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Review

Technical review of molecular markers and next-generation sequencing technology to manage plant pathogenic oomycetes

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To feed the world human population which is expected to reach 10 billion in the next three decades, agricultural sustainability is required for stable food production. However, crops always suffer from many biotic and abiotic stresses. Among them, plant pathogens often cause severe yield losses. Plant pathogenic oomycetes are one of the most destructive plant diseases, which include *Phytophthora infestans* in potato and tomato, *Phytophthora capsici* in peppers, *Phytophthora sojae* in soybean, *Phytophthora fragariae* var. *fragariae* in strawberry, *Plasmopara viticola* in grapevine, and *Pseudoperonospora cubensis* in cucurbits. Therefore, rapid, robust and sophisticated molecular technologies are required for accurate identification and characterization of the oomycetes, to manage crop diseases resistances. In addition, breeding highly disease resistant varieties is also essential for sustainable agriculture. Molecular marker technology, especially recent advanced next-generation sequencing-based methods, would provide helpful information to monitor the pathogen endemicity and to breed the resistant cultivars through a gene pyramiding strategy. In this review, there was focus on both conventional and novel genotyping techniques for oomycete characterization and resistant gene identification in crops, to discuss future outlook for successful disease management.

Key words: Oomycete plant pathogens, vegetable crops, genomics, molecular markers, next-generation sequencing technology.

INTRODUCTION

The world human population is expected to reach approximately 10 billion by 2050 (UN, 2015). To meet the challenges of poverty and the rising population, food production must be increased by at least 70% over the next three decades. Agricultural sustainability is threatened by a number of limiting factors such as water and nutrient deficiencies, infestations of insects and nematodes, and infections of plant pathogenic viruses, bacteria, fungi and oomycetes. Especially, the plant pathogens are responsible for severe yield losses in a wide range of crops throughout the world. Besides, global trade of crops among countries leads to the rapid spread

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Table 1. Characteristics of selected DNA-based molecular markers.

Marker	Dominance	Reproducibility	Precision	Speed	Relative amount of template DNA needed	Prior sequence information needed for primer design?	Restriction enzyme needed?
RFLP	Co-dominant	High	Medium	Low	High	No	Yes
RAPD	Dominant	Low	Low	High	Low	No	No
AFLP	Dominant	High	Medium	Low	High	No	Yes
SSR	Co-dominant	High	High	High	Low	Yes	No
ISSR	Dominant	Low	High	High	Low	No	No
SCAR	Co-dominant	High	High	High	Low	Yes	No
CAPS	Co-dominant	High	High	High	Low	Yes	Yes
SNP	Co-dominant	High	High	Very high	Low	Yes	No
SRAP	Dominant	High	High	High	Low	No	No
DNA sequencing	Co-dominant	High	High	Very high	Low	Yes	Yes

of plant pathogenic microorganisms and unprecedented disease outbreaks in hitherto unaffected croplands.

Molecular markers can be used for identification and taxonomic classification of species across all domains of life (Vignal et al., 2002; Singh et al., 2013). In modern plant breeding programs, a gene pyramiding strategies based on marker-assisted selection (MAS) can facilitate development of new varieties with desirable traits such as disease resistances. In addition, the molecular techniques help in discovering an array of plant disease resistance genes, which have been used for the management of several serious plant pathogens (Gururani et al., 2012). Furthermore, greater understanding of interactions between pathogens and host plants could facilitate disease outbreak forecasting and predictions of yields. In this decade, genome sequencing technology as well as the molecular marker techniques has been greatly advanced due to great advancements of next-generation sequencing (NGS) methods (Davey et al., 2011). For example, whole-genome sequencing analysis of many microorganisms including plant pathogens has contributed to understanding of pathogenicity, host preferences, secreted effector proteins and fungicide resistances of the pathogens (Grunwald et al., 2016). In this review, genomics of oomycete plant pathogens in important crops are summarized for future breeding, to overcome the disease-derived yield losses.

