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Review article

Review: Status and prospects of association mapping in grapevine

Javier Tello [*,1], Javier Ibáñez [2]

Instituto de Ciencias de la Vid y del Vino (CSIC, UR, Gobierno de La Rioja), Logroño 26007, Spain

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ABSTRACT

Thanks to current advances in sequencing technologies, novel bioinformatics tools, and efficient modeling solutions, association mapping has become a widely accepted approach to unravel the link between genotype and phenotype diversity in numerous crops. In grapevine, this strategy has been used in the last decades to understand the genetic basis of traits of agronomic interest (fruit quality, crop yield, biotic and abiotic resistance), of special relevance nowadays to improve crop resilience to cope with future climate scenarios. Genome-wide association studies have identified many putative causative *loci* for different traits, some of them overlapping well-known causal genes identified by conventional quantitative trait loci studies in biparental progenies, and/or validated by functional approaches. In addition, candidate-gene association studies have been useful to pinpoint the causal mutation underlying phenotypic variation for several traits of high interest in breeding programs (like berry color, seedlessness, and muscat flavor), information that has been used to develop highly informative and useful markers already in use in marker-assisted selection processes. Thus, association mapping has proved to represent a valuable step towards high quality and sustainable grape production. This review summarizes current applications of association mapping in grapevine research and discusses future prospects in view of current viticulture challenges.

1. Introduction

1.1. Grapevine: a worldwide relevant crop under new threats

According to the latest available statistics, worldwide vineyard surface accounts for 7.3 mha, with a total grape production of 77.8 mt that sustains worldwide wine elaboration and fresh grape and dried grape markets (O.I.V., 2021). Across the globe, there are about 6000–10,000 different grapevine (*Vitis vinifera* L.) cultivated genotypes (Wolkovich et al., 2018), but most of the worldwide grape production relies in the cultivation of a reduced number of them (Anderson and Nelgen, 2020). Forecast predictions indicate that traditional viticulture systems are strongly threatened by climate change conditions, as local climates will become increasingly mismatched with current viticultural practices (Hannah et al., 2013; Fraga et al., 2013). In addition, climate change may impact the known spatial distribution, biological patterns and reproductive cycles of different grapevine pests and pathogens, generating new uncertainties for grape and wine production markets (Caffarra et al., 2012; Savi et al., 2019). Multiple vineyard management strategies have been proposed to counteract some of the effects of climate change on grape production (Naulleau et al., 2021). However, they do not provide a long-term sustainable solution to overcome the plethora of expected problems linked to global warming, which include the shortening of the growing season with earlier phenological events, and the desynchronization of sugars, organic acids and phenolic compounds metabolism during grape ripening (Fraga et al., 2013). In addition,

Abbreviations: ABA, Abscisic acid; AM, Association mapping; CGAS, Candidate-gene association study; CRISPR, Clustered regularly interspaced short palindromic repeats; FDR, False discovery rate; *flb*, Fleshless berry; GWAS, Genome-wide association study; INDEL, Insertion/Deletion; LD, Linkage disequilibrium; MAS, Marker-assisted selection; MLM, Mixed linear model; MLMM, Multi-locus mixed model; MWAS, Metabolome-wide association study; NB-LRR, Nucleotide binding-leucine-rich repeat; Q-Q, Quantile–quantile; QTL, Quantitative trait locus; QTN, Quantitative trait nucleotide; RRM, Reiterated reproductive meristem; *SdI*, Seed development inhibitor; SNP, Single nucleotide polymorphism; SSR, Simple sequence repeat; SV, Structural variation; TWAS, Transcriptome-wide association study; *VIVC*, *Vitis* International Variety Catalogue.

* Correspondence to: Instituto de Ciencias de la Vid y del Vino (ICVV), Finca La Grajera, Ctra. de Burgos Km. 6 (LO-20 – Salida 13), Autovía del Camino de Santiago, 26007 Logroño, La Rioja, Spain.

E-mail address: javier.tello@icvv.es (J. Tello).

[1] ORCID: 0000-0002-6299-5563

[2] ORCID: 0000-0002-6286-5638

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viticulture makes use of a huge amount of fungicides, and regulations in many countries tend to reduce the use of pesticides in agriculture. As a result, many viticulturists will be forced to use alternative grapevine genetic resources (Töpfer and Trapp, 2022), as the substitution of traditional cultivars by better adapted genotypes might buffer the adverse effects of climate change on grape production and fruit quality (Morales-Castilla et al., 2020).

Shifting of grapevine cultivars to adapt viticulture systems to new climate conditions and new regulations requires the characterization of the diversity available in this crop. Phenotypic information, combined with genetic data, can provide useful knowledge on the genetic determinism of highly relevant traits. In this framework, association mapping studies provide an efficient strategy to analyze the genetic architecture of agriculturally and economically important traits. This knowledge can be used to speed up grapevine breeding and improvement programs to release novel cultivars capable to overcome current viticultural challenges. In this review, we (i) summarize how association mapping has been used to understand the genetic determinism of major traits of grapevine; (ii) critically discuss how these findings have been useful so far; and (iii) outline the challenges and opportunities that grapevine association mapping faces.

1.2. Grapevine breeding aims

A successful new grape variety should combine multiple characteristics that may differ according to its final use (table grape, wine grape, raisins). As recently reviewed (Delrot et al., 2020), table grape breeders aim to obtain new high-yielding seedless varieties with appealing fruit appearance (color, shape, size) and other good sensory features (sweetness-acidity balance, new flavors, firm texture). On the other hand, wine grape breeders intend to obtain novel balanced-yielding varieties whose fruits provide fermentable juices with an optimum composition (sugar, acids, phenolic compounds, aroma precursors) to obtain high quality wines. Regarding varieties for raisins, breeders aim to obtain high-yielding varieties with seedless and very sweet fruits, ideally with additional beneficial attributes (like some skin persistence, wrinkle presence, and meatiness) to produce the highest quality product after dehydration processes. Regardless its final use, grape breeding programs search for some level of resistance or tolerance to some of the most common biotic factor agents that threaten grape production: powdery mildew, downy mildew and phylloxera (caused by *Erysiphe necator*, *Plasmopara viticola*, *Daktulosphaira vitifoliae*, respectively). More recently, given the need of cultivars with adaptation potential to novel climate conditions, the evaluation of traits of resistance or tolerance to abiotic stresses (heat, drought, sunburn) is becoming common in grapevine breeding programs.

On the other hand, most vineyards over the world are grafted onto rootstocks, usually varieties from non-*vinifera Vitis* species or hybrids between non-*vinifera* and *vinifera*. The non-*vinifera* background provides resistance to biotic (phylloxera, nematodes) and abiotic (salinity, drought) stresses. Consequently, rootstocks breeding programs search for novel genotypes with high root resistance levels towards grape phylloxera and soil nematodes. As they also play a role in scion adaptation to abiotic stresses, rootstocks with beneficial traits to fight soil (*e.g.*: mineral deficiencies or excesses) and/or climate adversities (*e.g.*: drought, waterlogging, *etc.*) are aimed. In addition, novel genotypes with high rooting and good callus formation abilities, and good affinity for grafting are preferred (Delrot et al., 2020, Marín, et al. 2021).

