The Plant Cell, Vol. 21: 1877–1896, July 2009, www.plantcell.org

REVIEW

What Has Natural Variation Taught Us about Plant Development, Physiology, and Adaptation?

Carlos Alonso-Blanco,[a] Mark G.M. Aarts,[b] Leonie Bentsink,[c] Joost J.B. Keurentjes,[b,d,e] Matthieu Reymond,[f] Dick Vreugdenhil,[d,e] and Maarten Koornneef[b,f,1]

[a] Centro Nacional de Biotecnología, Consejo Superior de Investigaciones Científicas, Departamento de Genética Molecular de Plantas, Cantoblanco 28049 Madrid, Spain

[b] Laboratory of Genetics, Wageningen University, 6700 AH Wageningen, The Netherlands

[c] Molecular Plant Physiology Group, Institute of Environmental Biology, Utrecht University, 3584 CH Utrecht, The Netherlands

[d] Laboratory of Plant Physiology, Wageningen University, 6700 AR, Wageningen, The Netherlands

[e] Centre for Biosystems Genomics, 6708 PB Wageningen,The Netherlands

[f] Department of Plant Breeding and Genetics, Max Planck Institute for Plant Breeding Research, 50829 Cologne, Germany

Nearly 100 genes and functional polymorphisms underlying natural variation in plant development and physiology have been identified. In crop plants, these include genes involved in domestication traits, such as those related to plant architecture, fruit and seed structure and morphology, as well as yield and quality traits improved by subsequent crop breeding. In wild plants, comparable traits have been dissected mainly in *Arabidopsis thaliana*. In this review, we discuss the major contributions of the analysis of natural variation to our understanding of plant development and physiology, focusing in particular on the timing of germination and flowering, plant growth and morphology, primary metabolism, and mineral accumulation. Overall, functional polymorphisms appear in all types of genes and gene regions, and they may have multiple mutational causes. However, understanding this diversity in relation to adaptation and environmental variation is a challenge for which tools are now available.

INTRODUCTION

Intraspecific natural variation (hereinafter referred to as natural variation) may be broadly defined as the within-species phenotypic variation caused by spontaneously arising mutations that have been maintained in nature by any evolutionary process including, among others, artificial and natural selection. Thus, natural variation embraces the enormous diversity present within wild plant species as well as most of the genetic variants that are found in domesticated plants. Some of the phenotypic differences existing in wild or cultivated plants are due to single-gene (monogenic) allelic variants. However, most of the natural variation is quantitative and determined by molecular polymorphisms at multiple loci and genes (multigenic), which are referred to as quantitative trait loci (QTL) and quantitative trait genes (QTGs).

The natural variation present in crop plants has been exploited since their domestication thousands of years ago by the genetic manipulation of developmental traits and physiological features related to adaptation to agriculture. Methods for genetic analysis and mapping of natural quantitative variation were developed a few decades ago for crop species, in which many more studies have been performed than in wild plants. Currently, genomic resources have been developed for several herbaceous crop plants, such as rice (*Oryza sativa*), barley (*Hordeum vulgare*), and tomato (*Solanum lycopersicum*), enabling the identification of the genes and nucleotide polymorphisms underlying QTL involved in domestication, yield, biotic and abiotic stress, and quality traits (Doebley et al., 2006; Sang, 2009). In addition, the recent availability of the first genome sequences of cultivated perennial woody plants, such as poplar (*Populus* spp) and grapevine (*Vitis vinifera*; Tuskan et al., 2006; Jaillon et al., 2007), is increasing the scope of traits and processes whose natural variation can be dissected molecularly.

In addition, the analysis of natural variation in wild species has begun to elucidate the molecular bases of phenotypic differences related to plant adaptation to distinct natural environments and to determine the ecological and evolutionary processes that maintain this variation (Mitchell-Olds et al., 2007). The molecular approach to these questions has been applied mainly to the wild annual crucifer *Arabidopsis thaliana*, which has become a model plant for the study of natural variation (Mitchell-Olds and Schmitt, 2006). Its wide geographical and environmental distribution, combined with its small genome and the availability of unprecedented genetic and genome resources, have strongly facilitated its molecular analysis in the last decade. As a result, *A. thaliana* has provided the largest number of genes and nucleotide polymorphisms underlying natural variation of any plant species (Alonso-Blanco et al., 2005). However, the specific ecological niche and life history of *A. thaliana* limits the plant traits and

[1] Address correspondence to maarten.koornneef@wur.nl.
www.plantcell.org/cgi/doi/10.1105/tpc.109.068114

processes that can be approached in a single species. Therefore, new plant models phylogenetically related to *A. thaliana* (e.g., *Arabidopsis lyrata*; Clauss and Koch, 2006) as well as unrelated species (e.g., of the genera *Aquilegia* [Kramer, 2009], *Mimulus* [Wu et al., 2007], *Ipomoea* [Clegg and Durbin, 2003], and *Helianthus* [Rieseberg et al., 2003]) are beginning to be used in studies of natural variation and speciation.

Our understanding of plant biology has benefited tremendously from work done with artificially induced mutants in model species, as illustrated by *A. thaliana* mutants currently available for most genes, and mutant screenings continue to be useful in the identification of gene function (Page and Grossniklaus, 2002). Gene functions involved in plant survival and adaptation can be identified partially by induced mutant analyses of different wild genotypes, where mutants with reduced fitness are easily selected. However, current mutant collections have been obtained using a limited number of laboratory strains, which harbor only a small portion of *A. thaliana* natural variation. Interestingly, Clark et al. (2007) showed that ~9.4% of *A. thaliana* protein-coding genes are naturally absent or knocked out in wild accessions, limiting the mutant spectra that can be obtained from each accession. Therefore, natural variation provides a relevant complementary resource to discover novel gene functions as well as those allelic variants that specifically interact with the genetic background and/or the environment or alleles showing small effects on phenotype, particularly for traits related to plant adaptation (Benfey and Mitchell-Olds, 2008).

Genetic analyses of natural variation in plants currently are mainly performed by QTL mapping, often called linkage mapping, in which phenotypic variation is associated with allelic variation at molecular markers segregating in experimental mapping populations derived from directed crosses (Doerge, 2002). Thus, genomic regions accounting for trait variation are located in large physical intervals containing the causal QTLs. Further analyses of these regions with a combination of functional strategies allows the final identification of QTGs and nucleotide polymorphisms altering the function of those genes (reviewed in Koornneef et al., 2004; Alonso-Blanco et al., 2005; Weigel and Nordborg, 2005; González-Martínez et al., 2006). Association mapping, which involves looking for phenotype-genotype associations in a general population of individuals whose degree of relatedness or pedigree is unknown, is also becoming more popular and useful in plant systems, owing to improvements in statistical and analytical tools and in gene sequencing technology (see Myles et al., 2009).

The information gleaned from the various types of QTL analysis is extending the current concept of gene function based on a single wild-type allele and provides a more realistic and dynamic view of gene function by estimating the effects of different natural alleles depending on genetic background, environment, and evolutionary temporal scale. In addition, recent genetic analyses of large data sets generated by high-throughput profiling of mapping populations with "-omics" procedures (genomics, transcriptomics, metabolomics, proteomics, ionomics, or epigenomics) is allowing the genetic integration of several levels of molecular regulation of phenotypic trait variation. Thus, QTL and gene networks controlling natural variation are being inferred (Jansen et al., 2009).

In this review, we discuss the major contributions of the analysis of natural variation to our understanding of plant development and physiology. Given the large number of studies performed in the past, we do not aim to completely cover all traits analyzed so far, but to focus on several relevant phenotypes recently or extensively dissected in *A. thaliana* and major crop species. These traits include the timing of germination and flowering, plant growth and morphology, primary metabolism, and mineral accumulation. Detailed discussion of natural variation for secondary metabolites is covered by Kliebenstein (2009a), and various reviews have specifically described the natural variation involved in crop domestication and diversification (Doebley et al., 2006; Pourkheirandish and Komatsuda, 2007; Purugganan and Fuller, 2009; Sang, 2009), plant development (Alonso-Blanco et al., 2005), or resistance to pathogens (Holub, 2007). Here, we summarize the major genes and allelic variants currently known to participate in plant adaptation to different natural and agricultural environments through some modifications of plant development and physiology. The kind of mutations, molecular mechanisms, and gene networks involved in microevolution and adaptation of different plant species to changing environments are beginning to be elucidated. Consequently, new perspectives in our understanding of phenotype and pan-genome variation and evolution are emerging (Morgante et al., 2007).

DEVELOPMENTAL PROCESSES

Domestication of crop plants mainly has resulted in changes in traits related to floral and seed morphology, such as shattering, free-threshing, and seed coat color in cereals (Salamini et al., 2002, Dubcovsky and Dvorak, 2007), plant architecture-like branching patterns in maize (*Zea mays*) and rice (Izawa et al., 2009), fruit morphology-like size and shape in *Solaneaceae* crops (Tanksley, 2004), and seed dormancy, especially in domesticated cereals (Salamini et al., 2002). In addition, the analysis of natural variation has identified novel molecular mechanisms involved in the regulation of life history traits, such as seed dormancy and flowering time, by different environmental and endogenous clues. This section highlights some of the most important advances resulting from these studies.

Seed Dormancy and Germination

Most wild annual plant species, including *A. thaliana*, show substantial intraspecific natural variation for seed dormancy and germination properties, which is presumably involved in adaptation to different environments. Domestication has often led to a reduction of seed dormancy in crop plants, although considerable variation remains among cultivated varieties. The genetic bases of this variation have been approached mainly in *A. thaliana* and cereal plants, mostly in relation to environmental factors, such as temperature and light, and to endogenous hormonal signals, such as abscisic acid (ABA) and gibberellin (GA).

In *A. thaliana*, QTL mapping analyses of germination-related traits have been performed in relation to after-ripening

(Alonso-Blanco et al., 2003; Clerkx et al., 2004), light regimes (van der Schaar et al., 1997; Laserna et al., 2008; Meng et al., 2008), low temperature (Meng et al., 2008), or GA inhibitors (van der Schaar et al., 1997). Many of the loci are only detected in specific assays or conditions, indicating strong QTL by environment interactions. However, several QTLs colocate in different crosses, suggesting the presence of moderate frequency natural alleles with pleiotropic effects on dormancy and related traits, such as cold-tolerant germination and seed longevity (Clerkx et al., 2004; Meng et al., 2008). Particularly, the locus *DOG1* has been detected in three experimental populations (Alonso-Blanco et al., 2003; Clerkx et al., 2004; Laserna et al., 2008) and has been isolated, identifying a member of a small gene family of unknown molecular function (Bentsink et al., 2006; Table 1). *DOG1* induces seed dormancy and is specifically expressed during seed development. In addition, it has been shown that *DOG1* functional nucleotide polymorphism(s) affect its expression, dormant accessions having higher RNA levels than nondormant accessions (Bentsink et al., 2006). Furthermore, *DOG1* is involved in the ABA-mediated sugar signaling pathway in seedlings since glucose induces the expression of the *DOG1*/*GSQ5* Cvi allele, whereas Landsberg *erecta* and Columbia alleles do not respond (Teng et al., 2008). Thus, *DOG1* has provided the first gene involved in natural variation for seed dormancy and illustrates the value of this variation to identify previously unknown genes for this trait.

In cereals, several analyses have identified seed dormancy QTLs in crosses between cultivated varieties with low dormancy and between cultivated and dormant weedy accessions or wild relative species (Lin et al., 1998; Gu et al., 2005; Hori et al., 2007; Imtiaz et al., 2008). In particular, the large-effect locus *Sdr1* of rice might be orthologous to barley *SD4* and wheat (*Triticum aestivum*) 4AL loci (Lin et al., 1998). Detailed QTL characterizations have shown that some loci may control dormancy through seed maternal tissues, while others function in offspring tissue(s) (Gu et al., 2008). As in wheat, maternally inherited seed dormancy has been associated with the seed pigmentation color variation determined by the rice *Rc* locus (Gu et al., 2005), which encodes a bHLH transcription factor (Sweeney et al., 2006). In addition, rice QTLs have been found for germination at low temperature, and the first of such loci, *qLTG3-1*, has been recently isolated (Fujino et al., 2008). *qLTG3-1* encodes a protein of unknown function that is expressed in the embryo during seed germination. It has been suggested that *qLTG3-1* is involved in tissue weakening during seed germination, which is reduced in the nondormant rice accession bearing a loss-of-function deletion allele.

Genetic analyses of dormancy and germination also have been performed in other crop species, such as lettuce (*Lactuca sativa*; Argyris et al., 2005). Interestingly, an interspecific cross between *L. sativa* and *L. serriola* identified *Htg6.1* as a major effect locus involved in germination at high temperature (thermoinhibition), which colocates with germination QTLs for ABA sensitivity and GA response as well as with the ABA biosynthesis gene Ls-*CED4*. In addition, Ls-*CED4* is induced by high temperature only in the thermoinhibited cultivated species, which strongly supports Ls-*CED4* as candidate for *Htg6.1* (Argyris et al., 2008).

Flowering Time

Molecular studies of the natural variation in the annual species *A. thaliana*, pea (*Pisum sativum*), rice, barley, wheat, and maize have identified ~25 different causal genes and their nucleotide polymorphisms of major effect (Table 1). In addition, genetic analyses of flowering time or related traits have been performed in other annual plants, such as tomato (González-Martinez et al., 2006), biennial species like *Brassica* sp (Schranz et al. 2002), short-lived perennials like *Fragaria vesca* (Albani et al., 2004), and several long-lived woody trees (Frewen et al., 2000; Casasoli et al., 2006). These studies are identifying multiple candidate genes and polymorphisms, which allow comparative analyses among species with rather different environmental and ecological distributions as well as physiological and developmental behaviors.

A. thaliana is a facultative long-day species widely distributed in temperate regions of the Northern hemisphere. Two extreme flowering behaviors have been described among wild genotypes grown in laboratory conditions, which are considered winter (late) and spring (early) life habits because they show strong and weak vernalization responses, respectively. Nine genes have been isolated that contribute to *A. thaliana* natural variation for flowering time (Table 1). Among these, *FRI* and *FLC* are involved in the regulation of flowering by vernalization and were first identified because of this natural variation. *FLC* encodes a transcripition factor of the MADS family that represses flowering (Michaels and Amasino, 1999). Its expression is downregulated by the low temperature of winter through epigenetic mechanisms leading to histone methylation and chromatin modifications (reviewed in Sung and Amasino, 2005). *FRI* encodes a protein of unknown function that also represses flowering initiation by activating the expression of *FLC* (Figure 1; Johanson et al., 2000). Most winter annual genotypes carry active alleles of both genes, which interact epistatically to delay flowering, while many summer annual accessions bear partial or total loss-of-function alleles in one or both genes (Werner et al., 2005a). More than 25 *FRI* independent loss-of-function alleles have been described, which mainly encode truncated proteins, indicating that *FRI* loss-of-function has evolved multiple times from a late flowering ancestor (Johanson et al., 2000; Le Corre et al., 2002; Shindo et al., 2005). By contrast, several natural loss-of-function alleles of *FLC* with reduced gene expression are caused by independent insertions of transposon elements within the first regulatory intron (Gazzani et al., 2003; Michaels et al., 2003). Other rare alleles are produced by nonsense or splicing mutations predicted to generate truncated proteins (Werner et al., 2005a). Interestingly, it has been suggested that additional allelic variation in *FLC cis*-regulatory sequences that alters the efficiency of *FLC* chromatin silencing might contribute to the quantitative variation for vernalization response present among late flowering genotypes (Shindo et al., 2006).