ADVANCEMENT OF DNA MARKER TECHNOLOGIES

Traditional morphological and biochemical markers are hampered by their reliance on particular factors, for example, developmental stages and environmental conditions. In contrast, DNA markers provide stable results independent of the factors, hence, DNA analysis is the basis of a range of techniques in basic and applied researches (Collard et al., 2005). Since the 1980s, many types of DNA markers have been developed in accordance with advancement of DNA analysis technologies, for example, restriction fragment length polymorphism (RFLP), random amplified polymorphic DNA (RAPD), amplified fragment length polymorphism (AFLP), simple sequence repeat (SSR), inter-simple sequence repeat (ISSR), sequence characterized amplified region (SCAR), sequence related amplified polymorphism (SRAP) and cleaved amplified polymorphic sequence (CAPS) (Table 1). The DNA markers are used to detect polymorphisms between individuals in populations, determine genetic biodiversity among genotypes, and investigate plant-pathogen interactions (Patwardhan et al., 2014).

Due to NGS technology, genome-wide SNP discovery and genotyping have been enabled with high precision and accuracy, high-throughput performance and cost-effectiveness (Yang et al., 2016). This situation has made the classical DNA markers mentioned above (Vos et al., 1995; Jarne and Lagoda, 1996) to suffer from some constraints such as time- and cost-consuming.

In Figure 1, a possible experimental approach for genotyping, SNP discovery, and gene