1.3. Grapevine diversity and grapevine collections

The exploration of the genetic diversity of the *V. vinifera* germplasm has been the basis of many works, first through ampelographic (morpho-agronomic) descriptors (Boursiquot et al., 1995), and then with genetic markers, usually microsatellites (or simple sequence repeats, SSRs) and single nucleotide polymorphisms (SNPs) (Myles et al., 2011; Emanuelli et al., 2013; Bacilieri et al., 2013). The combination of traditional ampelographic descriptions with molecular-based profiling techniques has indicated the presence of 6000–10,000 different *V. vinifera* cultivars (Wolkovich et al., 2018), a number of difficult estimation due to the existence of many different homonyms and synonyms (This et al., 2006). Population genetic analyses indicate that this high diversity is strongly structured, and affected by the primary use of the cultivar (wine or table grape) and its geographical origin (Emanuelli et al., 2013; Bacilieri et al., 2013; Laucou et al., 2018). This genetic diversity is reflected in the high phenotypic variability available for multiple reproductive and quality traits, many of them of interest for grape breeding activities (Fig. 1). To cite some, berry weight and berry volume have been reported to vary by a ten- and 23-fold factor between grapevine cultivars, from 0.98 g and 0.5 cm^3 to 10.14 g and 11.5 cm^3, respectively (Houel et al., 2013), budburst date might vary up to 39 days between the earliest and the latest cultivars (Boursiquot et al., 1995), and white-berried cultivars might accumulate 5000–60,000 times less anthocyanins in berry skins than black-berried cultivars, and 10–100 times less compared to pink-berried cultivars (Arapitsas et al., 2015). Of the interest for association genetics studies, different works indicate a strong relationship between genetic structure and phenotypic diversity for some traits, due to preferential selection of alleles among genetic subgroups, derived from diversifying selection processes and/or genetic drift (Nicolas et al., 2016; Migicovsky et al., 2017; Sikuten et al., 2021).

Despite this high variability, only a small portion of the available cultivars is commercially exploited, and most of the genetic diversity is confined to germplasm collections (This et al., 2006). These collections have been used to define several core collections to represent global grapevine diversity, based on morphological traits or on genetic data (Emanuelli et al., 2013; Cunff et al., 2008; Barnaud et al., 2006). Recently, a panel of 279 grapevine cultivars capturing most of the genetic and phenotypic diversity from the Vassal grapevine collection (the largest and most diverse collection of grape cultivars available worldwide) has been proposed (Nicolas et al., 2016). The limited relatedness between the cultivars included in this panel and its global genetic structure facilitates the exploration of the genetic determinism of multiple agronomic traits *via* association mapping, as recently demonstrated (Flutre et al., 2022).

2. Grapevine genetic association studies

2.1. Linkage mapping vs association mapping

Most of the traits of interest for grapevine breeding show a complex quantitative inheritance (Vezzulli et al., 2019). These traits have been conventionally studied through linkage mapping (also termed quantitative trait *loci* (QTL) mapping) in segregating progenies, approach that has provided useful results on the genetic determinism of traits related to grapevine yield, phenology, berry composition, and resistance to pathogens and abiotic factors (Vezzulli et al., 2019). In specific cases, QTL mapping results have revealed an oligogenic control for some traits, like flower sex, berry color, muscat aroma, or seedlessness (Doligez et al., 2006; Cabezas et al., 2006; Dalbó et al., 2000; Doligez et al., 2002). Although QTL mapping has proved (and remains) to be a powerful tool to identify the genetic basis of multiple traits, it presents some limitations. An important one is that QTL mapping relies on the recombination events occurred during the development of the mapping progeny, usually not too large, which conventionally derives in wide QTL intervals of 10–20 cM (Zhu et al., 2008) that hinders the identification of the underlying responsible gene/s. This limitation can be partially solved by the use of larger progenies, but it increases the cost associated to plant maintenance, propagation and phenotyping. Additionally, QTL mapping results depend on the phenotypic diversity of the two parents for the trait of interest, which might be a reduced portion of that available at the species level (Xu et al., 2017).

An alternative approach to understand the global genetic

Fig. 1. Phenotypic diversity for bunch (size, shape, compactness) and berry (size, shape, color) traits in different grapevine cultivars (from left to right and top to bottom, representative bunches from cultivars 'Fogoneu', 'Sangiovese', 'Cabernet Sauvignon', 'Quiebratinajas Rojo', 'Graciano', 'Cornichon Blanc', 'Monastrell', 'Beba Roja', 'Pinot Meunier', 'Garganega', 'Ruby Seedless', 'Dominga', 'Listan Prieto', and 'Gewurztraminer'). Squares in the background have 1 cm^2.

architecture of a complex trait is linkage disequilibrium (LD)-based association mapping (AM). AM studies search for functional variation in a broader context, using an association panel of diverse genotypes selected by carrying most of the phenotypic variability available for the target trait at a species level (Zhu et al., 2008). The genetic diversity available in the genotypes of the association panel derives from numerous historical and evolutionary recombination events happened across generations, resulting in increased mapping resolution (Zhu et al., 2008; Myles et al., 2009). Thus, AM studies consider a greater allele number than QTL mapping studies, so results from this approach tend to be more general (Zhu et al., 2008). AM is of special interest for species with long generation cycles (like the grapevine), as it does not require the laborious, time-cost (and often expensive) process of establishing mapping progenies (Myles et al., 2009). As a result, AM has become the method of choice for many laboratories worldwide, a tendency that increases as sequencing technologies progress and new modeling approaches are developed.

AM performance relies on the LD between the genotyped markers and the functional polymorphism/s in the causative gene/s (Myles et al., 2009; Rafalski, 2010). Therefore, knowing the rate of LD decay over a specific genetic distance is fundamental to set the number of genetic markers needed to reach an adequate statistical power (Nicolas et al., 2016). Genome-wide LD estimations in the cultivated grapevine indicate it decays fastly, reaching r^2 values below 0.2 within short physical distances (Laucou et al., 2018; Nicolas et al., 2016; Marrano et al., 2017). This value implies the need of genotyping a large number of well-scattered genome-wide markers to overcome the underlying LD structure. In this line, at least one marker per Kb has been suggested to be needed for a proper genome-wide statistical power (Nicolas et al., 2016). For genome-wide association studies (see subsection 2.2), it implies the use of high-throughput genotyping methods, or whole genome resequencing technologies (Pavan et al., 2020). Once a significant association is detected, it is likely that the associated marker is physically close to the causal polymorphism, which eases the task of identifying the gene/s responsible of the phenotypic diversity (Ingvarsson et al., 2016).