QTL mapping studies have also shown that other loci, including homologs of *FRI* and *FLC*, affect the vernalization response (Figure 1). Natural loss-of-function alleles in two *FRI*-like genes (*FRL1* and *FRL2*; Schläppi, 2006) and one *FLC*-like gene named *FLM*/*FLW1* (Werner et al., 2005b) have been shown to produce early flowering. Additional flowering time QTLs affecting this

Table 1. Genes and Funtional Polymorphisms Involved in Natural Variation for Different Traits and Species

Plant Species	Locus/Gene	Phenotypic Effects	Molecular Function	Functional Nucleotide Polymorphism		Allelic Dysfunction	References
				Gene Position	Mutation		
A. thaliana	*DOG1*	Seed dormancy, sugar sensing	Unknown	Promoter	Unknown	ME	Bentsink et al. (2006)
Thale cress	*FRI*	Flowering	Unknown	Promoter, coding	Ins, Del, nonsense Subs	TP, ME	Johanson et al. (2000); Shindo et al. (2005)
	FRL1	Flowering	FRI-like	Coding	Nonsense Subs	TP	Schläppi (2006)
	FRL2	Flowering	FRI-like	Coding	Missense Subs	AP	Schläppi (2006)
	FLC	Flowering	MADS TF	Intron, coding	TE insertion, nonsense Subs	ME, TP	Michaels et al. (2003); Werner et al. (2005a)
	FLW1/FLM	Flowering	MADS TF	Promoter + coding	Gene Del	Null expression	Werner et al. (2005b)
	ART1/HUA2	Flowering, shoot morphology	RNA processing factor	Coding	Nonsense and missense Subs	TP, AP	Doyle et al. (2005); Wang et al. (2007)
	EDI/CRY2	Flowering, seedling growth, fruit size	Photoreceptor	Coding	Missense Subs	AP	El-Assal et al. (2001, 2004)
	PHYD	Flowering, seedling growth	Photoreceptor	Coding	Del	TP	Aukerman et al. (1997)
	PHYC	Flowering, seedling growth	Photoreceptor	Coding	Nonsense Subs	TP	Balasubramanian et al. (2006)
	PHYA	Seedling growth	Photoreceptor	Coding	Missense Subs	AP	Maloof et al. (2001)
	PHYB	Seedling growth	Photoreceptor	Coding	Missense Subs	AP	Filiault et al. (2008)
	TZP/Light5	Seedling growth	Zn knuckle protein	Coding	Ins	TP	Loudet et al. (2008)
	CAL	Flower morphology	MADS TF	Coding	Missense Subs	AP	Kempin et al. (1995)
	IIL1	Leaf morphology	Leu biosynthesis enzyme	Intron	Ins, Del	ME	Sureshkumar et al. (2009)
	GL1	Trichome formation	Myb TF	Coding	Del	ME	Hauser et al. (2001)
	PUB8	Self-incompatibility	U box protein	Promoter	Unknown	ME	Liu et al. (2007)
	MUM2	Seed mucilage	Galactosidase	Coding	Del	ME	Macquet et al. (2007)
	BRX	Root growth	Novel TF	Coding	Nonsense Subs	TP	Mouchel et al. (2004)
	LPR1	Root growth response to P	Multicopper oxidase	Promoter	Del	ME	Svistoonoff et al. (2007)
	INV	Sugar composition, root growth	Invertase	Unknown	Unknown	Unknown	Sergeeva et al. (2006)
	Small effect QTL	Biomass accumulation	Protein kinase	Unknown	Unknown	Unknown	Kroyman and Mitchell-Olds (2005)
	DM1	Hybrid incompatibility, disease resistance	NB-LRR proteins	Promoter + coding	Nonsense Subs, Del	AP	Bomblies et al. (2007)
	QTL3	Hybrid incompatibility, disease resistance	NB-LRR proteins	Unknown	Unknown	Unknown	Alcázar et al. (2009)
	LD1. 1	Genetic incompatiblity, embryogenesis	His biosynthesis enzyme	Promoter, coding	Nonsense Subs	ME, TP	Bikard et al. (2009)
	LD1.5	Genetic incompatiblity, embryogenesis	His biosynthesis enzyme	Promoter + coding	Gene Del	Null expression	Bikard et al. (2009)
	APR2	Sulfate accumulation	Sulfate reductase	Coding	Nonsense Subs	AP	Loudet et al. (2007)
	MOT1	Mo accumulation	Sulfate transporter	Promoter	Del	ME	Baxter et al. (2008)

(Continued)

Table 1. (continued).

Plant Species	Locus/Gene	Phenotypic Effects	Molecular Function	Functional Nucleotide Polymorphism		Allelic Dysfunction	References
				Gene Position	Mutation		
	HMA5	Cu toxicity	Cu ATPase transporter	Coding	Missense Subs	AP	Kobayashi et al. (2008)
	HKT1	Na accumulation	Na^+ transporter	Promoter	Del	ME	Rus et al. (2006)
A. lyrata	*FRI*	Flowering	FRI-like	Coding	Indel	AP	Kuittinen et al. (2008)
B. rapa	*BrFLC1*	Flowering	MADS TF	Unknown	Unknown	Unknown	Kole et al. (2001)
Turnip	*BrFLC2*	Flowering	MADS TF	Unknown	Unknown	Unknown	Schranz et al. (2002)
S. lycopersicum	*SUN*	Fruit shape	IQ67 domain protein	Coding + promotor	Gene duplication	ME	Xiao et al. (2008)
Tomato	*OVATE*	Fruit shape	Nuclear protein	Coding	Nonsense Subs	TP	Cong et al. (2002)
	FAS	Fruit shape	Yabby TF	Intron	Ins	ME	Cong et al. (2008)
	Fw2.2	Fruit size	Cell cycle control	Promoter	Subs, indel	ME	Frary et al. (2000)
	Sw4. 1	Seed size	Transporter	Unknown	Unknown	Unknown	Orsi and Tanksley (2009)
	Brix9-2-5/LIN5	Fruit sugar content	Invertase	Coding	Missense Subs	AP	Fridman et al. (2004)
	Cnr	Fruit ripening	SBP TF	Promoter	DNA methylation	ME	Manning et al. (2006)
Pisum sativum	*LF/PsTFL1c*	Flowering	TFL1-like protein	Promoter, coding	Gene Del	Null expression	Foucher et al. (2003)
Pea	*R*	Seed composition and morphology	Starch branching enzyme	Coding	TE insertion	TP, ME	Bhattacharyya et al. (1990)
Lynaria vulgaris Toadflax	*Lcyc*	Flower simetry	TCP TF	Promoter + coding	DNA methylation	ME	Cubas et al. (1999)
T. aestivum	*VRN1*	Flowering	AP1-like MADS TF	Promoter, intron	Del, Ins	ME	Yan et al. (2003)
Bread wheat	*VRN3*	Flowering	FT-like protein	Promoter	TE insertion	ME	Yan et al. (2006)
	Q	Seed free-thressing	AP2-like TF	Coding	Missense Subs	AP	Simons et al. (2006)
	RhtB1, *RhtD1*	Plant and leaf size	GAI-like protein	Coding	Nonsense Subs	TP	Peng et al. (1999)
	Gpc-B1/NAM-B1	Senescence; Zn, Fe, and protein content	NAC TF	Coding	Del, gen Del	TP	Uauy et al. (2006)
Triticum monococum	*VRN1*	Flowering	AP1-like MADS TF	Promoter	Del	ME	Yan et al. (2003)
Einkorn wheat	*VRN2*	Flowering	CCT domain protein	Promoter, coding	Missense Subs	AP	Yan et al. (2004a)
H. vulgare	*VRN2*	Flowering	CCT domain protein	Promoter + coding	Gene Del	Null expression	Yan et al. (2004a)
Barley	*VRN3*	Flowering	FT-like protein	Intron	Subs	ME	Yan et al. (2006)
	Ppd1	Flowering	Response regulator	Coding	Missense Subs	AP	Turner et al. (2005)
	Nud	Seed free-threshing	ERF TF	Promoter + coding	Gene Del	Null expression	Taketa et al. (2008)
	Vrs1	Seed number, ear morphology	HD TF	Coding	Ins	TP	Komatsuda et al. (2007)
	Bot1	Boron toxicity tolerance	Boron efflux transporter	Promoter + coding	Gene duplication	ME	Sutton et al. (2007
O. sativa	*qLTG3*	Germination	Unknown	Coding	Del	ME	Fujino et al. (2008)
Rice	*Rc*	Germination, seed color	bHLH TF	Coding	Del	TP	Sweeney et al. (2006)
	Hd1	Flowering	CO-like TF	Coding	Del, TE insertion	TP, ME	Yano et al. (2000); Doi et al. (2004)
	Hd3a	Flowering	FT-like protein	Unknown	Unknown	ME	Kojima et al. (2002)
	Hd6	Flowering	Protein kinase CK2	Coding	Nonsense Subs	TP	Takahashi et al. (2001)
	Ehd1	Flowering	Response regulator	Coding	Missense Subs	AP	Doi et al. (2004)
	Ghd7	Flowering, plant height, seed yield	CCT domain protein	Coding	Gene Del, nonsense Subs	Null expression	Xue et al. (2008)
	sh4	Shattering	Myb TF	Coding	Missense Subs	AP	Li et al. (2006)

(Continued)

Table 1. (continued).

Plant Species	Locus/Gene	Phenotypic Effects	Molecular Function	Functional Nucleotide Polymorphism		Allelic Dysfunction	References
				Gene Position	Mutation		
	qSH1	Shattering	HD TF	Promoter	Missense Subs	ME	Konishi et al. (2006)
	qSW5	Seed size	Unknown	Coding, promoter	Del	ME	Shomura et al. (2008)
	GW2	Seed size	RING protein	Coding	Del	TP	Song et al. (2007)
	GS3	Seed size	Unknown	Coding	Missense Subs	TP	Fan et al. (2006)
	Gn1a	Seed number	CK oxidase/ dehydrogenase	Promoter	Del	ME	Ashikari et al. (2005)
	Wx	Seed starch composition	Starch biosynthesis enzyme	Intron	Splice site Subs	TP	Isshiki et al. (1998)
	SKC1	Salt tolerance	HKT transporter	Coding	Missense Subs	AP	Ren et al. (2005)
Z. mays	*Vgt1*	Flowering	AP2-like TF	Promoter enhancer	TE insertion, indel	ME	Salvi et al. (2007)
Maize	*tb 1*	Inflorescence architecture	TCP TF	Promoter enhancer	Unknown	ME	Doebley et al. (1997)
	tga1	Seed morphology	SBP TF	Coding	Missense Subs	AP	Wang et al. (2005)
	Wx	Starch composition	Starch biosynthesis enzyme	Promoter, intron, coding	TE insertion	ME	Varagona et al. (1992)

TF: Transcription factor; TE: Transposable element; Subs: substitution; Ins: insertion; Del: deletion; TP: truncated protein; AP: altered protein; ME: Misexpression

response have been colocated with other *FLC* homologs in several crosses (Alonso-Blanco et al., 1998; O'Neill et al., 2008). Furthermore, loss- and gain-of-function alleles of another *FLC* regulator called *HUA2* likely contribute to this variation (Doyle et al., 2005; Wang et al., 2007).

In addition, natural variation for the flowering photoperiod response is caused by three photoreceptor genes, *CRY2*, *PHYC*, and *PHYD*, in *A. thaliana* (Table 1, Figure 1). Rare loss-of-function alleles of *PHYD* and *PHYC* as well as a gain-of-function of *CRY2* produce early flowering and reduced photoperiod response (Aukerman et al., 1997; El-Assal et al., 2001; Balasubramanian et al., 2006). Association mapping analyses suggest that haplotypes of *CRY2* and *PHYC* differing in eight amino acid substitutions might further contribute to this variation (Olsen et al., 2004; Balasubramanian et al., 2006).

QTL linkage mapping and association analyses of candidate genes also have been performed in other *Brassciaceae* species, showing that *FLC*-like genes probably contribute to the differentiation of annual and biennial habits in *Brassica rapa* (Schranz et al., 2002; Yuan et al., 2009) and that functional variants of a *FRI*-like gene of *A. lyrata* affects its vernalization requirement (Kuittinen et al., 2008). In addition, molecular analyses have identified the *LF* gene in another dicotyledonous crop species, pea, which is a long-day temperate legume that also responds to vernalization. Pea *LF* behaves as a flowering repressor that is homologous to *A. thaliana TFL1*, and a natural loss-of-function *LF* allele caused by a large deletion shows reduced photoperiod response (Foucher et al., 2003).

In the last few years, comparable progress has been achieved in understanding flowering time variation in several monocotyledonous grass species, including temperate cereals with similar photoperiod and vernalization responses to *A. thaliana* (Table 1). Two genes largely determine the life habit and vernalization response of barley and wheat. *VRN1* encodes a MADS box transcription factor homologous to the meristem identity protein AP1 of *A. thaliana* (Yan et al., 2003), and *VRN2* encodes a grass-specific putative transcription factor with a CCT domain (Yan et al., 2004b). *VRN1* promotes flowering and is speculated to be directly downregulated by vernalization, whereas *VRN2* is a repressor that reduces the expression of *VRN1* mediated by *VRN3*, a feedback regulatory loop among these genes accounting for their epistatic interactions (Figure 1; Distelfeld et al., 2009a). The early flowering spring habit of wheat and barley has been associated with more than 15 independent insertion and deletions in the first regulatory intron of *VRN1* (Yan et al., 2004a; Fu et al., 2005; Szucs et al., 2007) and with several loss-of-function alleles of *VRN2* (Distelfeld et al., 2009b). In addition, natural variation for the photoperiod response and its interaction with vernalization is determined by *VRN3* and *Ppd1*. *VRN3*, which is a homolog of *A. thaliana FT* encoding a long-distance flowering signal, is upregulated by long-day photoperiod and vernalization and activates *VRN1* expression (Yan et al., 2006). *Ppd1* encodes a pseudoresponse regulator that mediates the photoperiod upregulation of *VRN3* (Turner et al., 2005). Dominant mutations in the promoter and first intron of wheat and barley *VRN3* show increased expression and response to vernalization (Yan et al., 2006). By contrast, missense recessive mutations in the CCT domain of barley *Ppd-H1* likely cause late flowering

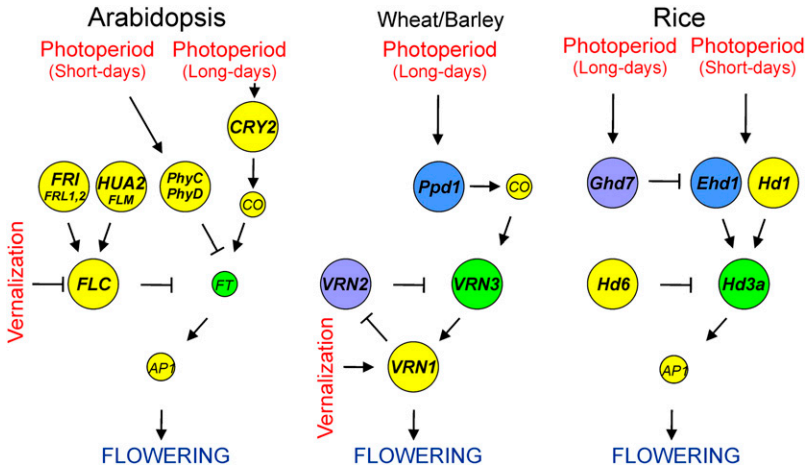

Figure 1. Gene Networks Involved in Natural Variation for Flowering Responses to Vernalization and Photoperiod signals in *A. thaliana*, Wheat, and Rice.

Diagrams do not represent full molecular models of flowering regulation, but they show gene network components and branches known to contribute to the natural intraspecific variation existing in these species. Yellow color represents genes that contribute to the variation in a single species, which do not present known homologous genes contributing to natural variation in other species. Green color depicts homologous genes that contribute to the variation in several species. Blue and purple indicate genes accounting for the variation in one species, which show homologous protein domains with genes contributing to the variation in another species. Given their large functional homology, *CO*, *FT*, and *AP1* homologs of the three species are included in the three diagrams, with small circles depicting genes that do not contribute to natural variation. See text for further details.

under long-day photoperiod (Turner et al., 2005). Moreover, another barley *FT* homolog has been proposed as a possible candidate for the *Ppd-H2* photoperiod QTL (Faure et al., 2007; Kikuchi et al., 2009).

