Structural, Functional and Genomic Diversity of Plant NLR proteins: an Evolved Resource for Rational Engineering of Plant Immunity.

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ABSTRACT:

Plants employ a diverse intracellular system of NLR (Nucleotide-binding, Leucine rich-Repeat) innate immune receptors to detect pathogens of all types. These receptors represent valuable agronomic traits that plant breeders rely on to maximize yield in the face of devastating pathogens. Despite their importance, the mechanistic underpinnings of NLR-based disease resistance remain obscure. The rapidly increasing numbers of plant genomes are revealing a diverse array of NLR-type immune receptors. In parallel, mechanistic studies are describing diverse functions for NLR immune receptors. In this review, we intend to broadly describe how the structural, functional and genomic diversity of plant immune receptors can provide a valuable resource for rational engineering of plant immunity.

Introduction: Layers of the plant immune system.

Plants have evolved an elaborate innate immune system to detect and limit the growth of potential pathogens. Lacking an adaptive immune system with mobile cells, each plant cell must be able to detect and defend appropriately against pathogens. Plants mount a sophisticated multilayered defense response including local physical barriers and chemical weapons, systemic signaling to prime uninfected cells and programmed cell death to limit pathogens that rely on living host cells. To present an appropriate response, plants must have a mechanism to identify microbes of all types and discriminate between friend and foe. To integrate signals from their biotic environment, plants rely on a diverse collection immune receptors often numbering in the hundreds

per genome (53; 59; 99). Despite their numbers, exactly how a limited set of genomically-encoded immune receptors can protect plants against a deluge of rapidly-evolving microbial pathogens remains unknown.

Plant immune receptors come in two broad classes that have been proposed to play complementary roles (55). The first class of immune receptors, termed Pattern Recognition Receptors (PRRs), monitors the extracellular environment for signals derived from microbes (25; 112). The PRR class is responsible for transducing recognition of pathogens across the plasma membrane to activate a defense response known as PAMP-triggered (pathogen-associated molecular patterns) immunity, or PTI (25; 134). PTI-activating signals are usually conserved, essential microbe-derived or generated molecules (15; 86). PRRs typically have an extracellular ligand-binding domain, a transmembrane-spanning domain, and an intracellular kinase domain (145). PTI is sufficient to render plants immune to a large number of potential pathogens. Microbes that are successful pathogens on a given host have evolved tools to defeat PTI. In many cases, these evolved tools are secreted or translocated proteins known as “effectors” or small molecule toxins (16; 119). The second layer of the plant immune system has evolved to defeat these evolved pathogens, by recognizing pathogen virulence tools as reliable indicators of pathogenesis. This second layer of defense is composed NLR-type (Nucleotide-binding, Leucine-rich Repeat or, alternatively, NOD-Like Receptor) immune receptors (139). These NLR receptors recognize evolved pathogens either directly by the presence or indirectly, by the activity of translocated effectors and toxins. This effector-triggered immunity (ETI) “reboots” plant immune responses dampened by pathogen manipulation and results in strong disease resistance, often associated with programmed cell death known as the hypersensitive response (HR) (26). In some interesting cases, the boundaries between PTI and ETI are less distinct and PRR-type receptors can behave genetically like ETI-triggering NLRs (113). Together PRRs and NLRs must be sufficient to recognize and discriminate between environmental microbes, symbionts and pathogens (47).

Since the rise of agriculture, farmers and breeders have selected for resistance traits to maximize yield by reducing losses to pathogens. The genetic behavior of these traits led to Flor’s gene-for-gene hypothesis which proposed single dominant genes in the plant somehow recognized single dominant genes in the pathogen (39). In the 20th century, researchers realized that the plant resistance traits are often encoded by NLR immune receptors. One of the most striking and unexpected findings was that immunity to pathogens of all kingdoms could be encoded by a single stereotyped class of immune receptor. Since then we have greatly expanded our knowledge of NLRs, but many basic mechanistic facts remain poorly understood. While commonalities between NLRs were striking when first discovered, intensive study has exposed a great deal of diversity in both their structure and function. As increasing numbers of genomes are sequenced,

evidence for NLR diversity at the species and population level is also rapidly accumulating. In this review we will focus on NLRs, their structural, functional and genomic diversity, and progress and prospects for engineered disease resistance.

NLRs are multi-domain molecular switches.

Upon their identification, plant NLR proteins were recognized to contain conserved domains in a stereotypical configuration: a variable N-terminal domain, a central nucleotide binding site (NBS) domain with similarity to the AAA-ATPase family and a C-terminal LRR. The variable N-terminal domains are typically a TIR (Toll-interleukin-1 receptor) or a CC (Coiled-Coil) domain (Figure 1). More recently, evolutionarily distinct classes of CC domains have been described, and many CC-type NLRs (CNLs) have been refined as RPW8-type CC-NLRs (CCr-NLRs or RNLs) based on their similarity to the CC-only disease resistance gene *RPW8* (24; 132; 144). How these domains interact during both the inactive resting state and the activated, signaling state remains unknown. How plant NLRs function is ultimately a difficult structural biology problem. Unfortunately, the structure of any full-length plant NLR has not yet been determined.

NLR proteins are proposed to function as multi-domain switches with inactive and active states driven by the nucleotide-bound status of the central NBS domain; binding to ADP promotes a closed, inactive conformation and binding to ATP promotes an open, active conformation (Figure 1) (reviewed in (12)). The basis for thinking of plant NLRs as NBS-driven switches is largely drawn from structurally-related NBS domains of animal proteins (56; 109). Homology modeling to the NBS domain of animal proteins such as the apoptosome component APAF1 reveal that NLRs contain conserved motifs with predictable functions (109). The P-loop nucleotide binding motif is required for nucleotide binding and can be reliably mutated to generate a loss of function mutant (7; 32; 111; 127). A second motif, characterized by the amino acid sequence MHD, can be mutated to generate gain of function autoactive alleles (7; 28; 50; 127). Despite the strikingly similar domain structure of plant and animal NLRs, as well as mechanistic similarities they are likely products of convergent evolution (117).

If the NBS domain is responsible for controlling the switch between resting and activated states of NLRs, which domain is responsible for signaling downstream? Deletion analysis of the various domains has found that for a number of NLRs the N-terminal CC, CCr or TIR domain is required and often sufficient for cell death signalling (10; 24; 76; 108). Thus the N-terminus is proposed to transduce the activation signal to downstream pathways. In the case of both CC and TIR domains, oligomerization of the N-terminus is proposed to be the critical event in activation. At the whole NLR level, oligomerization can be effector induced, as with the tobacco N gene (81) or with Arabidopsis RPP1 (97). Other NLRs, such as the RPS4/RRS1 complex appear to constitutively self-associate pre-activation, and then subsequently form post-activation

N-terminal multimers to activate defense (51) (Figure 1). Several dimeric CC and TIR structures now exist for NLR N-termini, but the exact conformations of resting and activated multimers and the extent of their oligomerization remains elusive (33; 138). How N-terminal domain multimers form in response to conformational change in the NBS in response to nucleotide binding remains an important unanswered question. While there is much agreement that NLRs behave as switches, exactly how these three domains respond to pathogens and activate cell death remains mechanistically unclear (77; 110).

NLRs can directly or indirectly recognize pathogen effectors

Evolved pathogens of all kingdoms deliver intracellular effector molecules to immunosuppress and manipulate the host. Thus, these effectors are excellent reliable signals for the plant to monitor. In many cases, NLRs can directly recognize pathogen effectors by binding to them (Figure 1). There do not appear to be generalizable rules to how or where NLRs bind pathogen effectors. The LRR of the rice CNL Pi-ta was first proposed as an effector binding domain (54). A role in substrate binding makes intuitive sense given the known role of LRRs as diverse substrate-binding platforms (40). Subsequently, LRRs have been found to directly bind diverse effectors and also to be under diversifying selection, presumably driven by effector diversity and diversification (44; 64). Beyond the LRR, other domains are also clearly regulating recognition. In the case of genes at the L locus of flax, TNLs with identical LRRs, but slightly divergent TIR domains have distinct specificities (34).

How effector-binding to the LRR (or other domains) opens NLRs and promotes oligomerization remains unclear. Analysis of alleles of the flax TNLs L6 and L7 suggest that in the absence of pathogens NLRs may be in an equilibrium in the “on” and “off” states, and that effectors stabilizes the active, ATP-bound state (9). Consistent with this model, for L6 and L7, the activating effector was found to bind inactive versions of the NLR more weakly than active forms (9). If closed, inactive NLRs have multiple points of intramolecular contact between or among domains, then effectors could bind to any of them and disrupt a closed state, or stabilize an open one.

NLRs can indirectly recognize pathogen effectors by guarding important immune targets

NLRs can also indirectly recognize the presence of pathogen effectors by monitoring their impact on host targets (Figure 1). This model was first proposed to explain the Pto/Prf/AvrPto system, where targeting of the Pto kinase by AvrPto is detected by the CNL Prf (118). This “guard hypothesis” proposes that by guarding important, conserved targets of pathogens (or decoys of targets) the plant immune system can detect all

pathogens without a separate, genomically encoded receptor for each pathogen (27). Another important outcome of the guard hypothesis is that we can better understand the plant immune system by knowing the set of proteins that evolution has selected to be guardees of NLRs. Indirect recognition can allow plants to detect mechanistically-distinct effectors that target the same host protein.

Downstream signalling events are not understood.

Surprisingly, the main function of NLRs, the downstream activation of disease resistance and cell death remains mechanistically obscure. How effector activation eventually is transduced into disease resistance, and often cell death, is unknown for any NLR. Downstream events have proven remarkably resistant to forward genetic analysis. The lack of mutable genes required for NLR signalling has prompted hypotheses of redundancy or lethality. An alternative is that the pathways are extremely direct and lack a downstream element. A direct action hypothesis proposes that NLRs are capable of directly activating immune responses and/or killing cells. Intriguingly, it has been proposed that the CNLs Rx1 and I-2 can bind and deform DNA in an effector-dependent manner (36; 37). How DNA binding and deformation by NLRs promotes an "immune-competent" state remains to be determined, but could represent an extremely direct and redundant pathway.

There are however a few identified genes that are required for NLR function. Chaperones such as HSP90, RAR1 and SGT1 are generally required for NLR protein accumulation (100). Genetic analysis of suppressors of autoactive NLRs has revealed a number of novel regulators of NLR homeostasis (reviewed in (72)). Signalling components downstream of NLR accumulation are more rare. Interestingly, the downstream genes appear to split NLR function by TIR vs CC class. All TNLs tested require a lipase-like gene called EDS1 (125). In addition to EDS1, TNLs also require EDS1-like family members such as PAD4 and SAG101, which function in complexes with EDS1 (121). These proteins interact with TNLs and shuttle in and out of the nucleus. Their biochemical function remains mysterious as conserved lipase catalytic residues are not required for supporting TNL immune function (121). CNLs do not appear to directly require EDS1, but several are strongly dependent on the function of NDR1, a protein with homology to integrins (62). Exactly how NDR1 is required for CNL function remains obscure and NDR1 function may not be limited to NLR signalling, as *ndr1* mutant plants also have altered responses to compatible *Pseudomonas syringae,* which lacks recognized ETI-triggering effectors (62).

