Review

A survey of dominant mutations in *Arabidopsis thaliana*

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Following the recent publication of a comprehensive dataset of 2400 genes with a loss-of-function mutant phenotype in *Arabidopsis (Arabidopsis thaliana)*, questions remain concerning the diversity of dominant mutations in *Arabidopsis*. Most of these dominant phenotypes are expected to result from inappropriate gene expression, novel protein function, or disrupted protein complexes. This review highlights the major classes of dominant mutations observed in model organisms and presents a collection of 200 *Arabidopsis* genes associated with a dominant or semidominant phenotype. Emphasis is placed on mutants identified through forward genetic screens of mutagenized or activation-tagged populations. These datasets illustrate the variety of genetic changes and protein functions that underlie dominance in *Arabidopsis* and may ultimately contribute to phenotypic variation in flowering plants.

Surveying dominant mutations

Mutation is a major source of genetic variation in natural populations. In addition, mutation plays an important role in genetic analysis, along with recombination, transformation, and genetic complementation. In light of the extraordinary advances made in genetic analysis over the past 100 years, it seems remarkable that comprehensive datasets of mutations in model genetic organisms cannot be readily obtained in a simplified format. Even a basic question such as 'which human, mouse, or *Drosophila* genes are associated with a recessive, dominant, loss-of-function, or gain-of-function mutant phenotype' cannot be resolved with a simple query, despite volumes of relevant information archived in genome databases. Because model organisms were developed in part to facilitate the identification of genes underlying phenotypes of interest in related species, continued advances in data curation are urgently needed to update information on genotype-to-phenotype associations for research biologists worldwide.

Toward this end, my laboratory recently published a comprehensive dataset of 2400 *Arabidopsis* genes with a loss-of-function mutant phenotype and a complementary dataset of 401 genes that exhibit a phenotype when disrupted in combination with a putative paralog [1]. Missing from those datasets are genes with only a dominant, gain-of-function mutant phenotype. We decided to focus initially on the consequences of a loss of gene function because those phenotypes are often the most straightforward to interpret. However, a convincing argument can be made that dominant mutants should not be ignored, particularly when genetic redundancy limits the number of genes that can be analyzed with a loss-of-function approach.

I therefore embarked on another literature curation effort for this review, focused this time on dominant mutant phenotypes. Because my own research on embryo-defective (*emb*) mutants of *Arabidopsis* [2,3] has limited my exposure to dominant mutations, for the obvious reason that most dominant lethals cannot be maintained or studied, I relied on extensive PubMed searches (http://www.ncbi.nlm.nih.gov) with appropriate keywords (*Arabidopsis*, dominant, semidominant, gain-of-function, activation tagged or tagging, haploinsufficient or haploinsufficiency, hypermorphic, antimorphic, and neomorphic) to uncover more than 1000 abstracts of promising publications, which were then evaluated for candidate genes. This approach resulted in three separate datasets: one for dominant mutations identified through screens of activation-tagged populations (93 genes), another for dominant mutations found by screening populations of mutagenized plants (92 genes), and a third for examples of haploinsufficiency (15 genes). Dominant enhancer and suppressor mutations were retained when a dominant phenotype was described for the second mutation in the absence of the first. Excluded from this analysis were dominant phenotypes that resulted from reverse genetic analysis of activation-tagged lines or from overexpression of a cloned gene of interest in transgenic plants. By focusing on the results of forward genetic screens, where mutant phenotypes are observed before the disrupted genes have been identified, information on the frequencies of different types of gene disruptions can be obtained and evaluated.

Several conclusions were reached from this analysis: (i) dominant mutant phenotypes are much less common than recessive phenotypes in *Arabidopsis*; (ii) alterations in transcription factors, hormone pathways, and signaling components are frequently encountered in dominant mutants identified through forward genetic screens; (iii) dominant phenotypes observed following chemical mutagenesis do not often result from elevated transcription of the affected gene; they tend to be caused instead by missense mutations that modify protein function or confer a dominant-negative effect on protein-protein interactions; (iv) there is virtually no overlap between the datasets of genes with dominant mutant phenotypes identified through chemical mutagenesis and activation tagging; and (v) in contrast to humans and yeast, few cases of haploinsufficiency have been documented in *Arabidopsis*; a single functional allele is therefore sufficient for most cellular functions.

