Molecular Pathogens 2024, Vol.15, No.1, 40-49
http://microbescipublisher.com/index.php/mp

Research Report Open Access

Genomic Approaches to Enhance Disease Resistance in Grapevine Breeding Programs

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Molecular Pathogens, 2024, Vol.15, No.1 doi: 10.5376/mp.2024.15.0005
Received: 29 Dec., 2023
Accepted: 31 Jan., 2024
Published: 20 Feb., 2024

Preferred citation for this article:
Huang J., and Li M.F., 2024, Genomic approaches to enhance disease resistance in grapevine breeding programs, Molecular Pathogens, 15(1): 40-49 (doi: 10.5376/mp.2024.15.0005)

Abstract Enhancing disease resistance in grapevine breeding programs is a key strategy for improving grape productivity and quality. This study provides an overview of grapevine diseases and their economic and agricultural impact, discusses traditional methods of disease control and their limitations, and introduces genomic tools and technologies such as high-throughput sequencing, genotyping and single nucleotide polymorphism (SNP) analysis, and genome-wide association studies (GWAS) used in grapevine breeding. It also explores the development and successful cases of marker-assisted selection (MAS) in grapevine breeding, elucidates the principles and advantages of genomic selection (GS), and its application in grapevine breeding. By examining the existing genomic technologies and strategies, this study emphasizes the importance of genomics in enhancing grapevine disease resistance and provides recommendations for future research. These genomic approaches not only offer new perspectives for grapevine breeding but also provide valuable references for disease-resistant breeding in other crops.

Keywords Disease resistance; Grapevine breeding; Genomic tools; Marker-assisted selection (MAS); Genomic selection (GS)

1 Introduction

Grapevine (*Vitis vinifera*) breeding has a long history, with initial efforts dating back to the early nineteenth century in North America and later in Europe, driven by the need to combat diseases such as mildews and phylloxera (Eibach and Töpfer, 2015). Traditional breeding techniques have primarily relied on phenotypic selection and the use of a limited number of molecular markers, which has made the process time-consuming and labor-intensive, often taking up to 25 years to release new cultivars (Brault et al., 2023). Despite these challenges, significant progress has been made in understanding grapevine genetics, which has paved the way for more efficient breeding methods.

Disease resistance is a critical trait in grapevine breeding due to the susceptibility of *Vitis vinifera* to various fungal diseases and insect pests, especially in cool, wet climates. Diseases such as downy mildew, powdery mildew, and grey mold cause substantial economic losses and necessitate the extensive use of agrochemicals, which is increasingly unsustainable in the context of global warming. Enhancing disease resistance not only reduces the reliance on chemical treatments but also contributes to the sustainability and economic viability of grapevine cultivation (Poland and Rutkoski, 2016; Capriotti et al., 2020).

This study aims to explore advances in genomic approaches that have the potential to revolutionize grape breeding programs by enhancing disease resistance. Specifically, it will examine the use of genomic prediction and selection methods, such as the genomic best linear unbiased predictor (GBLUP) and the least absolute shrinkage selection operator (LASSO), which have shown promise in accelerating the breeding process and improving the accuracy of selecting for disease resistance traits. This study will also discuss the integration of biotechnologies, including gene overexpression, gene silencing, and genome editing, which provide precise and efficient methods for introducing disease resistance traits into grape varieties. By synthesizing the latest research and developments, this study will provide a comprehensive understanding of how genomic approaches can enhance disease resistance in grape breeding programs, ultimately helping to develop more resilient and sustainable grape varieties.

2 Overview of Grapevine Diseases

2.1 Common pathogens affecting grapevines

Grapevines are susceptible to a variety of pathogens, with fungal and oomycete diseases being particularly prevalent. The most significant diseases include downy mildew (caused by *Plasmopara viticola*), powdery mildew (caused by *Erysiphe necator*), and grey mold (caused by *Botrytis cinerea*) (Agurto et al., 2017; Fröbel et al., 2019; Capriotti et al., 2020). These pathogens can cause severe damage to grapevine crops, leading to substantial economic losses (Figure 1).