Despite its advantages compared to conventional QTL mapping, AM presents some limitations, including high rates of spurious associations due to population structure and multiple testing. Spurious associations occur when a marker-trait association is declared as significant when it is not actually true (Zhu et al., 2008). Grapevine association panels are formed by a series of genotypes with varying levels of pedigree relationships, common geographical origin and breeding history (Zhu et al., 2008). Consequently, a prime risk of grapevine AM studies is the appearing of false positives when the trait correlates with the underlying genetic structure or pedigree relatedness between the individuals of the panel (Balding, 2006). Fortunately, this fact is a common problem for AM studies for many genetically structured species, and many statistical methods have been developed to reduce this effect (Tibbs Cortes et al., 2021), including the pioneer unified mixed linear model (MLM) (Yu et al., 2006). Besides, multiple testing is another issue that might hinder AM studies. As more markers are genotyped and tested, the probability to find spurious associations increases, which implies the need to set an appropriate significance threshold to detect only those markers truly associated with the target trait. Common approaches to overcome this limitation include the estimation of the false discovery rate (FDR), and the Bonferroni correction, which divides the desired significance threshold by the total number of markers tested (Tibbs Cortes et al., 2021). Nevertheless, it assumes independence between the tested markers (which is not habitual in AM studies (Tibbs Cortes et al., 2021; Zinelabidine et al., 2021) and derives into too stringent thresholds that increase the number of false negatives. However, different alternatives have been proposed to set a more realistic significance threshold to evaluate AM studies results, like those that consider the dependency among markers (Gao et al., 2010; Duggal et al., 2008) or heritability values (Kaler and Purcell, 2019).

2.2. *Association mapping: genome-wide vs candidate-gene studies*

Based on their scale and focus, AM studies can be classified into two categories: genome-wide and candidate-gene association studies (GWAS and CGAS, respectively) (Zhu et al., 2008; Rafalski, 2010). In general, GWAS are exploratory analyses used to reveal the genetic architecture of a trait, providing useful information regarding the number of causal *loci*, their distribution and location, and their interactions (Liu and Yan, 2019). GWAS search for significant associations using markers detected across the whole genome, typically single nucleotide polymorphisms (SNPs). On the other hand, CGAS are hypothesis-driven approaches that assume some previous understanding of the genetic architecture of the target trait and are not impacted by the global genome-wide LD. For CGAS, genetic markers are genotyped at a *locus* (typically, one gene) thought to be involved in the target trait (Myles et al., 2009). In

grapevine CGAS, candidate *loci*/genes have been commonly selected from previous genetic, biochemical and/or physiological studies (Royo et al., 2018; Cardoso et al., 2012; Tello et al., 2016). In the absence of previous information, candidate *loci* have been selected based on studies in related or in model species (Vargas et al., 2013a; Fernandez et al., 2014; Tello et al., 2020). CGAS are used to test the association between the genetic markers detected in the candidate *loci* and the phenotype, to ultimately move from QTLs to QTNs (quantitative trait nucleotides). Ideally, this approach will identify the genetic variants responsible for phenotypic variation, which can be very confidently used for marker-assisted selection (MAS) in breeding activities (Myles et al., 2009).

Either for GWAS or CGAS, the experimental workflow of AM studies follows a series of common stages, which are graphically depicted in Fig. 2. The first step consists in the selection of the individuals to be screened from the available germplasm. This selection must ideally represent all the phenotypic diversity existing for the target trait (Nicolas et al., 2016), maximizing if possible the frequency of minority classes to increase the statistical power of the association study (Vargas et al., 2016). As discussed above, the cultivated grapevine holds a great diversity for most of the traits that are relevant for breeding programs, so this stage is critical. Once selected, these individuals are phenotyped for the trait of interest and genotyped. For GWAS, genetic markers are randomly obtained from the whole genome using high-throughput sequencing technologies. These markers are then used to (i) test their association with the target trait (candidate variants), and (ii) evaluate the presence of confounding factors like population structure and family relatedness. CGAS typically involve the obtaining of two different sets of markers: (i) those used as candidate variants after the targeted sequencing of the candidate *locus* (or *loci*), and (ii) a series of neutral (typically microsatellite) markers, used to evaluate population structure and family relatedness effects (Zhu et al., 2008). In parallel, the diversity panel is phenotyped for the trait(s) of interest, ideally in different locations during several seasons to overcome environmental fluctuations. Depending on the traits of interest, they can be alternatively or additionally evaluated under controlled conditions, in dedicated greenhouses or phenotyping platforms (Coupel-Ledru et al., 2016). So far, most of the reported grapevine AM studies have used traits evaluated in the field by traditional phenotyping methods, which (in general) only allowed the description of a limited number of individuals. Although the development of high-throughput grapevine phenotyping technologies has increased rapidly in the last years (recently reviewed in (Cadle--Davidson et al., 2019)), this field of research still lags far behind genomics advances, and this step is currently considered the actual bottleneck in AM studies (Töpfer et al., 2011). Another critical step in AM studies is the selection of a modeling approach that fits our data and aims. As stated above, AM research was boosted by the MLM solution (Yu et al., 2006), extensively used in grapevine AM studies. Nowadays,

