can often be activated as modules of a program to fulfill a particular function.

To compare the networks generated by these two procedures, we required that they were equally informative, as quantified by their density (i.e., the total number of edges divided by the number of edges in a complete network on the same number of nodes). This also implies that the selection of the threshold values in the procedures for network generation has to guarantee an (almost) equal density. The density is a number ranging from 0 to 1, with 0 where there are no edges between any two nodes, and 1 when any two nodes are connected by an edge.

It can be shown that the null distribution for k is almost uniform; therefore, with 10,000 genes, k = 100 will ensure a significance level of $\alpha = 0.01$. Here, we present and discuss the results for k = 15. To examine the robustness of the findings, we also repeated the analysis for $k \in \{10,20\}$ (data not shown). To specify the threshold value τ, we determined the value of the PCC that ensured that the generated network was of (almost) equal density as the proximity network (as established based on the same dataset). For instance, $\tau = 0.91$ in the procedure for extraction of the relevance network corresponds to k = 15 in the procedure for generating proximity networks. These thresholds were applied to both the MW and MD gene expression profiles, and the resulting networks were compared and contrasted based on their network properties.

1.3 Analysis based on relevance networks

The proximity network generation and properties are described in the main text (Online Methods and Results sections). As already indicated above, the relevance networks were extracted so that their densities matched those of the proximity networks. This facilitates further comparative analysis between the two procedures for network generation. With the corresponding threshold value of $\tau = 0.92$, the MW relevance network is again sparser than the MD relevance network: 1,661 isolated nodes (i.e., nodes without any edge) in MW, and 105 isolated nodes in MD. The largest connected component in the MW network included 8,257 nodes, while in the MD network, this contained 10,439 nodes. The relevance networks have a characteristic heavy-tailed degree distribution. As a result, there was a finer community structure in both of the relevance networks (Supplemental Figures 9A and 9B online), with 152 communities with at least two nodes in the MW network and 27 in the MD network. In the MW relevance network, the largest community contained 2,662 nodes, while in the MD relevance network contained 4,665 nodes. Altogether, nine and four communities included more than 100 nodes in the MW and MD networks, respectively. The enrichment analysis largely matched that for the proximity networks.

Regarding the assortativity with respect to the contigs under selection pressure, our findings were similar to those from proximity networks: 0.010 for MW and 0.008 for MD. For assortativity with respect to the CVs, as in the case of proximity networks, we found that MW showed higher clustering of similar contigs (0.44) in comparison to MD (0.35). The findings regarding the centrality of the PS contigs were in line with those obtained from the proximity networks.

2. Gene-set enrichment analysis using MapMan

To characterize the molecular functions and biological processes of the *Phaseolus* contigs under study, the latest version that was available for MapMan and *Arabidopsis* (version 1.1 from January 2010, http://mapman.gabipd.org/) was used (Thimm et al., 2004). By using the sequence homology of *Phaseolus* contigs and *Arabidopsis* genes, a total of 13,228 contigs were assigned with MapMan bins, disregarding the 35 MapMan (sub-)bins that corresponded to '*not assigned*'. The *Phaseolus* contig-to-MapMan mapping that was obtained was further processed to include the parent bins and to remove inconsistencies, as described in Klie and Nikoloski (2012).

To further assess whether a particular set of contigs (i.e., members of network communities, PS contigs, or contigs up-regulated in the wild forms) is predominantly involved in similar molecular functions or biochemical processes in MW and MD, gene-set enrichment analysis (GSEA) was performed (Subramanian et al., 2005). Briefly, for a given set of contigs, it was statistically tested whether certain MapMan bins are over-represented within this particular group of contigs; i.e., over-enriched. Classically, hypergeometric tests are used to derive which MapMan bins are statistically significantly over-represented (Rivals et al., 2007). The enrichment results presented throughout this manuscript were obtained using the previously mentioned hypergeometric test and the Benjamini-Hochberg false discovery rate correction to obtain *p* values

(Benjamini and Hochberg, 1995), as implemented in the statistical environment R. For all of the enrichment tests, the significance level was set to 5%.

SUPPLEMENTAL METHODS 2

3. Survey of enriched gene functions for the MW and MD communities

To determine whether the network communities carry biological signals, the enriched gene functions for each of the communities determined were investigated (at a significance level of $\alpha = 0.01$) using the MapMan ontology. The communities corresponded to modular structures of largely different functions (Supplemental Table 3 online; Supplemental Data Sets 1B and 1C online). We investigated whether the different classes of genes that were over-represented in either MW or MD were shown to be involved in the domestication process, either through direct experiment or by implication on the basis of function. The results of this survey are reported below.