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Classification of dominant mutations

Unlike recessive mutant alleles, whose presence can be masked by a functional wild-type allele, dominant mutant alleles can be detected in both heterozygotes and homozygotes. With semidominant mutations, which exhibit incomplete dominance, the phenotype of heterozygotes is typically less severe than that of homozygotes. Unfortunately, the term 'semidominant' is not consistently used in the literature. Some mutants described as having a dominant mutant phenotype are in fact semidominant because heterozygotes and homozygotes can be distinguished. Such inconsistencies are also found here. The term 'semidominant' has been retained in some places, whereas elsewhere 'dominant' refers to all mutant alleles with a phenotype detected in heterozygotes. Although the terms 'gain-of-function' and 'dominant' are sometimes used interchangeably, they do not describe identical datasets. The most notable exceptions involve haploinsufficiency, where dominance is associated with a loss of gene function not fully compensated by a single wild-type allele. Because the term 'haploinsufficient' is more frequently used in some model organisms than others, comparisons between haploinsufficient genes in different species can be difficult.

Based on the classical genetic literature [4], dominant mutant alleles include hypermorphs (too much functional gene product), neomorphs (altered gene product with a novel function), and antimorphs (defective protein that interferes with functional proteins in a dominant-negative manner). These terms are informative but not widely used in the *Arabidopsis* community. Activation-tagged mutants are often described as overexpression mutants based on increased transcription driven by linked enhancer sequences. Dominant phenotypes may also result from inappropriate gene expression, epigenetic changes, increased protein or messenger RNA (mRNA) stability, and decreased micro RNA (miRNA) binding to target mRNAs. Because of these molecular ambiguities, interpreting the normal function of a gene of interest from its dominant mutant phenotype can be problematic.

Examples of haploinsufficiency

Haploinsufficiency refers to genetic loci where a single functional allele is not sufficient to meet the needs of the cell, and as a result, heterozygotes exhibit a mutant phenotype [5]. The most common explanation, based on the assumption that two functional alleles contribute more gene product than one, is that haploinsufficiency identifies cellular processes that are sensitive to dosage effects and changes in protein concentration [6]. Increased susceptibility to stochastic disruptions of the single functional allele in heterozygotes may also be involved [7]. The dominant mutant phenotype should in principle disappear following the introduction of a second functional allele into heterozygotes. However, this experimental approach is not often pursued. Haploinsufficiency has been studied in a variety of organisms, with recent attention focused on humans [8,9], *Drosophila* [10,11], and yeast [12,13].

Two factors have contributed to widespread interest in human haploinsufficiency: the proliferation of copy number variation (CNV) data in human populations [14] and a desire to understand the molecular basis of heritable human diseases [15]. Based on a recent dataset of ~300 human haploinsufficient genes identified through automated text searching and database mining [8], regulatory proteins and transcription factors are frequently involved, and affected individuals often exhibit developmental or neurological phenotypes. When compared with a dataset of ~1000 haplosufficient loci in humans, established by identifying gene disruptions tolerated by two or more individuals, haploinsufficient genes tend to be associated with increased transcription early in development, specialized patterns of gene expression, and proteins with more interactors than haplosufficient genes [9]. Haploinsufficiency may also help to explain phenotypes observed with large chromosomal deletions. One striking example is the 1.6 Mb deficiency in Williams syndrome that spans at least 25 genes on chromosome 7. Heterozygotes exhibit a complex spectrum of physical abnormalities and personality features that result from haploinsufficiency of several genes within the deletion [16]. Homozygotes for haploinsufficient loci typically exhibit more severe phenotypes, including early lethality, and are not widely characterized.

Haploinsufficiency in yeast has been addressed using heterozygous deletion strains to evaluate differential growth rates in liquid cultures [12,13]. Based on fitness profiling in batch cultures, approximately 3% of yeast genes appear to be haploinsufficient [12]. Molecular complexes associated with metabolic processes are frequently involved. With competition experiments using continuous cultures and multiple nutrient environments [13], up to 20% of yeast genes exhibit a haploinsufficient phenotype, depending on the medium. Haploinsufficiency in yeast is therefore frequently associated with subtle defects in growth rates under specialized conditions. Surprisingly, the prevalence of haploinsufficient loci in yeast and humans is increased for chromosomes associated with mating type or sex determination [17].