Figure 1 Infected grapevine plants (Adopted from Agurto et al., 2017)

Image caption: Right: powdery mildew development on a susceptible genotype; Left: leaf of resistant segregant carrying *RUN1* and/or *REN1* loci (Adopted from Agurto et al., 2017)

2.2 Economic and agricultural impact of diseases

The economic impact of grapevine diseases is profound, as they can drastically reduce yield and quality. For instance, downy mildew and powdery mildew are responsible for significant yield losses and necessitate extensive use of fungicides, which increases production costs and poses environmental risks (Feechan et al., 2013; Wan et al., 2020). The reliance on chemical treatments conflicts with sustainable agricultural practices, highlighting the need for resistant grapevine cultivars (Peressotti et al., 2010).

2.3 Traditional methods of disease control

Traditional methods of controlling grapevine diseases primarily involve the application of chemical fungicides. However, this approach has several drawbacks, including environmental pollution, development of pathogen resistance, and high costs. Breeding programs have also focused on introducing resistance genes from wild grapevine species into cultivated varieties. For example, resistance loci such as *Rpv10*, *RUN1*, and *REN1* have been introgressed to confer resistance to downy and powdery mildew. Despite these efforts, the durability of resistance remains a challenge due to the adaptability of pathogens (Peressotti et al., 2010; Merdinoglu et al., 2018). By integrating genomic approaches, such as gene overexpression, gene silencing, and genome editing, breeding programs can enhance disease resistance in grapevines more effectively and sustainably (Yin et al., 2022).

3 Genomic Tools and Technologies

3.1 High-throughput sequencing

High-throughput sequencing technologies have revolutionized the field of genomics by enabling the rapid and cost-effective sequencing of large genomes. In grapevine breeding, these technologies facilitate the identification

of genetic variations that are crucial for disease resistance. For instance, the re-sequencing of grapevine cultivars has led to the discovery of thousands of single nucleotide polymorphisms (SNPs), which are essential for genetic mapping and marker-assisted selection. Restriction site-associated DNA sequencing (RAD-seq) has been employed to analyze the genetic diversity of grapevine and identify genes related to disease resistance, such as those conferring resistance to white rot disease (Zhang et al., 2020).

3.2 Genotyping and SNP analysis

Genotyping and SNP analysis are critical components of modern grapevine breeding programs. SNPs are the most abundant type of DNA sequence polymorphisms and provide a robust framework for genetic studies. High-density SNP arrays and genotyping-by-sequencing (GBS) methods have been used to generate extensive SNP datasets, which are then utilized in genome-wide association studies (GWAS) to link genetic markers with phenotypic traits. For example, a study using GBS identified over 76 000 SNPs in Canadian Holstein cows, demonstrating the utility of this approach for complex trait improvement (Ibeagha-Awemu et al., 2016). In grapevine, SNP genotyping has been applied to cultivar identification, genetic diversity studies, and the construction of genetic maps, thereby enhancing the efficiency of breeding programs.

3.3 Genome-wide association studies (GWAS)

GWAS have become a powerful tool for identifying genetic loci associated with disease resistance in grapevine. By analyzing the association between SNPs and phenotypic traits across a large population, GWAS can pinpoint specific genomic regions that contribute to disease resistance. For instance, a high-resolution GWAS in wheat identified multiple quantitative trait loci (QTLs) associated with resistance to various diseases, providing valuable insights for breeding programs (Pang et al., 2021). Similarly, GWAS in grapevine have revealed significant SNPs linked to disease resistance, such as those associated with white rot disease (Zhang et al., 2020). The integration of GWAS with genomic selection (GS) models has further improved the predictive accuracy of breeding programs, as demonstrated by a study that combined GWAS and GS to achieve high prediction accuracies for complex traits in grapevine (Fodor et al., 2014).