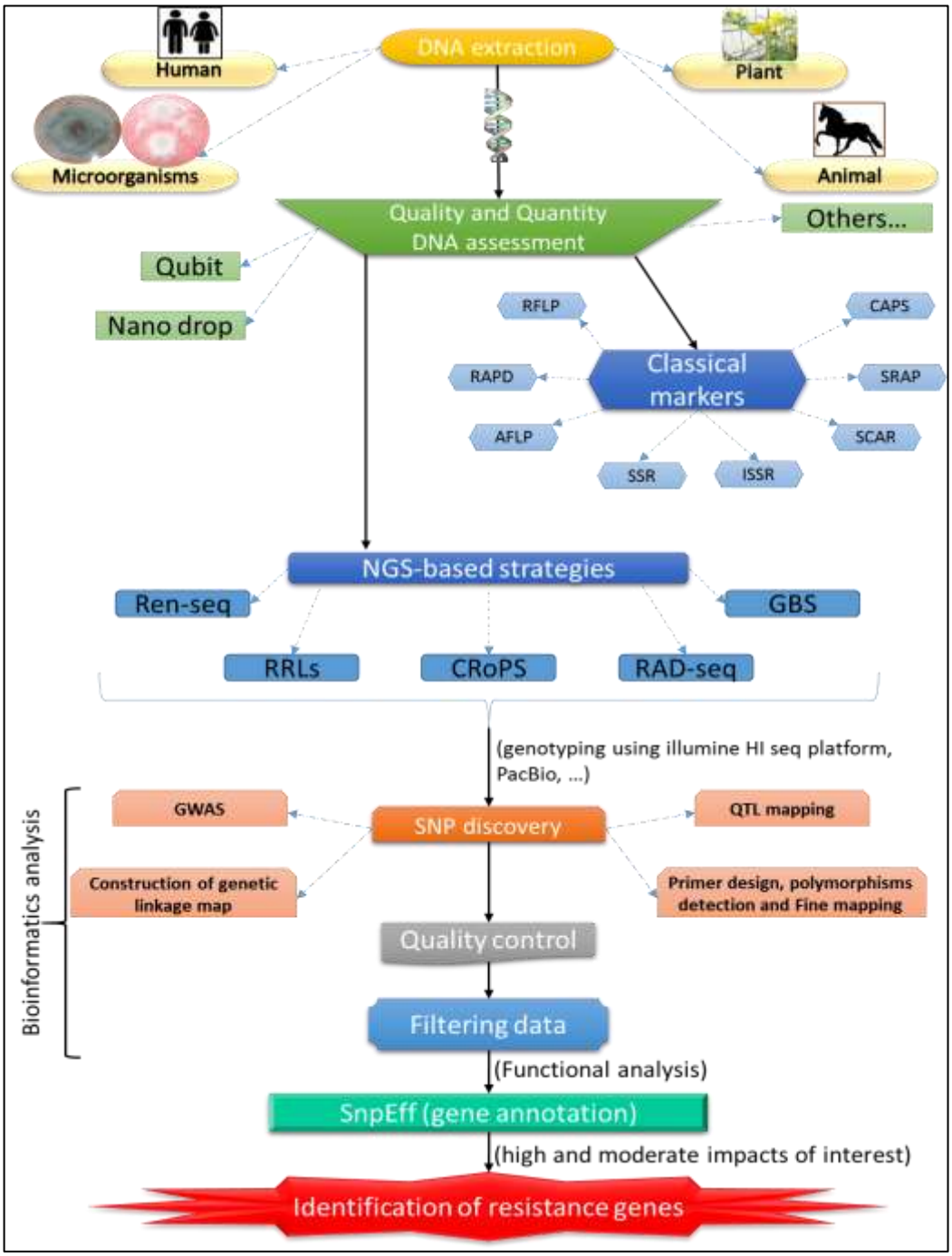

Figure 1. Workflow steps of NGS technology during identification of SNP markers and resistance loci.

identification with NGS strategies is presented. Even in non-model organisms in which genome sequences are not available (Baxter et al., 2011), NGS-based genome-wide genotyping technology has been widely applied for studies on SNP discovery, genetic variability, QTL mapping, candidate gene detection and genome-wide association study (GWAS) (Fu et al., 2014). NGS-based methods are suitable for genome-wide genotyping across large numbers of individuals, for example, reduced-representation libraries (RRLs) (Altshuler et al., 2000), complexity reduction of polymorphic sequences (CRoPS) (van Orsouw et al., 2007), restriction site-associated DNA sequencing (RAD-seq) (Baird et al., 2008) and genotyping-by-sequencing (GBS) (Elshire et al., 2011). In RRL sequencing technology, which has been originally developed in the human genome project (Altshuler et al.,