Extensive analyses are also identifying the molecular bases of the natural variation for flowering time of rice and maize. In contrast with *A. thaliana* and temperate cereals, these are tropical short-day photoperiod species with no significant response to vernalization. To date, five genes have been isolated as determining the large variation for photoperiod response in rice (Table 1). *Hd1* and *Hd3a* are flowering promoters, homologs of *A. thaliana CO* and *FT* genes (Yano et al., 2000; Kojima et al., 2002). Several *Hd1* loss-of-function alleles reduce the expression of *Hd3a* and produce late flowering under short days, which indicates a conservation of this photoperiod regulatory module in phylogenetically distant short- and long-day flowering species (Figure 1). In addition, *EhdD1* encodes a response regulator that independently upregulates *Hd3a* under short days (Doi et al., 2004). By contrast, *Ghd7* and *Hd6* encode a CCT domain protein and a CK2 kinase, respectively, which probably repress *Hd3a* under long-day photoperiod (Takahashi et al., 2001; Xue et al., 2008). Loss-of-function alleles of both genes produce early flowering, but additional alleles differing in several *Ghd7* missense substitutions have been suggested to further contribute to rice flowering natural variation. In maize, the *Vgt1* locus has been identified as accounting for the natural variation for flowering photoperiod response (Salvi et al., 2007). *Vgt1* is an ~2-kb noncoding *cis*-element that regulates the expression of an *AP2* homolog located 70 kb downstream and behaves as a flowering repressor. Several polymorphisms in the *Vgt1* region have been strongly associated with flowering time variation (Salvi et al., 2007; Ducrocq et al., 2008).

The identification of large-effect QTGs has shown that photoreceptor and regulatory genes of different classes, such as those encoding transcription factors or signal transduction components, account for a large portion of the natural variation for flowering time in different species. Comparisons among species with similar physiological and environmental requirements for flowering induction show that some homologous genes contribute to the intraspecific variation in related species of the same plant family (e.g., *FLC* and *VRN3* in *Brassicaceae* and grasses, respectively). Thus, parallel evolution of flowering time by mutations in homologous conserved genes is apparent in different groups of related species. However, comparisons among distant species from the same or different phylogenetic families show that natural variation for flowering responses to vernalization and photoperiod signals is mainly generated by allelic variation at different genes in each species, which are often highly divergent among species (Figure 1). Current results suggest that such convergent evolution of flowering responses is determined by species-specific genes showing analogous network positions in distant species (e.g., *FLC* and *VRN2*) and by homologous genes with partly differentiated functions (e.g., *AP1* and *VRN1*). However, photoperiod responses seem to involve more conserved genes among species (photoreceptors, *CO*, and *FT*) than those involved in vernalization (*FLC*, *VRN1*, and *VRN2*), suggesting stronger constrains for the evolution of photoperiod than vernalization responses. Given the well-documented climate changes across evolutionary time, it can be further speculated that these differential constraints have been influenced by a wider temporal prevalence of photoperiod than vernalization signals.

The availability of causal genes and polymorphisms enables the study of the evolutionary processes that generate and maintain flowering time variation within and among species (reviewed in

Roux et al., 2006; Mitchell-Olds et al., 2007). In crop species, fitness effects and adaptive values of genetic variants are often documented because segregating populations are grown in their natural agricultural environments (Izawa, 2007). Detailed analyses indicate that some loci affect not only heading date but several other fitness components, as shown with the effects of *Ghd7* on plant height, panicle size, and seed production (Xue et al., 2008). Geographical distributions of alleles of *Hd1*, *Ehd1*, and *Dgh7* from rice (Izawa, 2007; Xue et al., 2008) or *Vgt1* and *Dwarf8* from maize (Camus-Kulandaivelu et al., 2006; Ducrocq et al., 2008) show latitudinal and/or altitudinal clines, which suggests that they are involved in adaptation to different world regions. Current multilocus analyses of cultivated varieties are elucidating the role of flowering time allelic variation in regional adaptation and crop expansion during the few thousand years after domestication.

Similar studies have been initiated in *A. thaliana*, where in contrast with crop plants, several of the natural alleles identified in *CRY2*, *FLM*, *PhyC*, *PhyD*, or *HUA2* (Table 1) are found in a single accession; therefore, it is possible that they are rare deleterious alleles. However, analyses of nucleotide diversity of *CRY2*, *PhyC*, *FRI*, and *FLC* have detected highly differentiated haplotypic groups, suggesting that their allelic variation might be maintained by various types of selection (Olsen et al., 2004; Caicedo et al., 2004; Stinchcombe et al., 2004; Balasubramanian et al., 2006). Most of the large number of *FRI* loss-of-function alleles appear at very low frequency, suggesting that they have been generated recently, for example, after the last glaciation (Le Corre et al., 2002; Shindo et al., 2005). However, two of these alleles are widely distributed in Central Europe, supporting the notion that their frequency increased due to strong natural selection during the postglacial colonization of this region (Johanson et al., 2000; Toomajian et al., 2006). In addition, a Eurasian latitudinal cline of flowering time and vernalization sensitivity has been shown to be partly determined by interactions among *FRI*, *FLC*, and *PhyC* allelic variation, suggesting that these interactions contribute to latitudinal and local adaptation (Caicedo et al., 2004; Lempe et al., 2005; Balasubramanian et al., 2006). Supporting the adaptive value of this allelic variation, analysis of *FRI* and *FLC* alleles in field experiments performed under environments closer to their natural habitat than laboratory conditions show that the *FRI*/*FLC* epistatic interaction affects different fitness components depending on the season of germination (Korves et al., 2007). In addition, antagonistic pleiotropic effects of *FRI* allelic variation on different fitness components, such as flowering time and plant architecture, suggest that complex phenotypic pleiotropy accounts for the adaptive value of *FRI* alleles (Scarcelli et al., 2007). Similarly, the large pleiotropic effects described for photoreceptor genes and *HUA2* (Table 1) probably also contribute to the global adaptive value of their genetic variants. Thus, several demographical and selective processes seem to determine the natural variation for flowering time in crop and wild species, but their relative significance and molecular targets are just beginning to emerge.

Plant Architecture and Morphology

More than 20 loci of major effect have now been cloned for several domestication traits related to plant architecture, revealing that loss of functions of transcription factor genes (sometimes previously unknown) are often involved (Table 1). Examples are the rice shattering locus *sh4* encoding a Myb factor (Li et al., 2006), the rice shattering locus qSH1, and the six/two row locus *Vrs1* of barley encoding homeodomain transcription factors (Konishi et al., 2006; Komatsuda et al. 2007) and a *SBP* gene underlying the *teosite glume architecture1* (*tga1*) locus in maize (Wang et al., 2005). Gain-of-function alleles of genes encoding other transcription factors also have been identified. These are illustrated with the classical maize *tb1* and wheat *Rht1* genes involved in plant architecture, whose selected alleles show mutations in a *cis*-regulatory region or in the coding region, respectively (Doebley et al., 2006; Peng et al., 1999; Clark et al., 2006). In tomato, fruit size and shape strongly differ from the small and round fruits of ancestral wild species. Detailed QTL analyses (reviewed in Tanksley, 2004) have been followed up with the cloning of four major effect loci (Table 1). Thus, *FW2.2* and *OVATE* identified novel classes of genes (Frary et al., 2000; Liu et al., 2002), the *FAS* locus has recently found to be a Yabby-type cell fate gene (Cong et al., 2008), and *SUN* has been shown to encode an IQ67 domain protein (Xiao et al., 2008). An *ovate* nonsense allele causes fruits with a pear shape (Liu et al., 2002), while different regulatory mutations producing misexpression of *FW2.2*, *FAS*, and *SUN* lead to large fruit phenotypes. Furthermore, seed size loci have been isolated in several species, such as the rice *GW2* and *GS3* loci encoding an ubiquitin-E3-ligase and a transmembrane protein, respectively (Fan et al., 2006; Song et al., 2007), or the tomato *Sw4.1* locus encoding an ABC transporter (Orsi and Tanksley, 2009). On the other hand, a large number of QTL analyses have been described in many crops for other developmental and morphological traits related to yield and plant performance (e.g., http://www.gramene.org/ and http://www.sgn.cornell.edu/index.pl). The first genes underlying those loci have been identified mainly in rice (Sakamoto and Matsuoka, 2008; Weng et al., 2008) as illustrated with the *Gn1a* locus encoding a cytokinin dehydrogenase that affects grain number (Ashikari et al., 2005) or the pleiotropic *Ghd7* locus with effects on various yield components (Xue et al., 2008).

Developmental traits related to plant architecture and organ morphology also have been studied in *A. thaliana*, where natural variation for seed size (Alonso-Blanco et al.,1999), inflorescence architecture (Juenger et al., 2000), leaf morphology (Pérez-Pérez et al., 2002), and flower size (Juenger et al., 2005) have been described. Although none of the underlying genes have been cloned, microsynteny comparisons between tomato and *A. thaliana*, combined with functional analyses, suggest that a *Sw4.1* ortholog gene might underlie an *A. thaliana* seed size QTL (Orsi and Tanksley, 2009). Several QTLs have been detected for root growth and architecture (Mouchel et al., 2004; Loudet et al., 2005; Fitz Gerald et al., 2006), and the major effect locus *BRX* has identified a novel gene with unknown molecular function (Mouchel et al., 2004). In addition, developmental features present as monogenic traits in some *A. thaliana* accessions have identified non-sense mutations in the Myb transcription factor gene *GL1* causing glabrous phenotype (Hauser et al., 2001) and in the β-galactosidase gene corresponding to the *MUM2* locus, which reduces seed mucilage liberation after imbibition (Macquet et al., 2007).

Different strategies are revealing cryptic developmental genetic variation of *A. thaliana* that is only apparent under specific conditions (Table 1). It has been shown that differential expansion of an intronic trinucleotide repeat affects the expression of a Leu biosynthesis enzyme gene, hence causing aberrant leaf morphology defects that are mainly visible under short-day photoperiod and high temperature conditions (Sureshkumar et al., 2009). In addition, *A. thaliana* transgenic lines carrying the *SRK* and *SCR* genes that determine self-incompatibility in *A. lyrata* have been used to reveal a gene underlying pseudo-self-compatibility. Thus, it has been shown that polymorphisms in the promoter region of the previously uncharacterized gene *PLANT U-BOX8* regulating *SRK* transcript levels reduce its expression and cause such compatibility (Liu et al., 2007). These examples show how the analysis of morphological and developmental traits in crops and wild plants are identifying not only genes with allelic variants increasing fitness under particular conditions, but also cryptic genetic variation with unknown effects on plant adaptation.

VEGETATIVE GROWTH AND PHYSIOLOGY

Natural variation has been described extensively for general growth traits (e.g., biomass accumulation) as well as primary metabolism and mineral uptake and accumulation, and the complex molecular bases underlying these traits are beginning to be elucidated. Such studies are aiding our understanding of hybrid vigor (positive heterosis) and hybrid incompatibility (negative heterosis), which are of primary concern in agronomy, as well as specific metabolic pathways and physiological processes that affect crop growth and/or crop quality.

Growth and Biomass Accumulation

The complexity underlying the regulation of biomass accumulation is illustrated with the precise dissection of a small-effect QTL for this trait in *A. thaliana*, which includes two closely linked QTLs that have opposing effects on biomass accumulation within a small genomic region of 210 kb (Kroymann and Mitchell-Olds, 2005). In addition, the effect of both loci depends on the genetic background. Thus, a highly polygenic architecture involving genetic interactions has been speculated for biomass accumulation (Kroymann and Mitchell-Olds, 2005). Recently, significant progress has been made in understanding the genetic and molecular bases of growth traits that show positive or negative heterosis, as well as in finding genes contributing to the variation for growth interactions with abiotic environmental factors.

A large number of QTL studies are currently dissecting the genetic bases of positive heterosis or hybrid vigor, which is a growth trait observed in many hybrids of most species and a major plant breeding objective. Numerous QTLs with different levels of dominant, overdominant, and epistatic effects have been mapped for heterosis in maize (Frascaroli et al., 2007), rice (Li et al., 2001), tomato (Semel et al., 2006), rapeseed (*Brassica napus*) (Radoev et al., 2008), and *A. thaliana* (Kusterer et al., 2007; Melchinger et al., 2007). Comparisons of genomic sequences among maize inbred lines have shown extensive within-species lost of gene colinearity, with a large portion of genes being absent in some individuals (Fu and Dooner, 2002; Song and Messing, 2003). This lack of colinearity has led to a molecular hypothesis for the dominance model of heterosis and its counterpart inbreeding depression, where the presence of distinct genes in different lines might cause hybrid vigor (Fu and Dooner, 2002). In addition, overdominance frequently has been detected at the level of gene expression in hybrids of maize and *A. thaliana* (Song and Messing, 2003; Vuylsteke et al., 2005).

On the other hand, analyses of *A. thaliana* hybrids are identifying the molecular bases of a related fundamental evolutionary phenomenon, namely, negative heterosis or hybrid incompatibility (Table 1). Nearly 2% of *A. thaliana* intraspecific crosses yield hybrid plants expressing severe growth defects and leaf necrosis, which are due to epistatic interactions between two or three genes fitting the Dobshansky-Muller model of hybrid postzygotic isolation (Bomblies et al., 2007; Alcázar et al., 2009). Alleles of two different tandem repeats of *NB-LRR* disease resistance genes differing in sequence and gene copy number have been shown to cause these hybrid incompatibilities (Bomblies et al., 2007; Alcázar et al., 2009). Incompatible combinations are characterized by autoimmune-like responses and enhanced disease resistance, which depend on growth temperature and activation of the salicylic acid stress signaling pathway (Alcázar et al., 2009). In addition, embryo lethality segregating in crosses among wild *A. thaliana* genotypes is determined by an epistatic interaction between two paralogous genes encoding a key enzyme involved in His biosynthesis (Bikard et al., 2009). Thus, divergent evolution of particular duplicated genes appears as the main mechanism causing genetic incompatibilities at different postzygotic levels.

Several QTLs have been isolated that contribute to natural variation for growth responses to light or soil nutrient availability in *A. thaliana*. Analyses of light responses have shown that amino acid substitutions in photoreceptors, including phytochrome A (Maloof et al., 2001), phytocrome B (Filiault et al., 2008), cryptochome 2 (Botto et al., 2003), and probably phytochrome C (Balasubramanian et al., 2006), affect hypocotyl elongation in different light conditions. In addition, a tandem zinc knuckle/PLU3 (*TZP/LIGHT5*) domain-encoding gene has been shown to promote growth, associated with an insertion mutation appearing as a rare natural loss-of-function allele (Loudet et al., 2008). Furthermore, it has been shown that natural polymorphisms affecting the expression of *LPR1*, which encodes a multicopper oxidase, strongly influences the primary root growth response to phosphate starvation (Svistoonoff et al., 2007). Hence, it appears that mainly signal perception and transduction components have been involved in natural variation for growth environmental responses.

Primary Metabolism

Primary metabolism has been defined as "those essential reactions involving compounds that are formed as part of the normal anabolic and catabolic processes, which result in assimilation, respiration, transport, and differentiation processes that take place in most, if not all, cells of an organism" (Fernie and Schauer, 2009). Besides a wide range of intermediate compounds (e.g.,

compounds from glycolysis or Krebs cycle), primary metabolites include end products of metabolic pathways that accumulate in (harvestable) sink organs (e.g., seeds, fruits, and tubers) determining relevant crop quality traits related to nutritional content and composition. Recent molecular analyses of natural variation have identified a large number of genes encoding enzymes and have associated primary metabolism with phenotypic variation for morphology and growth-related traits (Lisec et al., 2008; Schauer et al., 2008).

Two decades ago, analyses of starch content in seeds of pea and cereals identified the genes underlying classical loci, such as Mendel's pea *rugosus* (*R*) and maize *Waxy*. These pioneering works illustrate the pleiotropic effects of primary metabolism on plant development. The *R* locus encodes a starch branching enzyme, whose recessive allele carrying a transposon insertion in the coding sequence has been widely spread in European cultivars due to the associated sweetness of the wrinkled pea phenotype (Bhattacharyya et al., 1990). Maize *Waxy* loci encode granule-bound starch biosynthesis enzymes, where multiple loss-of-function alleles caused by transposon insertions lead to a waxy appearance of kernels that reflect the lack of amylose in endosperm (Varagona et al., 1992). Moreover, a single splice donor site mutation in a homologous *Waxy* gene is responsible for the absence of amylose in glutinous rice varieties, which has been widely spread in East Asia associated with human cultural behaviors (Olsen and Purugganan, 2002).