4 Identification of Disease Resistance Genes

4.1 Mapping resistance loci

Mapping resistance loci is a critical step in identifying and utilizing disease resistance genes in grapevine breeding programs. Various studies have employed different mapping techniques to locate these loci. For instance, a physical map of the heterozygous grapevine 'Cabernet Sauvignon' was constructed, which included 29 727 BAC clones assembled into 1 770 contigs. This map facilitated the genome-wide mapping of candidate genes for disease resistance, revealing that *NBS-LRR* and *RLK* genes for host resistance were found in 424 contigs, with 133 of them assigned to chromosomes. A multi-tiered haplotype strategy was used to enhance phased assembly and fine-mapping of a disease resistance locus, specifically the *RPV33* locus conferring resistance to grapevine downy mildew, narrowing the candidate region to only 0.46 Mb (Zou et al., 2023). Another study focused on the *REN1* and *REN2* loci for powdery mildew resistance, using high-resolution genetic mapping to identify candidate resistance genes (Cadle-Davidson et al., 2016).

4.2 Functional genomics approaches

Functional genomics approaches are essential for understanding the roles of identified resistance genes. These approaches include transcriptome analysis, gene expression profiling, and functional validation through gene editing. For example, allele-specific RNA-seq analysis was employed to identify a cluster of three putative disease resistance RPP13-like protein 2 genes as candidates for the *RPV33* locus (Zou et al., 2023). In another study, the candidate-gene approach was applied to map QTLs for disease resistance in wheat, revealing that many minor resistance QTLs may be from the action of defense response genes. Deep sequencing of putative susceptibility genes in grapevine identified Single Nucleotide Polymorphisms (SNPs) that could be used for genomic-assisted breeding and tailored gene editing approaches for resistance to biotic stresses (Pirrello et al., 2021).

4.3 Candidate gene validation

Validating candidate genes is crucial to confirm their role in disease resistance. This can be achieved through various methods such as marker-assisted selection, gene knockout, and overexpression studies. For instance, the *REN11* locus from *Vitis aestivalis* was validated in a pseudo-testcross with the grandparent source of resistance, demonstrating its effectiveness in nearly all vineyard environments (Karn et al., 2021). Another study utilized positional cloning to map and clone disease resistance genes from the wild North American grape species *Muscadinia rotundifolia*, providing sequence information that can be used to design perfect genetic markers for marker-assisted selection. Additionally, genetic linkage maps displaying the chromosomal locations of microsatellite markers and *R*-gene candidates have been constructed, aiding in the identification of markers linked to genetic determinants of disease resistance.

5 Marker-Assisted Selection (MAS) in Grapevine Breeding

5.1 Development of molecular markers

The development of molecular markers is a critical step in the implementation of marker-assisted selection (MAS) in grapevine breeding. Molecular markers such as single nucleotide polymorphisms (SNPs) and microsatellite markers are commonly used due to their high polymorphism and reproducibility. Next-generation sequencing (NGS) technologies have significantly advanced the discovery of these markers, enabling high-throughput genotyping and the identification of trait-associated markers. For instance, the AmpSeq platform has been utilized to develop a MAS package for grapevine, targeting traits such as disease resistance and acylated anthocyanins (Yang et al., 2016). The genotyping-by-sequencing (GBS) approach has been employed to discover and genotype SNPs in crop genomes, providing a cost-effective and efficient tool for MAS (He et al., 2014).

5.2 Integration of MAS in breeding programs

Integrating MAS into grapevine breeding programs involves several steps, including the identification of trait-associated markers, genotyping of breeding populations, and selection of individuals carrying desirable alleles. MAS allows for the selection of traits at the seedling stage, thereby accelerating the breeding process and reducing costs. The use of MAS is particularly advantageous for traits controlled by single genes or major quantitative trait loci (QTLs) with large effects. For example, MAS has been successfully integrated into breeding programs for disease resistance in various crops, including wheat and barley, by targeting specific resistance genes and QTLs (Collins et al., 2018). The integration of MAS in grapevine breeding can similarly enhance the efficiency of selecting disease-resistant varieties.