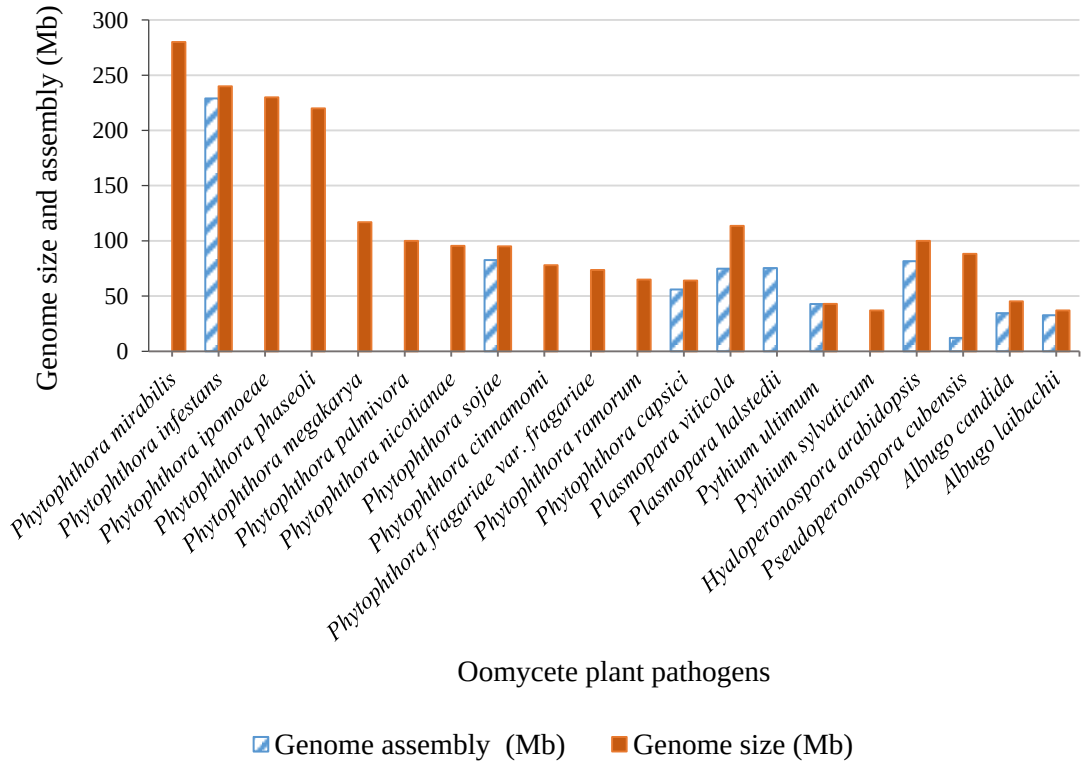

Figure 2. The genome size and assembly of selected plant pathogenic oomycetes.

2000), small genomic regions are sequenced for SNP discovery and genotyping. These techniques have been applied in other organisms including plants and animials (Van Tassell et al., 2008; Wiedmann et al., 2008; Gore et al., 2009; Hyten et al., 2010). On the other hand, CRoPS technology, another reduced-representation method, has mitigated the amounts of sequencing data to identify polymorphism in populations (van Orsouw et al., 2007). In RAD-Seq procedure, genome DNAs are cut with restriction enzymes into short DNA fragments, and sequenced to discover and genotype genome-wide SNPs (Baird et al., 2008). GBS is another approach for genotyping and developing novel molecular markers (Sonah et al., 2013; He et al., 2014). The library preparation is affordable, straightforward, rapid and precise (Elshire et al., 2011; Romay et al., 2013). Furthermore, in the fields of plant pathology and microbiology, through the NGS-based approaches, novel molecular markers associated with resistance genes were broadly identified (Devran et al., 2015). For example, resistance gene enrichment sequencing (RenSeq) is an effective genotyping technique with NGS technologies, in sequence variations of nucleotide binding-site leucine-rich repeat (NB-LRR) genes simultaneously identified (Jupe et al., 2013). Subsequently, the RenSeq approach has been widely applied to identify resistance genes in wheat and potato (Jupe et al., 2013; Steuernagel et al., 2016).

IDENTIFICATION OF KEY INTERACTIVE GENES BETWEEN PLANTS AND OOMYCETE PATHOGENS

Oomycetes are fungus-like eukaryotic microorganisms, many of which are pathogens to humans, animals and plants. Plant pathogenic oomycetes pose substantial threats to global food security. Among the oomycetes, *Phytophthora* is one of the largest genera containing almost 117 species (Martin et al., 2012), many of which cause severe disease outbreaks in horticultural, fruit, arable crops, forest trees and ornamental plants. In addition, *Plasmopara* and *Pseudoperonospora* also thrive on susceptible hosts and pose substantial risks to agriculture worldwide. To overcome the losses from the diseases, breeding new cultivars with resistance (R) genes to the pathogens is an effective strategy. However, the R-gene-derived resistances sometimes decay because of alterations of the plant pathogenic effector proteins, which suppress plant immunity system and modulate host cell functions (Hogenhout et al., 2009). Therefore, to combat the diseases completely, it there is need to understand molecular mechanisms of disease resistance as well as population dynamics of plant pathogens upon the temporal and spatial levels. The genome sequences of the several oomycete pathogens, sizes of which varied depending on the genera (Figure 2), would be useful for this purpose. In addition, methods to monitor and predict alternations of the effector genes are

Table 2. List of tomato late blight, *Phytophthora infestans* resistance genes.