Diversity of NLR domain structure

In spite of the fact that NLRs were initially recognized to have a stereotyped domain structure, sequencing of the Arabidopsis genome revealed an unexpected diversity in

NLR-like sequences (84). Not only full CNL and TNL receptors exist, but also "truncated" versions that could lack LRR or NBS-LRR domains (Figure 1). These truncated forms are reminiscent of truncated animal immune receptors such as Myd88, a TIR protein that serves as a cytoplasmic adapter for a number of Toll-like receptors. Myd88, and similar TIR adaptor proteins act downstream of multiple receptors to transduce receptor activation (90). In the case of truncated plant TNLs, their function appears to be more specific, although the number of cases tested remains low. RLM3, a TIR-NBS protein is the first example of a "truncated TNL" protein which is required for disease resistance (103). Other TIR-NBS proteins such as TN2 and CHS1 have loss of function or overexpression phenotypes consistent with immune receptors (123; 136; 142). The TIR-only protein RBA1 is required for cell death in response to the type III effector protein HopBA1 (Figure 1) (87). Exactly how truncated TNLs function in the immune system remains unclear, but a compelling hypothesis is that they form hetero-complexes with full-length TNLs. Consistent with a hetero-interaction hypothesis, *chs1* autoimmunity phenotypes were recently shown to require SOC3, a full-length TNL (Figure 1) (140).

Genomic pairs and "integrated domains" are a shortcut to novel virulence targets

The most important recent NLR discovery has been the realization that some NLRs function as genomically-linked pairs (20; 126; 137). These dual NLR systems are proposed to be made up of a signaling NLR and a receptor NLR (18). The signalling NLR behaves much like a traditional NLR and guards the receptor NLR. Remarkably, the receptor NLR behaves as an effector binding platform, containing unusual motifs (i.s. not CC/TIR, RPW8, NBS or LRR domains) that are recognized by pathogen effectors. Integrated domains can be found in many locations within an NLR (Figure 1). These effector-interacting NLR motifs have similarity to the intended pathogen virulence targets and have been referred to as "integrated domains", or "integrated decoys" (IDs) (18; 88). In the case of RPS4 and RRS1, the two molecules preexist as a complex, and the signaling TNL RPS4 is activated after the effector PopP2 acetylates an RRS1-integrated WRKY transcription factor domain (Figure 1). PopP2 "intended" targets are WRKY transcription factors; PopP2 acetylation targets the DNA-binding domain of WRKY transcription factors required for proper immune responses (69). Some RRS1 alleles are capable of recognizing both PopP2 and the sequence-unrelated effector AvrRps4, apparently through mechanistically distinct targeting of RRS1 (96). Similarly, CNLs such as RGA4/RGA5 also exist in genetically linked pairs that contain a decoy domain (RATX1/HMA, a putative metal-binding domain in RGA5) that is targeted by multiple effectors (19; 78).

As more plant genomes are made available, the list of atypical domains integrated into NLRs is rapidly expanding (Supplemental Table 1). These genomic pairs reveal important information solely through their primary sequence and can be identified

across the plant phylogeny (65). There are many useful hypotheses that follow from these observations. First, pairs at a locus (especially head to head) are now reasonably hypothesized to function as a unit. To test this hypothesis, mutations in one locus should suppress the second. Accordingly, transient reconstruction assays of paired loci should include both genes. Second, unusual domains should be considered as effector binding targets and their homologs as relevant to pathogenicity. Thus the universe of NLR IDs across the plant phylogeny is now a minimal set of pathogen virulence targets. Many of these IDs have not been previously indicated as pathogen virulence targets. These domains are a hypothesis generator based solely on genome sequences. While it has not yet been demonstrated, it remains an open possibility that some IDs may retain their former biochemical function (131).

Helpers and genetic interactions across NLR-type.

Canonically, NLRs have been associated with recognizing a specific pathogen and conferring qualitative disease resistance. More recently, “helper” NLRs have been identified that are required for (or “help”) the function of other NLRs. One of the first cloned NLRs was the N-gene in tobacco; a TNL that confers resistance to the tobacco mosaic virus (124). To identify other component of N-mediated disease resistance, Peart et al. performed a VIGS assay looking for loss of N-mediated cell death (92). This screen identified NRG1 as an CCr-containing RNL required for the function of the TNL N-gene. NRG1 is a member of a gene family that also includes ADR1 RNL proteins. Silencing NRG1 and ADR1 in combination resulted in loss of cell death mediated by the CNL Rx2, while single silencing constructs had no effect. Similar redundancy and cross-type interaction was reported in Arabidopsis for the ADR family (13). Interestingly, in Arabidopsis the function of ADR1-L2 as a helper NLR is independent of the p-loop, which is typically required for ETI across NLRs (13). Despite this functional divergence, the N-termini of ADR1 and NRG1 proteins are capable of triggering cell death, indicating that helpers may have functions as ETI-triggers as well as helpers for other NLRs (24). Intriguingly, RNL NRG1 helpers appear to have been co-retained or lost with TNLs multiple times during plant evolution (24). More recently, the NRC family of CNL helpers has been found to be required for clade-specific NLR function (130).

PigmR/PigmS: A novel genomically-paired NLR “helper” mechanism to reduce the cost of resistance

Not all helper NLRs are positive regulators of another NLR’s function. In rice, cloning of the rice blast gene *Pigm* revealed a novel, agronomically important mechanism imparted using a canonical CC-NBS-LRR domain structure (30). Deng, et al. found that *PigmR*, which encodes a CNL is responsible for broad-spectrum, durable resistance to rice blast. Interestingly, *PigmR* is found at an NLR cluster with an extremely closely related partner CNL *PigmS* (only four polymorphic AA between PigmR and PigmS).

Intriguingly, this genomically-linked pair does not follow the integrated decoy model of RPS4/RRS1. Instead, PigmS heterodimerizes with PigmR and suppresses PigmR-based resistance. This suppression apparently counteracts a cost of PigmR-mediated resistance, as it results in increased grain yield. The PigmS impact on productivity may be determined in a tissue-specific manner as while PigmR is constitutively expressed throughout the plant, PigmS is pollen-specific. This presents a novel, potentially engineerable, mechanism of NLR-improvement: tissue-specific expression of dominant-negative "inhibitor NLRs" to decrease fitness costs of NLRs.

Unveiling the diversity of NLR-coding genes

Much of the mechanistic study of NLR function described above has been derived from a limited number of model organisms and genes. With improvement of costs and capabilities of next-generation sequencing technologies, genomic approaches became front line resources to characterize NLR diversity across plant species and populations. To date, the NLR repertoires of over 100 species are available, or can be easily obtained from genome annotations (Supplemental Table 2 lists genome-wide NLR interrogation studies performed to date). Taken together, those repertoires allow extensive comparative analyses and the definition of evolutionary paths.

An intricate evolutionary history explains current diversity

Knowledge of NLR diversity and distribution can reveal novel sources of resistance with enormous biotechnological potential. Preliminary efforts towards characterization of NLR diversity started immediately after the first R-genes were cloned in the mid 1990's (8; 85; 124). At that time, comparative analysis focused on the LRR region, given the results from seminal studies showing significant clustering of nonsynonymous substitutions in that region (14; 34; 80; 89; 122), and the preliminary indications showing that *R* gene specificity was determined by LRRs (40; 54; 105). An early population-level study aimed at characterizing intraspecific NLR polymorphisms was developed in *Arabidopsis thaliana* by Bakker et al. in 2006. This study provided a snapshot of LRR domain diversity across 27 NLRs from 96 accessions of Arabidopsis (4). The methodological innovation, at the time, was to compare LRR polymorphisms to a genome-wide empirical distribution of polymorphisms, rather than to neutral models. This approach identified RPP13 as highly polymorphic and with signatures of balancing selection, adding to the already known genes under balancing selection: RPP1 (14), RPS2 (17), RPP5 (89), RPM1 (104), RPS5 (114), and elucidated seven more loci with weaker balancing selection signatures: AT1G56540, AT1G59780, AT3G50950, AT4G14370, AT4G14610, AT5G58120, and AT5Gg63020 (4). PCR-based approaches have been employed to address sequence recombination, conversion, indels and copy-number variation at particular gene clusters in species other than *A. thaliana* (5; 66; 67;

73). Those studies aimed to characterize the complex selective forces on the evolution of individual genes or clusters.

Genome-wide studies, such as those in *A. thaliana* (46) and rice (133) have provided a deeper insight into NLR distribution, diversity and evolution. In those studies, researchers found that genetically clustered NLR genes frequently swap sequences and are thus more polymorphic than singleton loci. Distinct evolutionary paths and rates for TIR- and non-TIR containing NLRs are apparent in *A. thaliana* (23). NLRs evolve rapidly, and copy number variants were more often found in NLR genes relative to the genome as a whole. 33.3 % of NLR-coding genes from the reference Col-0 accession appeared to be deleted in at least one of the 80 accessions, compared to 12.5% of genes in the entire genome (46). An equivalent number of NLRs must be absent from the Col-0 reference genome. This indicates that there is much to be learned from a deep dive into closely related genomes.

With the advent of second and third generation sequencing technologies, efforts definitively shifted towards genome-wide comparative studies. An early attempt to characterize genome-wide variation among 18 *A. thaliana* ecotypes employed paired-end Illumina reads and a combination of reference-based and *de novo* assembly (41). Bioinformatic limitations of short-read assembly forced authors to limit the analysis to single-copy regions homologous to the the reference (Col-0) genome. Accordingly, analysis of copy-number and structural variation was hampered, as well as the discovery of novel NLRs (93). The currently reported *A. thaliana* pan-NLRome (At-panNLRome)**,** defined as the union of NLR genes of the different ecotypes, is thus restricted to the genes known in a single genotype reference accession (Col-0) (93). Nevertheless, accumulated knowledge shows that the At-panNLRome expands beyond the Col-0 NLR repertoire (31; 89). An interesting example is the *A. thaliana DANGEROUS MIX2* (DM2) cluster, which in Col-0 contains two RPP1-like genes, but in Ler contains up to seven RPP1-like genes (21; 107). To date, it is still unknown if NLRs in the different DM2 loci contribute to recognition of different pathogens. Further expansion of the At-panNLRome will help describe how NLR genes expand and contract across populations in response to pathogen selective pressures.

The NLR content of the *A thaliana* Col-0 genome was first described in 2003 (83), since then our knowledge of NLR gene content across the plant phylogeny has rapidly expanded. Bioinformatic comparative analysis opened a new avenue for studying NLR genetic diversity and evolution. In a recent study, a panel of 6,000 NLR genes from 22 Angiosperm species were incorporated in a comparative analysis and phylogenetic reconstruction. The reported results elucidate how all currently known NLRs likely diversified from 23 NLRs belonging to three distinct ancestral TNL, CNL and RNL

lineages (99). A similar ancestral state reconstruction analysis using 38 sequenced species representing the six kingdoms of life (eubacteria, archaebacteria, fungi, protists, plants and animals) showed that the most basal plants analyzed had a very limited NLR repertoire (30 NLRs in *Physcomitrella patens* and 17 in *Selaginella moellendorffii*) (135). On the other hand, higher plant genomes typically encode numerous NLR genes, with hundreds of genes in gymnosperm and angiosperm genomes. Detailed analysis of plant lineages reveals expansion and contraction of particular NLR classes (99).

The scenario of NLR genes expansion and contraction is complex. While TNLs are expanded in Brassicaceae, the opposite is observed in Poaceae, with TNLdepletion and an expansion of the CNL class (Table 1). Family-level evolutionary paths are not that clear across the plant phylogeny. Comparative analysis of Fabaceae has shown multiple expansion and contraction events, leading to an increase in of NLRs in *Cajanus cajan* and *Medicago truncatula* and a decrease in the NLR repertoire of *Lotus japonicus*, *Phaseolus vulgaris* and *Cicer arietinum* (143). Interestingly, whole genome duplication does not seem to necessarily contribute to net increase the number of NLR genes. NLRs seem to be rather maintained in a dosage- or diploidization-sensitive scheme. In fact, the mechanisms governing NLR gene expansion and/or contraction in the different species might depend on the intraspecific diversity, widespread or restricted geographic distribution, ploidy, mating system (inbreeding or outcrossing), generation time and domestication history (in the case of crops).