In *Drosophila*, most haploinsufficient genes encode components of cytoplasmic ribosomes [10]. Loss of gene function results in a heterozygous *Minute* phenotype characterized by prolonged development, altered bristles, and reduced viability [11]. A recent survey based on chromosomal deletions with defined break points identified about 100 haploinsufficient genes in *Drosophila*: 49 associated with haplolethal or haplosterile *Minute* phenotypes, 28 with a less severe *Minute* phenotype, and 26 with other cellular or developmental phenotypes, including a handful of genes that encode dosage-sensitive muscle components, transcription factors, and regulatory proteins [10]. Thus, despite a rich history of genetic analysis, only a few haploinsufficient genes with specialized morphological phenotypes have been identified in *Drosophila*. For the vast majority of genes, a single copy appears to be sufficient for growth and development.

The growth of knockout heterozygotes in *Arabidopsis* has not been examined to the same extent as in yeast or *Drosophila*. Based on my direct experience with hundreds of embryo-defective mutants [3], most plants with a single functional copy of an *EMB* gene appear normal except for the segregation of defective seeds in selfed siliques. Mutants altered in cytoplasmic ribosomes exhibit a variety of recessive phenotypes [18], including embryo lethality,

but only a single dominant *Minute*-like locus has been documented in *Arabidopsis* [19]. A complete loss of cytoplasmic translation appears to result in 100% gametophyte lethality, which prevents the recovery of such mutant alleles from knockout collections [20]. The most common protein functions associated with haploinsufficiency in *Arabidopsis* and *Drosophila* are therefore different.

To identify examples of haploinsufficiency in *Arabidopsis*, I evaluated publications on semidominant mutant phenotypes [1] and queried PubMed with relevant terms. The resulting list of 15 genes (see Table S1 in the supplementary material online) is remarkably short and includes a variety of protein functions: transcriptional regulators [21–24], biosynthetic enzymes [25–28], ribosomal protein [19], iron transporter [29], protein importer [30], photoreceptor [31], histone [32], light harvesting complex subunit [33], and unknown [34]. The blue light photoreceptor encoded by the *ELONGATED HYPOCOTYL4* (*HY4*) locus described in the classical genetic literature can also be included [35,36]. Why have so few examples of haploinsufficiency been identified in *Arabidopsis*? One reason may be that plants are more tolerant of changes in ploidy level and gene dosage than other multicellular eukaryotes. Equally important is the fact that plants heterozygous for loss-of-function mutant alleles have frequently not been subjected to a thorough phenotypic characterization, and may in fact exhibit subtle phenotypes that have gone undetected. One future objective for large-scale phenotyping centers [37] might therefore be to focus on detailed comparisons of wild-type and heterozygous plants segregating for known loss-of-function mutant alleles.

Forward genetic screens of activation-tagged lines

Although T-DNA inserts and transposable elements have been used for more than 20 years to generate recessive, loss-of-function mutations in *Arabidopsis* [38,39], insertion agents can also lead to dominant, gain-of-function mutations through inappropriate expression of neighboring genes, particularly when the inserted sequence includes terminal enhancer elements [40,41]. This approach, known as activation tagging, has resulted in the establishment of large populations of transgenic *Arabidopsis* plants [41–46], which have then been subjected to a variety of forward genetic screens for mutant phenotypes of interest. To facilitate suppressor, enhancer, and conditional phenotype screens, some of these activation-tagged lines have been produced in specialized genetic backgrounds.

My literature curation identified 93 examples of *Arabidopsis* genes with a dominant or semidominant mutant phenotype resulting from T-DNA or transposon-activated gene expression (see Table S2 in the supplementary material online). This dataset excludes mutants described only briefly, during the creation of large populations of insertion lines, and mutants identified through reverse genetics. Each gene listed in Supplemental Table S2 is associated with a PubMed identification number for a relevant publication, along with the locus number, gene name, predicted protein function, insert location, description of mutant phenotype, focus of genetic screen, and availability of loss-of-function mutants. Fifty-four percent of these genes were discovered through forward genetic screens focused on altered plant morphology (Table 1). Another 36% were found through suppressor or enhancer screens, or experiments designed to identify conditional plant phenotypes. The remainder involved altered transgene expression or detection of altered cellular or biochemical phenotypes. In most cases, overexpression of the candidate gene in wild-type plants recapitulates the mutant phenotype. Inserted sequences are not always located immediately upstream of the activated gene, or with enhancer sequences oriented as expected relative to transcription initiation. In almost 20% of the activation-tagged lines with published mutant phenotypes, the insert is located downstream. Sometimes the distance upstream or downstream of the start codon is considerable [47–49]. Some inserts activate one gene while disrupting another [50–54]; others activate multiple linked genes [55,56]. In these cases, additional experiments are required to demonstrate that the dominant phenotype results from the activation of a single locus.