Recent quantitative analyses of natural variation for the content of primary metabolites in fruits of tomato interspecific crosses (Schauer et al., 2006) and in potato tubers (*Solanum tuberosum*; Menéndez et al., 2002) have found a large number of QTLs underlying the content of other carbohydrate metabolites. Isolation of a large-effect QTL for tomato sugar content identified the invertase encoding gene *LIN5*, where a single amino acid substitution alters its activity (Fridman et al., 2004). Based on colocation and genetic association, two tandemly repeated invertase genes, *invGE* and *invGF*, have been also suggested to underlie a cold-sweetening QTL in potato (Li et al., 2005).

Several studies have dissected the variation for primary metabolism of *A. thaliana* through the analysis of enzymatic activities and metabolite contents in different vegetative organs. QTLs have been found for the activity of multiple carbohydrate metabolism enzymes, some of them colocating with the corresponding structural genes, for example, phosphogluco-mutase (*PGM*) and hexokinase, which indicates *cis*-regulatory variation (Mitchell-Olds and Pedersen, 1998; Keurentjes et al., 2008b). Histochemical analysis further shows that certain *PGM* QTLs are tissue specific (Sergeeva et al., 2004). However, several enzymatic activity QTLs are located in different genomic regions, identifying *trans*-acting sequences. These loci might simultaneously coregulate several enzymes, hence revealing novel modes of carbohydrate metabolic regulation (Mitchell-Olds and Pedersen, 1998; Sergeeva et al., 2004; Keurentjes et al., 2008b). In addition, a vacuolar invertase has been found that contributes specifically to the natural variation for root elongation but not for hypocotyl length (Sergeeva et al., 2006). Similarly, QTLs have been identified for nitrogen- and sulfur-containing compounds, such as nitrate, sulfate, and free amino acids (Loudet et al., 2003, 2007). A large-effect QTG has been isolated for sulfate content, which corresponds to the *APR2* sulfate reductase gene (Loudet et al., 2007). *APR2* activity is altered by a single amino acid substitution, and the effects of this polymorphism interact with nitrogen availability, hence illustrating the interaction between sulfate assimilation and nitrogen metabolism. Furthermore, as described in the previous section, genes involved in Leu or His biosynthesis account for natural variation for severe zygotic (embryo) and postzygotic morphological defects (Bikard et al., 2009; Sureshkumar et al., 2009).

A. thaliana natural variation for untargeted metabololites from vegetative tissues has been dissected by quantifying high-throughput metabolic profiles in different mapping populations (Keurentjes et al., 2006; Meyer et al., 2007; Rowe et al., 2008). A large number of metabolite content QTLs (mQTLs) have been mapped, demonstrating that two- and three-way epistatic interactions determine a substantial proportion of this variation (Lisec et al., 2008; Rowe et al., 2008). Candidate genes have been proposed for a large proportion of detected mQTL based on the enzymatic activities involved in different biochemical pathways (Lisec et al., 2008). In addition, comparative analyses have shown colocation of QTLs for biomas accumulation and mQTL, supporting a link between growth and metabolic profiles (Lisec et al., 2008).

Mineral Accumulation

Most nutrients that plants need for growth and development are supplied as minerals to the roots, and they are classified as macronutrients (Ca, K, Mg, N, P, and S) or micronutrients (B, Cl, Fe, Mn, Co, Cu, Mo, Ni, and Zn) depending on the necessary quantities. The composition of mineral nutrients and trace elements (i.e., the inorganic component of an organism) is now referred to as the ionome (Salt et al., 2008). There is substantial natural variation for mineral use efficiency, root uptake, translocation from roots to shoots, and accumulation in the seed as storage and supply for the germinating seedling. This variation has been reported in many species, leading to breeding programs such as those aiming to improve zinc and iron status of cereal grains or tuber crops (www.harvestplus.org). Recent QTL analyses have identified six genes involved in the complex mechanisms controlling the variation for plant nutrition and mineral homeostasis (Table 1; Ghandilyan et al., 2006)

QTL studies in crop species have focused on seed or leaf mineral concentrations, mostly in rice, wheat, barley, *Brassica* species, and soybean (*Glycine max*). In cereals, mostly rice, QTLs have been mapped for grain minerals (Joppa et al., 1997; Garcia-Oliveira et al., 2009), flag leaf nitrogen (N) (Ishimaru et al., 2001) or phosphorous (P) uptake (Wissuwa et al., 2002), salt tolerance related to Na/K homeostasis (Lin et al., 2004), and grain accumulation of toxic Cd (Ueno et al., 2009). In *Brassica* crops, loci have been reported for phosphate concentrations in leaves and seeds of *B. rapa* (Zhao et al., 2008), for Ca and Mg concentrations in leaves of *B. oleracea* (Broadley et al., 2008), and for leaf mineral concentrations in *B. rapa* (Wu et al., 2008). In soybean, QTLs have been found for Ca and S concentrations in seeds (Panthee et al., 2006; Zhang et al., 2009). Three large-effect QTLs have been isolated in crops, which have identified several molecular mechanisms linking mineral content and other

physiological traits. The rice *SKC* gene encodes a Na^+ selective transporter, whose more active allele determined by missense mutations increases salt tolerance (Ren et al., 2005). A boron tolerance locus of barley corresponds to the boron efflux transporter gene *Bot1* that appears duplicated and overexpressed in a B tolerant accession (Sutton et al., 2007). In addition, the *Gpc-B1/NAM-B1* locus of wheat encodes a NAC transcription factor that regulates nutrient remobilization from leaves to developing grains (Uauy et al., 2006). It has been shown that nonfunctional alleles caused by different deletions are present in cultivated varieties, leading to delayed senescence and reduced protein, Zn, and Fe grain content.

Detailed analyses of the ionome in *A. thaliana* have shown considerable variation for leaf mineral concentrations under various mineral/metal supply conditions (Salt et al., 2008). QTLs have been identified for accumulation of different elements (Ca, Cu, Fe, K, Mg, Mn, Na, P, S, and Zn) in seeds, siliques, leaves, and roots under different growth conditions (Vreugdenhil et al., 2004; Waters and Grusak, 2008; Ghandilyan et al., 2009). Overall, these analyses show that mineral concentrations are controlled by a large number of loci with mostly moderate effect, which often interact strongly with growth environment. Interestingly, a strong P QTL has been colocated with a previously identified locus for phytate (myo-inositol-1,2,3,4,5,6-hexakisphosphate or IP6), the storage compound for P in seeds (Bentsink et al., 2003). However, only the *ERECTA* gene, encoding a receptor-like kinase for which a mutant allele segregates in mapping populations, has been demonstrated to affect mineral concentrations in these studies (Waters and Grusak, 2008; Ghandilyan et al., 2009).

In addition, *A. thaliana* QTL analyses have been focused on accumulation of specific minerals, including N (as nitrate; Loudet et al., 2003; Harada et al., 2004), K (Harada and Leigh, 2006), Cu (Kobayashi et al., 2008), Mo (Baxter et al., 2008), and Na (Rus et al., 2006). These studies have led to the isolation of three genes underlying large-effect QTLs, which also encode different mineral transport components. A root copper tolerance locus corresponds to the *HMA5* gene encoding a Cu-transporting ATPase. Several natural alleles differing in missense mutations in conserved motifs show lower activity and Cu translocation to the shoot (Kobayashi et al., 2008). A mitochondrial molybdenum transporter encoded by the nuclear *MOT1* gene underlies a shoot Mo concentration QTL. A deletion in *MOT1* promoter region has been associated with low gene expression and low shoot Mo concentration, suggesting that this regulatory mutation is the causal nucleotide polymorphism (Baxter et al., 2008). Finally, *HKT1* encodes a Na^+ transporter for which two loss-of-function alleles associated with promoter deletions produce lower root expression and enhanced shoot Na^+ levels in two coastal accessions (Rus et al., 2006).

Studies of *A. thaliana* mineral accumulation have inspired research on natural variation for exceptional zinc and/or cadmium accumulation in leaves of the related metal hyperaccumulator species *Arabidopsis halleri* and *Thlaspi caerulescens*. Several loci have been mapped in populations derived from crosses between *A. halleri* and *A. lyrata* (Courbot et al., 2007), one of them colocalizing with *HMA4*, a locus containing three copies of the Ah-*HMA4* gene that is essential for Zn hyperaccumulation and Cd tolerance in *A. halleri* (Hanikenne et al., 2008). In addition, multiple QTLs have been located for root or shoot Zn or Cd accumulation in F3 populations of *T. caerulescens* (Assunção et al., 2006; Deniau et al., 2006). Thus, comparative analyses with *A. thaliana* are not only assisting the isolation of genes underlying those loci but will also enable identification of the molecular bases of interspecific variation present in wild crucifers.

REVEALING THE VARIOUS LEVELS OF PHENOTYPIC REGULATION: NATURAL VARIATION FOR MOLECULAR TRAITS

The path from genotype to phenotype includes several molecular intermediate steps in the translation of genetic information, with regulation occurring at each of these levels (Keurentjes et al., 2008a). Extensive natural variation has been described for the amount of molecular components, such as gene transcripts (Vuylsteke et al., 2005; Kliebenstein et al., 2006a), protein abundance and activity (Chevalier et al., 2004; Cross et al., 2006), and metabolites (Kliebenstein et al., 2001; Cross et al., 2006). Quantitative genetic analyses of "-omics" data collected from mapping populations by so-called genetical genomics approaches (Jansen and Nap, 2001) have shown that much of this natural variation is genetically determined by specific expression QTL (eQTL), mQTL, or protein QTL (pQTL) (Keurentjes et al., 2008a). In addition, a portion of this variation is determined by epigenetic mechanisms of regulation, such as methylation and chromatin remodeling (He et al., 2004; Vaughn et al., 2007), which in turn can also result from DNA sequence polymorphisms (Johannes et al., 2008).

The genetic bases of natural variation for genome-wide gene expression have been approached systematically in *A. thaliana*, barley, and maize (Schadt et al., 2003; Vuylsteke et al., 2006; Keurentjes et al., 2007; West et al., 2007; Potokina et al., 2008b). Expression variation of ~30 to 40% of the segregating genes is regulated by an eQTL colocating with the gene encoding the mRNA, most of those local eQTLs being the result of *cis*-regulated genes (i.e., allele-specific expression). However, most variably expressed genes are regulated in trans by eQTLs located in distant genomic regions (*trans*-eQTLs) that often appear concentrated in a small number of regulatory hot spots (Keurentjes et al. 2007; West et al., 2007; Fu et al., 2009). *cis*-eQTLs show larger average effects than *trans*-eQTLs probably due to the stronger impact of direct *cis*-regulation on the target gene. In addition, it has been shown that QTLs for gene expression variation might depend on spatial and temporal regulation (Potokina et al., 2008a). The molecular identification of regulatory eQTLs is currently facilitated by statistical methods that combine the functional annotation of biological relevant gene sets, the genomic position of genes and eQTLs, and the coexpression of candidate regulators and target genes. In this way, complex genetic networks are constructed, which reveal many novel putative regulatory steps together with strong interconnectivity and epistasis (Kliebenstein et al., 2006b; Keurentjes et al., 2007; Druka et al., 2008). As described above, large-scale untargeted analyses of metabolic profiles have also revealed extensive

genetic variation for metabolite content in *A. thaliana* and tomato (Keurentjes et al., 2006; Schauer et al., 2006; Lisec et al., 2008). Large numbers of mQTLs have been mapped, although they show a lower average heritability than eQTL (Rowe et al., 2008).

The genetic dissection of natural variation for developmental and physiological traits is beginning to link phenotypic QTLs for complex traits with eQTL, mQTL, and pQTL (Keurentjes, 2009). Several studies, mostly in *A.thaliana*, have integrated information from different levels of molecular regulation to improve the elucidation of genetic control of quantitative traits (Hirai et al., 2004; Tohge et al., 2005; Meyer et al., 2007; Wentzell et al., 2007; Druka et al., 2008; Lisec et al., 2008). Thus, it has been shown that plant growth and development are interwoven with primary metabolism, regulation occurring at different levels, including gene expression, enzyme activity, and metabolite abundance (Keurentjes et al., 2008b). Although these studies often reveal direct relationships between the various levels of biological information, such a relationship is not always linear or present. This was illustrated recently with a system-wide analysis, wherein much of the natural genetic variation affecting gene expression or functional protein differences did not to appear to lead to phenotypic variation, a phenomenon known as phenotypic buffering (Fu et al., 2009). Interestingly, several loci have been identified as contributing to natural variation for the ability to buffer developmental processes through environmental canalization (Hall et al., 2007; Sangster et al., 2008). Hence, integrative analyses of multiple phenotypic and molecular regulatory levels are elucidating the mechanisms controlling developmental buffering and canalization, which are presumed to contribute to biological robustness of plant species and facilitate evolvability in changing environments (Queitsch et al., 2002; Kitano, 2004).

MOLECULAR TARGETS OF SELECTION FOR PLANT ADAPTATION: CURRENT AND FUTURE PROSPECTS

Nearly 100 genes underlying natural variation for plant development and growth have been identified in crop plants and *A. thaliana*. Most of them correspond to QTLs with large effects on trait variation and provide a first inventory of mechanisms, genes, and functional nucleotide polymorphisms that might be involved in plant adaptation to different agricultural or natural environments. They belong to all types of ontological classes, including transcription factors, signal transduction components, enzymes of primary and secondary metabolism, hormone metabolism and signaling, metal transporters, as well as genes with unknown functions. Interestingly, some of these genes had not been found previously in mutant screenings because common laboratory strains carry natural loss-of-function alleles, such as *FLC*, *FRI*, or *DOG1* in *A. thaliana*.

Nucleotide polymorphisms affecting the function of these genes are identifying the mutational mechanisms that generate natural variation. A large proportion of natural alleles carry null loss-of-function mutations, which are often produced by structural nonsense or insertion and deletion (indel) mutations (Alonso-Blanco et al., 2005). A particular class of these alleles corresponds to complete gene deletions or duplications caused by retrotransposition, recombination, and other molecular mechanisms, which may play a major role in heterosis of crop and wild species (Fu and Dooner, 2002; Song and Messing, 2003). A second type of common allele is a change-of-function allele produced by a missense mutation altering protein structure and function, such as described for photoreceptor genes (Table 1). In addition, multiple change-of-function alleles carrying regulatory mutations in three types of genomic regions affecting gene expression have been described for many traits and species. Most of these alleles show indels in their nearby promoter regions, in agreement with the large number of *cis*-eQTLs identified (Keurentjes et al., 2007; West et al., 2007). Second, gene expression changes are caused by unknown mutations located in distant 5′-regions of the genes as illustrated for maize *Tb1* (Clark et al., 2006) and *Vgt1* (Salvi et al., 2007). Third, expression alterations also appear to be produced by intronic mutations, including insertions of tranposons or differential expansion of microsatellite repeated sequences (Sureshkumar et al., 2009). Finally, although most natural alleles that have been described are caused by variation at the level of nucleotide sequence, natural epigenetic variation also contributes to heritable developmental and physiological variation, as indicated by stably inherited epialleles in the *LCyc* gene involved in *Linaria* flower morphology (Cubas et al., 1999) and in an SBP-box gene affecting tomato fruit ripening (Manning et al., 2006). This is supported by the considerable amount of natural variation found for DNA methylation (Riddle and Richards, 2005; Zhang et al., 2006b; Vaughn et al., 2007), which is partly mediated by small interfering RNAs also differing among accessions (Zhai et al., 2008). It is hypothesized that methylation and heterochromatinization mediated by different kinds of small interfering RNAs might *cis*- and *trans*-regulate gene expression and function in a more quantitative and reversible manner than sequence variation (Zhai et al., 2008).

All of these studies provide information on the particular classes of genes and alleles that might have been naturally or artificially selected for different traits (reviewed in Alonso-Blanco et al., 2005). For instance, as described by Purugganan and Fuller (2009), it seems that domestication is mainly associated with transcriptional activators and changes in transcriptional networks. By contrast, crop diversification after domestication involves a large proportion of genes encoding enzymes, with loss-of-function alleles differently contributing to crop domestication and diversification. Thus, we are beginning to understand how natural variation is generated and maintained depending on plant species, traits, environments, and selective forces. However, conclusive generalizations on evolutionary processes await systematic extensions of the following aspects of these analyses: (1) the number of species analyzed, particularly of wild plants; (2) the number of genes identified in each species; (3) the spectrum of allelic effects per gene; and (4) the estimates of genetic and environmental interactions.