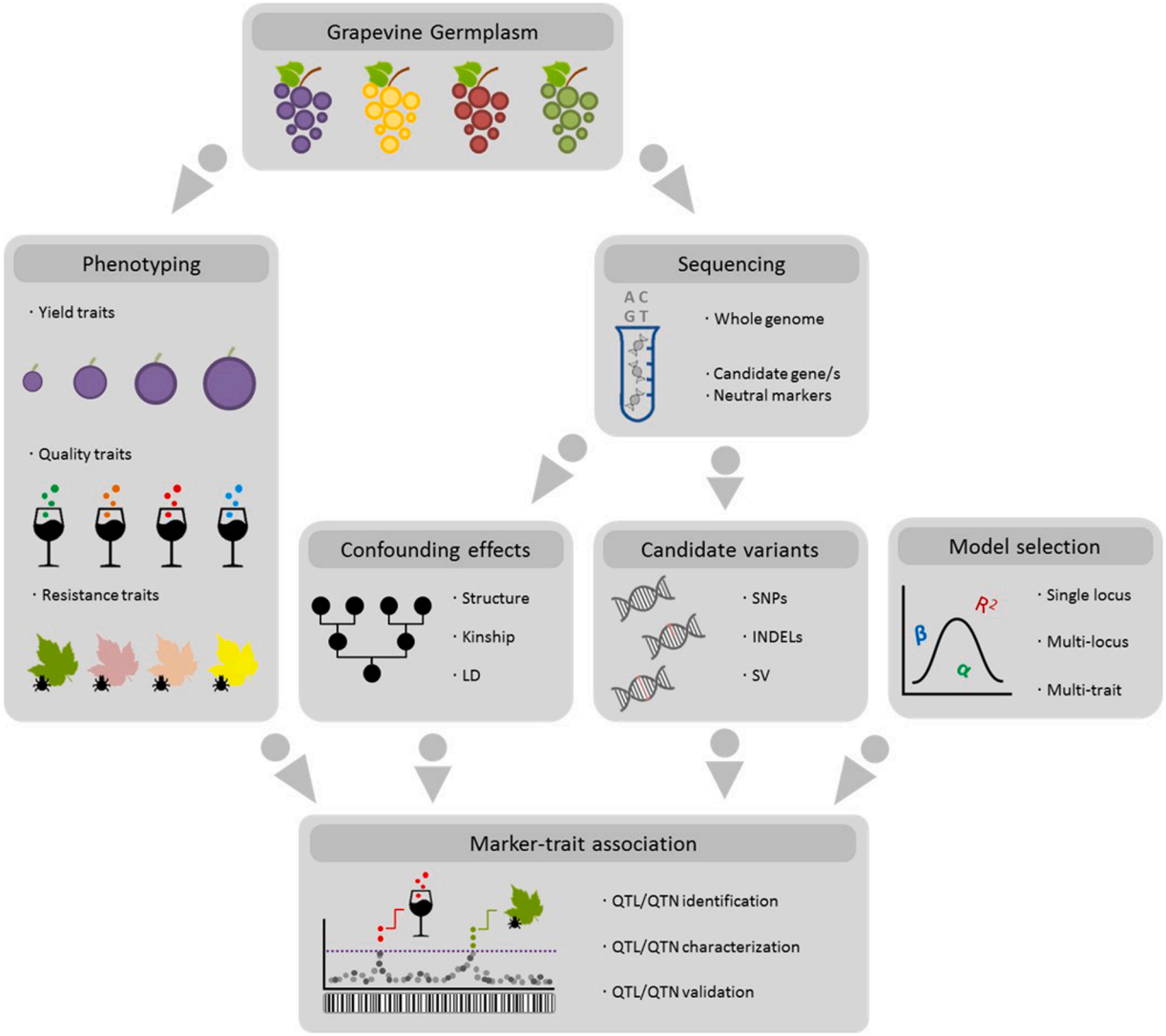

Fig. 2. Graphical overview of the main steps for conducting a linkage disequilibrium-based association mapping study in grapevine.

there is a trend towards the development of multi-locus models, which incorporate more than one candidate marker as covariates in the model (Liu et al., 2016a; Wang et al., 2016; Segura et al., 2012). More recently, several multi-trait multi-locus models have been developed too (Liu et al., 2016b), which are expected to provide a new dimension to understand the intricate biological processes underlying phenotypic diversity.

After genetic and phenotypic data collection and model selection, marker-trait association tests are conducted, usually in software packages that ease data processing and results interpretation (Bradbury et al., 2007; Purcell et al., 2007; Lipka et al., 2012). The outcome of these tests is a list of putative associations to be evaluated after setting a multiple testing-corrected p-value cutoff. In addition, each test is accompanied by the proportion of phenotypic variance explained by the marker after model fitting (Rafalski, 2010). AM results are usually summarized by quantile–quantile (Q-Q) and Manhattan plots, which ease the identification of true signals. For each modeled trait, Q-Q plots display the observed *vs* the null-expected p-values for all markers, so only associated markers deviate for the null expectation at the upper-right end of the plot. A systematic deviation from the diagonal observed in a Q-Q plot might be indicating problems with experimental data or an inappropriate model selection (Korte and Farlow, 2013). Manhattan plots display the $-log10$(p-value) of the association test *vs* the genomic position of the marker, so highly associated markers will appear as 'skyscrapers' along the plot (Kaler and Purcell, 2019). After the identification of these markers, the neighboring genomic regions are characterized through different approaches. They include the visualization of the local LD and common haplotype patterns (Barret et al., 2005), the evaluation of the effect of the associated polymorphism on gene sequence and protein function, and the evaluation of the likely effect of the polymorphism on gene expression if it is found in the promoter of the gene (Cingolani et al., 2012; Yachdav et al., 2014). Lastly, an integral step of an AM study is the independent validation of the hypothesis generated, as the risk of false positive associations is still present even under strong statistical evidence (Alseekh et al., 2021). This stage could be approached through a cross validation in alternative diversity panels, or in biparental progenies segregating at the associated polymorphism (Sonah et al., 2015). Another way is the functional validation of the association. In this regard, genome editing technologies such as the CRISPR/Cas9 system are suggested to provide determinant information for the confirmation (or rejection) of the causality hypothesized from the statistical correlation (Wang et al., 2017).

3. An overview of grapevine genome-wide and candidate-gene studies

Association tests have been used in plant genetics since the early 2000s, after the publication of some pioneer studies on maize and *Arabidopsis* populations (Flint-Garcia et al., 2003). Aware of its potential for identifying alleles and *loci* responsible for natural variation, first grapevine AM studies appeared shortly after that (This et al., 2007; Fournier-Level et al., 2009a). Since then, the number of works reporting results from AM studies has grown progressively (Fig. 3A). As for other crops, AM was initially used to explore the association between the allelic variation in the sequence of some candidate genes and trait diversity, whilst first GWAS were reported only when high-throughput sequencing technologies and new computational resources became available and cost-affordable. AM studies (both CGAS and GWAS) have been used to analyze very different traits, with a predominance of quality traits (*e.g.*: berry color, muscat aroma, seedlessness) over yield-related traits (*e.g.*: bunch weight, berry weight) or resistance traits (*e.g.*: pest resistance or cold tolerance). Other traits analyzed by AM are those related to phenology or leaf shape (Fig. 3B). Interestingly, both CGAS and GWAS have been published for all traits categories but for resistance traits, for which only GWAS are available. An overview of these studies can be found in Table 1 and Table 2, and the most relevant results are discussed in the following subsections.

3.1. Quality traits

The concept of grape quality is highly complex, and it depends on the aim of the fruit (wine or fresh consumption). For both uses, appropriate composition in terms of sugars, organic acids, phenolics and aromatic compounds relates to better fruit, juice and wine quality (Poni et al., 2018). In addition, medium-to-loose bunches are preferred for both wine and table grapes, as they are less prone to fungal diseases (Tello and Ibáñez, 2018). For table grapes, quality is also evaluated in terms of visual attributes (berry size, shape and color), berry texture, taste and seedlessness, and bunch size and shape (Wei et al., 2002). Although vineyard management techniques can, to some extent, modify part of some of these traits, they are varietal features under strong genetic control.