5.3 Case studies of MAS success

Several case studies highlight the success of MAS in breeding programs. In wheat, MAS has been effectively used to incorporate resistance genes such as *Lr34* and *Yr36* for rust resistance, and *Fhb1* for Fusarium head blight resistance (Miedaner and Korzun, 2012; Arruda et al., 2016). In lupin, a co-dominant, sequence-specific marker linked to anthracnose resistance was developed and successfully implemented in the Australian lupin breeding program. In grapevine, the AmpSeq platform has been employed to develop a MAS package for traits including disease resistance, demonstrating the potential of MAS to enhance grapevine breeding (Yang et al., 2016). These examples underscore the utility of MAS in improving disease resistance and other agronomically important traits in various crops. By leveraging molecular markers and integrating MAS into breeding programs, grapevine breeders can achieve more precise and efficient selection of disease-resistant varieties, ultimately enhancing the sustainability and productivity of grapevine cultivation.

6 Genomic Selection (GS) and Its Applications

6.1 Principles of genomic selection

Genomic Selection (GS) is a modern breeding approach that leverages genome-wide markers to predict the genetic value of breeding candidates. Unlike traditional marker-assisted selection (MAS), which focuses on a few significant markers, GS considers the effects of all markers across the genome simultaneously. This

comprehensive approach allows for the capture of both major and minor gene effects, making it particularly effective for traits controlled by multiple genes. The principle of GS is based on the creation of a training population (TP) that is both phenotyped and genotyped. Statistical models are then trained on this data to predict the performance of untested individuals, thereby accelerating the breeding cycle and increasing genetic gain (Rutkoski et al., 2015).

6.2 Advantages of GS over MAS

GS offers several advantages over MAS, particularly in the context of complex traits. GS uses genome-wide markers, capturing the effects of both major and minor genes, which is crucial for traits with a complex genetic architecture (Merrick et al., 2021; 2022). Studies have shown that GS models generally have higher prediction accuracies compared to MAS. For instance, GS models for disease resistance in wheat achieved an accuracy of 0.72, significantly higher than MAS models. By predicting the genetic value of breeding candidates early in the breeding cycle, GS can significantly reduce the time required to develop new varieties. The ability to select superior genotypes more accurately and rapidly leads to higher genetic gains per unit of time. This has been demonstrated in various crops, including maize, rice, and wheat (Bassi et al., 2016).

6.3 Implementing GS in grapevine breeding

Implementing GS in grapevine breeding involves several key steps and considerations. A diverse and representative training population must be developed. This population should be both phenotyped for relevant traits and genotyped using high-density markers. Statistical models, such as genomic best linear unbiased prediction (gBLUP) and Bayesian methods, are trained on the TP data. These models are then validated using cross-validation techniques to ensure their accuracy and robustness (Huang et al., 2019). Once the models are validated, they can be used to predict the genetic value of untested individuals. Breeding candidates with the highest predicted values are selected for further breeding or direct use (Cappetta et al., 2020). GS can be combined with other advanced technologies, such as hyperspectral imaging and high-throughput phenotyping, to further enhance selection accuracy and efficiency (Crossa et al., 2017; Merrick et al., 2022).

In grapevine breeding, GS has the potential to revolutionize the selection process by enabling the rapid and accurate identification of disease-resistant genotypes. This is particularly important for traits like resistance to Pierce's disease and dagger nematode, which are controlled by multiple genes (Gaspero and Cattonaro, 2010; Viana et al., 2016). By integrating GS into breeding programs, grape breeders can accelerate the development of new, disease-resistant varieties, ultimately improving grapevine health and productivity.