As more plant genomes are sequenced, comparative analyses of NLRs and NLRomes will provided a better understanding of its diversity and evolutionary history. For that, the establishment of rigorous and reproducible analysis pipelines will be key. In some cases, analyses of the NLR content reported by different groups can be strikingly inconsistent (Table 1). The observed variance might be due, at least in some cases, to the use of different genome annotation versions, or to which bioinformatic tools and settings are used to perform the analysis. Use and reporting of standardized methods could reduce variance reported between publications and facilitate comparisons [see SIDEBAR].

Good practices for Genome-wide identification of NLRs.

Exploratory descriptions of NLR repertoires provide a valuable glimpse at the species-level NLR diversity and allow comparative NLRome analysis across the different taxonomic clades (3; 60; 65; 95; 99). To that end, a variety of bioinformatic tools have proven useful to identify NLR genes from genome sequences and annotated gene models. Available methods include *ab initio* predictors, identification of functional domains or motifs, similarity searches against databases, PCR amplification with

partially degenerated primers, and R-gene enrichment and sequencing (several studies in Supplementary Table 2 use those methods).

Accurate identification of protein domains in a collection of sequences is critical to defining and organizing proteins into families. Multidomain NLR proteins can be further classified according to domain architectures. To this end, hidden Markov model (HMM) profiles have become a popular means to identify protein domains. High quality, manually curated and biologically relevant HMM profiles for a wide range of domains are available via Pfam (38), TIGRFAM (48) and SMART (71). Each HMM profile in the Pfam-A database contains curated bit score thresholds (38).

One limitation in reproducibly defining NLRomes, may simply be the lack of a unified definition for NLR-coding genes. Given the current mechanistic understanding of plant NLR biology, a putative NLR-coding gene would contain either an NB-ARC, or TIR, or RPW8 domain. LRR domains commonly occur in other protein families and should not be considered part of the primary definition of NLRs. CC folds can't be easily detected using domain profiles, and often require secondary structure prediction such as Paircoil2 (79), MARCOIL (29), COILS (75), MultiCoil (129), and PCOILS (45). The different CC prediction tools generate slightly different outputs, but their union and/or intersections can be informative and assist identification of high probability CC signatures.

Criteria for defining NLRs has changed as our mechanistic understanding of NLR has deepened. Historically, NB-ARC alignments and NB-ARC motifs have been used to discriminate between TIR, or non-TIR NLRs (40; 82; 91). When the first NB-LRR and RPW8 NLRs were reported (132), it became relevant to distinguish between CC-NB-LRRs, RPW8-NB-LRRs and NB-LRRs. A curated RPW8 HMM profile is available from Pfam-A, allowing distinction between CC and CCr classes. TIR and TIR-NB proteins are increasingly being described with immune receptor-like function (discussed above), thus a broader definition of "NLR" is likely warranted. Recent reports have also pointed to the importance of considering TIR_2 domains in addition to TIR domains when defining NLRs (95).

Resistance from relatives in the post genomic era

Plant species with major agricultural and economic interest frequently have large and complex genomes. Therefore, cheap and efficient methods to identify NLRs at a genome-wide level are invaluable. R-gene enrichment and sequencing (RenSeq) is a method that allows selective sequencing of NLR-containing genomic fragments (42; 58). The method allows the definition of the NLRome of any plant by using an RNA bait

library (complementary to known or partially annotated NLRs from related species) combined with a HT sequencing platform (typically Illumina, Pacbio or Nanopore) (43; 57). The technique reduces the overall complexity of the genomic sample, and allows focused sequencing on the enriched gene family.

RenSeq technology allowed refinement of NLR gene annotations, as well as the identification of 317, 105 and 126 previously unreported NLRs in *S. tuberosum* DM clone, *S. lycopersicum* Heinz 1706 and *S. pimpinellifolium* LA1589, respectively (1). Most of the novel genes mapped to unannotated or gapped regions of the genomes. RenSeq allowed thus the definition of previously unidentified or incomplete NLR clusters, in which the novel genes were found to reside (1; 2; 58; 94; 115). This technique can also be applied to plant species for which there is no available draft genome. RenSeq applied to wild relatives of tomato allowed the identification of markers that cosegregated with resistance to *Phytophtora infestans* (58). RenSeq combined with long read Single Molecule Real Time (SMRT) sequencing is effective at resolving NLR clusters that are notoriously difficult to sequence. (42; 43; 128). RenSeq has also been successfully used to enrich NLR cDNAs, allowing transcript validation of 167 *S. lycopersicum* Heinz 1706 and 154 *S. pimpinellifolium* LA1589 NLRs (1). Identification of sources of resistance from wild relatives, or ancestral progenitors from the primary geographic diversity centers will provide novel NLR variants to further increase the disease resistance gene pool available for breeding programs (70; 120)

NLR transfers between genomes

Understanding NLR diversity at the mechanistic and genomic levels provides an invaluable resource for breeding and, eventually, rationally engineering disease resistance. Traditionally, sources of resistance have been selected for, or found in closely related genomes. Plant genomes have followed independent evolutionary paths and each has a unique set of immune receptors. To what extent are immune receptors transferable between more distant genomes? To what extent will genomic studies define a pan-NLRome allowing the use of these diverse products of evolution from across the kingdom as resistance traits?

The first example of interfamily immune receptor transfer was between Arabidopsis and the solanaceous plants *Nicotiana benthamiana* and Tomato (68). EFR is a PRR receptor-like kinase that perceives the bacterial PAMP EF-Tu (elf18 peptide), but it is only present in the Brassicaceae. After transferring it into solanaceous genomes, EFR was able to confer responsiveness to elf18. Importantly, it also resulted in strong bacterial disease resistance in tomato. NLRs can also be transferred between genomes. Rice genomes don’t have a known resistance specificity for *Xanthomonas*

oryzae pv. *oryzicola*. After identifying a disease resistance trait in maize, Zhao, et al. were able to transfer RXO1, a CNL, into rice and generate resistant plants (141).

Even further phylogenetic distances are possible. The monocot CNL *MLA1* has been transferred from barley into the dicot Arabidopsis (74). Amazingly, MLA1 is functional in Arabidopsis and recognizes the pathogen effector AVRa1. This result indicates that the machinery required for NLR function can be conserved over extremely large phylogenetic distances. A high level of conservation is also supported by the general feasibility of transient assays in *Nicotiana* and the conservation of *Nicotiana* EDS1 function to support phylogenetically distant Arabidopsis TIR and TNL functions (87; 126).

There are likely limits to the transfer of immune receptors. To serve as useful traits NLRs must be functional and properly regulated. Functionality requires that the NLR can integrate into a largely unknown system required for recognition and downstream function. Proper regulation is required to ensure that NLRs do not have negative impacts on fitness via autoactivity. Autoactivity is a frequent outcome of transgenic expression of NLRs. This is likely due to the idiosyncratic nature of transgenic lines and resulting over- or mis-expression. In other cases the autoactivity may be genetically determined. In the case of the “Dangerous Mix” loci, incompatibilities can be revealed by outcrosses of Arabidopsis genomes that have undergone independent evolution (11). Several of these loci map to NLR immune receptors and may reflect drift between NLRs and guardees that results in inappropriate physical interaction and the resulting autoactivity (21). Thus, in the case of NLRs that guard host proteins, there may be a limitation based on conservation between the guardee and the adopted guardee in the new genome. NLRs themselves may form incompatible heteromeric complexes and one NLR may activate a second when they encounter each other via outcrossing (116). In other cases, NLRs may negatively regulate each other. Transfer of the rye *Pm8* resistance gene into wheat is limited in some genotypes by the dominant action of the wheat *Pm3* resistance gene (52). As both genes are CNLs, it is intriguing to speculate that the suppression is via the formation of an inappropriate, inactive heteromeric receptor complex.

NLR tinkering: fine tuning responses

Existing NLRs can also be tinkered with, to either expand recognition or tune responsiveness. An early attempt at modifying NLR specificity mutagenized the Rx CNL in ordered to expand recognition of potato virus X strains (35). By using random mutagenesis targeted at the LRR, they were able to find Rx mutants that could recognize not only the wild-type version of PVX coat protein (CP), but also mutant CP that could evade wild-type Rx. Interestingly, the Rx mutants now also recognized CP from the distantly-related poplar mosaic virus (PoMV). One of the mutants, Rx N846D,

displayed systemic necrosis when challenged with PoMV, demonstrating a cost to increased recognition. Further mutagenesis of Rx N846D was able to find new mutations that were able to convert the systemic necrosis into a strong resistance able to control PoMV (49). Interestingly, while N846D is located in the LRR, the suppressing mutations are in the NBS domain, suggesting an interdomain contact. Similar attempts to generate expanded specificities for the potato NLR R3a were able to expand recognition to “stealthy” versions of the AVR3a effector (22; 98).

Study of the wheat CNL Pm3 indicates that the NBS domain of NLRs are tuned in their responses and that this tuning can be downstream of “triggerability” (106). In this case, immune output can be altered independently of propensity to be activated by mutation of only two residues in the ARC2 subdomain. This is consistent with a hypothesis that initial pathogen detection is translated into an appropriately tuned resistance response. These two tuning residues are surface exposed in NBS models, but higher order true structures of the NBS in combination with other domains will be required to understand how they are promoting an ATP-bound active conformation. By all indications, NLRs have multiple intramolecular interactions that can be tuned for a combination of activation and output strength.

NLR re-engineering: building better mousetraps

Beyond single point mutations, more extensive re-engineering of NLRs has also been attempted. Domain swaps between closely related NLRs (such as Rx1 and Gpa2) can result in a corresponding specificity swap (101). Domain swaps indicate that NBS and LRR intramolecular interactions are critical for maintaining the resting state of NLRs to avoid inappropriate, elicitor-independent activation (102). These Rx1/Gpa2 domain swaps used existing specificities to engineer NLR function, what are the prospects for novel specificities?

Recently, breakthrough studies of the RPS5 system has presented an excellent opportunity to rationally engineer NLR immune recognition. In this case, the CNL RPS5 indirectly recognizes AvrPphB proteolytic cleavage of the decoy kinase protein PBS1. The elegant solution described by Kim et al, is that replacement of the AvrPphB cleavage site with an engineered protease site will allow an unmodified RPS5 to activate defenses to novel proteases (61). By engineering the guardee they were able to obviate problems of autoactivation created by modifying the NLR itself. But even with a WT NLR, there are likely issues that will have to be solved for any engineered PBS1/RPS5 system. The authors found that activation of RPS5 defenses against turnip mosaic virus (TuMV) (using an engineered PBS1 cleaved by TuMV Nla protease) was slower than needed to limit systemic spread. They proposed that the plasma membrane localization of WT RPS5 may be inappropriate for detection of an effector protease found mostly in the nucleus. If these sorts of pathogen-specific issues can be overcome,

the abundance of protease effectors in pathogen effector repertoires suggests that RPS5/PBS1 may be a widely useful NLR engineering approach.