- MADS-BOX. The MADS-BOX class of genes, which includes *APETALA1* (AP1; Mandel et al., 1992; Gustafson-Brown et al., 1994) and *CAULIFLOWER* (*CAL*; Kempin et al., 1995), have been shown to control the specification of floral meristem identity (Alvarez-Buylla et al., 2006). In maize, a domestication candidate gene, *GRMZM2G448355* (Hufford et al., 2012), is an ortholog of the Os*MADS56* gene, which delays flowering under long-day conditions in rice (Ryu et al., 2009). Interestingly, the evolution of the domesticated cauliflower (*B. oleracea* spp. *botrytis*) appears to be associated with mutations in the MADS-BOX floral meristem identity genes *CAL* and *AP1* (Kempin et al., 1995; Lowman and Purugganan, 1999).

- bZIP, WRKY. Drought responses include the induction of proteins belonging to several transcription factor and regulator families used in the reprogramming of the transcriptome to initiate adaptation strategies (Ramanjulu and Bartels, 2002), such as the bZIP, the MYB transcription factors, WRKY, and zinc-finger proteins. The bZIP transcription factor family induces transcription by binding to upstream abscisic-acid-responsive elements (Ramanjulu and Bartels, 2002), and differential expression of a member of this transcription-factor family was observed in a leaf subtractive cDNA library of a drought-sensitive genotype of wheat (*TTD-22*; Ergen and Budak, 2008). It is worth noting that several bZIP genes have been postulated to be involved in domestication. In maize, the *OPAQUE 2* (*O2*) gene, for example, was shown to encode a transcriptional activator that has a role in alterations to the grain phenotype during domestication (Henry et al., 2005). In addition, studies of natural variations in the seed dormancy in *Arabidopsis* led to the cloning of a QTL, *DELAY OF GERMINATION 1* (*DOG1*), which affects embryonic dormancy (Bentsink et al., 2006). *DOG1* encodes a member of a plant-specific protein family with a domain shared by the D class bZIP DNA-binding proteins (Sugimoto et al., 2010).

Interestingly, members of the WRKY family of proteins (Eulgem and Somssich, 2007) that are well-known for their roles in response to several abiotic stresses (Ramanjulu and Bartels, 2002) were almost exclusively induced in a drought-tolerant emmer wheat genotype (TR39477; Ergen and Budak, 2008). A number of transcription factors including many from the WRKY, AP2/EREBP, and MYB families, are also involved in leaf senescence (Eulgem et al., 2000; Chen et al., 2002).

The maternally expressed *Arabidopsis* WRKY transcription factor *TRANSPARENT TESTA GLABRA 2* (*TTG2*) appears to have a controlling role in seed size via the integument growth pathway; the seed length of a *ttg2* mutant is much smaller than the wild-type (Garcia et al., 2005).

Duplicated WRKY genes have been maintained in wild and cultivated plant species in the course of selection during domestication and polyploidization (Petitot et al., 2008). However, the majority of the WRKY genes analyzed respond to pathogen attack and to the endogenous signaling molecule salicylic acid (Eulgem and Somssich, 2007).

- Trihelix. The rice *Shattering 1* (*SHA1*) gene that encodes a GT-1-type factor has an important role in the activation of cell separation, and a mutation in the trihelix domain resulted in the elimination of seed shattering in cultivated rice (Lin et al., 2007). All of the the domesticated rice cultivars analysed harbor the mutant *sha1* gene, and have thus lost the ability to shed their seeds at maturity.

- Xylan. The cell wall mediates growth responses and often acts as the first barrier in interactions with a wide range of environmental factors (Stebbins, 1992; Somerville et al., 2004). Selection during the domestication process produced changes in the cell wall structure and composition; in this regard, in the study of Zhang et al. (2012), it was shown that the wild rice Yuanj has a reduced level of xylan associated with a less upright growth habit. Domestication appears to have conferred an increased level of xylan backbone to cultivated rice plants, along with an erect growth habit.

- Raffinose family. The most common of the raffinose family oligosaccharides (RFOs) are raffinose (RFO-trisaccharide) and stachyose (RFO-tetrasaccharide). The RFOs have diverse roles in plants, as they are used for transport and storage of carbon, and as solutes for the protection against abiotic stress (Bachmann et al., 1994; Haritatos et al., 1996; Taji et al., 2002). In many plant species, raffinose is also stored in high amounts in seeds, where it is thought to have an additional role in desiccation tolerance (Obendorf, 1997). The sucrose and RFO content in seeds might determine and indicate their storing capacity. Tahir et al. (2012) reported variations in relative concentrations of stachyose and raffinose between wild and domesticated lentil genotypes.