Remarkably, more than 40% of the activated genes encode transcriptional regulators, and 75% encode proteins involved with transcriptional control, signaling pathways, or hormone biosynthesis or response (Table 2). These percentages exceed those found in the genome as a whole [57] and in the dataset of *Arabidopsis* genes with a loss-of-function mutant phenotype [1]. In two exceptional cases (*JAGGED AND WAVY* and *JABBA*), the insert results in overexpression of a locus encoding an miRNA, which then targets a transcription factor, resulting in reduced function [58,59]. The dataset also includes a number of membrane-localized transporters, several enzymes, and a handful of proteins with unknown functions. Strikingly absent from the dataset are most proteins with basic cellular or metabolic functions. Overall, these results indicate that genes with specialized functions in regulating growth and development are most likely to generate an overexpression phenotype that can be readily detected with forward genetics. Of course, this conclusion

Table 1. Forward genetic screens used to identify dominant mutations in *Arabidopsis*[a]

		Number of genes identified		
Category[b]	Type of genetic screen performed	Activation tagging	Mutagenesis	Total %
M	Altered plant morphology	50	28	42.2
C	Conditional plant phenotype	19	41	32.4
SE	Suppressor; enhancer screen	15	16	16.8
T	Altered transgene expression	3	2	2.7
O	Other	6	5	5.9
	Totals	93	92	100.0

[a]Excludes 15 examples of genes that exhibit haploinsufficiency.

[b]Refer to Tables S2 and S3 in the supplementary material online for specific gene assignments.

Table 2. Classification of protein functions disrupted by dominant mutations in *Arabidopsis*[a]

		Number of genes identified		
Category[b]	Proposed or confirmed function of gene product	Activation tagging	Mutagenesis	Total %
A	Hormone biosynthesis, signaling pathways	15	16	16.8
B	Aux/IAA transcriptional repressor proteins	0	9	4.9
C	Other transcriptional regulators	40	16	30.3
D	Other signaling pathway components	15	9	13.0
E	Tubulins: cytosolic microtubule monomers	0	8	4.3
F	Synthesis of other macromolecular polymers	1	6	3.8
G	Other biosynthetic enzymes	0	11	5.9
H	Light receptor proteins	0	3	1.6
I	Membrane transporters; ATPases	5	6	5.9
J	Other functions (22 proteins; 1 tRNA; 2 miRNA)	17	8	13.5
	Total identified through forward genetic screens	93	92	100.0

[a]Excludes 15 examples of genes that exhibit haploinsufficiency.

[b]Refer to Tables S2 and S3 in the supplementary material online for specific gene assignments.

may be influenced somewhat by the types of screens performed and the mutant phenotypes chosen for detailed analysis.

Activation tagging has long been promoted as an effective method to uncover genes with mutant phenotypes that are missed through loss-of-function genetic screens [41], either because functional redundancy prevents the phenotype from being observed in the first place, or because knockout alleles result in early lethality, which is often thought to preclude more detailed analysis. With a dataset of activation-tagged mutants identified through forward genetics in hand, these assumptions can finally be evaluated. For 48% of the genes in supplemental Table S1, a recessive, loss-of-function allele is known to exhibit a mutant phenotype. Frequently, this phenotype is the opposite of that described for the activation-tagged mutant, consistent with expectations. For 22% of activation-tagged genes with mutant phenotypes, I could not determine whether a loss-of-function mutant had been isolated or characterized. For another 11% of these genes, phenotype information was limited to RNA interference (RNAi) lines. That leaves 18 genes (19%) with a documented gain-of-function phenotype but no obvious loss-of-function phenotype. This number is probably lower than originally predicted. An alternative approach, being pursued in the private sector, is to overexpress a specific class of regulatory genes such as transcription factors or signaling components, and then score these plants for phenotypes of interest. Based on the trends observed with activation-tagged mutants identified to date, such an approach is likely to generate a wide range of interesting and informative phenotypes. How frequently activation tagging results in desirable phenotypes not observed in loss-of-function mutants remains to be determined.