3.1.1. Berry color

Doubtless, berry color is the trait that has received more attention from the grapevine scientific community. This trait has a high

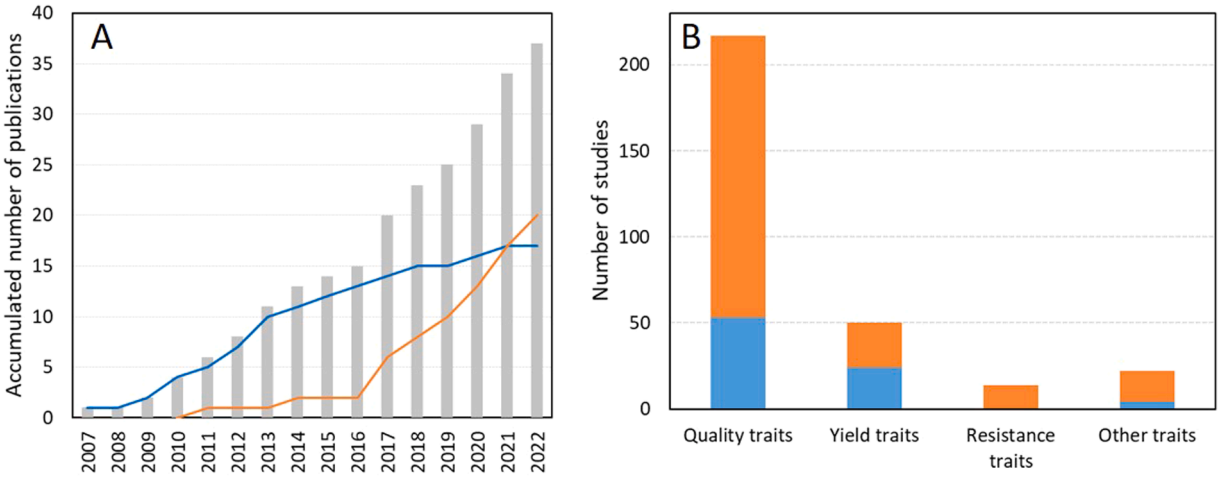

Fig. 3. Number of linkage disequilibrium-based association mapping studies in grapevine published per year (A) and trait category (B). In A, the accumulated number of publications reporting candidate-gene association studies (CGAS) and/or genome-wide association studies (GWAS) per year is shown as blue and orange lines, respectively. In B, the number of studies showing results on quality, yield, resistance, and other traits is depicted. Publications for CGAS and GWAS are shown in blue and orange, respectively.

Table 1
Candidate-gene association studies (CGAS) in grapevine.

Trait category[a]	Trait/s	Population size	Candidate gene/s	No. Markers	Reference
Q	Berry color	168	*VviMybA1*	46	(This et al., 2007)
Q	Anthocyanins	141	*VviMybA1*, *VviMybA2*, *VviMybA3*, *VviMybA4*	78	(Fournier-Level et al., 2009a)
Q	Muscat flavor	148	*VviDXS*	102	(Emanuelli et al., 2010)
Q	Methylated anthocyanins	50	*VviAOMT1 VviAOMT2*	37	(Fournier-Level et al., 2011)
Q	Berry color; Anthocyanins	149	15 genes	124	(Cardoso et al., 2012)
Q	Proanthocyanidins	141	9 genes	110	(Huang et al., 2012)
Q	Proanthocyanidins	141	*VviCob-like*, *VviGat-like*, *VviMybC2-L1*	81	(Carrier et al., 2013)
Q	Muscat flavor	92	*VviDXS*	22	(Yang et al., 2017b)
Q	Seedlessness	124	*VviAGL11*	537	(Royo et al., 2018)
Q/Y	Inflorescences number; Cluster width; Cluster length; Cluster weight; Peduncle lentgh; Berry width; Berry length; Berry weight; Berry volume; Color index; Juice yield; Flesh firmness; Force at 10%; Force at 20%; Rupture force; Rupture slope; Rupture area; Deformation rate	96	*VviPel*	32	(Vargas et al., 2013a)
Q/Y	Inflorescences number; Cluster width; Cluster length; Cluster weight; Peduncle lentgh; Berry width; Berry length; Berry weight; Berry volume; Color index; Juice yield; Force at 10%; Force at 20%; Rupture force; Rupture slope; Rupture area; Deformation rate	127	*VviGAI1*	15	(Vargas et al., 2013b)
Y	Berry weight	38	*flb* region	447	(Houel et al., 2010)
Y	Berries; Berry length; Berry volume; Berry weight; Berry width; Cluster length; Cluster weight; Cluster width; Seeds	114	*VviNAC26*	69	(Tello et al., 2015b)
Y	Cluster compactness; First ramification length; Berries	114	183 genes	7032	(Tello et al., 2016)
Y	Cluster compactness; Peduncle length; Rachis length; First ramification length; Second ramification length; Third ramification length; Fourth ramification length; Pedicel length	114	*VviUCC1*	80	(Tello et al., 2020)
Y	Berries; Coulure; Flower number; Fruitset; Millerandage; Seeds	114	289 genes	15,309	(Zinelabidine et al., 2021)
Y/O	Budburst; Flowering; Veraison; Maturity; Yield; Berry weight; Cluster length; Cluster width; Cluster weight; Cluster compactness	140	*VviTFL1A*	60	(Fernandez et al., 2014)

[a] Q: Quality-related trait; Y: Yield-related trait; O: Others

commercial relevance for both wine and table grapes, so understanding how individual berries get their final color and how it is affected by genetic and environmental factors is essential. Early genetic studies in biparental progenies indicated that berry color variation is mostly controlled by a single *locus* on chromosome 2 (Doligez et al., 2002; Lijavetzky et al., 2006), which was soon narrowed to a 200-kb region that clusters a series of *VviMybA* transcription factor genes (Fournier-Level et al., 2009b; Walker et al., 2007). As expected given this oligogenic control, this major *locus* has been easily detected in different GWAS (Myles et al., 2011; Laucou et al., 2018; Migicovsky et al., 2017; Flutre et al., 2022; Guo et al., 2019), which also indicates the presence of strong selection processes at this *locus* during grapevine selection and breeding processes.