- MYB. Anthocyanin accumulation is controlled through the coordinated expression of genes encoding the anthocyanin biosynthetic pathway enzymes. From studies in a diverse array of plant species, it is apparent that this coordinated expression is controlled at the transcriptional level, usually by an R2R3 MYB and/or a basic helix-loop-helix transcription factor (Mol et al., 1996; Winkel-Shirley, 2001). More recently, advances have been achieved in apple (*Malus* × *domestica*) where the R2R3 MYB tanscriptional factors responsible for apple anthocyanin accumulation were identified (Espley et al., 2007). In a study seeking to examine the control of apple fruit skin anthocyanins (Ban et al., 2007), Md-MYBA was isolated from a pale red-skinned apple cultivar and characterized in a deep red-skinned cultivar.

A member of the MYB transcription factor family proteins that is involved in the control of several biological functions upon biotic and abiotic stresses (Lee et al., 2007) was differentially induced in a drought-sensitive genotype of wheat (TTD-22; Ergen and Budak 2008).

A gene identified in rice as producing a non-shattering phenotype (*sh4*) has a MYB3 DNA binding domain, which suggests that it is a transcription factor. A single SNP that leads to a single conserved amino-acid change has resulted in a change in function, which appears to result in either the incomplete formation of the abscission zone (Li et al., 2006) or the failure to initiate cell degradation (Lin et al., 2007). In the case of rice, two independent genetic pathways to nonshattering have occurred. The nonshattering phenotype probably came after other mutations that were associated with an increase in grain size and the waxy phenotype (Shomura et al., 2008), which supports the idea that the mutation arose in the domesticated population of rice.

- ZF-HD. Abscission is a process that is often implicated in domestication. Nakano et al. (2013) examined the transcriptomes of three tomato flower pedicel regions, the abscission zone and the flanking proximal and distal regions. They identified 89 genes that were preferentially expressed in the abscission zone compared to both the proximal and distal regions. These genes included several transcription factors that regulate apical or axillary shoot meristem activity. Nine genes belonging to seven transcription factor families were identified, among which there was a zinc-finger homeodomain (ZF-HD) family gene (*CK715116*). In particular, this gene encodes a protein with sequence similarity to the *Arabidopsis* ZF-HD family gene *HOMEOBOX PROTEIN33* product, which is involved in the abscisic acid response pathway (Wang et al., 2011).

4. Gene-function investigation

A survey of the function of a subset of PS contigs was carried out to investigate whether they are known to be associated to the domestication process in other species, using either direct experimentation or because of their function. In particular, we focused our survey on the 380 contigs that had the highest selection index (290), and considering also different patterns of polymorphism, all of the 23 PS contigs with alternative allelic states in MW and MD, and all of the 67 PS contigs that are monomorphic in MW and polymorphic in MD. Almost all of these contigs investigated had a BLASTX e-value ≤$10e^{-4}$, with few exceptions (six contigs had an e-value ≤$10e^{-2}$ and their functions were not relevant to domestication).

4.1 Contigs with the highest selection indices

The survey of the function of 221 annotated contigs among the 290 with the highest selection indices resulted in the following main points:

- Genes involved in "light" response pathway: Under directional selection, several genes were identified as involved in light perception or signaling and circadian and rhythm determination (*PHYA*, *EARLY FLOWERING4-Like 3*), photoperiod response (*GIGANTEA*), photoperiod adaptation (*DWARF IN LIGHT*), and timing of bolting and flowering (*VERNALIZATION INDEPENDENCE 5*, *AROGENATE DEHYDRATASE 1*, *AGAMOUS-LIKE8*). Another gene that was under positive selection, *KANADI2* (that together with *K1* modulates *PIN1*, a gene that, in turn, encodes an auxin transport protein), is a target (as also for *AGAMOUS* [see below] and other genes) of *LEAFY*, a master gene that has a central role in the regulation of the transition from vegetative growth to flower formation (Winter et al., 2011). *BRIZ1* is another interesting gene here, which has been shown to be comprised in the interval of Flt-2L QTL for flowering time in barley (Chen et al., 2009a). This QTL comprises Hv-*AP2*, which is highly similar to the wheat domestication gene Q (Förster et al., 2013). Finally, there is the *HIGH MOBILITY GROUP A* (*HMGA*) gene that encodes a DNA binding protein that interacts with A/T-rich stretches of DNA. Although this specific gene has an unknown function, it should be noted that other proteins, such as AHL22, that contain an AT-hook motif in *Arabidopsis* regulate flowering initiation by modifying the *FLOWERING LOCUS T* chromatin (Yun et al., 2012).