With respect to circumventing lethality in loss-of-function mutants, I found only three cases (At1g49770, At2g47430, and At4g00220) where forward genetics identified an activation-tagged mutant disrupted in a gene known to be required for embryo or gametophyte development [60–62]. Furthermore, I have long maintained that lethal mutants are often quite informative [2,63], and that alternative methods such as RNAi or gene silencing can be used to observe the consequences of a partial loss of gene function. Activation tagging has therefore identified a wide range of genes with informative phenotypes, associated many of these genes with important regulatory pathways, and greatly facilitated genetic analysis in *Arabidopsis*, but not always for the exact reasons originally envisioned.

Forward genetic screens of mutagenized populations

Dominant mutations can also be identified following chemical mutagenesis, irradiation, or insertion events not associated with activation tagging. Ninety-two examples of genes with a dominant mutant phenotype identified in this manner are listed in supplemental Table S3. In addition to locus and gene identifiers, PubMed references, protein functions, descriptions of mutant phenotypes, and information on genetic screens and loss-of-function alleles, the molecular changes that underlie each dominant phenotype are specified. Because ethyl methanesulfonate (EMS) was often used to generate these mutations, the presence of missense mutations is not unexpected. Of the 92 genes included in the dataset, 68 are associated with missense mutations that alter protein function. In at least two cases (At1g51950 and At3g26744), identical missense mutations in the same gene were identified in different genetic screens [64–67]. Another common scenario, with 12 examples identified here, involves truncated proteins generated through nonsense or frameshift mutations, deletions, altered RNA splice sites, or insertions that create a shortened transcript. In four noteworthy cases [*PHABULOSA*, *PHAVOLUTA*, *INCURVATA4*, and *REVOLUTA* (*REV*)], a missense mutation changes the protein sequence, but the phenotype results from reduced efficiency of miRNA binding to the altered mRNA [68–72]. Dominant phenotypes can also result from hypomethylation of key regulatory genes (At4g16890 and At4g25530), improved mRNA stability (At3g01120 and At5g60890), modification of upstream regulatory sequences (At1g21970 and At1g65620), and antisense transcript formation (At1g74260) [73–80]. One particularly intriguing mechanism involves a mutation in the anticodon of a redundant $tRNA^{Ala}$ that causes alanine to be replaced by valine in a subset of polypeptides produced by heterozygotes [81].

Why do these changes result in a dominant mutant phenotype rather than a recessive phenotype? Table 3 summarizes the range of mechanisms that appear to be involved. Altered protein interactions and complex

Table 3. Underlying causes of dominant mutant phenotypes in *Arabidopsis*[a]

Category[b]	Genes	Apparent cause of dominant mutant phenotype
A	10	Increased transcription; enhanced mRNA stability
B	18	Enhanced protein stability; reduced feedback inhibition
C	13	Altered polymerization of macromolecules
D	14	Altered protein interactions, complex formation
E	7	Constitutively active protein
F	18	Altered protein function or interaction; missense mutation
G	6	Altered protein function or interaction; truncated protein
H	6	Other mechanism involved
	92	Total identified through forward genetic screens

[a]Limited to phenotypes identified in mutagenized populations.Excludes activation-tagged mutants and examples of haploinsufficiency.

[b]Refer to Table S3 in the supplementary material online for specific gene assignments.

formation are frequently invoked and are likely to be responsible for additional cases that remain to be clarified. In a common scenario, the mutant protein fails to associate properly with other proteins in the cell and forms a poisoned complex that interferes with normal cellular functions. This dominant-negative effect has been well studied in model genetic organisms [82,83]. Some dominant-negative alleles in *Arabidopsis* produce truncated proteins; others encode proteins with a single amino acid substitution. By definition, dominant-negative alleles should have a stronger impact on the phenotype of heterozygotes than null alleles and, depending on the level of genetic redundancy, the phenotype should more closely resemble that of knockout homozygotes than overexpression lines. Several such examples are included in supplemental Table S3. One common method used to distinguish between loss-of-function and gain-of-function mutations in *Arabidopsis* involves crosses with tetraploid plants [84,85]. However, demonstrating that a defective protein complex, and not some other change in protein function, is responsible for the mutant phenotype can be difficult.