S/N	Gene name	Wilde type	Accession	Chromosome	References
1	*Ph-1*	*Solanum pimpinellifolium*	West Virginia 19 and 731	7	Peirce (1971)
2	*Ph-2*	*S. pimpinellifolium*	West Virginia 700	10	Moreau et al. (1998)
3	*Ph-3*	*S. pimpinellifolium*	L3708	9	Chunwongse et al. (2002)
4	*Ph-4*	*S. habrochaites*	LA1033	2	Kole et al. (2006)
5	*Ph-5.1*	*S. pimpinellifolium*	PI270443	1	Merk et al. (2012) and Merk and Foolad (2012)
6	*Ph-5.2*	*S. pimpinellifolium*	PI270443	10	Merk et al. (2012) and Merk and Foolad (2012)

also essential. Also, genetic and genomic analyses of plant pathogens would lead to new strategies for integrated disease management of high aggressive races, which would breakdown existing resistant varieties. The current status of knowledge on important crops and the corresponding pathogens are summarized as follows.

Tomato and potato- *Phytophthora infestans*

Late blight of tomato (*Solanum lycopersicum*) and potato (*Solanum tuberosum*) are caused by the heterothallic oomycete pathogen, *P. infestans* (Mont.) de Bary, also known as a pathogen of the Irish potato famine in the 1840s (Aragaki and Uchida, 2001; Abad and Abad, 2003). *P. infestans* can completely destroy tomato and potato plants within a few days after infection. Unfortunately, pathogenic races of *P. infestans* have been altered in each season and growing areas (Arafa et al., 2017). Therefore, multiple resistance varieties of tomato and potato have been developed by introgression of R genes from the wild relatives. In tomato, six major and race-specific R genes have been identified from the wild relatives, which are *Ph-1*, *Ph-2*, *Ph-3*, *Ph-4*, *Ph-5.1* and *Ph-5.2* (Table 2). Among them, *Ph-3* derived from *Solanum pimpinellifolium* L3708 confers a high level resistance against a broad-spectrum of *P. infestans* genotypes. On the other hand, in potato, eleven resistance genes (*R1*–*R11*) were identified from a wild potato relative, *S. demissum*, and *R1*, *R2*, *R3*, *R4* and *R10* were broadly used in potato breeding programs (Vleeshouwers et al., 2011). Furthermore, new QTLs for *P. infestans* resistance have been reported in *S. pimpinellifolium*, *Solanum habrochaites*, and *Solanum pennellii* for tomato, and in *Solanum bulbocastanum* and *Solanum phureja* for potato. Moreover, RAD-Seq technology was used to identify SNP markers from a tomato wild relative, *S. pimpinellifolium* (Chen et al., 2014). Genetic linkage maps were constructed, and a QTL associated with late blight resistance was detected on chromosome 2. Recently, a resistance locus to an Egyptian isolate of *P. infestans* from *S. habrochaites* (Arafa et al. 2018) was also identified, in which the established analytic pipeline for ddRAD-Seq was employed (Shirasawa et al., 2016). However, most of these resistance genes might be subsequently disrupted by new pathotypes, which have been generated due to the unstableness of the *P. infestans* genomes caused by movements of transposable elements, mitotic recombinations and dispensable chromosomes (Judelson, 2002). Therefore, rapid detection methods and easy monitoring technologies of late blight would be beneficial for pathogen control to reduce yield losses of crops. For example, mitochondrial DNA (mtDNA) haplotypes detected by the RG57 RFLP marker as well as RAPD and AFLP have been used as DNA makers to examine the population diversity of *P. infestans* isolates. Subsequently, SSRs and SNPs have been also applied to investigate population structures and to monitor alterations of effector proteins of *P. infestans*. More recently, NGS-based genotyping methods including reduced representative sequencing techniques and whole-genome shotgun (WGS) approaches are used to characterize *P. infestans* isolates. A GBS approach has also been applied to detect genetic variability within four clonal lineages (US-8, US-11, US-23 and US-24) of *P. infestans*, where 3,774, 4,363, 5,070 and 4,353 SNPs were discovered, respectively (Hansen et al., 2016). These findings are considered a clear indication that the GBS method is adequately a useful method for high-resolution analysis of population structure of *P. infestans*, which would contribute to reduction in epidemiology of late blight globally. Furthermore, whole-genome resequencing strategy has also been used for six genomes of four *Phytophthora* species (*P. infestans, P. ipomoeae, P. mirabilis* and *P. phaseoli*) to detect 746,744 SNPs and to estimate genomic evolutionary rates in the genus, *Phytophthora* (Raffaele et al., 2010). This study suggested that the evolutionary level among the tested isolates