Among these genes, *GIGANTEA* (*GI*) has a pivotal role in the photoperiod response, as it controls flowering under long days in a circadian clock-controlled flowering pathway. In *Arabidopsis*, *GI* acts earlier than *CONSTANS* (*CO*) and *FLOWERING TIME* (*FT*) in the pathway, by increasing the levels of *CO* and *FT* mRNA (Mizoguchi et al., 2005). Literature surveys have shown that the genes with which *GI* interacts directly (i.e., *FT*, *CO*) were targets of selection during the domestication in crops like rice (*DTH CONSTANS*-like, Wu et al., 2013; and *Hd1 CONSTANS* homolog, Takahashi and Shimamoto, 2011) and sunflower (*HaFT1* and paralogs, Blackman et al., 2011). In pea, Hecht et al. (2007) identified *LATE BLOOMER 1* (*LATE1*) as the pea ortholog of *Arabidopsis GI*, and showed that it is necessary for promotion of flowering, production of a mobile flowering stimulus, and induction of an *FT* homolog under long-day conditions. Moreover, several other genes involved in flowering time were selected under domestication, such as in rice, wheat, barley, maize, rapeseed, sunflower, lentil, pea and sorghum (see Lenser and Theißen, 2013; Olsen and Wendel, 2013, for reviews). Interestingly, in *Arabidopsis*, it has been shown that *GIGANTEA* and *EARLY FLOWERING 4* (*ELF4*) show differential phase-specific genetic influences over a diurnal cycle (Kim et al., 2012), and that *GI* is epistatic to *ELF4* in flowering time determination, while *ELF4* is epistatic to *GI* in hypocotyl growth regulation. Moreover, *GI* and *ELF4* have a synergistic or additive effect on endogenous clock regulation. Kim et al. (2012), which suggests that this might allow diversity in the regulation of circadian physiological outputs to be achieved, including flowering time and hypocotyl growth. However, the present study is the first that reports that *GI* was selected during the process of domestication, while a putative transcriptional regulator that potentially functions in the Phytochrome A light signaling pathway was shown to be under selection during domestication of soybean (*E1* gene; Xia et al., 2012). This congruence is relevant, as the recent divergence of flowering-related genes in three legume species has been documented (*Glycine soya, Lotus japonicus*, *Medicago truncatula*; Kim et al., 2013).

AGL8 is another gene of outstanding interest. In *Arabidopsis*, it is negatively regulated by *APETALA 1*. The homolog of *APETALA 1* in wheat has been found to be selected under domestication (Yan et al., 2003; Golovnina et al., 2010). Moreover, *AGAMOUS* occupies a nodal position between the "floral induction" pathway and the "floral identity genes and meristem maintenance" pathway that control the formation of stamens, carpels, ovule and fruit development, and that determine the flowers across all angiosperms (Lenser and Theißen, 2013). Mutations in this "input-output" gene might alter a trait (or a series of traits) in a way that might otherwise only be achieved by concerted mutations within several upstream or downstream genes simultaneously, and it is for this reason that it is regarded as a good example to explain the molecular basis of convergent evolution during domestication (Lenser and Theißen, 2013).

Furthermore, the homolog of *AGL8* in soybean is considered as one of the three candidates for a major QTL for flowering time on chromosome 6 (Zhang et al., 2013).

- Genes that are pivotal to ensure correct hormonal perception, transport or biosynthesis: *TINY2* is an AP2/ERF (APETALA/Ethylene-responsive factor). In *Glycine max*, this gene regulates the Gm-*GA2ox4* gene, causing dwarfism (Suo et al., 2012). Another gene, At-*GRXS17*, has a critical role in redox homeostasis and hormone perception, to mediate temperature-dependent post-embryonic growth (Cheng et al., 2011); its mutants are altered in their perception of the phytohormone auxin and its polar transport. The *PIN3* gene encodes an auxin transport protein that is crucial for correct cellular coordination, and has a direct involvement in gravitropism and phototropism. It is implicated in the shade avoidance response regulated by phyA (here also found under selection) and phyB (Devlin et al., 2003). Moreover, *PIN* interacts with *INDEHISCENT* (*IND*) in regulation of the separation layer cells. The gene *WALL ARE THIN 1* is involved in numerous processes, such as auxin polar transport, positive regulation of auxins, regulation of meristem growth, anthocyanin accumulation in tissues in response to UV light, cell-wall organization and secondary cell-wall biogenesis in fibers, cell growth, regulation of cell size, root hair elongation, root morphogenesis, water transport, response to salt stress, and stem elongation (Ranocha et al., 2010). The gene *FRAGILE FIBER 1* (*FRA1*) is also an interesting candidate, as its mutants show altered orientation of cellulose microfibrils and reduced mechanical strength of fibers. Moreover, phylogenetic studies have shown that the rice gene *GIBBERELLIN INSENSITIVE DWARF1* (*GDD1*) is most similar to *At5g47820* (*FRA1*) of *Arabidopsis*. Mutation of rice *GDD1*, which encodes a kinesin-like protein that binds to a gibberellic acid biosynthesis gene promoter, leads to dwarfism with impaired cell elongation (Li et al., 2011). *FRA1* appears to be located 0.4 cM downstream of the *DINAGZ* QTL (a QTL for fiber digestibility) of chromosome 5 (Barriere et al., 2005). Finally, we found that apyrase 2 (*APY2*) is under selection. At-*APY1* and At-*APY2* have key roles in pollen germination and vegetative growth (Wu et al., 2007; Wolf et al., 2007). In *Arabidopsis*, the *apy1* and *apy2* double knock-out showed failed pollen germination. Moreover, lines silenced under RNA interference showed a dwarf phenotype in overall vegetative growth, and had dramatically reduced growth of the primary root and etiolated hypocotyls (Wu et al., 2007), and abnormal cotyledons (Wolf et al., 2007). Recent studies have indicated that a critical step connecting apyrase suppression to growth suppression is the inhibition of polar auxin transport (Liu et al., 2012). *AHP1* has a role in cytokinin signaling and affects multiple aspects of plant development. Cytokinins have diverse functions that include control of meristem activity, hormonal cross-talk, nutrient acquisition, responses to light (interactions with *PHYB*) and various stress responses (Jones et al., 2010; Brenner et al., 2012). Together with four other *AHP* genes and a histidine kinase, *CYTOKININ-INDEPENDENT1* (*CKI1*) gene, *AHP1* is implicated in the regulation of female gametophyte development and vegetative growth (Deng et al., 2010). Furthermore, a quintuple *ahp* mutant showed various abnormalities in growth and development, including reduced fertility, increased seed size, reduced vascular development, and a shortened primary root (Deng et al., 2010).