Increased protein stability is another explanation for a dominant pattern of inheritance. In select cases, this involves reduced feedback inhibition [86–88]. More frequently, it results from a reduction in protein degradation associated with amino acid substitutions in protein interaction domains. The most striking example in *Arabidopsis* involves auxin/indole-3-acetic acid (Aux/IAA) proteins. Missense mutations in nine different *Aux/IAA* genes lead to a dominant mutant phenotype [64,89,90]. A tenth example was published recently [91]. Altered polymerization of tubulin, actin, or cellulose explains the dominance of missense mutations in 13 other *Arabidopsis* genes [92–96]. In fact, tubulins and Aux/IAA proteins account for almost 20% of the protein functions encoded by dominant mutant alleles identified following mutagenesis (Table 2). Other protein functions include biosynthetic enzymes, membrane transporters, ATPases, and light receptor proteins.

Similar to results obtained with activation tagging, more than half of the protein functions associated with dominant mutant alleles identified in mutagenized populations involve transcriptional control, signaling pathways, or hormone biosynthesis or response. However, the molecular mechanisms that give rise to the mutant phenotype differ considerably. Unlike activation tagging, where inappropriate gene expression consistently underlies the mutant phenotype, enhanced transcription is rarely involved with dominant alleles identified following mutagenesis. Only a single example of a point mutation in a promoter that leads to elevated transcription is included in supplemental Table S3 [78]. Remarkably, this locus [*ASYMMETRIC LEAVES2 (AS2)*] also represents the sole overlap between datasets of genes identified by mutagenesis and activation tagging. In another case [*LEAFY COTYLEDON1 (LEC1)*], an upstream deletion results in enhanced gene expression [79]. Overall, single point mutations in promoters do not readily give rise to dominant mutant phenotypes in *Arabidopsis*. This is consistent with recent evolutionary studies in *Drosophila*, where certain morphological differences between related species required a series of cumulative changes in upstream regulatory sequences [97]. By contrast, four examples of point mutations in miRNA binding sites within transcripts encoding regulatory proteins are included here. This suggests that miRNA-mediated regulatory pathways represent effective targets for random genetic changes that can rapidly impact morphology and plant evolution.

In contrast to most of the genes uncovered through activation tagging, several genes associated with induced dominant mutations in *Arabidopsis* represent classical genetic loci with known loss-of-function phenotypes. These include three elongated hypocotyl loci (*HY3*, *HY4*, and *HY8*) [98–100], several genes with vegetative or reproductive phenotypes (*AS2*, *REV*, and *APETALA2*) [71,78,101], and the *LEC1* gene required for embryogenesis [79]. A novel allele [102] of another well-characterized gene [103] required for growth and development [*ABNORMAL SUSPENSOR1/DICER-LIKE1 (SUS1/DCL1)*] is excluded here because the subtle molecular changes identified in heterozygotes do not meet the published criteria for a mutant phenotype [1].

How do the phenotypes of dominant and recessive mutants identified through forward genetics compare? When phenotypes are assigned to the four prioritized groups (essential, morphological, cellular-biochemical, and conditional; see Table S4 in the supplementary material online) previously described [1], the most obvious difference is the scarcity of dominant mutants defective in essential genes (Figure 1). More intriguing are the similarities in group assignments for dominant mutants identified following mutagenesis and activation tagging, and the similar percentages of dominant and recessive mutants with cellular-biochemical and conditional phenotypes. Whether significant differences can be found in the frequencies of more specialized phenotypes remains to be determined. Although saturation for mutant phenotypes has not been reached, and additional examples of dominant mutants with novel phenotypes should be uncovered in the future, it appears that with the exception of lethals, both dominant and recessive mutations in *Arabidopsis* are associated with a wide range of informative phenotypes.