In most cases, our understanding of how an NLR functions is limited. In the case of RPS5 and PBS1 years of research was required to adequately understand how to use it as an NLR engineering platform (63). The recent discovery of paired NLRs with integrated domains (described above) suggests a powerful shortcut for identifying engineering targets. NLR pairs are relatively easy to identify and are present in many plant genomes. Importantly, following the model of RPS4 and RRS1, if integrated domains are effector decoys, then we will not have to genetically identify an unknown guardee. The loci should be transferable to novel genomes, and as they contain both components of the receptor complex (receptor NLR and signaling NLR). As they define a complete receptor complex, they should be less susceptible to problems arising from incompatibility due to independent evolution. Recent study by Bailey et al. indicates that NLRs with integrated domains are quickly gaining and losing novel unsual domains (3) , and thus may be rapidly changing specificity within a conserved receptor context. It will be extremely informative to understand what mutations in the canonical NLR domains are required to accomodate a novel ID. These mutations will undoubtedly be critical for both maintenance of the resting state and/or appropriate activation in response to effector modification of the ID. Replacement of an ID with a novel effector target or with a homologous one derived from the recipient genome may be a viable approach to engineering NLRs.

Unanswered Questions and Outlook

Many of the basic questions about NLR function remain unanswered. A better understanding of how individual NLR domains interact with one another is critical to understanding how the molecules function as a switch. This is important for limiting the costs of inappropriate activation, as well as for understanding pathogen specificity and strength of response. We need to understand how NLRs activate downstream events: how disease resistance and cell death are triggered remains, remarkably, a black box. How do NLRs homo and hetero-oligomerize to generate an immune system? To what extent do the two tiers of the immune system (NLRs and PRRs) functionally cooperate to form an immune system? Can we identify characteristics of NLRs that promote durable resistance?

Rational engineering of immune receptors is an increasingly achievable goal. By mechanistically understanding how NLRs function, we will be able to modify existing NLRs or generate novel receptor systems that recognize pathogens of interest. By exploring the breadth and depth of plant NLR natural variation, we will expand our toolbox of deployable disease resistance traits. Accelerating climate change is predicted to generate novel pathogen/plant interactions, demanding rapid responses by plant

breeders (6). Rational design of plant immune systems will be one tool, of many, that enables agricultural systems to keep pace with pathogens.

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TERMS AND DEFINITIONS:

ETI - Effector-Triggered Immunity.
PAMP - Pathogen-Associated Molecular Pattern.
PTI - PAMP-Triggered Immunity.
NLR - Nucleotide-binding Leucine-Rich Repeat or NOD-Like Receptor.
TIR - Toll/interleukin-1 receptor.
TNL - TIR-containing NLR.
CC - Coiled-Coil.
CNL - CC-containing NLR.
RNL - RPW8-containing NLR
PRR - Pattern Recognition Receptors.
HR - Hypersensitive Response.
LRR - Leucine-Rich Repeat.
NBS - Nucleotide-Binding Site.
IDs - Integrated Domains, or Integrated Decoys.
Pan-NLRome - union of all the NLRs found in a collection of individuals (same population, species, family, etc).
At-panNLRome - Arabidopsis thaliana pan-NLRome.
HMM - Hidden Markov Model.
RenSeq - Resistance-gene ENrichment and SEQuencing.
SMRT - Single Molecule Real Time.
MBP - Mapping by Sequencing.
SNP - Single Nucleotide Polymorphisms.

RELATED RESOURCES:

- The Plant Resistance Genes database (PRGdb). http://prgdb.org
- Public release of RenSeq assemblies from 69 accessions of *Arabidopsis thaliana*, and R-genes from four Nicotiana and four Solanum species. http://2blades.org/resources/
- Wikipedia List of sequenced plant genomes (last Updated in October 2017). https://en.wikipedia.org/wiki/List_of_sequenced_plant_genomes

SIDEBAR:

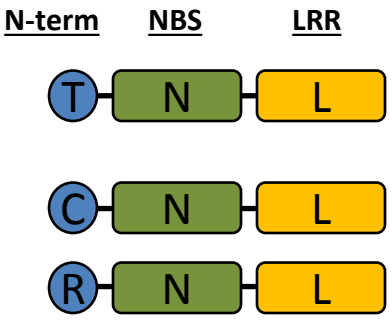
Checklist for genome-wide NLR interrogation studies:

- HMM profiles are powerful tools to identify functional domains.
- Curated HMM profile databases include Pfam-A, Panther, SMART, TIGRFAM, among many others.
- HMMER and InterproScan are currently the most used bioinformatic tools to detect functional domains.
- Consider using multiple secondary structure prediction tools to detect proteins likely to present a coiled-coil fold, and report the probability cut-off.
- To facilitate reproducibility, authors should include model specific cut-offs included in curated HMM databases and report software and database versions, as well as genome annotation release.

Figure 1 draft

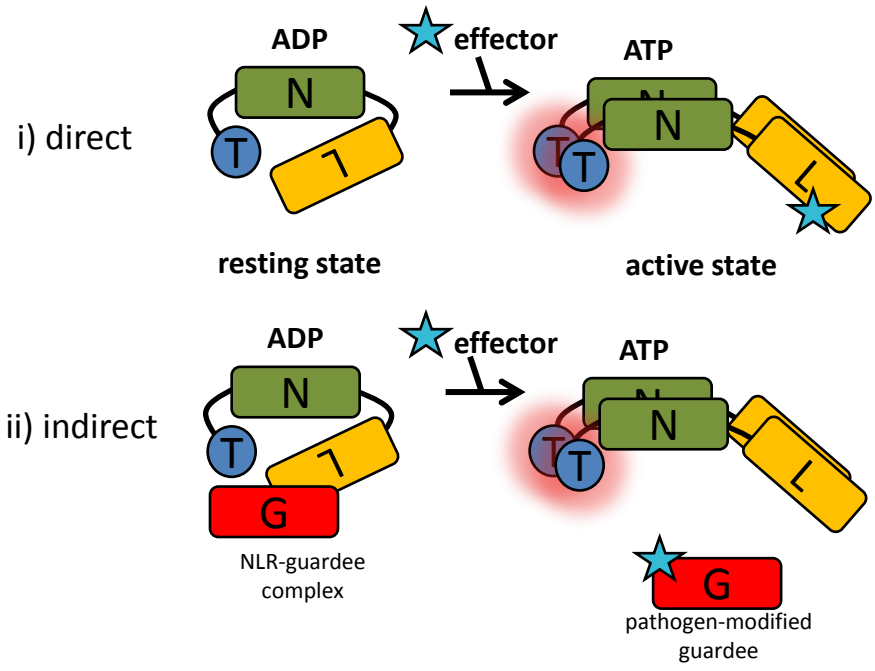
a

many NLRs have a stereotypical domain organization



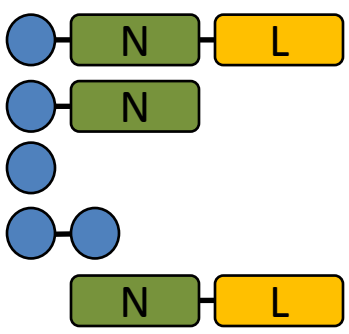
b

NLRs directly and indirectly recognize effectors



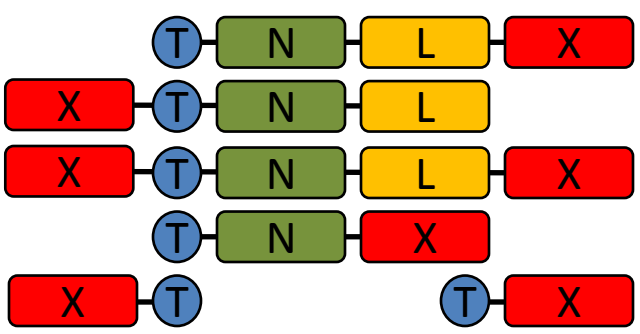
c

NLRs also exist in diverse domain combinations



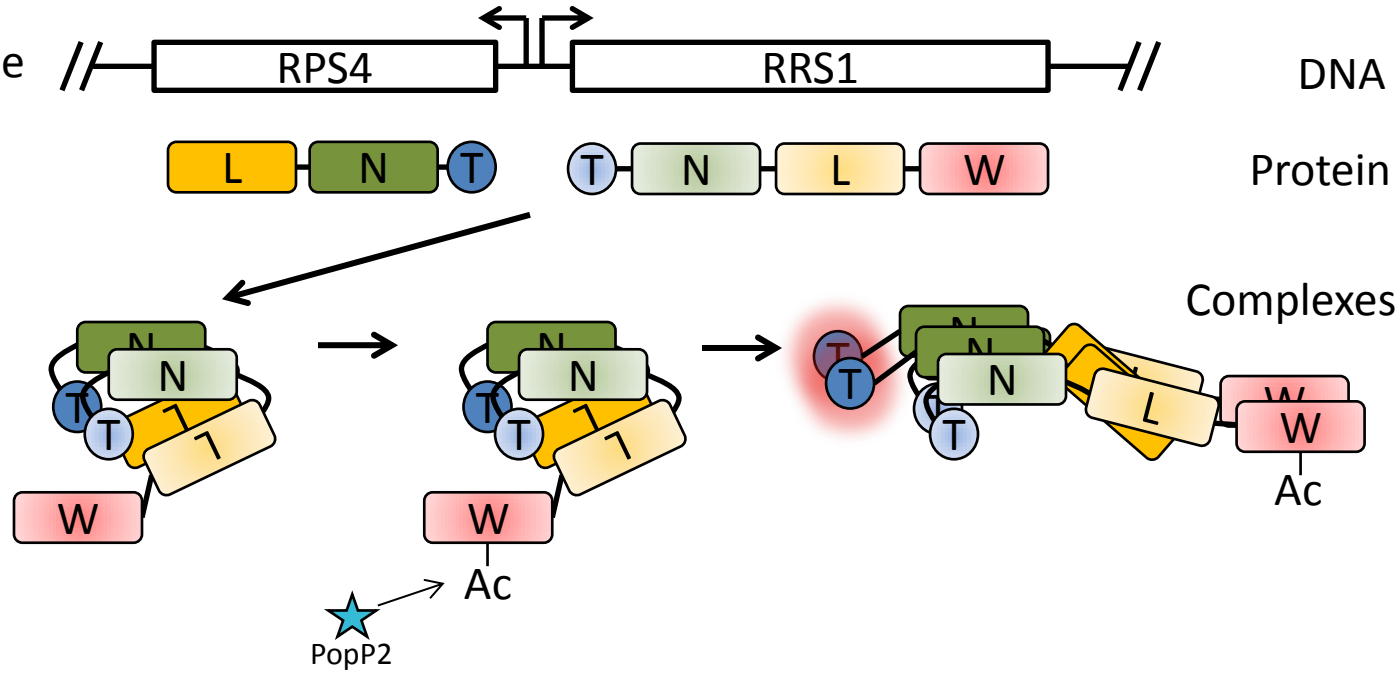
d

NLRs can contain unusual integrated domains



Genomically-paired NLRs combine an signaling NLR and a receptor NLR that contains a decoy domain

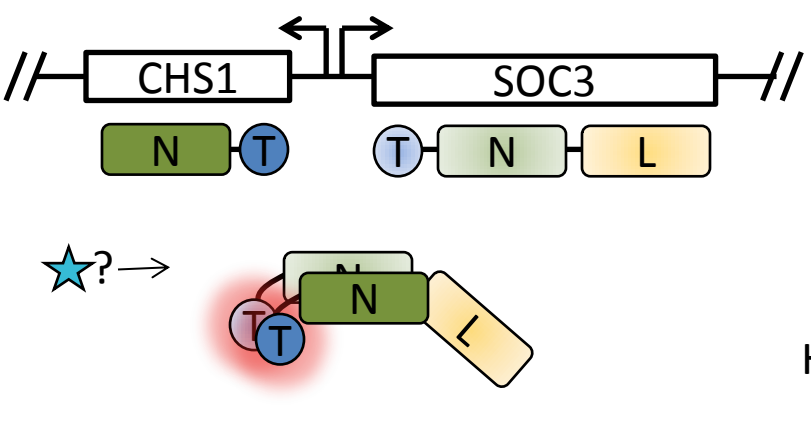
e



f

"truncated" NLRs may function in hetero-oligomeric immune complexes

i) Autoactivity of *chs1-1* requires neighboring TNL SOC3



ii) TIR-only RBA1 functions as a receptor?