As indicated by Lenser and Theißen (2013), despite this seeming plurality of the domestication targets, two strategies have been repeatedly applied to promote the dwarfing habit in different species: alteration of the meristem identity to cause determinate growth (Salamini, 2003), or as the above-mentioned genes also suggest for *P. vulgaris*, interference with hormone metabolism or signaling (McGarry et al., 2012). In addition to the modulation of gibberellic acid signaling that is mainly seen in rice (Itoh et al., 2004; Asano et al., 2007, 2011), barley (Jia et al., 2009) and wheat (Doebley et al., 2006), interference with brassinosteroid signal transduction and with polar auxin transport has been shown to cause a semi-dwarfing growth habit in agronomically important varieties of barley (Chono et al., 2003) sorghum (Multani et al., 2003), and pearl millet (Parvathaeni et al., 2013). However, although in soybean and the common bean, *TERMINAL FLOWER* determines the growth habit and has been shown to be under selection during domestication (Tian et al., 2010; Kwak et al., 2012), it was not on our list of candidates.

- Genes involved in seed development and traits: Some of these genes are important for correct embryo development (*YODA*, Lukowitz et al., 2004; *POR*, Mathur, 2004; *AKRP*, Tzafrir et al., 2004; *BRIZ1*, Hsia and Callis, 2010; *EMB1211*, Liang et al., 2010; *IAA12*, Bureau et al., 2010), and others can affect the seed chemical composition, like for seed protein (*IAA12*, Yonekura et al., 2010), oil (*IAA12*, Kondo et al., 2010; and *LRR-RLK*) and fat (*FATB*, Molina et al., 2008) content,

and for seed maturation (*SEC14p*, Huang et al., 2013) and germination (*DOF6,* Rueda-Romero et al., 2012; *TKL,* Arc et al., 2012; *BGAL3*, Bui et al., 2011*; RBOHB*, Müller et al., 2009). Effects of domestication on these traits are inconceivable, as human selection might have led to seeds with development, maturation and germination that are more adapted to cultivation and field conditions. Moreover, during domestication, variations in seed chemical characteristics were also observed in several cases, such as, for example, the case of the *WAXY* gene in rice, maize, barley, sorghum, millet, and amaranth (Olsen and Wendel, 2013).

- Three genes have roles in the carbon/nitrogen (C/N) balance response: The first of these is a *trans*-membrane gamma-aminobutyrate (GABA) transporter. There is growing evidence that in plants the GABA shunt has a major role in primary C/N metabolism (Fait et al., 2008; Masclaux-Daubresse et al., 2008). The second is *TSD2* (*TUMOROUS SHOOT DEVELOPMENT2*), which encodes a putative methyltransferase with an essential role in cell adhesion that coordinates plant development (Krupková et al., 2007) and appears to be a critical modulator of the C/N nutrient balance response in *Arabidopsis* (Gao et al., 2008). Finally, a transketolase (AT3G60750) is among 16 genes involved in N nutrition and C metabolism up-regulated by NO_3^- (Girin et al., 2007). It has been shown that the transcribed segments of undomesticated plant genomes are the most N poor, with genomes and proteomes with signatures of N limitation (Acquisti et al., 2009). In this context, adaptation to N availability at the whole-plant level is highly conceivable, which would justify a role also for these genes during domestication.