Understanding the ecological and evolutionary significance of natural variation requires precise evaluation of their role in adaptation to particular environments, which is just beginning to be approached. Based on their presence in a single wild genotype and their relative large effects, some of the *A. thaliana* natural alleles are probably deleterious variants segregating in natural populations. This has been suggested for loss-of-function

alleles of *HUA2* and *LIGHT5*, found only in a subset of lines derived from the same parental accession (Doyle et al., 2005; Loudet et al., 2008). Similarly, the *BRX* loss-of-function allele has not been found in genotypes collected in the same geographical site where this variant was originally sampled many years before (Shindo et al., 2008). As described above for flowering time, demonstrating that natural variation in specific genes is involved in adaptation is currently addressed by combining population and evolutionary genetic analyses with detailed phenotypic studies of fitness-related traits. Analysis of the amount and pattern of nucleotide diversity may show potential signatures of selection, hence suggesting different evolutionary mechanisms to maintain such variation. This is illustrated with the identification of selective sweeps in several domestication genes of crop plants (Purugganan and Fuller, 2009) and with the highly differentiated haplotypes found in some *A. thaliana* photoreceptor genes (Olsen et al., 2004; Balasubramanian et al., 2006). However, demographical history also affects the patterns of DNA sequence diversity; therefore, other studies are necessary to test adaptive effects of such alleles. On one hand, detailed phenotypic characterizations under natural and agricultural conditions are detecting fitness effects of particular alleles or genotypes (Tian et al., 2003; Shindo et al., 2008; Wilczek et al., 2009). In addition, comparisons of differentiation among local populations for quantitative traits (Q_{ST}) and nucleotide polymorphisms (F_{ST}) might further assist the detection of selection signatures on particular genes (Le Corre, 2005; Stenoien et al., 2005). On the other hand, association analyses of nucleotidic and phenotypic diversity with environmental variation might identify environmental factors driving phenotypic selection. It is expected that new extensive collections of *A. thaliana* wild genotypes recently developed from several world regions (Jorgensen and Mauricio, 2004; Stenoien et al., 2005; Schmid et al., 2006; Beck et al., 2008; Picó et al., 2008) will facilitate estimations of allele frequencies, geographical distributions, and genetic associations with environmental factors.

In the past decade, the analysis of natural variation in crop plants and *A. thaliana* has provided an unprecedented amount of information on the genetic and molecular mechanisms that determine intraspecific variation and adaptation. It can be anticipated that this trend will continue in the next decade, especially with the broad implementation of "-omics" technologies for the precise analysis of natural variation at different levels. First, high-throughput genotyping will enable the development of new genetic mapping strategies, such as genome-wide association (Azanzana et al. 2005; Nordborg and Weigel, 2008; Waugh et al., 2009), which is expected to provide higher mapping resolution. Second, comparisons of thousands of whole-genome sequences from genotypes of the same species will provide a dynamic perspective of a species' genome in terms of pangenomes (Morgante et al., 2007). Third, common integration of QTLs and genes causing phenotypic variation with those affecting the various levels of molecular variation will provide complete (genome-wide and whole organisms) phenotypic regulatory networks. The latter should include not only eQTL, mQTL, and pQTL estimated at particular points but also molecular fluxes in those networks. Finally, extension of the analysis of natural variation to other crop and wild species will allow deep comparisons among species. Such comparative intraspecific and interespecific studies will elucidate the mechanisms involved in the evolution of plant development and physiology at higher levels, including those of speciation and species diversification in relation to earth changing environments.

ACKNOWLEDGMENTS

We apologize to those authors whose work could not be discussed due to space limitations. Research in our laboratories was supported by the European Research Area-Plant Genomics program Grant 034B ARABRAS and the Max Planck Society (M.R. and M.K.), Grants GEN2006-27786-E/VEG and BIO2007-62632 from the Ministerio de Ciencia e Innovación of Spain (C.A.-B.), the Netherlands Organization for Scientific Research, VENI scheme (JK and LB), and the Centre for Biosystems Genomics (Netherlands Genomics Initiative; J.J.B.K. and D.V.).

Received April 21, 2009; revised June 10, 2009; accepted June 11, 2009; published July 2, 2009.

REFERENCES

Albani, M.C., Battey, N.H., and Wilkinson, M.J. (2004). The development of ISSR-derived SCAR markers around the *SEASONAL FLOWERING LOCUS* (*SFL*) in *Fragaria vesca.* Theor. Appl. Genet. **109:** 571–579.

Alcázar, R., García, A.V., Parker, J.E., and Reymond, M. (2009). Incremental steps toward incompatibility revealed by Arabidopsis epistatic interactions modulating salicylic acid pathway activation. Proc. Natl. Acad. Sci. USA **106:** 334–339.

Alonso-Blanco, C., Bentsink, L., Hanhart, C.J., Blankestijn-De Vries, H., and Koornneef, M. (2003). Analysis of natural allelic variation at seed dormancy loci of *Arabidopsis thaliana.* Genetics **164:** 711–729.

Alonso-Blanco, C., Blankestijn-de Vries, H., Hanhart, C.J., and Koornneef, M. (1999). Natural allelic variation at seed size loci in relation to other life history traits of *Arabidopsis thaliana.* Proc. Natl. Acad. Sci. USA **96:** 4710–4717.

Alonso-Blanco, C., El-Assal, S.E., Coupland, G., and Koornneef, M. (1998). Analysis of natural allelic variation at flowering time loci in the Landsberg erecta and Cape Verde Islands ecotypes of *Arabidopsis thaliana.* Genetics **149:** 749–764.

Alonso-Blanco, C., Mendez-Vigo, B., and Koornneef, M. (2005). From phenotypic to molecular polymorphisms involved in naturally occurring variation of plant development. Int. J. Dev. Biol. **49:** 717–732.

Aranzana, M.J., et al. (2005). Genome-wide association mapping in Arabidopsis identifies previously known flowering time and pathogen resistance genes. PLoS Genet. **1:** e60.

Argyris, J., Dahal, P., Hayashi, E., Still, D.W., and Bradford, K.J. (2008). Genetic variation for lettuce seed thermoinhibition is associated with temperature-sensitive expression of abscisic acid, gibberellin, and ethylene biosynthesis, metabolism, and response genes. Plant Physiol. **148:** 926–947.

Argyris, J., Truco, M.J., Ochoa, O., Knapp, S.J., Still, D.W., Lenssen, G.M., Schut, J.W., Michelmore, R.W., and Bradford, K.J. (2005). Quantitative trait loci associated with seed and seedling traits in *Lactuca.* Theor. Appl. Genet. **111:** 1365–1376.

Ashikari, M., Sakakibara, H., Lin, S., Yamamoto, T., Takashi, T., Nishimura, A., Angeles, E.R., Qian, Q., Kitano, H., and Matsuoka, M. (2005). Cytokinin oxidase regulates rice grain production. Science **309:** 741–745.

Assunção, A.G., Pieper, B., Vromans, J., Lindhout, P., Aarts, M.G., and Schat, H. (2006). Construction of a genetic linkage map of *Thlaspi caerulescens* and quantitative trait loci analysis of zinc accumulation. New Phytol. **170:** 21–32.

Aukerman, M.J., Hirschfeld, M., Wester, L., Weaver, M., Clack, T., Amasino, R.M., and Sharrock, R.A. (1997). A deletion in the *PHYD* gene of the *Arabidopsis* Wassilewskija ecotype defines a role for phytochrome D in red/far-red light sensing. Plant Cell **9:** 1317–1326.

Balasubramanian, S., Sureshkumar, S., Agrawal, M., Michael, T.P., Wessinger, C., Maloof, J.N., Clark, R., Warthmann, N., Chory, J., and Weigel, D. (2006). The *PHYTOCHROME C* photoreceptor gene mediates natural variation in flowering and growth responses of *Arabidopsis thaliana.* Nat. Genet. **38:** 711–715.

Baxter, I., Muthukumar, B., Park, H.C., Buchner, P., Lahner, B., Danku, J., Zhao, K., Lee, J., Hawkesford, M.J., Guerinot, M.L., and Salt, D.E. (2008). Variation in molybdenum content across broadly distributed populations of *Arabidopsis thaliana* is controlled by a mitochondrial molybdenum transporter *MOT1*. PLoS Genet. **4:** e1000004.

Beck, J.B., Schmuths, H., and Schaal, B.A. (2008). Native range genetic variation in *Arabidopsis thaliana* is strongly geographically structured and reflects pleistocene glacial dynamics. Mol. Ecol. **17:** 902–915.

Benfey, P.N., and Mitchell-Olds, T. (2008). From genotype to phenotype: Systems biology meets natural variation. Science **320:** 495–497.

Bentsink, L., Jowett, J., Hanhart, C.J., and Koornneef, M. (2006). Cloning of DOG1, a quantitative trait locus controlling seed dormancy in Arabidopsis. Proc. Natl. Acad. Sci. USA **103:** 17042–17047.

Bentsink, L., Yuan, K., Koornneef, M., and Vreugdenhil, D. (2003). The genetics of phytate and phosphate accumulation in seeds and leaves of *Arabidopsis thaliana*, using natural variation. Theor. Appl. Genet. **106:** 1234–1243.

Bhattacharyya, M.K., Smith, A.M., Ellis, T.H., Hedley, C., and Martin, C. (1990). The wrinkled-seed character of pea described by Mendel is caused by a transposon-like insertion in a gene encoding starch-branching enzyme. Cell **60:** 115–122.

Bikard, D., Patel, D., Le Mette, C., Giorgi, V., Camilleri, C., Bennett, M.J., and Loudet, O. (2009). Divergent evolution of duplicate genes leads to genetic incompatibilities within *A. thaliana*. Science **323:** 623–626.

Bomblies, K., Lempe, J., Epple, P., Warthmann, N., Lanz, C., Dangl, J.L., and Weigel, D. (2007). Autoimmune response as a mechanism for a Dobzhansky-Muller-type incompatibility syndrome in plants. PLoS Biol. **5:** e236.

Botto, J.F., Alonso-Blanco, C., Garzaron, I., Sanchez, R.A., and Casal, J.J. (2003). The Cape Verde Islands allele of *cryptochrome 2* enhances cotyledon unfolding in the absence of blue light in Arabidopsis. Plant Physiol. **133:** 1547–1556.

Broadley, M.R., Hammond, J.P., King, G.J., Astley, D., Bowen, H.C., Meacham, M.C., Mead, A., Pink, D.A.C., Teakle, G.R., Hayden, R.M., Spracklen, W.P., and White, P.J. (2008). Shoot calcium and magnesium concentrations differ between subtaxa, are highly heritable, and associate with potentially pleiotropic loci in *Brassica oleracea.* Plant Physiol. **146:** 1707–1720.

Caicedo, A.L., Stinchcombe, J.R., Olsen, K.M., Schmitt, J., and Purugganan, M.D. (2004). Epistatic interaction between Arabidopsis FRI and FLC flowering time genes generates a latitudinal cline in a life history trait. Proc. Natl. Acad. Sci. USA **101:** 15670–15675.

Camus-Kulandaivelu, L., Veyrieras, J.B., Madur, D., Combes, V., Fourmann, M., Barraud, S., Dubreuil, P., Gouesnard, B., Manicacci, D., and Charcosset, A. (2006). Maize adaptation to temperate climate: Relationship between population structure and polymorphism in the Dwarf8 gene. Genetics **172:** 2449–2463.

Casasoli, M., Derory, J., Morera-Dutrey, C., Brendel, O., Porth, I., Guehl, J.M., Villani, F., and Kremer, A. (2006). Comparison of quantitative trait loci for adaptive traits between oak and chestnut based on an expressed sequence tag consensus map. Genetics **172:** 533–546.

Chevalier, F., Martin, O., Rofidal, V., Devauchelle, A.D., Barteau, S., Sommerer, N., and Rossignol, M. (2004). Proteomic investigation of natural variation between Arabidopsis ecotypes. Proteomics **4:** 1372–1381.

Clark, R.M., Wagler, T.N., Quijada, P. (2006). A distant upstream enhancer at the maize domestication gene tb1 has pleiotropic effects on plant and inflorescence architecture. Nat. Genet. **38:** 594–597.

Clark, R.M., et al. (2007). Common sequence polymorphisms shaping genetic diversity in *Arabidopsis thaliana.* Science **317:** 338–342.

Clauss, M.J., and Koch, M.A. (2006). Poorly known relatives of *Arabidopsis thaliana.* Trends Plant Sci. **11:** 449–459.

Clegg, M.T., and Durbin, M.L. (2003). Tracing floral adaptations from ecology to molecules. Nat. Rev. Genet. **4:** 206–215.

Clerkx, E.J.M., El Lithy, M.E., Vierling, E., Ruys, G.J., Blankestijin-De Vries, H., Groot, S.P.C., Vreugdenhil, D., and Koornneef, M. (2004). Analysis of natural allelic variation of Arabidopsis seed germination and seed longevity traits between the accessions Landsberg *erecta* and Shakdara, using a new recombinant inbred line population. Plant Physiol. **135:** 432–443.

Cong, B., Barrero, L.S., and Tanksley, S.D. (2008). Regulatory change in YABBY-like transcription factor led to evolution of extreme fruit size during tomato domestication. Nat. Genet. **40:** 800–804.

Courbot, M., Willems, G., Motte, P., Arvidsson, S., Roosens, N., Saumitou-Laprade, P., and Verbruggen, N. (2007). A major quantitative trait locus for cadmium tolerance in *Arabidopsis halleri* colocalizes with HMA4, a gene encoding a heavy metal ATPase. Plant Physiol. **144:** 1052–1065.

Cross, J.M., von Korff, M., Altmann, T., Bartzetko, L., Sulpice, R., Gibon, Y., Palacios, N., and Stitt, M. (2006). Variation of enzyme activities and metabolite levels in 24 Arabidopsis accessions growing in carbon-limited conditions. Plant Physiol. **142:** 1574–1588.

Cubas, P., Vincent, C., and Coen, E. (1999). An epigenetic mutation responsible for natural variation in floral symmetry. Nature **401:** 157–161.

Deniau, A., Pieper, B., Ten Bookum, W., Lindhout, P., Aarts, M., and Schat, H. (2006). QTL analysis of cadmium and zinc accumulation in the heavy metal hyperaccumulator *Thlaspi caerulescens.* Theor. Appl. Genet. **113:** 907–920.

Distelfeld, A., Li, C., and Dubcovsky, J. (2009a). Regulation of flowering in temperate cereals. Curr. Opin. Plant Biol. **12:** 178–184.

Distelfeld, A., Tranquilli, G., Li, C., Yan, L., and Dubcovsky, J. (2009b). Genetic and molecular characterization of the VRN2 loci in tetraploid wheat. Plant Physiol. **149:** 245–257.

Doebley, J.F., Gaut, B.S., and Smith, B.D. (2006). The molecular genetics of crop domestication. Cell **127:** 1309–1321.

Doerge, R.W. (2002). Mapping and analysis of quantitative trait loci in experimental populations. Nat. Rev. Genet. **3:** 43–52.

Doi, K., Izawa, T., Fuse, T., Yamanouchi, U., Kubo, T., Shimatani, Z., Yano, M., and Yoshimura, A. (2004). Ehd1, a B-type response regulator in rice, confers short-day promotion of flowering and controls FT-like gene expression independently of Hd1. Genes Dev. **18:** 926–936.

Doyle, M.R., Bizzell, C.M., Keller, M.R., Michaels, S.D., Song, J., Noh, Y.S., and Amasino, R.M. (2005). HUA2 is required for the expression of floral repressors in *Arabidopsis thaliana.* Plant J. **41:** 376–385.

Druka, A., et al. (2008). Towards systems genetic analyses in barley: Integration of phenotypic, expression and genotype data into GeneNetwork. BMC Genet. **9:** 73.

Dubcovsky, J., and Dvorak, J. (2007). Genome plasticity a key factor in

the success of polyploid wheat under domestication. Science **316:** 1862–1866.

Ducrocq, S., Madur, D., Veyrieras, J.B., Camus-Kulandaivelu, L., Kloiber-Maitz, M., Presterl, T., Ouzunova, M., Manicacci, D., and Charcosset, A. (2008). Key impact of Vgt1 on flowering time adaptation in maize: Evidence from association mapping and ecogeographical information. Genetics **178:** 2433–2437.