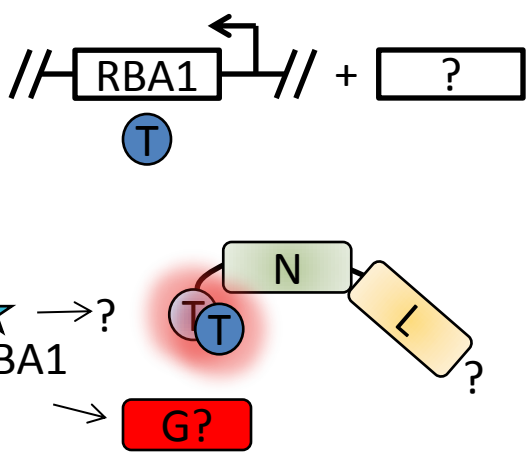
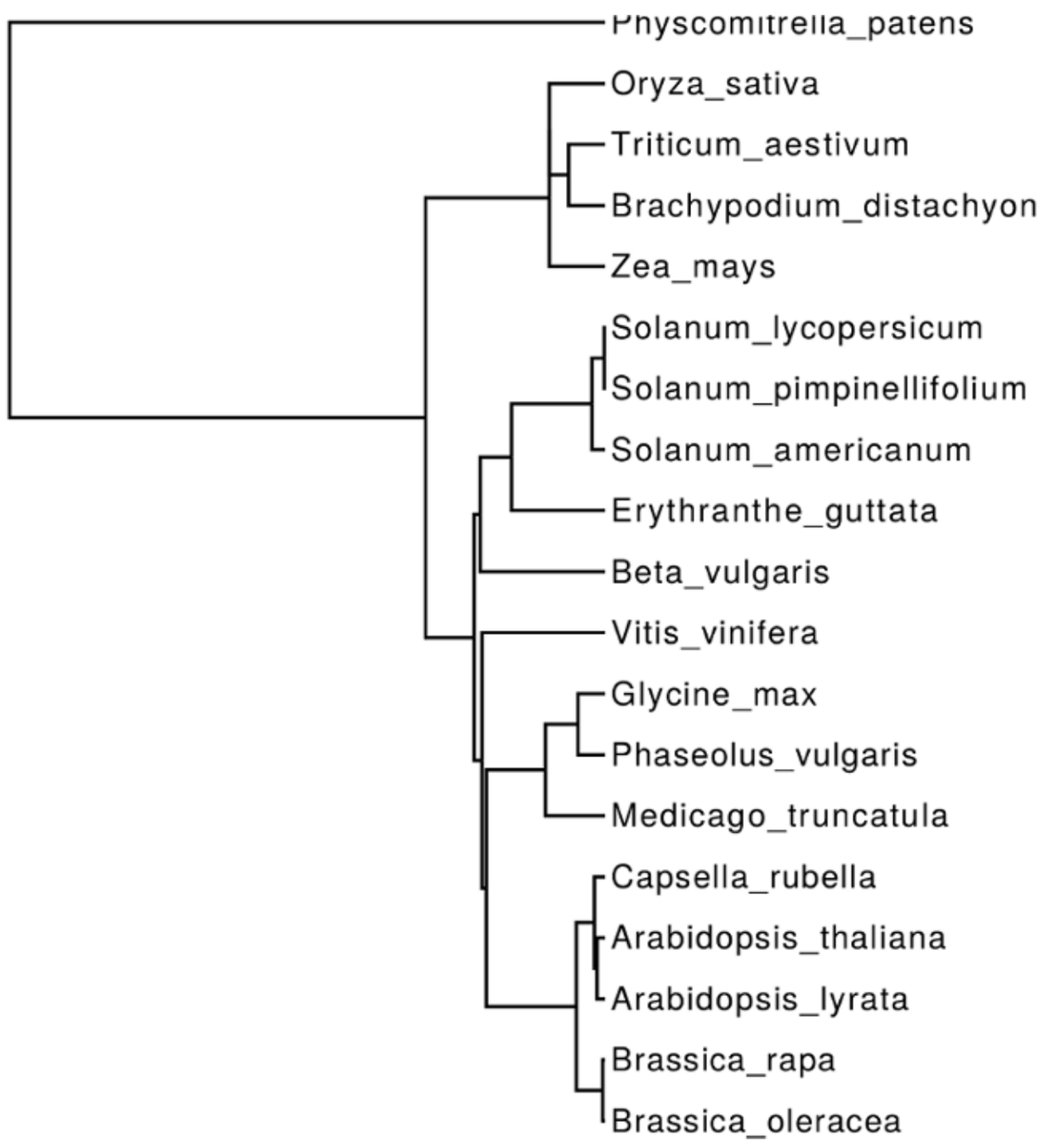


Figure 1) NLRs are modular switches. (a) typical plant NLRs contain a variable N-terminal domain, either TIR (T), Coiled-coil (C) or RPW8-like (R) domain followed by an NBS domain (N) and Leucine-rich repeat domain (L). (b) NLRs undergo conformation switching depending on ADP/ATP binding state induced/stabilized by effector (or guardee) trigger. Multimerization of N-terminus is required and often sufficient for signaling (red glow). The exact multimerization state is not known, but is shown here only as dimeric for graphical clarity. Detection of pathogen effectors can either be direct (i) or indirectly via modification of a host guardee protein (G). (c) Plant genomes contain a diverse array of NLR domain combinations. (d) Plant genomes contain NLRs with unusual "integrated domains" (X). Integrated domains can occur in many locations in the NLR domain structure. Example shown are from Arabidopsis. (e) NLRs with integrated domains are often found as pairs divergently expressed at a single genomic locus. In the case of RPS4/RRS1, effector (PopP2) targeting and acetylation of the integrated WRKY decoy domain (W) in RRS1 activates RPS4 to activate defense responses. The exact stoichiometry and orientation of RRS1 and RPS4 pre and post activation are unknown, but RPS4 and RRS1 interact pre-activation and the post-activation complex requires RPS4-RPS4 TIR self-association to signal. (f) Truncated NLRs likely function in hetero-oligomeric immune complexes. (f;i) Autoactivity triggered by the TN mutant *chs1-1* requires full length TNL SOC3. CHS1 and SOC3 also occur in a genomic pair. SOC3 physically interacts with CHS1, but it is unclear if this pair also functions to recognize a pathogen effector. (f;ii) RBA1 encodes a TIR-only protein that triggers cell-death in response to the pathogen effector HopBA1. While RBA1 and HopBA1 co-immunoprecipitate, they may not interact directly and could require unknown components such as a putative guardee or an unknown partner TNL.

Species	Reference	Data Source	NB	NB-LRR	TIR	TIR-LRR	TIR-NB	TIR-NB-LRR	CC-NB	CC-NB-LRR	RPW8	RPW8-NB	RPW8-NB-LRR
Physcomitrella patens	Kim et al. 2012	JGI, v1.1	28	12	2	-	-	1	0	0	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v3	87	49	-	-	2	4	-	-	-	-	-
Oryza sativa	Zhou et al. 2004	Bai et al. 2002; Genbank; BLAST; GRAMENE; *ab initio* annotations	45	320	-	-	3	-	7	160	-	-	-
	Kim et al. 2012	MSU, v6.1	36	167	2	-	0	0	40	333	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v7	595	438	-	-	0	0	-	-	-	-	-
	Nepal et al. 2017	JGI, Phytozome	-	-	-	-	-	-	149 *				
Triticum aestivum	Bouktila et al. 2015	NCBI; *ab initio* annotation	1	96	-	-	-	-	5	334	-	-	-
	Sarris et al. 2016	Ensembl, MIPS v22	1224	627	-	-	0	0	-	-	-	-	-
Brachypodium distachyon	Tan and Wu 2012	brachypodium.org, v1.2	12	16	-	-	-	-	48	157	-	-	-
	Kim et al. 2012	JGI, v1	12	47	1	-	0	0	18	107	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v2.1	501	357	-	-	0	0	-	-	-	-	-
Zea mays cv. B73	Cheng et al. 2012	maizesequence.org; *ab initio* annotation	7	31	-	-	0	0	11	58	-	-	-
	Kim et al. 2012	maizegdb.org, v4a.53	16	31	3	-	0	0	9	63	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v6a	191	105	-	-	0	0	-	-	-	-	-
Solanum lycopersicum Heinz 1706	Andolfo et al. 2014	RenSeq	57	88	10	1	3	26	14	107	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, iTAGv2.3	264	137	-	-	5	19	-	-	-	-	-
Solanum pimpinellifolium LA1589	Andolfo et al. 2014	RenSeq	122	78	12	1	6	14	34	32	-	-	-
Solanum americanum SP2271	Witek et al. 2016	RenSeq	-	-	-	-	-	100	-	528	-	-	-
Mimulus guttatus	Kim et al. 2012	JGI, v1	5	53	1	-	0	0	12	67	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v2	344	190	-	-	0	0	-	-	-	-	-
Beta vulgaris	Dohm et al. 2014	Genome annotation	22	56	-	-	-	1	26	32	-	-	-
Vitis vinifera	Yu et al. 2014	Genoscope	36	159	10	-	14	97	26	203	-	-	-
	Kim et al. 2012	Genoscope	34	133	22	-	26	99	22	254	-	-	-
	Zheng et al. 2016	NCBI/Phytozome, v8	182	130	75	-	7	14	75	69	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, Genoscope12X	323	256	-	-	3	18	-	-	-	-	-
Glycine max	Kim et al. 2012	JGI, v1	11	127	35	-	12	140	0	122	-	-	-
	Shao et al. 2014	JGI, Phytozome v1.1	42	145	-	-	24	124	8	109	-	1	9
	Zheng et al. 2016	NCBI/Phytozome, v1.1	156	70	53	-	68	67	46	68	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, Wm82.a2.v1	784	669	-	-	49	254	-	-	-	-	-
Phaseolus vulgaris	Shao et al. 2014	JGI, Phytozome, v1	3	100	-	-	13	76	9	128	-	0	5
	Zheng et al. 2016	NCBI/Phytozome, v1	59	20	57	-	9	1	40	31	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v1	406	381	-	-	15	98	-	-	-	-	-
Medicago truncatula	Kim et al. 2012	medicago.org, v3	95	132	98	-	47	142	15	139	-	-	-
	Shao et al. 2014	JGI, Phytozome, v3	111	145	-	-	49	121	16	94	-	0	8
	Yu et al. 2014	medicago.org,	328	-	92	-	38	118	25	152	-	-	-
	Zheng et al. 2016	NCBI/Phytozome, 3.5v5	193	102	44		127	44	44	49	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, Mt4.0v1	1074	893	-	-	63	361	-	-	-	-	-
Capsella rubella	Y.-M. Zhang et al. 2016	JGI, Phytozome, Aug. 2013	8	41	-	-	9	31	4	32	-	1	9
	Sarris et al. 2016	JGI, Phytozome v10, v1	152	127	-	-	11	40	-	-	-	-	-
Arabidopsis thaliana Col-0	Kim et al. 2012	TAIR9	6	26	40	-	18	98	2	48	-	-	-
	Yu et al. 2014	TAIR10	26	20	46	-	17	79	8	17	-	-	-
	Y.-M. Zhang et al. 2016	JGI, Phytozome, Aug. 2013	2	13	-	-	14	80	3	40	-	1	5
	Sarris et al. 2016	JGI, Phytozome v10, TAIR10	213	182	-	-	18	105	-	-	-	-	-
Arabidopsis lyrata	Y.-M. Zhang et al. 2016	JGI, Phytozome, Aug. 2013	15	31	-	-	17	92	6	27	-	0	5
	Kim et al. 2012	JGI, v1	13	36	41	-	18	98	2	33	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v1	204	163	-	-	19	96	-	-	-	-	-
Brassica rapa	Y.-M. Zhang et al. 2016	JGI, Phytozome, Aug. 2013	8	29	-	-	22	83	7	35	-	0	7
	Yu et al. 2014	brassicadb.org/brad/,	29	27	42	-	23	93	15	19	-	-	-
	Sarris et al. 2016	brassicadb.org/brad/, v1.2	207	164	-	-	22	92	-	-	-	-	-
Brassica oleracea	Yu et al. 2014	ocri-genomics.org/bolbase/	53	24	82		29	40	5	6			
	Golicz et al. 2016	Pangenome	114	97			41	132	30	25	2 **	3 **	