- Genes involved in responses to environmental stresses: Several genes have homologs that encode proteins that are involved in biotic stresses (Ribosomal protein S14p/S29e family protein, Mitsuya et al., 2009; a tautomerase/MIF superfamily protein, Bricchi et al., 2012; HSF A4A, Kuśnierczyk et al., 2007; SIZ1, Lee et al., 2007; G6PDH1, Asai et al., 2011; Siddappaji et al., 2013). In this case, there are genes that control programmed cell death and are involved in innate immunity responses (*MKS1*, Andreasson et al., 2005; *WRKY4*, Lai et al., 2008; *ERD2*, Xu et al., 2012), and also in systemic acquired resistance (*ROF2*, Lin et al., 2012a; Copper transport protein family [*AT5G52740*], Ascencio-Ibáñez et al., 2008). Among the genes that are involved in biotic stress responses, *MKS1* and *WRKY4* are involved in the mitogen-activated protein kinase (MAPK) pathway. This is one of the main phosphorylation pathways that plants use in biotic and abiotic stress resistance. Specifically, the MAPK cascade and WRKY transcription factor functions act in response to both fungal and bacterial pathogens (Asai et al., 2002). In the case of abiotic stress, there are common genes involved in: drought tolerance or osmotic stress (RING E3 Ub ligase, Ryu et al., 2010; Cho et al., 2011; *CYCLIN H*, Zhou et al., 2013; *ERD2*, Taji et al., 1999; *SIZ1*, Catala et al., 2007), in stomata aperture/ closure (*SPHK1*, Worral et al., 2008; Guo et al., 2012), and in the control of abscissic acid synthesis (*AT5G04250*, encoding a cysteine proteinase superfamily protein, Jensen et al., 2013), response to heat (*Hsp70b*, Sung et al., 2001; *CPN10*, Kant et al., 2008; *HSFA4A*, Riechmann et al., 2000), cold (*STA1*, Lee et al., 2006), and salt (*ERD2*, Taji et al., 1999; *CYCLIN H*, Zhou et al., 2013) Stresses. Some other genes are also involved in the response to nutrient starvation (*SIZ1*, Miura et al., 2005, 2011) and in the tolerance to toxic metals in the soil, in particular to aluminum (*BCB*, Ezaki et al., 2000, 2001). The involvement of fast-evolving genes implicated in biotic and abiotic stress has recently been documented in tomato (Koenig et al., 2013). Moreover, metal tolerance is a trait found under domestication in different crops like wheat, rye, sorghum and corn, and constitutes an evident convergent selection during crop domestication (Lenser and Theißen, 2013).

Other genes that do not fall into these categories:

- *RKF1*; This RECEPTOR-LIKE KINASE IN FLOWERS gene showed the highest signal for directional selection. Twenty-five percent of the selectively expressed genes in pollen are included in the signal-transduction category. Most of these genes (26 of 37) encode putative protein kinases. *RKF1* is an example of the pollen-specific receptor kinases that are possibly involved in signaling events (Takahashi et al., 1998).

- *RPF1*; this gene encodes for RNA PROCESSING FACTOR 1 (RPF1), which is implicated in the restoration of cytoplasmic male sterility. This nuclear gene goes through mitochondrial RNA processing that leads to a protein that prevents pollen abortion. This trait is mitochondrially inherited, and it has been observed in various plant species (Holzle et al., 2011). Another gene that

is essential for pollen development and that has a crucial role in male gametophyte development and male fertility is *ATMGT9* (Chen et al., 2009b), which encodes a magnesium transporter that has been shown to have a role in local adaptation to serpentine soils (high heavy-metal content, low calcium-to-magnesium ratios) in *Arabidopsis lyrata* (Turner et al., 2010).

- The homolog of *YABBY5* (*YAB5*); *YAB5* is involved in the molecular determination of abscission in tomato fruit, a trait that is also under domestication (Nakano et al., 2013). Moreover, recently, a *YAB* homologue gene, *SH1*, and its homologs, was identified in the regulation of seed shattering in cereal species, including sorghum, rice and maize (Lin et al., 2012b). In sorghum, the shattering is determined by a single gene (*SH1*) that encodes a YABBY transcription factor. In maize and rice, these encode YABBY-LIKE transcription factors (Lin et al., 2012b).

- A gene encoding proteins that belong to the transducin/WD40 repeat-like superfamily. This gene is involved in the responses to the auxin stimulus and has also been implicated in defense responses (Rodrigues et al., 2013). In *Arabidopsis*, it is involved in several processes, including cell-chromatin silencing by RNA interference, glucuronoxylan metabolic processes, gravitropism, hydrogen peroxide biosynthetic processes, meiotic DNA double-strand break formation, meiotic chromosome segregation, organ morphogenesis, positive regulation of organelle organization, protein desumoylation, reciprocal meiotic recombination, regulation of anion channel activity, regulation of chromosome organization, sister chromatid cohesion, tissue development, vegetative-to-reproductive phase transition of the meristem, and xylan biosynthetic processes.