El-Assal, E.-D.S., Alonso-Blanco, C., Peeters, A.J.M., Raz, V., and Koornneef, M. (2001). A QTL for flowering time in Arabidopsis reveals a novel allele of *CRY2.* Nat. Genet. **29:** 435–440.

Fan, C., Xing, Y., Mao, H., Lu, T., Han, B., Xu, C., Li, X., and Zhang, Q. (2006). GS3, a major QTL for grain length and weight and minor QTL for grain width and thickness in rice, encodes a putative transmembrane protein. Theor. Appl. Genet. **112:** 1164–1171.

Faure, S., Higgins, J., Turner, A., and Laurie, D.A. (2007). The *FLOWERING LOCUS T-like* gene family in barley (*Hordeum vulgare*). Genetics **176:** 599–609.

Fernie, A.R., and Schauer, N. (2009). Metabolomics-assisted breeding: A viable option for crop improvement? Trends Genet. **25:** 39–48.

Filiault, D.L., Wessinger, C.A., Dinneny, J.R., Lutes, J., Borevitz, J.O., Weigel, D., Chory, J., and Maloof, J.N. (2008). Amino acid polymorphisms in Arabidopsis phytochrome B cause differential responses to light. Proc. Natl. Acad. Sci. USA **105:** 3157–3162.

Fitz Gerald, J.N., Lehti-Shiu, M.D., Ingram, P.A., Deak, K.I., Biesiada, T., and Malamy, J.E. (2006). Identification of quantitative trait loci that regulate Arabidopsis root system size and plasticity. Genetics **172:** 485–498.

Foucher, F., Morin, J., Courtiade, J., Cadioux, S., Ellis, N., Banfield, M.J., and Rameau, C. (2003). DETERMINATE and LATE FLOWERING are two TERMINAL FLOWER1/CENTRORADIALIS homologs that control two distinct phases of flowering initiation and development in pea. Plant Cell **15:** 2742–2754.

Frary, A., Nesbitt, T.C., Grandillo, S., Knaap, E., Cong, B., Liu, J., Meller, J., Elber, R., Alpert, K.B., and Tanksley, S.D. (2000). fw2.2: A quantitative trait locus key to the evolution of tomato fruit size. Science **289:** 85–88.

Frascaroli, E., Cane, M.A., Landi, P., Pea, G., Gianfranceschi, L., Villa, M., Morgante, M., and Pe, M.E. (2007). Classical genetic and quantitative trait loci analyses of heterosis in a maize hybrid between two elite inbred lines. Genetics **176:** 625–644.

Frewen, B.E., Chen, T.H., Howe, G.T., Davis, J., Rohde, A., Boerjan, W., and Bradshaw, H.D., Jr. (2000). Quantitative trait loci and candidate gene mapping of bud set and bud flush in populus. Genetics **154:** 837–845.

Fridman, E., Carrari, F., Liu, Y.S., Fernie, A.R., and Zamir, D. (2004). Zooming in on a quantitative trait for tomato yield using interspecific introgressions. Science **305:** 1786–1789.

Fu, D., Szucs, P., Yan, L., Helguera, M., Skinner, J.S., von Zitzewitz, J., Hayes, P.M., and Dubcovsky, J. (2005). Large deletions within the first intron in VRN-1 are associated with spring growth habit in barley and wheat. Mol. Genet. Genomics **273:** 54–65.

Fu, H., and Dooner, H.K. (2002). Intraspecific violation of genetic colinearity and its implications in maize. Proc. Natl. Acad. Sci. USA **99:** 9573–9578.

Fu, J., et al. (2009). System-wide molecular evidence for phenotypic buffering in Arabidopsis. Nat. Genet. **41:** 166–167.

Fujino, K., Sekiguchi, H., Matsuda, Y., Sugimoto, K., Ono, K., and Yano, M. (2008). Molecular identification of a major quantitative trait locus, qLTG3-1, controlling low-temperature germinability in rice. Proc. Natl. Acad. Sci. USA **105:** 12623–12628.

Garcia-Oliveira, A.L., Tan, L., Fu, Y., and Sun, C. (2009). Genetic identification of quantitative trait loci for contents of mineral nutrients in rice grain. J. Integr. Plant Biol. **51:** 84–92.

Gazzani, S., Gendall, A.R., Lister, C., and Dean, C. (2003). Analysis of the molecular basis of flowering time variation in Arabidopsis accessions. Plant Physiol. **132:** 1107–1114.

Ghandilyan, A., Ilk, N., Hanhart, C., Mbengue, M., Barboza, L., Schat, H., Koornneef, M., El-Lithy, M., Vreugdenhil, D., Reymond, M., and Aarts, M.G.M. (2009). A strong effect of growth medium and organ type on the identification of QTLs for phytate and mineral concentrations in three *Arabidopsis thaliana* RIL populations. J. Exp. Bot. **60:** 1409–1425.

Ghandilyan, A., Vreugdenhil, D., and Aarts, M.G.M. (2006). Progress in the genetic understanding of plant iron and zinc nutrition. Physiol. Plant. **126:** 407–417.

González-Martinez, S.C., Krutovsky, K.V., and Neale, D.B. (2006). Forest-tree population genomics and adaptive evolution. New Phytol. **170:** 227–238.

Gu, X.Y., Kianian, S.F., Hareland, G.A., Hoffer, B.L., and Foley, M.E. (2005). Genetic analysis of adaptive syndromes interrelated with seed dormancy in weedy rice (*Oryza sativa*). Theor. Appl. Genet. **110:** 1108–1118.

Gu, X.Y., Turnipseed, E.B., and Foley, M.E. (2008). The *qSD12* locus controls offspring tissue-imposed seed dormancy in rice. Genetics **179:** 2263–2273.

Hall, M.C., Dworkin, I., Ungerer, M.C., and Purugganan, M. (2007). Genetics of microenvironmental canalization in *Arabidopsis thaliana*. Proc. Natl. Acad. Sci. USA **104:** 13717–13722.

Hanikenne, M., Talke, I.N., Haydon, M.J., Lanz, C., Nolte, A., Motte, P., Kroymann, J., Weigel, D., and Krämer, U. (2008). Evolution of metal hyperaccumulation required cis-regulatory changes and triplication of HMA4. Nature **453:** 391–395.

Harada, H., Kuromori, T., Hirayama, T., Shinozaki, K., and Leigh, R.A. (2004). Quantitative trait loci analysis of nitrate storage in Arabidopsis leading to an investigation of the contribution of the anion channel gene, AtCLC-c, to variation in nitrate levels. J. Exp. Bot. **55:** 2005–2014.

Harada, H., and Leigh, R.A. (2006). Genetic mapping of natural variation in potassium concentrations in shoots of *Arabidopsis thaliana.* J. Exp. Bot. **57:** 953–960.

Hauser, M.-T., Harr, B., and Schlötterer, C. (2001). Trichome distribution in *Arabidopsis thaliana* and its close relative *Arabidopsis lyrata*: Molecular analysis of the candidate gene *GLABROUS1.* Mol. Biol. Evol. **18:** 1754–1763.

He, Y., Doyle, M.R., and Amasino, R.M. (2004). PAF1-complex-mediated histone methylation of FLOWERING LOCUS C chromatin is required for the vernalization-responsive, winter-annual habit in Arabidopsis. Genes Dev. **18:** 2774–2784.

Hirai, M.Y., Yano, M., Goodenowe, D.B., Kanaya, S., Kimura, T., Awazuhara, M., Arita, M., Fujiwara, T., and Saito, K. (2004). Integration of transcriptomics and metabolomics for understanding of global responses to nutritional stresses in *Arabidopsis thaliana.* Proc. Natl. Acad. Sci. USA **101:** 10205–10210.

Holub, E.B. (2007). Natural variation in innate immunity of a pioneer species. Curr. Opin. Plant Biol. **10:** 415–424.

Hori, K., Sato, K., and Takeda, K. (2007). Detection of seed dormancy QTL in multiple mapping populations derived from crosses involving novel barley germplasm. Theor. Appl. Genet. **115:** 869–876.

Imtiaz, M., Ogbonnaya, F.C., Oman, J., and van Ginkel, M. (2008). Characterization of quantitative trait loci controlling genetic variation for preharvest sprouting in synthetic backcross-derived wheat lines. Genetics **178:** 1725–1736.

Ishimaru, K., Kobayashi, N., Ono, K., Yano, M., and Ohsugi, R. (2001). Are contents of Rubisco, soluble protein and nitrogen in flag leaves of rice controlled by the same genetics? J. Exp. Bot. **52:** 1827–1833.

Isshiki, M., Morino, K., Nakajima, M., Okagaki, R.J., Wessler, S.R., Izawa, T., and Shimamoto, K. (1998). A naturally occurring functional allele of the rice waxy locus has a GT to TT mutation at the 5′ splice site of the first intron. Plant J. **15:** 133–138.

Izawa, T. (2007). Adaptation of flowering-time by natural and artificial selection in Arabidopsis and rice. J. Exp. Bot. **58:** 3091–3097.

Izawa, T., Konishi, S., Shomura, A., and Yano, M. (2009). DNA changes tell us about rice domestication. Curr. Opin. Plant Biol. **12:** 185–192.

Jaillon, O., et al. (2007). The grapevine genome sequence suggests ancestral hexaploidization in major angiosperm phyla. Nature **449:** 463–467.

Jansen, R.C., and Nap, J.P. (2001). Genetical genomics: The added value from segregation. Trends Genet. **17:** 388–391.

Jansen, R.C., Tesson, B.M., Fu, J., Yang, Y., and McIntyre, L.M. (2009). Defining gene and QTL networks. Curr. Opin. Plant Biol. **12:** 241–246.

Jiménez-Gomez, J.M., Alonso-Blanco, C., Borja, A., Anastasio, G., Angosto, T., Lozano, R., and Martinez-Zapater, J.M. (2007). Quantitative genetic analysis of flowering time in tomato. Genome **50:** 303–315.

Johannes, F., Colot, V., and Jansen, R.C. (2008). Epigenome dynamics: A quantitative genetics perspective. Nat. Rev. Genet. **9:** 883–890.

Johanson, U., West, J., Lister, C., Michaels, S., Amasino, R., and Dean, C. (2000). Molecular analysis of FRIGIDA, a major determinant of natural variation in Arabidopsis flowering time. Science **290:** 344–347.

Joppa, L.R., Du, C., Hart, G.A., and Hareland, G.A. (1997). Mapping gene(s) for grain protein in tetraploid wheat (*Triticum turgidum* L.) using a population of recombinant inbred chromosome lines. Crop Sci. **37:** 1586–1589.

Jorgensen, S., and Mauricio, R. (2004). Neutral genetic variation among wild North American populations of the weedy plant *Arabidopsis thaliana* is not geographically structured. Mol. Ecol. **13:** 3403–3413.

Juenger, T., Pérez-Pérez, J.M., Bernal, S., and Micol, J.L. (2005). Quantitative trait loci mapping of floral and leaf morphology traits in *Arabidopsis thaliana*: Evidence for modular genetic architecture. Evol. Dev. **7:** 259–271.

Juenger, T., Purugganan, M., and Mackay, T.F.C. (2000). Quantitative trait loci for floral morphology in *Arabidopsis thaliana.* Genetics **156:** 1379–1392.

Keurentjes, J.J.B. (2009). Genetical metabolomics: closing in on phenotypes. Curr. Opin. Plant Biol. **12:** 223–230.

Keurentjes, J.J.B., Fu, J., de Vos, C.H., Lommen, A., Hall, R.D., Bino, R.J., van der Plas, L.H.W., Jansen, R.C., Vreugdenhil, D., and Koornneef, M. (2006). The genetics of plant metabolism. Nat. Genet. **38:** 842–849.

Keurentjes, J.J.B., Fu, J., Terpstra, I.R., Garcia, J.M., van den Ackerveken, G., Snoek, L.B., Peeters, A.J.M., Vreugdenhil, D., Koornneef, M., and Jansen, R.C. (2007). Regulatory network construction in Arabidopsis by using genome-wide gene expression quantitative trait loci. Proc. Natl. Acad. Sci. USA **104:** 1708–1713.

Keurentjes, J.J.B., Koornneef, M., and Vreugdenhil, D. (2008a). Quantitative genetics in the age of omics. Curr. Opin. Plant Biol. **11:** 123–128.

Keurentjes, J.J.B., Sulpice, R., Gibon, Y., Steinhauser, M.C., Fu, J., Koornneef, M., Stitt, M., and Vreugdenhil, D. (2008b). Integrative analyses of genetic variation in enzyme activities of primary carbohydrate metabolism reveal distinct modes of regulation in *Arabidopsis thaliana.* Genome Biol. **9:** R129.

Kikuchi, R., Kawahigashi, H., Ando, T., Tonooka, T., and Handa, H. (2009). Molecular and functional characterization of *PEBP* genes in barley reveal the diversification of their roles in flowering. Plant Physiol. **149:** 1341–1353.

Kitano, H. (2004). Biological robustness. Nat. Rev. Genet. **5:** 826–837.

Kliebenstein, D.J. (2009a). Advancing genetic theory and application by metabolic QTL analysis. Plant Cell **21:** 1637–1646.

Kliebenstein, D.J. (2009b). Quantitative genomics: Analyzing intraspecific variation using global gene expression polymorphisms or eQTLs. Annu. Rev. Plant Biol. **60:** 93–114.

Kliebenstein, D.J., Kroymann, J., Brown, P., Figuth, A., Pedersen, D., Gershenzon, J., and Mitchell-Olds, T. (2001). Genetic control of natural variation in Arabidopsis glucosinolate accumulation. Plant Physiol. **126:** 811–825.

Kliebenstein, D.J., West, M.A., van Leeuwen, H., Kim, K., Doerge, R.W., Michelmore, R.W., and St Clair, D.A. (2006a). Genomic survey of gene expression diversity in *Arabidopsis thaliana.* Genetics **172:** 1179–1189.

Kliebenstein, D.J., West, M.A., van Leeuwen, H., Loudet, O., Doerge, R.W., and St Clair, D.A. (2006b). Identification of QTLs controlling gene expression networks defined a priori. BMC Bioinformatics **7:** 308.

Kobayashi, Y., Kuroda, K., Kimura, K., Southron-Francis, J.L., Furuzawa, A., Kimura, K., Iuchi, S., Kobayashi, M., Taylor, G.J., and Koyama, H. (2008). Amino acid polymorphisms in strictly conserved domains of a P-type ATPase HMA5 are involved in the mechanism of copper tolerance variation in Arabidopsis. Plant Physiol. **148:** 969–980.

Kojima, S., Takahashi, Y., Kobayashi, Y., Monna, L., Sasaki, T., Araki, T., and Yano, M. (2002). Hd3a, a rice ortholog of the Arabidopsis FT gene, promotes transition to flowering downstream of Hd1 under short-day conditions. Plant Cell Physiol. **43:** 1096–1105.

Kole, C., Quijada, P., Michael, S.D., Amasino, R., and Osborn, T.C. (2001). Evidence for homology of flowering-time genes *VFR2* from *Brassica rapa* and *FLC* from *Arabidopsis thaliana.* Theor. Appl. Genet. **102:** 425–430.

Komatsuda, T., et al. (2007). Six-rowed barley originated from a mutation in a homeodomain-leucine zipper I-class homeobox gene. Proc. Natl. Acad. Sci. USA **104:** 1424–1429.

Konishi, S., Izawa, T., Lin, S.Y., Ebana, K., Fukuta, Y., Sasaki, T., and Yano, M. (2006). An SNP caused loss of seed shattering during rice domestication. Science **312:** 1392–1396.

Koornneef, M., Alonso-Blanco, C., and Vreugdenhil, D. (2004). Naturally occurring genetic variation in *Arabidopsis thaliana.* Annu. Rev. Plant Biol. **55:** 141–172.

Korves, T.M., Schmid, K.J., Caicedo, A.L., Mays, C., Stinchcombe, J.R., Purugganan, M.D., and Schmitt, J. (2007). Fitness effects associated with the major flowering time gene FRIGIDA in *Arabidopsis thaliana* in the field. Am. Nat. **169:** E141–E157.