Given this solid knowledge, AM studies have aimed to identify the *VviMybA* mutations causing berry color variation. *VviMybA1* is the major determinant of berry color, as it modulates the transcription of *VviUFGT* (UDP-glucose:flavonoid 3-O-glucosyltransferase), a key point in the pathway involved in anthocyanins accumulation in berry skins (Fournier-Level et al., 2009b). In this sense, different functional and genetic analyses indicated that the presence of a retrotransposon (*Gret1*) in the promoter region of *VviMybA1* disrupts anthocyanins biosynthesis, leading to non-colored berries (Lijavetzky et al., 2006; Kobayashi et al., 2005). Accordingly, the leading role of the *Gret1-VviMybA1* retrotransposon on berry color determination has been supported by AM findings (This et al., 2007; Fournier-Level et al., 2009a). Interestingly, additional *VviMybA1* polymorphisms contributing to berry color variation have been indicated, including two SNPs causing a non-synonymous modification in the VviMybA1 protein structure (Fournier-Level et al., 2009a). Another *VviMybA* gene known to have a relevant role on berry color is *VviMybA2*, which also regulates *VviUFGT* activity (Walker et al., 2007). Via AM, up to 12 *VviMybA2* sequence polymorphisms were found to associate significantly with berry anthocyanin concentration, three of them causing a non-synonymous change in the VviMybA2 protein structure (Fournier-Level et al., 2009a). Significant associations have been also indicated for *VviMybA3* sequence polymorphisms (Fournier-Level et al., 2009a). However, its functional contribution to berry skin color is less evident (Walker et al., 2007), and it has been related to berry flesh pigmentation (Zhang et al., 2018). Lastly, no association between berry color (or anthocyanin content) and *VviMybA4* sequence polymorphisms have been reported (Fournier-Level et al., 2009a), supporting the suggested lack of activity of this gene in grape berries (Walker et al., 2007). Besides, additional AM studies indicate that other *loci* beyond the *VviMybA* cluster on chromosome 2 might be involved on the fine regulation of grapevine berry color (Cardoso et al., 2012).

3.1.2. Muscat flavor

The scent of muscat varieties has been greatly appreciated since ancient times, and still is an important trait when breeding new table and wine grape varieties. This unique flavor is due to the presence of a series of monoterpenoids (mainly linalool, geraniol, nerol, citronellol and α-terpineol) with low olfactory perception thresholds (Ribereau-Gayon et al., 1975), which are synthesized and accumulated during grape development and ripening (Fenoll et al., 2009). Multiple genetic studies in biparental progenies revealed a QTL of major effect on chromosome 5 controlling this trait (Doligez et al., 2006; Wang et al., 2020; Battilana et al., 2009; Duchene et al., 2009). This oligogenic control has been also supported by up to five independent GWAS performed in different grapevine collections (Laucou et al., 2018; Migicovsky et al., 2017; Guo et al., 2019; Liang et al., 2019; Yang et al., 2017a). This genomic region co-localizes with a 1-deoxy-D-xylulose 5-phosphate synthase (*VviDXS1*) gene (Battilana et al., 2009; Duchene et al., 2009) which codes for the first enzyme of the plastidial pathway of terpene biosynthesis, acting upstream in the biosynthesis of aromatic

Table 2
Genome-wide association studies (GWAS) in grapevine.

Trait category	Trait/s	Population size	No. Markers	Reference
Q	Berry color	289	5110	(Myles et al., 2011)
Q	Muscat flavor	96	187	(Yang et al., 2017a)
Q	Seedlessness	199	414,223	(Zhang et al., 2017a)
Q	Berry shape	279	566,129	(Zhang et al., 2022a)
Q	Berry cracking	287	601,261	(Zhang et al., 2022b)
Q	Seed-to-berry ratio	88	6.86 M	(Magris et al., 2021)
Q/R/Y/O	Yield components; Organic acids; Aroma precursors; Polyphenols; Water stress indicators	279	63,000	(Flutre et al., 2022)
Q/Y	Berry development; Cluster size; Cluster density; Berry weight; Berry flesh texture; Berry color; Berry shape; Berry flavor	179	32,311	(Guo et al., 2019)
Q/Y	Berry shape; Seeds; Cluster compactness; Berry composition; Aromatic composition; Berry weight; Brix	472	8.73–9.07 M	(Liang et al., 2019)
Q/Y	Cluster weight; Berry weight; Yield; Clusters per plant; Brix; pH	86	26,893	(Marrano et al., 2018)
Q/Y/O	Berry firmness; Berry length; Berry shape; Berry size; Berry weight; Berry width; Cluster density; Cluster length; Cluster size; Cluster weight; Cluster width; Brix; Muscat aroma; Seed number; Seed weight; Seedlessness; Skin color; Titratable acidity; Bloom date; Budburst date; Leaf date; Veraison; First cluster node; Flower sex; Leaf hair; Leaf size; Naked vein; Peduncle length; Petiolar sinus; Shoot color intensity; Shoot hair; Tip anthocyanin	1817	9114	(Migicovsky et al., 2017)
Q/Y/O	Flower sex; Berry color; Seeds; Flavor; Phenology; Fertility; Cluster weight; Berry weight	783	10,207	(Laucou et al., 2018)
R	Resistance to *Coniella diplodiella*	81	160	(Zhang et al., 2017b)
R	Resistance to *Colletotrichum* spp.	350	77,126	(Jang et al., 2020)
R	Resistance to *Plasmopara viticola*	132	12,825	(Sargolzaei et al., 2020)
R	Resistance to *Coniella diplodiella*	386	88,877	(Zhang et al., 2020)
R	Leaf bristles; Leaf hairs; Leaf domatia size; Leaf domatia density; Leaf domatia depth	399	4523	(LaPlante et al., 2021)
R	Drought resistance	100	7133	(Trenti et al., 2021)
R	Cold tolerance	118	1.04 M	(Wang et al., 2021)
O	Leaf shape; Venation pattern	961	6114	(Chitwood et al., 2014)

[1] Q: Quality-related trait; R: Resistance-related trait (abiotic/biotic); Y: Yield-related trait; O: Others.

monoterpenoids (Battilana et al., 2009).

The detailed analysis of the *VviDXS1* gene sequence in a collection of 148 grapevine cultivars revealed 101 polymorphisms (94 SNPs and 7 INDELs), three of which were found to yield a significant association with berry taste variation in a CGAS (Emanuelli et al., 2010). One of these SNPs was found to cause a non-neutral amino acid substitution (K284N) in VviDXS1 that affects protein kinetics and increases monoterpenoids levels in muscat cultivars (Battilana et al., 2011). Furthermore, the role of K284N on muscat flavor has been recently supported by an alternative CGAS (Yang et al., 2017b). Given the interest of this trait for breeding activities and germplasm characterization, a series of *VviDXS1* allele-specific markers for this trait have been designed (Emanuelli et al., 2014), which have been already used for targeting muscat-flavored grapevine genotypes (Merkouropoulos et al., 2016; Morcia et al., 2021).

3.1.3. Organic acids

Organic acids affect the sensory properties of grapes and the quality of wines (Dai et al., 2011). The final concentration of organic acids is a primary factor of must quality, and it differs between *V. vinifera* L. varieties (Bigard et al., 2018). Fruit composition is also affected by climate conditions, as well as by cultural practices, which hinders the analysis of its genetic basis. Different QTL studies in biparental progenies indicate that sugars and organic acids composition at harvest time is a complex quantitative trait, controlled by a large number of enzymes likely connected on a highly complex regulatory network (Houel et al., 2015; Chen et al., 2015; Bayo-Canha et al., 2019; Duchene et al., 2020; Reshef et al., 2022). A recent work has explored the genetic basis of organic acids berry content *via* GWAS in a panel of 279 grapevine cultivars (Flutre et al., 2022). Among other findings, authors indicated an associated genomic region in chromosome 3 for citrate levels, which co-localizes with several candidate genes likely involved in citrate metabolism, including five allene oxide synthases genes, and the long chain acyl coA synthase 2 gene. For malate levels, authors found significant associations with a series of SNPs in chromosomes 9, 12 and 18. The *locus* found in chromosome 9 was previously indicated in a biparental progeny (Bayo-Canha et al., 2019), and it has been linked to the presence of a chloroplastic glyoxylate/succinic semialdehyde reductase 2 gene, enzyme involved in malate acid metabolism.