Interestingly, a WD40 protein in *G. max* is involved in seed development (Joshi et al., 2013). Moreover, a *WD40* (or *WUSCHEL*, as this has not been definitely identified) gene acts to determine the number of locules (fruit size) in tomato, a trait that was under selection in this crop during domestication (Muños et al., 2011; Ranc et al., 2012). Moreover, a WD40 protein is involved in pigmentation in *Sorghum bicolor* (Wu et al., 2012).

- Two genes are homologous of genes that control the color of the “edible part”, a trait that has often been affected by domestication in several herbaceous (potato, rice) and tree crops (orange and grapevine). Again, it is also considered an example of molecular convergence underlying domestication-related phenotypic changes (Lenser and Theißen, 2013; Olsen and Wendel, 2013). The first is *BCH1* that is involved in hydroxylation of beta-carotene (Tian et al., 2003), and is implicated in the pathway that confers color to tomato and pepper (Paran and van der Knaap, 2007). A major QTL for carrot color has been found for the pigment content that is mainly determined by two genes (*Y* and *Y2*) that are associated with domestication in carrot (wild, white; domesticated, orange). The other gene, *ATCDC5*, has been shown to have a key role in plant development, secondary metabolism, hormone signal transduction, disease resistance, and abiotic stress tolerance. However, it has also been observed that the CDC5 transcription factor binds a deleted region of the *DFR-A* onion gene. Interestingly, mutations in this gene were associated with the changed colors of onion after the domestication process (Song et al., 2014).

- A gene related to yield. This encodes a leucine-rich repeat protein kinase family protein (*AT2G26730*). Wild rice (*Oryza rufipogon*) has an important role by contributing to modern rice breeding. Song et al. (2009) sequenced and analyzed a 172-kb genomic DNA region of wild rice around the RM5 locus, which is associated with the yield QTL *yld1.1*. As suggested previously, two putative receptor-like protein kinase genes (one of which is *AT2G26730*) were key suspects for *yld1.1* (Song et al., 2009).

4.2 Contigs monomorphic in MW and polymorphic in MD

We also investigated the 47 annotated contigs among the 67 PS contigs that were polymorphic in MD and monomorphic in MW:

- *ELF4-L2* (*EARLY FLOWERING4-Like 2*); This gene is involved in the control of the circadian rhythm, and also functions as part of the light-input pathway. In *Pisum sativum*, Liew et al. (2009) isolated an ortholog of the *Arabidopsis ELF4-L2* (*DIE NEUTRALIS*, *DNE*) locus, and confirmed that this gene inhibits flowering under noninductive short-day conditions. *DNE* has a role in diurnal and/or circadian regulation of several clock genes, including the pea *GI* ortholog *LATE BLOOMER 1(LATE1)*.

- *KAN1* (*KANADI1*) (that together with *K2* modulates, in turn, the *PIN1* gene, which encodes an auxin transport protein); This gene is a target of *LEAFY*, a master gene that has a central role in the regulation of the transition from vegetative growth to flower formation. Interestingly, while *ELF4-L3* and *KAN2* are under selection toward a reduction in diversity in the domesticated form, for *ELF4-L2* and *KAN1* the opposite is true; i.e., they have evolved toward an increase in diversity in the domesticated forms.

- *MYB102*; De Vos et al. (2006) showed that At-*MYB102* has a role in defense against caterpillars. This genes is also involved in wounding and osmotic stress responses; interestingly, herbivore-damaged plants also suffer from water loss (De Vos et al., 2006).

- *KUP6* (*K^+ uptake transporter 6*); Osakabe et al. (2013) demonstrated that the KUP potassium transporter family has important roles in water-stress responses and growth in plants; moreover, KUP-type K^+ transporters are induced by different stresses with an osmotic component, and specifically inhibit cell expansion while enhancing drought tolerance.

- *APC*; In rice, *APC* controls *RSS1*, which is important for maintenance of the shoot meristem under abiotic stress conditions, and is also thought to control tolerance responses to salt, drought, and cold (Ogawa et al., 2011).

- *ETT* (*ETTIN MUTATIONS*); other names *AUXIN RESPONSE TRANSCRIPTION FACTOR3* (*ARF3*); This gene positively regulates *FIL* (required for the “super-replum” phenotype) activity during leaf development (Garcia et al., 2006; Sorefan et al., 2009). Moreover, in *Arabidopsis*, González-Reig et al. (2012) hypothesized that subtle changes in the expression of the antagonistic factors involved in auxin efflux can produce drastic changes in the size of the different tissue types, including the variability of fruit shape in Brassicaceae and other related species. Another example is in rice, where at least two *ARF*s have been detected as selected genes, and where it has been suggested that these genes can be targeted by domestication selection for enhanced growth responses and productivity (Wang et al., 2010).