fluctuated based on copy number variations (CNVs), frequency of SNPs and the ratio of non-synonymous to synonymous substitutions. Yoshida et al. (2013) also used the genome sequencing approach to compare between ancient and modern populations of *P. infestans*, to detect 4.5 million SNPs and follow up the historical trajectory of clonal linages to comprehend the epidemiology of this destructive plant pathogen. They also presented the evolutionary process of *P. infestans* populations since the occurrence of Irish potato famine.

Pepper- *Phytophthora capsici*

P. capsici is a soil-borne plant pathogenic oomycete; this pathogen infects a wide range of host crops. *P. capsici* is considered as a major limiting factor for crop productions (Lamour and Kamoun, 2009; Roy et al., 2009; Zeng et al., 2009). Especially in pepper (*Capsicum annuum*), root, stem and foliar blights are caused by *P. capsici*. In the pepper genome, resistance loci for *P. capsici*, *Phyt-1*, *Phyt-2* and *Phyt-3* as well as *Phyto.5.2*, have been identified through a QTL mapping research. Recently, a novel resistance gene, *PhR10*, has been identified using NGS technology with Illumina HiSeq 2500 platform (Xu et al., 2016). This race specific gene can be used for breeding programs for resistant varieties to *Phytophthora* root rot with a marker-assisted selection. However, *P. capsici* readily undergoes sexual reproduction to develop new races. The new genotypes adapt to challenging environmental conditions by breakdown of pesticides. Therefore, it is important to assess *P. capsici* population dynamics and to identify new races rapidly. To date, molecular markers based on RFLP (Forster et al., 1990), mtDNA haplotypes (Martin et al., 2012), RAPDs (Yin et al., 2012), AFLPs (Hulvey et al., 2010), SSRs (del Castillo-Múnera et al., 2013) and SNPs (Gobena et al., 2012) have been available. More recently, Fulcher et al. (2014) applied the GBS approach for genotyping of *P. capsici* population to discover 368,356 SNPs. GBS has been also used to investigate population structure and genetic dynamics of *P. capsici* where 23,485 high-quality SNPs tightly linked to temporal dynamics and mating types are identified over the genome of *P. capsici* (Carlson et al., 2017).

Soybean- *Phytophthora sojae*

Root rot in soybean (*Glycine max*) is caused by *P. sojae* Kaufm. and Gerd. *P. sojae* attacks soybean plants at all developmental stages from seedling to harvest across a range of varieties (Malvick and Grunden, 2004; Kato, 2010). Soybean has at least 14 R genes, which have been used to develop *P. sojae* resistant cultivars (Burnham et al., 2003). Two R genes, *Rps8* and *Rps3*, tightly linked to each other can be used to breed new varieties, conferring durable resistance through the gene pyramiding strategy. QTL analyses have shown new resistance gene loci, *Rps1-k* (Kasuga et al., 1997; Salimath and Bhattacharyya, 1999) and *RpsYu25* (Sun et al., 2011), and novel QTLs indicating partial resistance for *Phytophthora* root and stem rot (Lee et al., 2013). The partial resistance loci have been also reported on chromosomes 3, 13 and 19 where seven QTLs were detected (Schneider et al., 2016). Therefore, pyramiding many minor genes as well as usage of R genes are efficacious ways to increase the resistance level to *P. sojae*. On the other hand, an avirulence gene, *Avr1a* in *Phytophthora* has been identified in the genome of *Ph. sojae*. This information would be useful to understand interactions between soybean and *P. sojae* (MacGregor et al., 2002). A whole genome resequencing analysis has been performed to predict effects of sequence variations on the functions of the avirulence genes, *Avr1a* and *Avr1c* (Na et al., 2014). Additionally, this study confirmed that NGS-based methods are workable techniques for breeding programs, and genetic and genomics research could be widely applied in release soybean breeding to increase crop immune system against oomycete pathogens.