Kramer, E.M. (2009). Aquilegia: A new model for plant development, ecology, and evolution. Annu. Rev. Plant Biol. **60:** 261–277.

Kroymann, J., and Mitchell-Olds, T. (2005). Epistasis and balanced polymorphism influencing complex trait variation. Nature **435:** 95–98.

Kuittinen, H., Niittyvuopio, A., Rinne, P., and Savolainen, O. (2008). Natural variation in *Arabidopsis lyrata* vernalization requirement conferred by a FRIGIDA indel polymorphism. Mol. Biol. Evol. **25:** 319–329.

Kusterer, B., Muminovic, J., Utz, H.F., Piepho, H.-P., Barth, S., Heckenberger, M., Meyer, R.C., Altmann, T., and Melchinger, A.E. (2007). Analysis of a triple testcross design with recombinant inbred lines reveals a significant role of epistasis in heterosis for biomass-related traits in Arabidopsis. Genetics **175:** 2009–2017.

Laserna, M.P., Sanchez, R.A., and Botto, J.F. (2008). Light-related loci controlling seed germination in L*er* x Cvi and Bay-0 x Sha recombinant inbred-line populations of *Arabidopsis thaliana.* Ann. Bot. (Lond.) **102:** 631–642.

Le Corre, V. (2005). Variation at two flowering time genes within and among populations of *Arabidopsis thaliana*: Comparison with markers and traits. Mol. Ecol. **14:** 4181–4192.

Le Corre, V., Roux, F., and Reboud, X. (2002). DNA polymorphism at the FRIGIDA gene in *Arabidopsis thaliana*: Extensive nonsynonymous variation is consistent with local selection for flowering time. Mol. Biol. Evol. **19:** 1261–1271.

Lempe, J., Balasubramanian, S., Sureshkumar, S., Singh, A., Schmid, M., and Weigel, D. (2005). Diversity of flowering responses in wild *Arabidopsis thaliana* strains. PLoS Genet. **1:** 109–118.

Li, C., Zhou, A., and Sang, T. (2006). Rice domestication by reducing shattering. Science **311:** 19361939.

Li, L., Strahwald, J., Hofferbert, H.-R., Lubeck, J., Tacke, E., Junghans, H., Wunder, J., and Gebhardt, C. (2005). DNA variation at the invertase locus *invGE/GF* is associated with tuber quality traits in populations of potato breeding clones. Genetics **170:** 813–821.

Li, Z.K., Luo, L.J., Mei, H.W., Wang, D.L., Shu, Q.Y., Tabien, R., Zhong, D.B., Ying, C.S., Stansel, J.W., Khush, G.S., and Paterson, A.H. (2001). Overdominant epistatic loci are the primary genetic basis of inbreeding depression and heterosis in rice. I. Biomass and grain yield. Genetics **158:** 1737–1753.

Lin, H.X., Zhu, M.Z., Yano, M., Gao, J.P., Liang, Z.W., Su, W.A., Hu, X.H., Ren, Z.H., and Chao, D.Y. (2004). QTLs for Na^+ and K^+ uptake of the shoots and roots controlling rice salt tolerance. Theor. Appl. Genet. **108:** 253–260.

Lin, S.Y., Sasaki, T., and Yano, M. (1998). Mapping quantitative trait loci controlling seed dormancy and heading date in rice, *Oryza sativa L.*, using backcross inbred lines. Theor. Appl. Genet. **96:** 997–1003.

Lisec, J., Meyer, R.C., Steinfath, M., Redestig, H., Becher, M., Witucka-Wall, H., Fiehn, O., Torjek, O., Selbig, J., Altmann, T., and Willmitzer, L. (2008). Identification of metabolic and biomass QTL in *Arabidopsis thaliana* in a parallel analysis of RIL and IL populations. Plant J. **53:** 960–972.

Liu, J., Van Eck, J., Cong, B., and Tanksley, S.D. (2002). A new class of regulatory genes underlying the cause of pear-shaped tomato fruit. Proc. Natl. Acad. Sci. USA **99:** 13302–13306.

Liu, P., Sherman-Broyles, S., Nasrallah, M.E., and Nasrallah, J.B. (2007). A cryptic modifier causing transient self-incompatibility in *Arabidopsis thaliana.* Curr. Biol. **17:** 734–740.

Loudet, O., Chaillou, S., Merigout, P., Talbotec, J., and Daniel-Vedele, F. (2003). Quantitative trait loci analysis of nitrogen use efficiency in Arabidopsis. Plant Physiol. **131:** 345–358.

Loudet, O., Gaudon, V., Trubuil, A., and Daniel-Vedele, F. (2005). Quantitative trait loci controlling root growth and architecture in *Arabidopsis thaliana* confirmed by heterogeneous inbred family. Theor. Appl. Genet. **110:** 742–753.

Loudet, O., Michael, T.P., Burger, B.T., Le Metté, C., Mockler, T.C., Weigel, D., and Chory, J. (2008). A zinc knuckle protein that negatively controls morning-specific growth in *Arabidopsis thaliana.* Proc. Natl. Acad. Sci. USA **105:** 17193–17198.

Loudet, O., Saliba-Colombani, V., Camilleri, C., Calenge, F., Gaudon, V., Koprivova, A., North, K.A., Kopriva, S., and Daniel-Vedele, F. (2007). Natural variation for sulfate content in *Arabidopsis thaliana* is highly controlled by APR2. Nat. Genet. **39:** 896–900.

Macquet, A., Ralet, M.-C., Loudet, O., Kronenberger, J., Mouille, G., Marion-Poll, A., and North, H.M. (2007). A naturally occurring mutation in an *Arabidopsis* accession affects a β-D-falactosidase that increases the hydrophilic potential of rhamnogalacturonan I in seed mucilage. Plant Cell **19:** 3990–4006.

Maloof, J.N., Borevitz, J.O., Dabi, T., Lutes, J., Nehring, R.B., Redfern, J.L., Trainer, G.T., Wilson, J.M., Asami, T., Berry, C.C., Weigel, D., and Chory, J. (2001). Natural variation in light sensitivity of Arabidopsis. Nat. Genet. **29:** 441–446.

Manning, K., Tor, M., Poole, M., Hong, Y., Thompson, A.J., King, G.J., Giovannoni, J.J., and Seymour, G.B. (2006). A naturally occurring epigenetic mutation in a gene encoding an SBP-box transcription factor inhibits tomato fruit ripening. Nat. Genet. **38:** 948–952.

Melchinger, A.E., Piepho, H.-P., Utz, H.F., Muminovic, J., Wegenast, T., Torjek, O., Altmann, T., and Kusterer, B. (2007). Genetic basis of heterosis for growth-related traits in Arabidopsis investigated by testcross progenies of near-isogenic lines reveals a significant role of epistasis. Genetics **177:** 1827–1837.

Menéndez, C.M., Ritter, E., Schäfer-Pregl, R., Walkemeier, B., Kalde, A., Salamini, F., and Gebhardt, C. (2002). Cold sweetening in diploid potato: mapping quantitative trait loci and candidate genes. Genetics **162:** 1423–1434.

Meng, P.H., Macquet, A., Loudet, O., Marion-Poll, A., and North, H. (2008). Analysis of natural allelic variation controlling *Arabidopsis thaliana* seed germinability in respons to cold and dral: Identification of three major quantitative trait loci. Mol. Plant **1:** 145–154.

Meyer, R.C., Steinfath, M., Lisec, J., Becher, M., Witucka-Wall, H., Torjek, O., Fiehn, O., Eckardt, A., Willmitzer, L., Selbig, J., and Altmann, T. (2007). The metabolic signature related to high plant growth rate in *Arabidopsis thaliana.* Proc. Natl. Acad. Sci. USA **104:** 4759–4764.

Michaels, S.D., and Amasino, R.M. (1999). *FLOWERING LOCUS C* encodes a novel MADS domain protein that acts as a repressor of flowering. Plant Cell **11:** 949–956.

Michaels, S.D., He, Y., Scortecci, K.C., and Amasino, R.M. (2003). Attenuation of FLOWERING LOCUS C activity as a mechanism for the evolution of summer-annual flowering behavior in Arabidopsis. Proc. Natl. Acad. Sci. USA **100:** 10102–10107.

Mitchell-Olds, T., and Pedersen, D. (1998). The molecular basis of quantitative genetic variation in central and secondary metabolism in Arabidopsis. Genetics **149:** 739–747.

Mitchell-Olds, T., and Schmitt, J. (2006). Genetic mechanisms and evolutionary significance of natural variation in Arabidopsis. Nature **441:** 947–952.

Mitchell-Olds, T., Willis, J.H., and Goldstein, D.B. (2007). Which evolutionary processes influence natural genetic variation for phenotypic traits? Nat. Rev. Genet. **8:** 845–856.

Morgante, M., De Paoli, E., and Radovic, S. (2007). Transposable elements and the plant pan-genomes. Curr. Opin. Plant Biol. **10:** 149–155.

Mouchel, C.L.F., Briggs, G.C., and Hardtke, C.S. (2004). Natural genetic variation in Arabidopsis identifies *BREVIS RADIX*, a novel regulator of cell proliferation and elongation in the root. Genes Dev. **18:** 700–714.

Myles, S., Peiffer, J., Brown, P., Ersoz, E., Zhang, Z., Costich, D.E., and Buckler, E.S. (2009). Association mapping: critical considerations shift from genotyping to experimental design. Plant Cell **21:** in press.

Nordborg, M., and Weigel, D. (2008). Next-generation genetics in plants. Nature **456:** 720–723.

O'Neill, C., Morgan, C., Kirby, J., Tschoep, H., Deng, P., Brennan, M., Rosas, U., Fraser, F., Hall, C., Gill, S., and Bancroft, I. (2008). Six new recombinant inbred populations for the study of quantitative traits in *Arabidopsis thaliana.* Theor. Appl. Genet. **116:** 623–634.

Olsen, K.M., Halldorsdottir, S.S., Stinchcombe, J.R., Weinig, C., Schmitt, J., and Purugganan, M.D. (2004). Linkage disequilibrium mapping of Arabidopsis *CRY2* flowering time alleles. Genetics **167:** 1361–1369.

Olsen, K.M., and Purugganan, M.D. (2002). Molecular evidence on the origin and evolution of glutinous rice. Genetics **162:** 941–950.

Orsi, C.H., and Tanksley, S.D. (2009). Natural variation in an ABC transporter gene associated with seed size evolution in tomato species. PLoS Genet. **5:** e1000347.

Page, D.R., and Grossniklaus, U. (2002). The art and design of genetic screens: *Arabidopsis thaliana.* Nat. Rev. Genet. **3:** 124–136.

Panthee, D., Pantalone, V., Sams, C., Saxton, A., West, D., Orf, J., and Killam, A. (2006). Quantitative trait loci controlling sulfur containing amino acids, methionine and cysteine, in soybean seeds. Theor. Appl. Genet. **112:** 546–553.

Peng, J., et al. (1999). 'Green revolution' genes encode mutant gibberellin response modulators. Nature **400:** 256–261.

Pérez-Pérez, J.M., Serrano-Cartagena, J., and Micol, J.L. (2002). Genetic analysis of natural variations in the architecture of *Arabidopsis thaliana* vegetative leaves. Genetics **162:** 893–915.

Picó, F.X., Mendez-Vigo, B., Martinez-Zapater, J.M., and Alonso-Blanco, C. (2008). Natural genetic variation of *Arabidopsis thaliana* is geographically structured in the Iberian peninsula. Genetics **180:** 1009–1021.

Potokina, E., Druka, A., Luo, Z., Moscou, M., Wise, R., Waugh, R., and Kearsey, M. (2008a). Tissue-dependent limited pleiotropy affects gene expression in barley. Plant J. **56:** 287–296.

Potokina, E., Druka, A., Luo, Z., Wise, R., Waugh, R., and Kearsey, M. (2008b). Gene expression quantitative trait locus analysis of 16,000 barley genes reveals a complex pattern of genome-wide transcriptional regulation. Plant J. **53:** 90–101.

Pourkheirandish, M., and Komatsuda, T. (2007). The importance of barley genetics and domestication in a global perspective. Ann. Bot. (Lond.) **100:** 999–1008.

Purugganan, M.D., and Fuller, D.Q. (2009). The nature of selection during plant domestication. Nature **457:** 843–848.

Queitsch, C., Sangster, T.A., and Lindquist, S. (2002). Hsp90 as a capacitor of phenotypic variation. Nature **417:** 618–624.

Radoev, M., Becker, H.C., and Ecke, W. (2008). Genetic analysis of heterosis for yield and yield components in rapeseed (*Brassica napus* L.) by quantitative trait locus mapping. Genetics **179:** 1547–1558.

Ren, Z.-H., Gao, J.-P., Li, L.-G., Cai, X.-L., Huang, W., Chao, D.-Y., Zhu, M.-Z., Wang, Z.-Y., Luan, S., and Lin, H.-X. (2005). A rice quantitative trait locus for salt tolerance encodes a sodium transporter. Nat. Genet. **37:** 1141–1146.

Riddle, N.C. and Richards, E.J. (2005). Genetic variation in epigenetic inheritance of ribosomal RNA gene methylation in Arabidopsis. Plant J. **41:** 524–532.

Rieseberg, L.H., Raymond, O., Rosenthal, D.M., Lai, Z., Livingstone, K., Nakazato, T., Durphy, J.L., Schwarzbach, A.E., Donovan, L.A., and Lexer, C. (2003). Major ecological transitions in wild sunflowers facilitated by hybridization. Science **301:** 1211–1216.

Roux, F., Touzet, P., Cuguen, J., and Le Corre, V. (2006). How to be early flowering: An evolutionary perspective. Trends Plant Sci. **11:** 375–381.

Rowe, H.C., Hansen, B.G., Halkier, B.A., and Kliebenstein, D.J. (2008). Biochemical networks and epistasis shape the *Arabidopsis thaliana* metabolome. Plant Cell **20:** 1199–1216.

Rus, A., Baxter, I., Muthukumar, B., Gustin, J., Lahner, B., Yakubova, E., and Salt, D.E. (2006). Natural variants of *AtHKT1* enhance Na^+ accumulation in two wild populations of Arabidopsis. PLoS Genet. **2:** e210.

Sakamoto, T. and Matsuoka, M. (2008). Identifying and exploiting grain yield genes in rice. Curr. Opin. Plant Biol. **11:** 209–214.

Salamini, F., Ozkan, H., Brandolini, A., Schafer-Pregl, R., and Martin, W. (2002). Genetics and geography of wild cereal domestication in the near east. Nat. Rev. Genet. **3:** 429–441.

Salt, D.E., Baxter, I., and Lahner, B. (2008). Ionomics and the study of the plant ionome. Annu. Rev. Plant Biol. **59:** 709–733.

Salvi, S., et al. (2007). Conserved noncoding genomic sequences associated with a flowering-time quantitative trait locus in maize. Proc. Natl. Acad. Sci. USA **104:** 11376–11381.

Sang, T. (2009). Genes and mutations underlying domestication transitions in grasses. Plant Physiol. **149:** 63–70.

Sangster, T.A., Salathia, N., Undurraga, S., Milo, R., Schellenberg, K., Lindquist, S., and Queitsch, C. (2008). HSP90 affects the expression of genetic variation and developmental stability in quantitative traits. Proc. Natl. Acad. Sci. USA **105:** 2963–2968.

Scarcelli, N., Cheverud, J.M., Schaal, B.A., and Kover, P.X. (2007). Antagonistic pleiotropic effects reduce the potential adaptive value of the *FRIGIDA* locus. Proc. Natl. Acad. Sci. USA **104:** 16986–16991.

Schadt, E.E., et al. (2003). Genetics of gene expression surveyed in maize, mouse and man. Nature **422:** 297–302.

Schauer, N., Semel, Y., Balbo, I., Steinfath, M., Repsilber, D., Selbig, J., Pleban, T., Zamir, D., and Fernie, A.R. (2008). Mode of inheritance of primary metabolic traits in tomato. Plant Cell **20:** 509–523.

Schauer, N., et al. (2006). Comprehensive metabolic profiling and phenotyping of interspecific introgression lines for tomato improvement. Nat. Biotechnol. **24:** 447–454.