(*) Contains non-TIR (RPW8, CC, NBS-LRR)

(**) Number of genes detected in the gene models provided by the authors using a conservative hmmscan with PfamA RPW8 and NB-ARC --cut_tc thresholds



Species	Reference	Data Source	NB	NB-LRR	TIR	TIR-LRR	TIR-NB	TIR-NB-LRR	CC-NB	CC-NB-LRR	RPW8	RPW8-NB	RPW8-NB-LRR
Physcomitrella patens	Kim et al. 2012	JGI, v1.1	28	12	2	-	-	1	0	0	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v3	87	49	-	-	2	4	-	-	-	-	-
Oryza sativa	Zhou et al. 2004	Bai et al. 2002; Genbank; BLAST; GRAMENE; *ab initio* annotations	45	320	-	-	3	-	7	160	-	-	-
	Kim et al. 2012	MSU, v6.1	36	167	2	-	0	0	40	333	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v7	595	438	-	-	0	0	-	-	-	-	-
	Nepal et al. 2017	JGI, Phytozome	-	-	-	-	-	-	149 *				
Triticum aestivum	Bouktila et al. 2015	NCBI; *ab initio* annotation	1	96	-	-	-	-	5	334	-	-	-
	Sarris et al. 2016	Ensembl, MIPS v22	1224	627	-	-	0	0	-	-	-	-	-
Brachypodium distachyon	Tan and Wu 2012	brachypodium.org, v1.2	12	16	-	-	-	-	48	157	-	-	-
	Kim et al. 2012	JGI, v1	12	47	1	-	0	0	18	107	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v2.1	501	357	-	-	0	0	-	-	-	-	-
Zea mays cv. B73	Cheng et al. 2012	maizesequence.org; *ab initio* annotation	7	31	-	-	0	0	11	58	-	-	-
	Kim et al. 2012	maizegdb.org, v4a.53	16	31	3	-	0	0	9	63	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v6a	191	105	-	-	0	0	-	-	-	-	-
Solanum lycopersicum Heinz 1706	Andolfo et al. 2014	RenSeq	57	88	10	1	3	26	14	107	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, iTAGv2.3	264	137	-	-	5	19	-	-	-	-	-
Solanum pimpinellifolium LA1589	Andolfo et al. 2014	RenSeq	122	78	12	1	6	14	34	32	-	-	-
Solanum americanum SP2271	Witek et al. 2016	RenSeq	-	-	-	-	-	100	-	528	-	-	-
Mimulus guttatus	Kim et al. 2012	JGI, v1	5	53	1	-	0	0	12	67	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v2	344	190	-	-	0	0	-	-	-	-	-
Beta vulgaris	Dohm et al. 2014	Genome annotation	22	56	-	-	-	1	26	32	-	-	-
Vitis vinifera	Yu et al. 2014	Genoscope	36	159	10	-	14	97	26	203	-	-	-
	Kim et al. 2012	Genoscope	34	133	22	-	26	99	22	254	-	-	-
	Zheng et al. 2016	NCBI/Phytozome, v8	182	130	75	-	7	14	75	69	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, Genoscope12X	323	256	-	-	3	18	-	-	-	-	-
Glycine max	Kim et al. 2012	JGI, v1	11	127	35	-	12	140	0	122	-	-	-
	Shao et al. 2014	JGI, Phytozome v1.1	42	145	-	-	24	124	8	109	-	1	9
	Zheng et al. 2016	NCBI/Phytozome, v1.1	156	70	53	-	68	67	46	68	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, Wm82.a2.v1	784	669	-	-	49	254	-	-	-	-	-
Phaseolus vulgaris	Shao et al. 2014	JGI, Phytozome, v1	3	100	-	-	13	76	9	128	-	0	5
	Zheng et al. 2016	NCBI/Phytozome, v1	59	20	57	-	9	1	40	31	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v1	406	381	-	-	15	98	-	-	-	-	-
Medicago truncatula	Kim et al. 2012	medicago.org, v3	95	132	98	-	47	142	15	139	-	-	-
	Shao et al. 2014	JGI, Phytozome, v3	111	145	-	-	49	121	16	94	-	0	8
	Yu et al. 2014	medicago.org,	328	-	92	-	38	118	25	152	-	-	-
	Zheng et al. 2016	NCBI/Phytozome, 3.5v5	193	102	44		127	44	44	49	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, Mt4.0v1	1074	893	-	-	63	361	-	-	-	-	-
Capsella rubella	Y.-M. Zhang et al. 2016	JGI, Phytozome, Aug. 2013	8	41	-	-	9	31	4	32	-	1	9
	Sarris et al. 2016	JGI, Phytozome v10, v1	152	127	-	-	11	40	-	-	-	-	-
Arabidopsis thaliana Col-0	Kim et al. 2012	TAIR9	6	26	40	-	18	98	2	48	-	-	-
	Yu et al. 2014	TAIR10	26	20	46	-	17	79	8	17	-	-	-
	Y.-M. Zhang et al. 2016	JGI, Phytozome, Aug. 2013	2	13	-	-	14	80	3	40	-	1	5
	Sarris et al. 2016	JGI, Phytozome v10, TAIR10	213	182	-	-	18	105	-	-	-	-	-
Arabidopsis lyrata	Y.-M. Zhang et al. 2016	JGI, Phytozome, Aug. 2013	15	31	-	-	17	92	6	27	-	0	5
	Kim et al. 2012	JGI, v1	13	36	41	-	18	98	2	33	-	-	-
	Sarris et al. 2016	JGI, Phytozome v10, v1	204	163	-	-	19	96	-	-	-	-	-
Brassica rapa	Y.-M. Zhang et al. 2016	JGI, Phytozome, Aug. 2013	8	29	-	-	22	83	7	35	-	0	7
	Yu et al. 2014	brassicadb.org/brad/,	29	27	42	-	23	93	15	19	-	-	-
	Sarris et al. 2016	brassicadb.org/brad/, v1.2	207	164	-	-	22	92	-	-	-	-	-
Brassica oleracea	Yu et al. 2014	ocri-genomics.org/bolbase/	53	24	82		29	40	5	6			
	Golicz et al. 2016	Pangenome	114	97			41	132	30	25	2 **	3 **	

(*) Contains non-TIR (RPW8, CC, NBS-LRR)

(**) Number of genes detected in the gene models provided by the authors using a conservative hmmscan with PfamA RPW8 and NB-ARC --cut_tc thresholds

Table 1 Legend

Survey of the number of NLR proteins in 19 plant species. The total number of NBS genes in each domain arrangement was retrieved from the indicated papers. One asterisk indicates reported non-TIR NLRs. Two asterisks refer to domains present in the fasta sequences provided by the authors, but not explicitly presented in the respective publication. HMMER with Trusted Cutoff threshold was used to retrieve RPW8 domains. Table rows are colored according to taxonomic family, with different shades for each species. Yellow, Poaceae; Orange, Solanaceae; Blue, Fabaceae; and Green, Brassicaceae. The phylogeny of the species listed in the table was obtained from timetree.org.

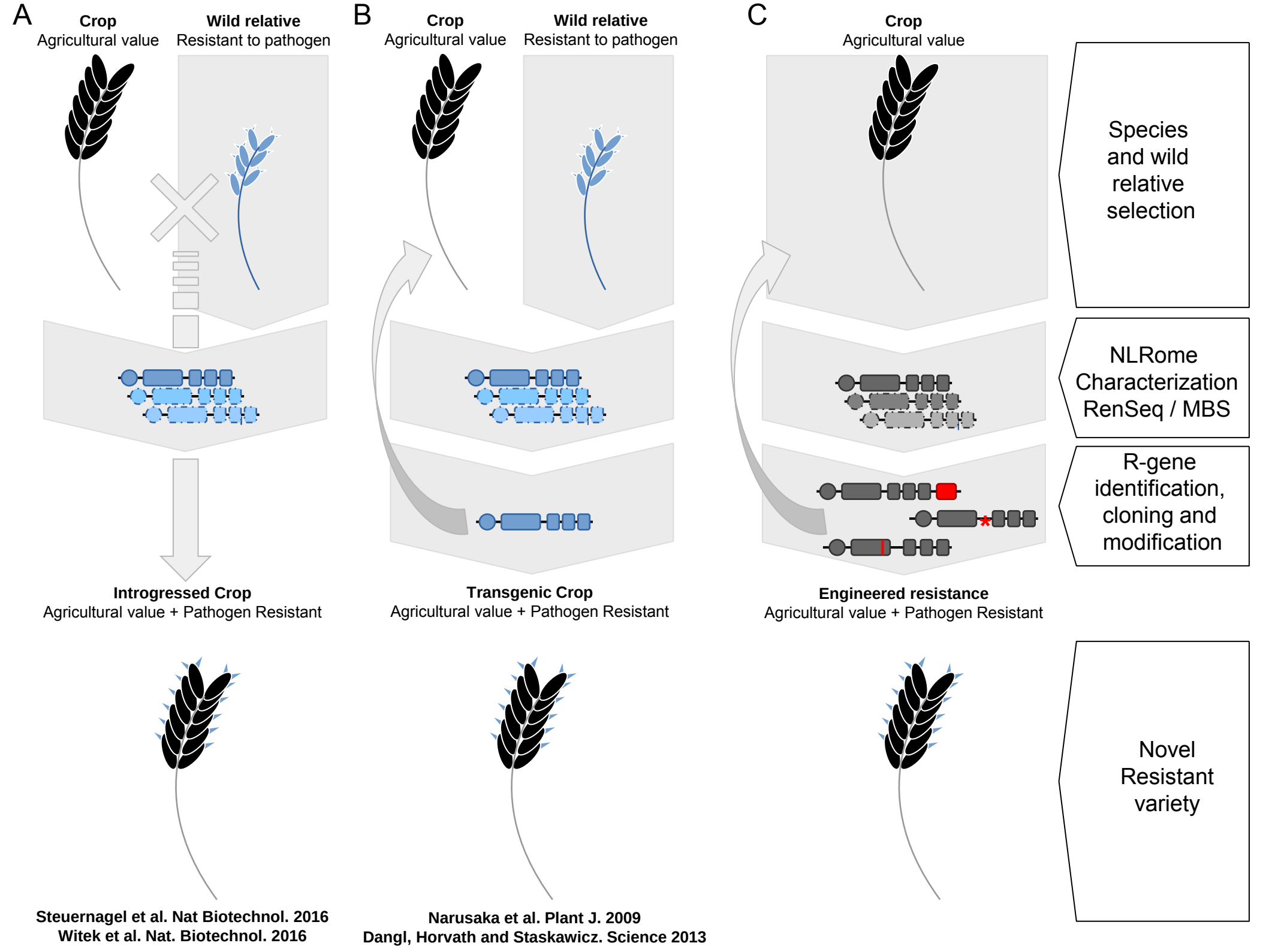
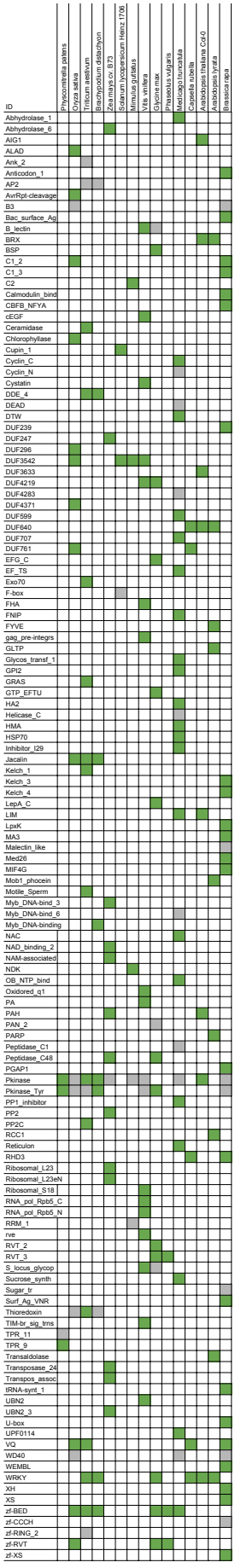