- Transducin/WD40 repeat-like superfamily protein; This is involved in the response to the auxin stimulus and it is also implicated in defense responses (Rodrigues et al., 2013). A WD40 protein in *G. max* is involved in seed development (Joshi et al., 2013). Moreover, a WD40 protein probably acts together with the *WUSCHEL* gene to determine the number of locules (lc) in tomato, a trait that was under selection in this crop during domestication (Muños et al., 2011; Ranc et al., 2012). Also in this case, it must be noted that members of this family protein have also been selected in the opposite direction; i.e., towards a reduction of diversity in the domesticated form (see above).

- Squamosa BP-like (*SPL*); So far, *SPL* has also been functionally linked to diverse developmental processes, such as seed germination and seedling development (Martin et al., 2010), leaf and plastocron development (Moreno et al., 1997), juvenile-to-adult and floral phase transitions (Cardon et al., 1997; Wu and Poethig, 2006; Gandikota et al., 2007; Wang et al., 2009), fruit ripening (Manning et al., 2006), copper homeostasis (Kropat et al., 2005; Yamasaki et al., 2009), programmed cell death (Stone et al., 2005), domestication (Wang et al., 2005; Preston and Hileman, 2013), and grain yield (Jiao et al., 2010; Miura et al., 2010).

- GRAS transcription factor family; This family includes monoculm1 (*moc1*), which was characterized from a rice mutant that had almost no branching (Li et al., 2003). In rice, *moc1* affects all branching meristems, so that both vegetative and inflorescence branching are severely curtailed (Doust, 2007). This gene is necessary for axillary meristem initiation. It is related to the *LATERAL SUPPRESSOR* gene (*LAve S* and *ls* in the model dicot plant systems of *Arabidopsis* and tomato, respectively), which controls aspects of branching.

- Other genes *ALEURAIN-LIKE PROTEASE* (*AALP*) and *SENESCENCE ASSOCIATED GENE2* (*SAG2*); In *Arabidopsis*, these are involved in senescence (Grbić, 2003).

4.3 Contigs fixed for alternative alleles in MW and MD

Finally, we specifically focused on the 19 annotated contigs among the 23 PS contigs that were fixed for alternative alleles in MW and MD. Some of these genes are involved in responses to biotic stress, such as insect responses (*JAZ*, also known as *TIFY*, Kazan and Manners, 2012; Schweizer et al., 2013) and responses to bacteria (*LOL2*, Epple et al., 2003). Another gene, which encodes a

GDSL-like lipase, is mainly involved in the response to water deprivation (Boyce et al., 2003). Two other genes are also interesting: the ribosomal protein L36 in *Lycopersicon pimpillinelifolium* co-maps with a QTL for wall thickness, and in *L. esculentum* for flavonoid content (Okmen et al., 2011). Finally, *CHC1* is predicted to encode a protein that belongs to the chromodomain remodeling complex. In *Arabidopsis*, two RNA-interference knock-down lines have a dwarf phenotype and reduced rates of *Agrobacterium*-mediated transformation. The low rate of root-mediated transformation might result from altered root morphology or reduced root growth rates (Crane and Gelvin, 2007; Campi et al., 2012). This genes has been suggested to enhance plant growth (De et al., 2012). Other details of these genes are reported below:

- *JAZ12* (also known as *TIFY3B*); In *Arabidospis*, this gene is involved in the jasmonic-acid-mediated signaling pathway, positive regulation of the flavonoid biosynthetic process, regulation of the plant-type hypersensitive response and the response to wounding. The JAZ/TIFY protein has MYC2, MYC3, MYC4 and NINJA as its interacting co-repressors and transcription factors (Kazan and Manners, 2012). Recently, it was shown that *Arabidopsis* basic helix-loop-helix transcription factors MYC2, MYC3, and MYC4 regulate glucosinolate biosynthesis, and insect performance and feeding behavior (Schweizer et al., 2013).

- Ribosomal protein L36; This is involved in DNA-dependent transcription and elongation, and ribosome biogenesis and translation. In *Arabidopsis*, it is ethylene regulated (De Paepe et al., 2004). This gene co-maps with a QTL for wall thickness in *L. pimpillinelifolium* and flavonoid content in *L. esculentum* (Okmen et al., 2011).

- *CHC1* (*CLATHRIN HEAVY CHAIN1*); In *Arabidopsis*, *CHC1* is predicted to encode a protein that belongs to the chromodomain remodeling complex (Crane and Gelvin, 2007; Campi et al., 2012). Two RNA-interference knock-down lines have a dwarf phenotype and reduced rates of *Agrobacterium*-mediated transformation. The low rate of root-mediated transformation might result from altered root morphology or reduced root growth rates. This gene is among those for complexes of AN3-interacting proteins. *AN3* is an “intrinsic yield gene” in *Arabidopsis*. Their use has been suggested for plant growth (De et al., 2012).

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