7 Biotechnological Approaches

7.1 CRISPR/Cas9 and genome editing

CRISPR/Cas9 technology has revolutionized the field of plant genetics, offering precise and efficient genome editing capabilities. In grapevine breeding, CRISPR/Cas9 has been employed to enhance disease resistance by targeting specific genes associated with susceptibility to pathogens. For instance, the CRISPR/Cas9 system has been used to confer resistance to grapevine leafroll-associated virus 3 (GLRaV-3) by expressing FnCas9 and LshCas13a, which inhibit the virus through RNA-targeting mechanisms (Jiao et al., 2022). Additionally, DNA-free genome editing using CRISPR/Cas9 ribonucleoprotein complexes has been demonstrated, allowing for the regeneration of edited protoplasts into whole plants without introducing foreign DNA, thus addressing regulatory concerns related to genetically modified organisms (Najafi et al., 2022). Furthermore, CRISPR/Cas9-mediated targeted mutagenesis has been successfully applied to generate biallelic mutations in the first generation of grape plants, enhancing resistance to *Botrytis cinerea* by knocking out the VvWRKY52 transcription factor gene (Wang et al., 2017).

7.2 Transgenic approaches

Transgenic approaches involve the introduction of foreign genes into the grapevine genome to confer disease resistance. These methods have been pivotal in developing grapevine varieties with enhanced resistance to fungal

and oomycete pathogens. For example, transgenic constructs expressing genes that limit pathogen growth or silence plant susceptibility genes have been optimized and applied to Vitis species, significantly reducing their susceptibility to diseases such as downy mildew, powdery mildew, and grey mold (Capriotti et al., 2020). The use of Agrobacterium-mediated transformation has been a common method for introducing these transgenes into grapevine, providing a robust platform for developing disease-resistant cultivars.

7.3 RNA interference (RNAi)

RNA interference (RNAi) is a powerful tool for silencing specific genes involved in disease susceptibility or pathogen virulence. In grapevine breeding, RNAi has been employed to downregulate genes that act as virulence effectors in pathogens, thereby enhancing the plant's defense mechanisms. This biotechnological approach has shown promise in controlling fungal and oomycete diseases by targeting and silencing critical genes in the pathogens, thus preventing their proliferation and reducing disease incidence (Figure 2) (Capriotti et al., 2020). The application of RNAi technology in grapevine breeding programs represents a complementary strategy to traditional breeding and other biotechnological methods, offering a holistic approach to disease management.