A
Crop
Agricultural value
Wild relative
Resistant to pathogen
Introgressed Crop
Agricultural value + Pathogen Resistant
B
Crop
Agricultural value
Wild relative
Resistant to pathogen
Transgenic Crop
Agricultural value + Pathogen Resistant
C
Crop
Agricultural value
Engineered resistance
Agricultural value + Pathogen Resistant
Species and wild relative selection
NLRome Characterization RenSeq / MBS
R-gene identification, cloning and modification
Novel Resistant variety
Steuernagel et al. Nat Biotechnol. 2016
Witek et al. Nat. Biotechnol. 2016
Narusaka et al. Plant J. 2009
Dangl, Horvath and Staskawicz. Science 2013

Figure 2 legend:

Plant NLR repertoires at the service of pathogen resistance engineering. (A) Wild relatives of an interesting crop might exhibit useful disease resistance phenotypes. NLR sequencing with RenSeq or MBP (Mapping by sequencing, Gina et al. Nature Communications 2017) allows the identification of crop and wild relative NLR repertoires. Comparative analysis of presence-absence, SNP and InDel polymorphisms assist the identification of NLR(s). Upon identification of the R-gene(s) in a resistant wild relative, resistance can be introgressed into the crop by hybridization and consecutive backcrosses. RenSeq might be a valuable tool to reduce genome complexity and assist selection of progeny. (B) When the crop and the wild relative are sexually incompatible, the NLR(s) can be cloned from the wild relative (or a more phylogenetically distant genome) and introduced the desired crop via transgenesis. (C) In the future, the accumulated knowledge in NLR domain swapping, integrated decoys, pathogen effector targets and point-mutation alleles will be used to engineer novel resistances. Pathogen effector targets might be incorporated into an already existent NLR-ID, in order to create a novel sensor. Modification of NLR-associated guardees or decoys (such as PBS1, not shown) are also possible.


ID
Physcomitrella patens
Oryza sativa
Triticum aestivum
Brachypodium distachyon
Zea mays cv. B73
Solanum lycopersicum Heinz 1706
Mimulus guttatus
Vitis vinifera
Glycine max
Phaseolus vulgaris
Medicago truncatula
Capsella rubella
Arabidopsis thaliana Col-0
Arabidopsis lyrata
Brassica rapa
Abhydrolase_1
Abhydrolase_6
AIG1
ALAD
Ank_2
Anticodon_1
AP2
AvrRpt-cleavage
B3
Bac_surface_Ag
B_lectin
BRX
BSP
C1_2
C1_3
C2
Calmodulin_bind
CBFB_NFYA
cEGF
Ceramidase
Chlorophyllase
Cupin_1
Cyclin_C
Cyclin_N
Cystatin
DDE_4
DEAD
DTW
DUF239
DUF247
DUF296
DUF3542
DUF3633
DUF4219
DUF4283
DUF4371
DUF599
DUF640
DUF707
DUF761
EFG_C
EF_TS
Exo70
F-box
FHA
FNIP
FYVE
gag_pre-integrs
GLTP
Glycos_transf_1
GPI2
GRAS
GTP_EFTU
HA2
Helicase_C
HMA
HSP70
Inhibitor_I29
Jacalin
Kelch_1
Kelch_3
Kelch_4
LepA_C
LIM
LpxK
MA3
Malectin_like
Med26
MIF4G
Mob1_phocein
Motile_Sperm
Myb_DNA-bind_3
Myb_DNA-bind_6
Myb_DNA-binding
NAC
NAD_binding_2
NAM-associated
NDK
OB_NTP_bind
Oxidored_q1
PA
PAH
PAN_2
PARP
Peptidase_C1
Peptidase_C48
PGAP1
Pkinase
Pkinase_Tyr
PP1_inhibitor
PP2
PP2C
RCC1
Reticulon
RHD3
Ribosomal_L23
Ribosomal_L23eN
Ribosomal_S18
RNA_pol_Rpb5_C
RNA_pol_Rpb5_N
RRM_1
rve
RVT_2
RVT_3
S_locus_glycop
Sucrose_synth
Sugar_tr
Surf_Ag_VNR
Thioredoxin
TIM-br_sig_trns
TPR_11
TPR_9
Transaldolase
Transposase_24
Transpos_assoc
tRNA-synt_1
UBN2
UBN2_3
U-box
UPF0114
VQ
WD40
WEMBL
WRKY
XH
XS
zf-BED
zf-CCCH
zf-RING_2
zf-RVT
zf-XS

Supplemental Table 1 Legend:

Atypical domains detected NLR genes from different plant species. Data obtained from Sarris et al. BMC Biology 2016. Green boxes show overrepresented in NLRs compared to the rest of the genomes, using significant Fisher's exact test p-value lower than 0.05. Grey boxes indicate fusion of the respective domain fusion to at least one NLR, but no enrichment.

Supplemental Table 2

Species	Year	NLR-report	References
Oryza sativa ssp. japonica cultivar Nipponbare	2004, 2006, 2010, 2012, 2017	Yes	(Monosi et al. 2004) (Zhou et al. 2004) (S. Yang et al. 2006) (J. Li et al. 2010) (Luo et al. 2012) (Nepal et al. 2017) (Sarris et al. 2016) (Kroj et al. 2016)
Oryza sativa ssp indica cv 93-11	2015	Yes	(S. Singh et al. 2015)
Oryza sativa ssp indica cv HR-12	2016	Yes	(Mahesh et al. 2016)
Oryza sativa ssp japonica	2015	Yes	(S. Singh et al. 2015)
Oryza brachyantha	2015	Yes	(S. Singh et al. 2015)
Oryza nivara	2014	Yes	(Q.-J. Zhang et al. 2014)
Oryza glaberrima	2014	Yes	(Q.-J. Zhang et al. 2014)
Oryza barthii	2014	Yes	(Q.-J. Zhang et al. 2014)
Oryza glumaepatula	2014	Yes	(Q.-J. Zhang et al. 2014)
Oryza meridionalis	2014	Yes	(Q.-J. Zhang et al. 2014)
Medicago truncatula	2003, 2008, 2011, 2014, 2016, 2017	Yes	(D. J. Bertioli et al. 2003) (Ameline-Torregrosa et al. 2008) (Young et al. 2011) (Shao et al. 2014) (Zheng et al. 2016) (Kroj et al. 2016) (Sarris et al. 2016) (Nepal et al. 2017)
Vitis vinifera	2007, 2008, 2016	Yes	(Velasco et al. 2007) (S. Yang et al. 2008) (Zheng et al. 2016) (Kroj et al. 2016) (Sarris et al. 2016)
Vitis davidii	2017	Yes	(Y. Zhang et al. 2017)
Carica papaya	2008, 2009, 2016	Yes	(Ming et al. 2008) (Porter et al. 2009) (Y.-M. Zhang et al. 2016) (Kroj et al. 2016) (Sarris et al. 2016)
Sorghum bicolor	2009, 2010, 2012, 2014, 2016	Yes	(Paterson et al. 2009) (J. Li et al. 2010) (Luo et al. 2012) (Mace et al. 2014) (Xiping Yang and Wang 2016) (Kroj et al. 2016) (Sarris et al. 2016)
Zea mays	2010, 2012, 2016	Yes	(J. Li et al. 2010) (Luo et al. 2012) (Cheng et al. 2012)

			(Kroj et al. 2016) (Sarris et al. 2016)
Brachypodium distachyon	2010, 2012, 2016	Yes	(J. Li et al. 2010) (Luo et al. 2012) (Tan and Wu 2012) (Sarris et al. 2016) (Kroj et al. 2016)
Glycine max	2003, 2011, 2014, 2016, 2017	Yes	(D. J. Bertioli et al. 2003) (Xiaohui Zhang et al. 2011) (Shao et al. 2014) (Y.-H. Li et al. 2014) (Zheng et al. 2016) (Kroj et al. 2016) (Sarris et al. 2016) (Nepal et al. 2017)
Glycine soja	2016	Yes	(Zheng et al. 2016)
Solanum tuberosum group phureja	2011, 2012	Yes	(Potato Genome Sequencing Consortium et al. 2011) (Lozano et al. 2012)
Solanum tuberosum	2013, 2016	Yes	(Jupe et al. 2013) (Kroj et al. 2016) (Sarris et al. 2016)
Solanum americanum	2016	Yes	(Witek et al. 2016)
Solanum lycopersicum	2013, 2014, 2016	Yes	(G. Andolfo et al. 2013) (Jupe et al. 2013) (Giuseppe Andolfo et al. 2014) (Kroj et al. 2016)(Sarris et al. 2016)
Phaseolus vulgaris	2003, 2014, 2016 2017	Yes	(D. J. Bertioli et al. 2003) (Schmutz et al. 2014) (Shao et al. 2014) (Vlasova et al. 2016) (Zheng et al. 2016) (Sarris et al. 2016) (Kroj et al. 2016) (Jing Wu et al. 2017) (Richard et al. 2017) (Nepal et al. 2017)
Cajanus cajan	2010, 2012, 2014, 2016	Yes	(Varshney et al. 2010) (N. K. Singh et al. 2012) (Shao et al. 2014) (Zheng et al. 2016) (Kroj et al. 2016)
Corchorus olitorius cv. JRO-524 (Navin)	2017	Yes	(Sarkar et al. 2017)
Capsicum annuum	2014, 2017	Yes	(S. Kim et al. 2014) (S. Kim et al. 2017)
Solanum melongena	2012 (PCR), 2014, 2015	Yes	(Zhuang, Zhou, and Wang 2012) (Xu Yang et al. 2014) (Reddy et al. 2015) (Di Donato et al. 2017)