Strawberry- *Phytophthora fragariae var. fragariae*

P. fragariae Hickman var. *fragariae* Wilcox & Duncan causes red core disease in *Rubus* species (Wilcox, 1989) including strawberry (*Fragaria* x *ananassa*) (Hickman, 1941), which leads to complete destruction and death of the plants. The genome sequence of *P. fragariae* is available to understand virulence, aggressiveness and evolution of this destructive pathogen (Gao et al., 2015). In strawberry, two R genes, *Rpf1* and *Rpf2*, have been reported as resistance loci (Haymes et al., 1997; Haymes et al., 2000; Gelvonauskienė et al., 2007; Mathey, 2013; Van de Weg, 1997).

Grapevine- *Plasmopara viticola*

In grapevine (*Vitis vinifera*), downy mildew disease is caused by *P. viticola* (Berk. and Curt.) Berl. and de Toni. This pathogen can infect all the green tissues of grapevine, causing substantial losses in crop productivity and quality (Gessler et al., 2011). An R gene, *Rpv3*, is responsible for the hypersensitive response against *P. viticola* in resistant grapevine genotypes (Bellin et al., 2009). Another R gene, *Rpv8*, a major QTL responsible for *P. viticola* resistance, has been identified from a grape wild relative, *Vitis amurensis* Rupr. Pyramiding of two genes, *Rpv3* and *Rpv12*+, in one line was an effective strategy to overcome downy mildew disease (Venuti et al., 2013). However, *P. viticola* exhibits extensive genetic variability (Gobbin et al., 2006), and several genotypes

3. Molecular markers used in characterization of oomycete plant pathogens.

Pathogen	Disease	Number of isolates investigated	Molecular marker	Number of polymorphic molecular markers	Number of groups obtained	Isolate origins	References
Phytophthora infestans	Late blight	326	RAPD	9	19	Canada	Punja et al. (1998)
		170	AFLPs	135	No data	Mexico	Flier et al. (2003)
		655	RFLP RG-57 probe	1	3 (8)[a]	Taiwan	Chen et al. (2009)
		32	SNP	102 by objective criteria 167 by eye	No data	Africa, Asia, Europe, North America and South America	Abbott et al. (2010)
		100	RFLP RG-57 probe	1	No data	China	Guo et al. (2010)
		104	RAPD	6	10	China, Korea and Japan	Xuanzhe and Shengjun (2010)
		200	SSR	9	169	Nordic European countries	Brurberg et al. (2011)

can be discovered from a single field (Gobbin et al., 2003). Therefore, a high-throughput genotyping is required to gain new insight into the genetic structure of *P. viticola* population (Stark-Urnau et al., 2000). For example, SNP and SSR markers have been used for the genetic variation study of *P. viticola* strains (Delmotte et al., 2011). Recently, Yin et al. (2017) employed the whole genome sequencing approach to identify pathogenicity genes and effector proteins that are associated with virulence of *P. viticola*. Moreover, NGS-based methods clarifies the origin and evolution patterns of *P. viticola*, which is completely different from *Hyaloperonospora arabidopsidis*, a pathogen for *Arabidopsis* downy mildew.

Cucurbitaceae- *Pseudoperonospora cubensis*

The family Cucurbitaceae suffers from approximately 45 diseases caused by viruses, bacteria, fungi, and oomycetes (Lebeda et al., 2006). Among them, *P. cubensis* [(Berk. and Curt.) Rost.] causes downy mildew disease. *P. cubensis* infects approximately 20 cucurbit genera, including cucumber (*Cucumis sativus*), watermelon (*Citrullus lanatus*), pumpkin (*Cucurbita maxima*), squash (*Cucurbita pepo*) and melon (*Cucumis melo*) (Lebeda and Urban, 2007). The GBS technique distinguishes *P. cubensis* from the relative, *Pseudoperonospora humuli* (Summers et al., 2015; Lee et al., 2016). Numbers of QTLs for *P. cubensis* resistance has been identified in cucumber (Pang et al., 2013; Yoshioka et al., 2014), while a resistance locus, *ILdm*, has been found from a wild relative of cucumber, *Cucumis hystrix* (Guo et al., 2011).