3.1.4. Seedlessness

Seedlessness is one of the most prized traits in table grapes and raisins. Seedless cultivars can be grouped into two major groups: stenospermocarpic (resulting after an early abortion of the embryo development) and parthenocarpic (resulting after ovary growth without fertilization) (Royo et al., 2018). Unlike parthenocarpy, stenospermocarpy can produce berries of a relevant size for the table grape market. Therefore, breeders aim for novel stenospermocarpic cultivars. This interest led to the early exploration of the genetic basis of this trait through multiple QTL mapping studies in biparental progenies (from

either seedless × seedless (embryo rescue is required) or seeded × seedless varieties). All these works found a major causative *locus* on chromosome 18 (near the VMC7F2 SSR marker) controlling seed content traits related to stenospermocarpic seedlessness variation: number of seeds, total fresh and dry weight of seeds, and seed traces (Cabezas et al., 2006; Doligez et al., 2002; Mejia et al., 2007; Costantini et al., 2008). This major *locus* was named as the *SdI locus*, for Seed development Inhibitor (Lahogue et al., 1998). Further analyses pointed out the grapevine AGAMOUS-LIKE11 (*VviAGL11*) gene as the functional candidate underlying the *SdI locus* (Costantini et al., 2008; Mejia et al., 2011), and some markers based on *VviAGL11* sequence variations were designed for breeding aims (like p3_VvAGL11) (Mejia et al., 2011). More recently, an Arg-197Leu missense substitution has been revealed as the functional mutation responsible for stenospermocarpic seedlessness (Royo et al., 2018).

So far, GWAS analysis for stenospermocarpic seedlessness have reported contradictory results. Whilst some works easily detected the *SdI locus* (Zhang et al., 2017a), others failed to detect it (Laucou et al., 2018; Migicovsky et al., 2017), probably to the high genetic structuration of this trait. Nevertheless, these three GWAS concurred in the identification of some significant signals in chromosome 6 associated with seedlessness, in a region that partially co-localizes with a previously reported QTL for seed traits (Costantini et al., 2008). It points out the interest of studying this genomic region to explore its role on the genetic determination of grapevine stenospermocarpic seedlessness.

3.1.5. Berry shape

Berry shape is another important feature for table grape breeding programs. In general, table grape consumers find elongated berries attractive, as well as those with unconventional shapes (Wycislo et al., 2008). Despite the great natural diversity available for this trait (from globose to horn-shaped and finger-shaped berries) (O.I.V., 2009), and the large phenotypic variation that might arise in segregating populations (Wycislo et al., 2008), only few works tackle its genetic basis.

So far, two studies have explored the genetic determinism of berry shape *via* GWAS. These works indicate that it might be controlled by multiple QTLs (of probably, minor effect) scattered in all chromosomes. Using a diversity panel of 334 *Vitis* accessions and 9.1 million genome-wide SNPs obtained from whole-genome resequencing, significant associations with berry shape variation were found in virtually all chromosomes (Liang et al., 2019). Following this work, authors highlighted a non-synonymous mutation in a putative *SERINE/THREONINE-PROTEIN KINASE* gene located in chromosome 7 associated with this trait. In another work, up to 122 SNPs (on all 19 chromosomes) were found to associate with different berry shape metrics, using phenotypic data from 279 grape varieties and 566,129 SNPs for genome-wide testing (Zhang et al., 2022a). The most relevant associations revealed that berry shape variation could be affected by a set of genes related to transcription processes, cell wall metabolism, plant hormones, ubiquitin ligases and, agreeing with the previous work (Liang et al., 2019), a series of serine/threonine protein kinases. Plant serine/threonine protein kinases are suggested to promote changes in metabolism, gene expression and cell growth and division in response to hormonal and environmental stimuli (Hardie, 1999). Nevertheless, the physiological role of grapevine serine/threonine protein kinases is poorly understood, as well as their suggested involvement in berry shape determination.

3.1.6. Berry texture and berry cracking

Berry texture comprises multiple sensory attributes, including skin friability, skin thickness, and flesh firmness (Rolle et al., 2011). This trait is determinant in the breeding of new table grape varieties, as consumers prefer grapes with firm and crisp texture. However, this trait is less important for cultivars aimed for winemaking (Sato and Yamada, 2003). Significant differences for berry texture-related traits can be found between *V. vinifera* L. table and wine grape cultivars (Sato and Yamada, 2003), indicating the effect of diversifying selection processes for this trait (Migicovsky et al., 2017). Quantitative genetics analyses performed in biparental progenies indicate a complex genetic control of berry texture-related traits (Carreño et al., 2015; Correa et al., 2016). On the contrary, only one *locus* in chromosome 16 has been pointed out for berry texture by GWAS (Guo et al., 2019). This genomic region harbors two genes related to calcium metabolism, an essential nutrient in cell wall composition with an important role on grape firmness (Balic et al., 2014). As stated before, there is a strong correlation between berry texture traits and population structure (Migicovsky et al., 2017). Therefore, the use of a too stringent population-corrected MLM model might have hindered the detection of additional potentially causal *loci* (Guo et al., 2019). Another limiting factor might have been the qualitative assessment of the trait, as berry texture was subjectively rated as soft, medium soft, slightly firm, or very firm.

Following a targeted approach, the association between *VviGAI1* and *VviPel* gene polymorphisms with berry texture attributes has been tested (Vargas et al., 2013a, 2013b). *VviGAI1* works as a negative regulator of gibberellin action, having pleiotropic effects in multiple grapevine developmental processes (Vargas et al., 2013b). Association results suggested that *VvGAI1* could be involved in berry firmness variation, affecting berry texture-related traits like deformation rate, and rupture force. Besides, *VviPel* codes for a pectate lyase, enzyme linked to fruit softening during ripening in many crops. Agreeing with this function, significant associations between multiple *VviPel* polymorphisms and the phenotypic variation of berry texture have been detected (Vargas et al., 2013a), including one non-synonymous SNP predicted to cause a modification in VviPel secondary structure.