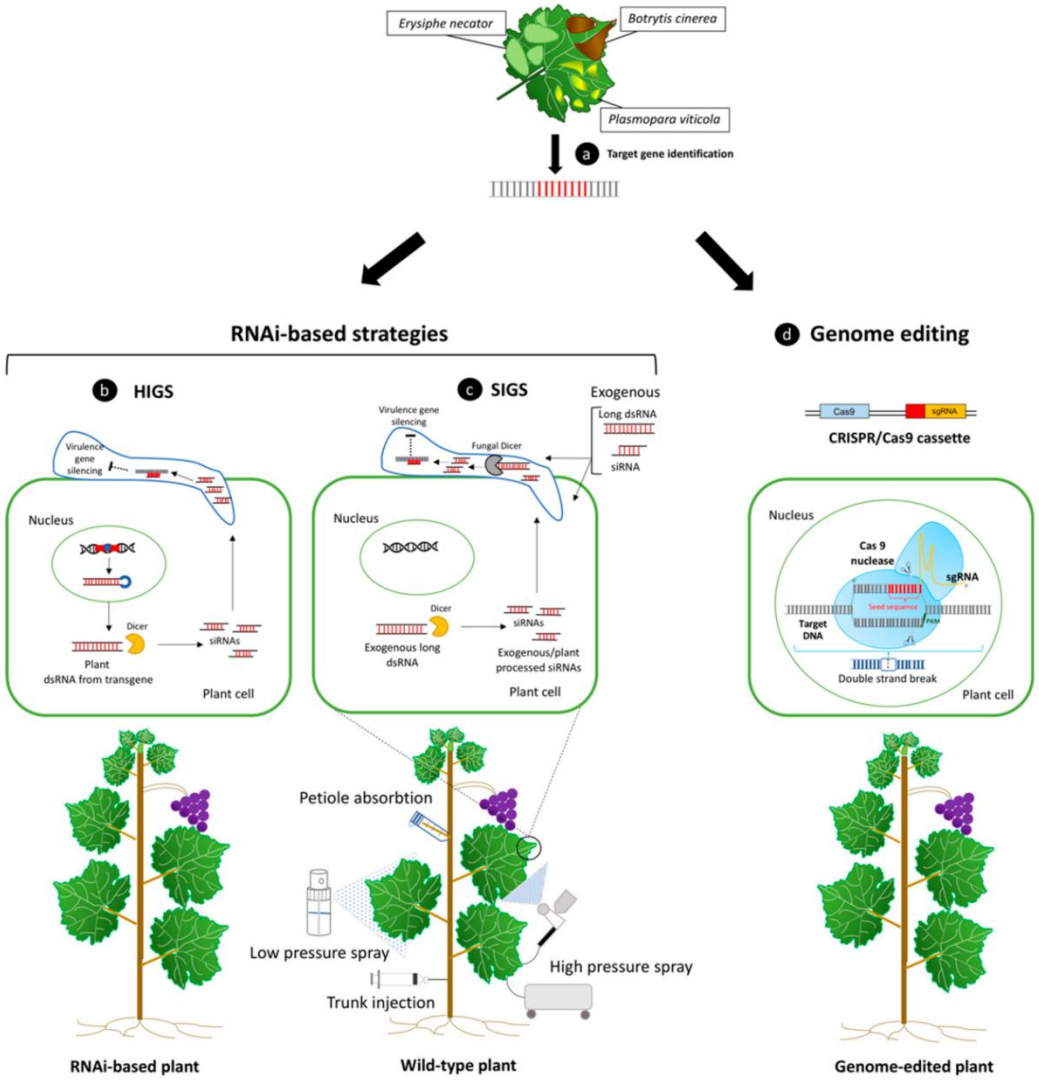

Figure 2 RNAi machinery (Adopted from Capriotti et al., 2020)

Image caption: In addition to trans/cisgenesis methods, the expression of RNAi gene constructs in the plant, the exogenous applications of double strand RNA (dsRNA) molecules targeting host/pathogen genes, or plant genome editing, represent valid alternatives to enhance plant immunity during pathogenesis (Adopted from Capriotti et al., 2020)

RNAi is based on two main strategies: master-induced gene silencing (HIGS) and spray-induced gene silencing (SIGS). In HIGS, transgenic plants are engineered to express double-stranded RNA (dsRNA) against pathogen genes. These dsRNAs are recognized and cleaved into small interfering RNAs (siRNAs) within plant cells by the Dicer protein, which downregulates the expression of the target gene. In SIGS, dsRNA is sprayed directly on the surface of plants and pathogens. These molecules can be taken up by both cells and, depending on the delivery method used, the dsRNA can be processed by the RNAi machinery of the plant and/or the pathogen, resulting in downregulation of virulence genes and reducing the harmful effects of the pathogen.

8 Challenges and Future Directions

8.1 Technical and practical challenges

The integration of genomic approaches in grapevine breeding programs faces several technical and practical challenges. One significant issue is the complexity of grapevine genomes, which complicates the identification and manipulation of resistance genes. For instance, while marker-assisted selection has been successful in identifying major resistance genes, these genes are often vulnerable to breakdown due to rapid changes in pathogen races. The genetic architecture of resistance is shifting towards a more complex model involving multiple minor genes, making breeding for durable resistance more challenging. Another practical challenge is the need for efficient gene transfer procedures and the optimization of biotechnological techniques, such as gene overexpression and gene silencing, to ensure that modifications do not introduce undesired traits. The development of new resistant varieties is a long-term and costly process, requiring significant resources and time (Merdinoglu et al., 2018).