FUTURE DIRECTION OF BREEDING STRATEGIES FOR PLANT DISEASE RESISTANCE

Plant diseases are one of the main threats to global food security and sustainable agriculture. Identifying and tracking oomycete plant pathogens are critical for breeding programs for disease resistances in a range of crop species. Moreover, identification of resistance genes for crops would be required for effective integrated disease management (Table 3).

The plant disease resistances could be classified into two major categories: (i) qualitative or race-specific resistance (vertical resistance) controlled by single resistance genes (major genes or R genes), and (ii) quantitative resistance or field resistance (horizontal resistance) regulated by multiple minor genes (Poland et al., 2009). Therefore, the gene pyramiding strategy has a potential to develop varieties with durable resistance against multiple plant pathogens.

To understand molecular mechanisms of plant disease infection, responses of plants, and the interaction from both aspects of pathogens and hosts would be essential to control plant disease and maintain stability of food productions. Advancement of NGS technology enables analyzing genetic variations of pathogens and crops at whole genome level. The information would provide a beneficial knowledge in both evolutionary researches on oomycete pathogens

Table 3. Contd.

		117	mtDNA	Not available	1	Thailand	Jaimasit and Prakob (2011)
		134	SSR	15	40	China	Wu et al. (2012)
		119	SSR	12	11	United Kingdom	Stroud et al. (2015)
		24	RAPD	7	6	Illinois	Islam et al. (2005)
Phytophthora capsici	Phytophthora root rot	41	SNP	8	No data	Argentina	Gobena et al. (2012)
		51	ISSR	13	7	China	Li et al. (2012)
		98	SSR	193	2 (10)	China	Pei-Qing et al. (2013)
		400[b]	RAPD and RFLP	250	22	Australia	Whisson et al. (1995)
		99	RFLP	5	15	Australia and USA	Drenth et al. (1996)
Phytophthora sojae	Root rot	55	RAPD	23	4	Illinois, Indiana, Iowa and Minnesota	Meng et al. (1999)
		558[c]	AFLP, CAP and RAPD	16	No data	USA	MacGregor et al. (2002)
		96	RAPD	2	79	Germany	Stark-Urnau et al. (2000)
		97	SSR	4	15	Italy	Gobbin et al. (2003)
Plasmopara viticola	Downy mildew	54	AFLP and SSR	200	43	Germany, Italy, France and Switzerland	Scherer and Gisi (2006)
		93	SSR	1	234	Japan	Mochizuki et al. (2012)
		96	SSR	35	89	France, Germany and USA	Rouxel et al. (2012)
		30	AFLP	4	No data	Greece, Czech, Netherlands, and France	Sarris et al. (2009)
Pseudoperonospora cubensis	Downy mildew	262	SSR	5	5	Canada and USA	Naegele et al. (2015)
		78	ISSR and SRAP	24	No data	Turkey, Israel and the Czech Republic	Polat et al. (2014)
		No data	SNP	7	No data	South Korea	Lee et al. (2016)

[a]Numbers in parentheses indicate sub-groups and sub-genotypes; [b]F2 populations of two crosses (200 individuals for each cross) between different races of *Phytophthora sojae*; [c]F2 populations generated from two avirulent (48FPA18 and P6497) and two virulent (25MEX4 and P7064) *P. sojae* parents.

and the interactions between the pathogens and their hosts (Yin et al., 2017). Also, NGS-based genotyping techniques would confer diagnosis methods to monitor new diseases. Unambiguously, NGS technology is expected to provide useful information on adequate plant breeding programs for desirable traits such as resistance genes discovery. The plants are deeply nested with plausible future perspectives to overcome plant disease challenges in different host species. Interactive, integrative and comparative researches on plant pathology, breeding, genetics and genomics would pave way for successful disease management.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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