	(PCR), 2017		
Solanum torvum	2014	Yes	(Xu Yang et al. 2014)
Solanum pennellii	2016	Yes	(Stam, Scheikl, and Tellier 2016)
Nicotiana glauca	2016	Yes	(Long et al. 2016)
Nicotiana noctiflora	2016	Yes	(Long et al. 2016)
Nicotiana cordifolia	2106	Yes	(Long et al. 2016)
Nicotiana knightiana	2016	Yes	(Long et al. 2016)
Nicotiana setchellii	2016	Yes	(Long et al. 2016)
Nicotiana tomentosiformis	2016	Yes	(Long et al. 2016)
Nicotiana tabacum	2014	Yes	(Sierro et al. 2014)
Nicotiana sylvestris	2014	Yes	(Sierro et al. 2014)
Nicotiana tomentosiformis	2014	Yes	(Sierro et al. 2014)
Arachis ipaensis	2016, 2017	Yes	(David John Bertioli et al. 2016) (Hui Song et al. 2017)
Arachis duranensis	2003, 2016, 2017	Yes	(Bertioli et al. 2003) (David John Bertioli et al. 2016) (Hui Song et al. 2017)
Daucus carota	2016	Yes	(Iorizzo et al. 2016)
Cicer arietinum	2006, 2016, 2017	Yes	(Palomino et al. 2006) (Zheng et al. 2016) (Kroj et al. 2016) (Sharma, Rawat, and Suresh 2017)
Vicia faba	2006	Yes	(Palomino et al. 2006)
Lotus japonicus	2003, 2015, 2016	Yes	(D. J. Bertioli et al. 2003) (H. Song et al. 2015) (Zheng et al. 2016) (Kroj et al. 2016)
Arachis cardenasii	2003	Yes	(D. J. Bertioli et al. 2003)
Arachis hypogaea var. Tatu	2003	Yes	(D. J. Bertioli et al. 2003)
Arachis stenosperma	2003	Yes	(D. J. Bertioli et al. 2003)
Arachis simpsonii	2003	Yes	(D. J. Bertioli et al. 2003)
Lactuca sativa	2004, 2009, 2015, 2017	Yes	(Plocik, Layden, and Kesseli 2004) (McHale et al. 2009) (Christopoulou et al. 2015) (Reyes-Chin-Wo et al. 2017)
Helianthus annuus	2004, 2008	Yes	(Plocik, Layden, and Kesseli 2004) (Radwan et al. 2008)
Cichorium intybus	2004	Yes	(Plocik, Layden, and Kesseli 2004)
Cucumis melo	2005, 2012, 2014, 2016,	Yes	(van Leeuwen et al. 2005) (Garcia-Mas et al. 2012) (González et al. 2014) (Natarajan et al. 2016) (Casacuberta, Puigdomènech, and Garcia-Mas 2016)
Cucumis sativus	2009, 2013, 2016	Yes	(Sanwen Huang et al. 2009) (Wan et al. 2013) (Kroj et al. 2016) (Sarris et al. 2016)

Arabidopsis thaliana	2003, 2011, 2014, 2015, 2016, 2017	Yes	(Meyers 2003) (Y.-L. Guo et al. 2011) (Gan et al. 2011) (Peele et al. 2014) (Y.-M. Zhang et al. 2016) (Zapata et al. 2016) (Kroj et al. 2016) (Sarris et al. 2016) (Nepal et al. 2017)
Arabidopsis lyrata	2011, 2014, 2015, 2016	Yes	(Y.-L. Guo et al. 2011) (Peele et al. 2014) (Y.-M. Zhang et al. 2016) (Buckley et al. 2016) (Sarris et al. 2016)
Capsella rubella	2012, 2014, 2016	Yes	(Gos, Slotte, and Wright 2012) (Peele et al. 2014) (Y.-M. Zhang et al. 2016) (Sarris et al. 2016)
Capsella grandiflora	2012, 2016	Yes	(Gos, Slotte, and Wright 2012) (Sarris et al. 2016)
Brassica rapa	2009, 2014, 2016	Yes	(Mun et al. 2009) (P. Wu et al. 2014) (Peele et al. 2014) (Yu et al. 2014) (Y.-M. Zhang et al. 2016) (Sarris et al. 2016)
Eutrema salsugineum (Thellungiella salsuginea)	2014, 2016	Yes	(Peele et al. 2014) (Y.-M. Zhang et al. 2016) (Sarris et al. 2016)
Brassica napus	2014, 2016	Yes	(Chalhoub et al. 2014) (Sarris et al. 2016)
Camelina sativa	2013	Yes	(Liang et al. 2013)
Brassica oleracea	2014, 2016	Yes	(Yu et al. 2014) (Golicz et al. 2016)
Aquilegia coerulea	2011	Yes	(Collier, Hamel, and Moffett 2011)
Ananas comosus	2016	Yes	(Xiaodan Zhang, Liang, and Ming 2016)
Malus domestica	2010, 2014, 2015, 2016	Yes	(Velasco et al. 2010) (Arya et al. 2014) (Zhong et al. 2015) (Kroj et al. 2016) (Sarris et al. 2016)
Arabidopsis halleri	2016	Yes	(Suryawanshi et al. 2016)
Triticum aestivum	2015, 2016	Yes	(Bouktila et al. 2015) (Sarris et al. 2016)
Citrus sinensis	2013, 2015, 2016	Yes	(Q. Xu et al. 2013) (Wang et al. 2015) (Kroj et al. 2016)
Citrus clementina	2015	Yes	(Wang et al. 2015)

Eucalyptus grandis	2014, 2015, 2016	Yes	(Myburg et al. 2014) (Christie et al. 2015) (Sarris et al. 2016)
Fragaria vesca	2013, 2015, 2016	Yes	(J. Li et al. 2013) (Zhong et al. 2015) (Sarris et al. 2016)
Pyrus bretschneideri	2012, 2015	Yes	(Jun Wu et al. 2013) (Zhong et al. 2015)
Prunus persica	2013, 2015, 2016	Yes	(International Peach Genome Initiative et al. 2013) (Zhong et al. 2015) (Van Ghelder and Esmenjaud 2016) (Sarris et al. 2016)
Prunus mume	2012, 2015	Yes	(Q. Zhang et al. 2012) (Zhong et al. 2015)
Rubus occidentalis	2016	Yes	(VanBuren et al. 2016)
Gossypium raimondii	2012, 2013, 2015, 2016, 2017	Yes	(Paterson et al. 2012) (Wei et al. 2013) (Chen et al. 2015) (Kroj et al. 2016) (Sarris et al. 2016) (Xiang et al. 2017)
Gossypium arboreum	2014, 2017	Yes	(F. Li et al. 2014) (Xiang et al. 2017)
Theobroma cacao	2011, 2014, 2016	Yes	(Argout et al. 2011) (F. Li et al. 2014) (Kroj et al. 2016) (Sarris et al. 2016)
Hibiscus syriacus	2017	Yes	(Y.-M. Kim et al. 2017)
Gossypium hirsutum	2017	Yes	(Xiang et al. 2017)
Gossypium barbadense	2017	Yes	(Xiang et al. 2017)
Linum usitatissimum	2011 (review) 2013, 2016	Yes	(Dodds and Thrall 2009) (Kale et al. 2013) (Sarris et al. 2016)
Musa acuminata ssp malaccensis	2008, 2016	Yes	(Azhar and Heslop-Harrison 2008) (W. Wu et al. 2016) (Kroj et al. 2016)
Musa balbisiana	2008, 2016	Yes	(Azhar and Heslop-Harrison 2008) (W. Wu et al. 2016) (Kroj et al. 2016)
Musa itinerans	2016	Yes	(W. Wu et al. 2016)
Musa schizocarpa	2008	Yes	(Azhar and Heslop-Harrison 2008)
Musa textilis	2008	Yes	(Azhar and Heslop-Harrison 2008)
Musa velutina	2008	Yes	(Azhar and Heslop-Harrison 2008)
Musa ornata	2008	Yes	(Azhar and Heslop-Harrison 2008)
Marchantia polymorpha	2012	Yes	(Xue et al. 2012)
Nelumbo nucifera	2013	Yes	(R. Z. Jia, Ming, and Zhu 2013)
Physcomitrella patens	2012,	Yes	(Yue et al. 2012)

	2016		(Xue et al. 2012) (Kim et al. 2012) (Kroj et al. 2016) (Sarris et al. 2016)
Panicum virgatum	2013, 2016	Yes	(Q. Zhu, Bennetzen, and Smith 2013) (Frazier et al. 2016)
Populus trichocarpa	2006, 2008, 2010, 2016, 2017	Yes	(Tuskan et al. 2006) (Kohler et al. 2008) (Germain and Séguin 2011) (Kroj et al. 2016) (Nepal et al. 2017) (Sarris et al. 2016)
Ricinus communis	2014, 2016	Yes	(Sood et al. 2014) (Kroj et al. 2016) (Sarris et al. 2016)
Jatropha curcas	2014	Yes	(Sood et al. 2014)
Setaria italica	2014, 2016	Yes	(Y. B. Zhu et al. 2014) (Zhao et al. 2016) (Kroj et al. 2016) (Sarris et al. 2016)
Selaginella moellendorffii	2012, 2016	Yes	(Yue et al. 2012) (Kroj et al. 2016) (Sarris et al. 2016)
Hordeum vulgare	2016	Yes	(Andersen et al. 2016) (Kroj et al. 2016) (Sarris et al. 2016)
Aegilops tauschii	2013	Yes	(J. Jia et al. 2013)
Amborella trichopoda	2016	Yes	(Kroj et al. 2016)
Coffea canephora	2016	Yes	(Kroj et al. 2016)
Elaeis guineensis	2016	Yes	(Kroj et al. 2016)
Manihot esculenta	2016	Yes	(Kroj et al. 2016) (Sarris et al. 2016)
Picea abies	2016	Yes	(Kroj et al. 2016)
Phoenix dactylifera	2015, 2016	Yes	(Hazzouri et al. 2015) (Kroj et al. 2016)
Coccomyxa subellipsoidea C-169	2016	Yes	(Sarris et al. 2016)
Micromonas pusilla	2016	Yes	(Sarris et al. 2016)
Mimulus guttatus	2012, 2016	Yes	(J. Kim et al. 2012) (Sarris et al. 2016)
Ostreococcus lucimarinus	2016	Yes	(Sarris et al. 2016)
Triticum urartu	2016	Yes	(Sarris et al. 2016)
Volvox carteri	2016	Yes	(Sarris et al. 2016)
Pinus monticola	2012	Yes	(Yue et al. 2012)
Juglans regia	2016	Yes	(Martínez-García et al. 2016)
Dimocarpus longan	2017	Yes	(Lin et al. 2017)
Actinidia chinensis	2013	Yes	(Shengxiong Huang et al. 2013)
Citrullus lanatus	2013	Yes	(S. Guo et al. 2013)
Ziziphus jujuba	2014	Yes	(Liu et al. 2014)

Morus notabilis	2013	Yes	(He et al. 2013)
Solanum aethiopicum gr. Gilo	2012 (PCR), 2015 (PCR)	Yes	(Zhuang, Zhou, and Wang 2012) (Reddy et al. 2015)
Solanum linnaeanum,	2012 (PCR)	Yes	(Zhuang, Zhou, and Wang 2012)
Solanum integrifolium	2012 (PCR)	Yes	(Zhuang, Zhou, and Wang 2012)
Solanum sisymbriifolium	2012 (PCR)	Yes	(Zhuang, Zhou, and Wang 2012)
Solanum khasianum	2012 (PCR)	Yes	(Zhuang, Zhou, and Wang 2012)
Solanum viarum	2015 (PCR)	Yes	(Reddy et al. 2015)
Capsicum baccatum	2017	Yes	(S. Kim et al. 2017)
Capsicum chinense	2017	Yes	(S. Kim et al. 2017)
Hevea brasiliensis	2016	Yes	(Lau et al. 2016)
Beta vulgaris	2014	Yes	(Dohm et al. 2014)
Spinacia oleracea	2017	Yes	(C. Xu et al. 2017)
Pinus taeda	2014	Yes	(Neale et al. 2014)

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