8.2 Ethical and regulatory considerations

The use of genomic technologies in grapevine breeding also raises ethical and regulatory concerns. The deployment of genetically modified organisms (GMOs) in agriculture is subject to strict regulations in many countries, which can hinder the adoption of new biotechnological methods (Pirrello et al., 2022). There are also societal concerns regarding the safety and environmental impact of GMOs, which need to be addressed through transparent communication and rigorous safety assessments. The potential for resistance breakdown, as observed with the emergence of resistance-breaking isolates in grapevine downy mildew, highlights the need for careful management and monitoring of resistant varieties to prevent the spread of virulent pathogen strains.

8.3 Future trends in genomic breeding

Looking forward, several trends are expected to shape the future of genomic breeding in grapevines. One promising direction is the use of CRISPR/Cas9 technology for precise genome editing, which has already shown success in enhancing resistance to powdery mildew by targeting susceptibility genes. Another trend is the shift from marker-assisted selection to genomic selection, which involves whole-genome prediction models and can improve the accuracy and efficiency of breeding for complex traits such as disease resistance (Poland and Rutkoski, 2016). Additionally, the integration of biotechnological strategies, such as RNA interference (RNAi) and the pyramiding of multiple resistance genes, can provide a more holistic approach to disease management (Agurto et al., 2017; Capriotti et al., 2020). The continued exploration and characterization of existing germplasm will be crucial for developing new varieties that can perform well under diverse environmental conditions and meet market demands (Gaspero and Cattonaro, 2010). By addressing these challenges and leveraging emerging technologies, grapevine breeding programs can enhance disease resistance and contribute to sustainable viticulture practices.

9 Concluding Remarks

The application of genomic approaches in grapevine breeding programs has shown significant promise in enhancing disease resistance. The use of CRISPR/Cas9-mediated mutagenesis has been effective in inducing targeted mutations in grapevine genes, such as *VvMLO3*, resulting in enhanced resistance to powdery mildew. The availability of the grapevine reference genome has facilitated the use of marker-assisted selection, allowing

breeders to select plants based on DNA sequences associated with desirable traits, thus improving the efficiency of breeding programs. Techniques such as gene overexpression, gene silencing, and RNA interference have been employed to control fungal and oomycete diseases in grapevines, demonstrating the potential of these methods to enhance disease resistance. The integration of genomic prediction methods, such as GBLUP and LASSO, has shown variability in predictive abilities across traits, but overall, it has accelerated the breeding process by identifying superior individuals for specific breeding programs. The pyramiding of resistance genes, such as *RUN1* and *REN1*, has led to improved defense responses and enhanced resistance to powdery mildew in grapevines.

Genomic approaches are crucial in modern grapevine breeding programs for several reasons. Genomic tools allow for precise manipulation and selection of resistance genes, significantly reducing the time and resources required for traditional breeding methods. By targeting specific genes associated with disease resistance, genomic approaches can create grapevine varieties that are more resilient to pathogens, reducing the need for chemical treatments and promoting sustainable agriculture. Genomic studies provide insights into the molecular basis of pathogen specificity and resistance mechanisms, enabling the development of more durable resistance strategies.

To further advance the field of grapevine breeding for disease resistance, the following recommendations are proposed. Increase the availability and characterization of genomic resources, including reference genomes and high-density marker arrays, to support more comprehensive genomic studies. Combine genomics with other omics technologies, such as transcriptomics and proteomics, to gain a deeper understanding of the complex interactions between grapevines and pathogens. Focus on the pyramiding of multiple resistance genes and the identification of multi-disease resistance QTLs to develop grapevine varieties with broad-spectrum and durable resistance. Foster collaboration between plant geneticists, pathologists, and breeders to ensure the effective translation of genomic research into practical breeding applications. Continue to refine genomic prediction models and explore the use of diverse training populations to improve the accuracy and reliability of predictions for complex traits. By addressing these recommendations, future research can build on the current advancements and further enhance the resilience of grapevine cultivars to various diseases, ultimately contributing to more sustainable and productive viticulture.

Acknowledgments

Thanks to the reviewing experts for their guidance on the the manuscript.

Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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