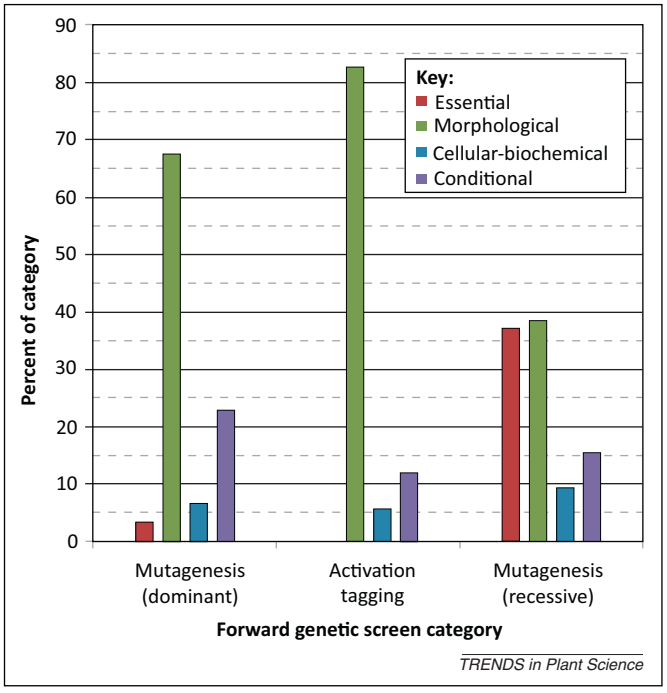

Figure 1. Phenotype group assignments for dominant and recessive mutants of *Arabidopsis* identified through forward genetic screens. Each gene is assigned to a single phenotype group as described in [1]. Number of genes involved: mutagenesis (dominant), 92; activation tagging, 93; mutagenesis (recessive), 1042.

Future directions

Several challenges remain to be addressed in the future. First, the relative frequencies of genes associated with dominant and recessive mutant phenotypes need to be compared among a variety of model eukaryotes, including *Arabidopsis*. This will require the establishment of curated datasets for other model organisms comparable to those available for *Arabidopsis*. One might expect that dominant mutations resulting from inappropriate gene expression will be most common in organisms with active transposable elements, and that dominant mutations overall will be particularly common in humans, where haploinsufficiency is frequently encountered, heterozygotes are often evaluated for subtle changes in complex phenotypes, and rare mutations that result in dominant or semidominant phenotypes are readily identified. A second challenge will be to incorporate information on overexpression lines and dominant mutations identified through reverse genetics to establish a comprehensive dataset of *Arabidopsis* genes associated with dominant phenotypes. By excluding such examples here, I focused attention on phenotypes identified through forward genetics and avoided skewing the dataset with genes of special interest to certain investigators. Of course, different promoters associated with the same gene may lead to different phenotypes, thereby complicating future analyses of overexpression lines. Another challenge will be to update and curate the current dataset. Several relevant examples of *Arabidopsis* genes with dominant or gain-of-function phenotypes were not discussed here. These include novel, gain-of-function mutations with a recessive pattern of inheritance [104–106], a semidominant phenotype (*peapod*) that results from deletion of two adjacent genes [107], several dominant mutant alleles (e.g., *cryptochrome2* and *agamous-like6*) identified by crossing different wild-type accessions [108,109], and a missense mutation found through a forward genetic screen in *Brassica* [110] that phenocopies the equivalent dominant-negative transgene in *Arabidopsis* [111].

Finally, as genomic and phenotypic data on *Arabidopsis* accessions continue to increase, the challenge will be to identify those mutant alleles, dominant or recessive, that are associated with phenotypic variation in natural populations. One recent example involves allelic variation at the *ACCELERATED CELL DEATH6* (*ACD6)* locus [112]. The dominant mutant allele, first identified in the laboratory [113], enhances pathogen resistance in natural populations, but also impacts fitness through reduced biomass of mature leaves. Other classical genetic loci of *Arabidopsis* are likely to affect growth and development within natural populations as well. In fact, natural variation offers a vast resource of informative alleles, both dominant and recessive, for future studies [114,115]. In conclusion, with the combined datasets of 2600 *Arabidopsis* genes that exhibit a dominant or recessive phenotype now in hand, the stage is set to uncover a wide range of genes that underlie phenotypic variation and morphological evolution in flowering plants.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tplants.2012.08.006.

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