Schläppi, M.R. (2006). FRIGIDA LIKE 2 is a functional allele in Landsberg erecta and compensates for a nonsense allele of FRIGIDA LIKE 1. Plant Physiol. **142:** 1728–1738.

Schmid, K.J., Torjek, O., Meyer, R., Schmuths, H., Hoffmann, M.H., and Altmann, T. (2006). Evidence for a large-scale population structure of *Arabidopsis thaliana* from genome-wide single nucleotide polymorphism markers. Theor. Appl. Genet. **112:** 1104–1114.

Schranz, M.E., Quijada, P., Sung, S.B., Lukens, L., Amasino, R., and Osborn, T.C. (2002). Characterization and effects of the replicated flowering time gene *FLC* in *Brassica rapa.* Genetics **162:** 1457–1468.

Semel, Y., Nissenbaum, J., Menda, N., Zinder, M., Krieger, U., Issman, N., Pleban, T., Lippman, Z., Gur, A., and Zamir, D. (2006). Overdominant quantitative trait loci for yield and fitness in tomato. Proc. Natl. Acad. Sci. USA **103:** 12981–12986.

Sergeeva, L.I., Keurentjes, J.J., Bentsink, L., Vonk, J., van der Plas, L.H., Koornneef, M., and Vreugdenhil, D. (2006). Vacuolar invertase regulates elongation of *Arabidopsis thaliana* roots as revealed by QTL and mutant analysis. Proc. Natl. Acad. Sci. USA **103:** 2994–2999.

Sergeeva, L.I., Vonk, J., Keurentjes, J.J.B., van der Plas, L.H.W., Koornneef, M., and Vreugdenhil, D. (2004). Histochemical analysis reveals organ-specific quantitative trait loci for enzyme activities in Arabidopsis. Plant Physiol. **134:** 237–245.

Shindo, C., Aranzana, M.J., Lister, C., Baxter, C., Nicholls, C., Nordborg, M., and Dean, C. (2005). Role of FRIGIDA and FLOWERING LOCUS C in determining variation in flowering time of Arabidopsis. Plant Physiol. **138:** 1163–1173.

Shindo, C., Bernasconi, G., and Hardtke, C.S. (2008). Intraspecific competition reveals conditional fitness effects of single gene polymorphism at the Arabidopsis root growth regulator *BRX.* New Phytol. **180:** 71–80.

Shindo, C., Lister, C., Crevillen, P., Nordborg, M., and Dean, C. (2006). Variation in the epigenetic silencing of FLC contributes to natural variation in Arabidopsis vernalization response. Genes Dev. **20:** 3079–3083.

Simons, K.J., Fellers, J.P., Trick, H.N., Zhang, Z., Tai, Y.S., and Faris, J.D. (2006). Molecular characterization of the major wheat domestication gene Q. Genetics **172:** 547–555.

Song, R., and Messing, J. (2003). Gene expression of a gene family in maize based on noncollinear haplotypes. Proc. Natl. Acad. Sci. USA **100:** 9055–9060.

Song, X.J., Huang, W., Shi, M., Zhu, M.Z., and Lin, H.X. (2007). A QTL for rice grain width and weight encodes a previously unknown RING-type E3 ubiquitin ligase. Nat. Genet. **39:** 623–630.

Stenoien, H.K., Fenster, C.B., Tonteri, A., and Savolainen, O. (2005). Genetic variability in natural populations of *Arabidopsis thaliana* in northern Europe. Mol. Ecol. **14:** 137–148.

Stinchcombe, J.R., Weinig, C., Ungerer, M., Olsen, K.M., Mays, C., Halldorsdottir, S.S., Purugganan, M.D., and Schmitt, J. (2004). A latitudinal cline in flowering time in *Arabidopsis thaliana* modulated by the flowering time gene FRIGIDA. Proc. Natl. Acad. Sci. USA **101:** 4712–4717.

Sung, S., and Amasino, R.M. (2005). Remembering winter: Toward a molecular understanding of vernalization. Annu. Rev. Plant Biol. **56:** 491–508.

Sureshkumar, S., Todesco, M., Schneeberger, K., Harilal, R., Balasubramanian, S., and Weigel, D. (2009). A genetic defect caused by a triplet repeat expansion in *Arabidopsis thaliana.* Science **323:** 1060–1063.

Sutton, T., Baumann, U., Hayes, J., Collins, N.C., Shi, B.-J., Schnurbush, T., Hay, A., Mayo, G., Pallotta, M., Tester, M., and Langridge, P. (2007). Boron-toxicity tolerance in barley arising from efflux transporter amplification. Science **318:** 1446–1449.

Svistoonoff, S., Creff, A., Reymond, M., Sigoillot-Claude, C., Ricaud, L., Blanchet, A., Nussaume, L., and Desnos, T. (2007). Root tip contact with low-phosphate media reprograms plant root architecture. Nat. Genet. **39:** 792–796.

Sweeney, M.T., Thomson, M.J., Pfeil, B.E., and McCouch, S. (2006). Caught red-handed: Rc encodes a basic helix-loop-helix protein conditioning red pericarp in rice. Plant Cell **18:** 283–294.

Szucs, P., Skinner, J.S., Karsai, I., Cuesta-Marcos, A., Haggard, K.G., Corey, A.E., Chen, T.H., and Hayes, P.M. (2007). Validation of the VRN-H2/VRN-H1 epistatic model in barley reveals that intron length variation in VRN-H1 may account for a continuum of vernalization sensitivity. Mol. Genet. Genomics **277:** 249–261.

Takahashi, Y., Shomura, A., Sasaki, T., and Yano, M. (2001). Hd6, a rice quantitative trait locus involved in photoperiod sensitivity, encodes the alpha subunit of protein kinase CK2. Proc. Natl. Acad. Sci. USA **98:** 7922–7927.

Taketa, S., et al. (2008). Barley grain with adhering hulls is controlled by an ERF family transcription factor gene regulating a lipid biosynthesis pathway. Proc. Natl. Acad. Sci. USA **105:** 4062–4067.

Tanksley, S.D. (2004). The genetic, developmental, and molecular bases of fruit size and shape variation in tomato. Plant Cell **16:** S181–S189.

Teng, S., Rognoni, S., Bentsink, L., and Smeekens, S. (2008). The Arabidopsis GSQ5/DOG1 Cvi allele is induced by the ABA-mediated sugar signalling pathway, and enhances sugar sensitivity by stimulating ABI4 expression. Plant J. **55:** 372–381.

Tian, D., Traw, M.B., Chen, J.Q., Kreitman, M., and Bergelson, J. (2003). Fitness costs of R-gene-mediated resistance in *Arabidopsis thaliana.* Nature **423:** 74–77.

Tohge, T., et al. (2005). Functional genomics by integrated analysis of metabolome and transcriptome of Arabidopsis plants over-expressing an MYB transcription factor. Plant J. **42:** 218–235.

Toomajian, C., Hu, T.T., Aranzana, M.J., Lister, C., Tang, C., Zheng, H., Zhao, K., Calabrese, P., Dean, C., and Nordborg, M. (2006). A nonparametric test reveals selection for rapid flowering in the Arabidopsis genome. PLoS Biol. **4:** e137.

Turner, A., Beales, J., Faure, S., Dunford, R.P., and Laurie, D.A. (2005). The pseudo-response regulator Ppd-H1 provides adaptation to photoperiod in barley. Science **310:** 1031–1034.

Tuskan, G.A., et al. (2006). The genome of black cottonwood, *Populus trichocarpa* (Torr. & Gray). Science **313:** 1596–1604.

Uauy, C., Distelfeld, A., Fahima, T., Blechl, A., and Dubcovsky, J. (2006). A NAC gene regulating senescence improves grain protein, zinc, and iron content in wheat. Science **314:** 1298–1301.

Ueno, D., Kono, I., Yokosho, K., Ando, T., Yano, M., and Ma, J.F. (2009). A major quantitative trait locus controlling cadmium translocation in rice (*Oryza sativa*). New Phytol. **182:** 644–653.

van der Schaar, W., Alonso-Blanco, C., Leon-Kloosterziel, K.M., Jansen, R.C., an Ooijen, J.W., and Koornneef, M. (1997). QTL analysis of seed dormancy in Arabidopsis using recombinant inbred lines and MQM mapping. Heredity **79:** 190–200.

Varagona, M.J., Purugganan, M., and Wessler, S.R. (1992). Alternative splicing induced by insertion of retrotransposons into the maize waxy gene. Plant Cell **4:** 811–820.

Vaughn, M.W., et al. (2007). Epigenetic natural variation in *Arabidopsis thaliana.* PLoS Biol. **5:** e174.

Vreugdenhil, D., Aarts, M.G.M., Koornneef, M., Nelissen, H., and Ernst, W.H.O. (2004). Natural variation and QTL analysis for cationic mineral content in seeds of *Arabidopsis thaliana*. Plant Cell Environ. **27:** 828–839.

Vuylsteke, M., Daele, H., Vercauteren, A., Zabeau, M., and Kuiper, M. (2006). Genetic dissection of transcriptional regulation by cDNA-AFLP. Plant J. **45:** 439–446.

Vuylsteke, M., van Eeuwijk, F., Van Hummelen, P., Kuiper, M., and Zabeau, M. (2005). Genetic analysis of variation in gene expression in *Arabidopsis thaliana.* Genetics **171:** 1267–1275.

Wang, H., Nussbaum-Wagler, T., Li, B., Zhao, Q., Vigouroux, Y., Faller, M., Bomblies, K., Lukens, L., and Doebley, J.F. (2005). The origin of the naked grains of maize. Nature **436:** 714–719.

Wang, Q., Sajja, U., Rosloski, S., Humphrey, T., Kim, M.C., Bomblies, K., Weigel, D., and Grbic, V. (2007). HUA2 caused natural variation in shoot morphology of *A. thaliana.* Curr. Biol. **17:** 1513–1519.

Waters, B.M., and Grusak, M.A. (2008). Whole-plant mineral partitioning throughout the life cycle in *Arabidopsis thaliana* ecotypes Columbia, Landsberg erecta, Cape Verde Islands, and the mutant line ysl1ysl3. New Phytol. **177:** 389–405.

Waugh, R., Jannink, J.-L., Muehlbauer, G.J., and Ramsay, L. (2009). The emergence of whole genome association scans in barley. Curr. Opin. Plant Biol. **12:** 218–222.

Weigel, D., and Nordborg, M. (2005). Natural variation in Arabidopsis. How do we find the causal genes? Plant Physiol. **138:** 567–568.

Weng, J., et al. (2008). Isolation and initial characterization of GW5, a major QTL associated with rice grain width and weight. Cell Res. **18:** 1199–1209.

Wentzell, A.M., Rowe, H.C., Hansen, B.G., Ticconi, C., Halkier, B.A., and Kliebenstein, D.J. (2007). Linking metabolic QTLs with network and cis-eQTLs controlling biosynthetic pathways. PLoS Genet. **3:** e162.

Werner, J.D., Borevitz, J.O., Uhlenhaut, N.H., Ecker, J.R., Chory, J., and Weigel, D. (2005a). FRIGIDA-independent variation in flowering time of natural *Arabidopsis thaliana* accessions. Genetics **170:** 1197–1207.

Werner, J.D., Borevitz, J.O., Warthmann, N., Trainer, G.T., Ecker, J.R., Chory, J., and Weigel, D. (2005b). Quantitative trait locus mapping and DNA array hybridization identify an FLM deletion as a cause for natural flowering-time variation. Proc. Natl. Acad. Sci. USA **102:** 2460–2465.

West, M.A., Kim, K., Kliebenstein, D.J., van Leeuwen, H., Michelmore, R.W., Doerge, R.W., and St Clair, D.A. (2007). Global eQTL mapping reveals the complex genetic architecture of transcript-level variation in Arabidopsis. Genetics **175:** 1441–1450.

Wilczek, A.M., et al. (2009). Effects of genetic perturbation on seasonal life history plasticity. Science **323:** 930–934.

Wissuwa, M., Wegner, J., Ae, N., and Yano, M. (2002). Substitution mapping of Pup1: A major QTL increasing phosphorus uptake of rice from a phosphorus-deficient soil. Theor. Appl. Genet. **105:** 890–897.

Wu, C.A., Lowry, D.B., Cooley, A.M., Wright, K.M., Lee, Y.W., and Willis, J.H. (2007). Mimulus is an emerging model system for the integration of ecological and genomic studies. Heredity **100:** 220–230.

Wu, J., Yuan, Y.-X., Zhang, X.-W., Zhao, J., Song, X., Li, Y., Li, X., Sun, R., Koornneef, M., Aarts, M., and Wang, X.-W. (2008). Mapping QTLs for mineral accumulation and shoot dry biomass under different Zn nutritional conditions in Chinese cabbage (*Brassica rapa L. ssp. pekinensis*). Plant Soil **310:** 25–40.

Xiao, H., Jiang, N., Schaffner, E., Stockinger, E.J., and van der Knaap, E. (2008). A retrotransposon-mediated gene duplication underlies morphological variation of tomato fruit. Science **319:** 1527–1530.

Xue, W., Xing, Y., Weng, X., Zhao, Y., Tang, W., Wang, L., Zhou, H., Yu, S., Xu, C., Li, X., and Zhang, Q. (2008). Natural variation in Ghd7 is an important regulator of heading date and yield potential in rice. Nat. Genet. **40:** 761–767.

Yan, L., Fu, D., Li, C., Blechl, A., Tranquilli, G., Bonafede, M., Sanchez, A., Valarik, M., Yasuda, S., and Dubcovsky, J. (2006). The wheat and barley vernalization gene VRN3 is an orthologue of FT. Proc. Natl. Acad. Sci. USA **103:** 19581–19586.

Yan, L., Helguera, M., Kato, K., Fukuyama, S., Sherman, J., and Dubcovsky, J. (2004a). Allelic variation at the VRN-1 promoter region in polyploid wheat. Theor. Appl. Genet. **109:** 1677–1686.

Yan, L., Loukoianov, A., Blechl, A., Tranquilli, G., Ramakrishna, W., SanMiguel, P., Bennetzen, J.L., Echenique, V., and Dubcovsky, J. (2004b). The wheat VRN2 gene is a flowering repressor down-regulated by vernalization. Science **303:** 1640–1644.

Yan, L., Loukoianov, A., Tranquilli, G., Helguera, M., Fahima, T., and Dubcovsky, J. (2003). Positional cloning of the wheat vernalization gene VRN1. Proc. Natl. Acad. Sci. USA **100:** 6263–6268.

Yano, M., Katayose, Y., Ashikari, M., Yamanouchi, U., Monna, L., Fuse, T., Baba, T., Yamamoto, K., Umehara, Y., Nagamura, Y., and Sasaki, T. (2000). Hd1, a major photoperiod sensitivity quantitative trait locus in rice, is closely related to the *Arabidopsis* flowering time gene CONSTANS. Plant Cell **12:** 2473–2484.

Yuan, Y.X., Wu, J., Sun, R.F., Zhang, X.W., Xu, D.H., Bonnema, G., and Wang, X.W. (2009). A naturally occurring splicing site mutation in the *Brassica rapa* FLC1 gene is associated with variation in flowering time. J. Exp. Bot. **60:** 1299–1308.

Zhai, J., Liu, J., Liu, B., Li, P., Meyers, B.C., Chen, X., and Cao, X. (2008). Small RNA-directed epigenetic natural variation in *Arabidopsis thaliana*. PLoS Genet. **4:** e1000056.

Zhang, B., Chen, P., Shi, A., Hou, A., Ishibashi, T., and Wang, D. (2009). Putative quantitative trait loci associated with calcium content in soybean seed. J. Hered. **100:** 263–269.

Zhang, X., Yazaki, J., Sundaresan, A., Cokus, S., Chan, S.W., Chen, H., Henderson, I.R., Shinn, P., Pellegrini, M., Jacobsen, S.E., and Ecker, J.R. (2006b). Genome-wide high-resolution mapping and functional analysis of DNA methylation in Arabidopsis. Cell **126:** 1189–1201.

Zhao, J., Jamar, D.C.L., Lou, P., Wang, Y., Wu, J., Wang, X., Bonnema, G., Koornneef, M., and Vreugdenhil, D. (2008). Quantitative trait loci analysis of phytate and phosphate concentrations in seeds and leaves of *Brassica rapa.* Plant Cell Environ. **31:** 887–900.