Berry cracking is a physiological disorder that affects the appearance of the fruit, causing relevant economic losses in the grape industry (Zhang et al., 2022b). Recently, its genetic basis has been explored *via* GWAS using a set of 287 grapevine varieties (*V. vinifera* L. and interspecific hybrids), which were evaluated to their resistance to berry cracking. GWAS results revealed that this physiological disorder is a complex trait controlled by multiple *loci*, most of them in chromosomes 1, 2, 3 and 18. Following this work, these *loci* co-localized with some genes involved in cell wall metabolism and some transcription factors, which arise as candidate genes likely involved in the occurrence of berry cracking.

3.1.7. Bunch compactness and size

Bunch compactness (or bunch density) and size affect the commercial value of both wine and table grapes. Grape growers prefer medium-to-loose bunches, as compact bunches are more susceptible to rots that reduce crop yield and impact grape quality (Tello and Ibáñez, 2018). Table grape consumers demand bunches with adequate compactness and size, features that also affect the industrial processing of table grapes (*e.g.*: washing, handling, transportation) (Wei et al., 2002). Consequently, the inclusion of the traits involved in bunch architecture determination is becoming a common practice in clonal selection and breeding programs. As observed for berry shape and berry texture, bunch compactness has suffered from divergent selection processes in table and in wine grape cultivars (Migicovsky et al., 2017; Tello et al., 2015a), and table grape cultivars are significantly less compact than cultivars for winemaking (Migicovsky et al., 2017). As a result, bunch compactness is a highly structured trait. Bunch compactness and size reflect a complex interaction between three main features (rachis architecture, berry number, and berry dimensions), each with their own genetic architecture (Tello et al., 2015a). Due to their relevance in yield determination, works on berry number and berry size/weight will be exposed in subsections 3.2.1 and 3.2.2.

To our knowledge, only one work has explored the genetic determination of bunch compactness *via* GWAS (Liang et al., 2019). This work found only one SNP associated with trait variation, using 9068,232 SNPs and visual qualitative assessments of bunch compactness in a collection of 222 *Vitis* accessions. This result contrasts with the complex genetic architecture found for this trait in diverse biparental progenies (Richter

et al., 2019; Correa et al., 2014). In this sense, the detection of additional associated *loci* might be hampered by the use of an over stringent structure-corrected modeling approach and/or the visual system used for bunch compactness rating.

On the other hand, different CGAS for bunch compactness are available. The comparative transcriptomic study between some loose and compact variants of the same cultivar revealed 183 candidate genes putatively involved in bunch compactness phenotypic variation (Grimplet et al., 2017, 2019), which were subsequently used for a CGAS (Tello et al., 2016). Association results indicated that some of these genes might play a role in bunch compactness and/or rachis architecture traits. They included a gene coding for an abscisic acid (ABA) 8′-hydroxylase located in chromosome 7, the MADS-box gene *AG3* (also known as *SEEDSTICK* or *AGL11*) in chromosome 18, and a gene coding for an uclacyanin-I protein (VviUCC1) located in chromosome 12. Within them, the further analysis of *VviUCC1* pointed out two SNPs significantly associated with bunch compactness variation and diverse rachis metrics (Tello et al., 2020). These results agreed with the suggested function of uclacyanin-I proteins in different plant species, as they are thought to be involved in the development of plant fibers *via* lignin formation and/or deposition (Nersissian et al., 1998).

Given the major role of *TERMINAL FLOWER 1* (*TFL1*) in the establishment of inflorescence architecture in *Arabidopsis* and other crops (Liu et al., 2013; Prusinkiewicz et al., 2007), the allelic variance of its closest homolog in grapevine (*VviTFL1A*) was used to explore its association with bunch dimensions using a core collection of 140 individuals (Fernandez et al., 2014). MLM and MLMM association results indicated the presence of a sequence INDEL explaining part of the phenotypic variance for bunch width. This result is in line with the increase in bunch width observed after the phenotypic characterization of the RRM somatic variant related to *VviTFL1A* overexpression (Fernandez et al., 2010). Using a similar approach, the association between *VviPel* sequence polymorphisms and bunch dimensions revealed the existence of two SNPs associated with bunch width and bunch length (Vargas et al., 2013a). According to authors, *VviPel* could affect bunch dimensions in the early inflorescence growth, probably contributing to cell enlargement processes. On the other hand, only one suggestive association between a SNP located in chromosome 5 and the phenotypic variation observed for bunch size in a diversity panel of 179 grape genotypes has been found *via* GWAS (Guo et al., 2019). This SNPs co-localizes with an AMSH-like ubiquitin thioesterase 3-like gene, which codes for an enzyme involved with cellular trafficking in *Arabidopsis* (Isono et al., 2010).

3.2. Yield traits

Consistent yield is essential for viticulturists, winemakers and the grape processing industry. Grape yield per vine is determined by three main traits: (i) the number of bunches per vine, (ii) the number of berries per bunch, and (iii) berry weight (Carmona et al., 2008). Studies in biparental progenies indicate that the genetic determination of these three yield components is highly complex (Fanizza et al., 2005), being shaped by multiple endogenous and exogenous regulatory factors (Li-Mallet et al., 2016). The number of bunches per vine and the number of berries per bunch are the major sources of seasonal variation in grape yield (Li-Mallet et al., 2016), which hinders the analysis of their genetic basis due to their sensitivity to environmental conditions (Fanizza et al., 2005). In fact, for the number of bunches per vine only very preliminary data has been recently provided by GWAS (Flutre et al., 2022; Marrano et al., 2018). On the contrary, berry weight shows less genotypic sensitivity to environment variation than the other grape yield components (Fanizza et al., 2005), and different AM studies (both GWAS and CGAS) can be found in the literature for this trait.

3.2.1. Berries per bunch

The number of berries per bunch depends on the initial number of flowers per inflorescence and the fruit set rate, and both show great variation among varieties (Ibáñez et al., 2020). The phenotypic variation found for this trait (and for five related features: coulure, flower number, fruit set rate, millerandage and seed number) in a set of 114 cultivars was tested against the allelic diversity found in 15,309 SNPs from 289 candidate genes (Zinelabidine et al., 2021), which were selected from previous transcriptome profiling experiments and/or according to their functional annotation (Grimplet et al., 2017, 2019). MLM results indicated that berry number variation associates with several SNPs located in the gene sequence of three transcription factors: *VviNAC26* (or *VviNAP*), *VviMYB108b* (or *VviMYB78*), and *VviAGL6* (in chromosomes 1, 7 and 16, respectively). Different sources of evidence indicate that *VviNAC26* plays an important role in grapevine flower, seed and fruit development (Fernandez et al., 2006; Zhang et al., 2021; Tello et al., 2015b). In Arabidopsis, *AtMYB108* is thought to affect pollen viability and anther filaments development (Mandaokar and Browse, 2008). Lastly, *AGL6* genes are known to be involved in floral organogenesis, including male and female gametophytes development (Dreni and Zhang, 2016). Altogether, these works indicate that the genes found by AM might have a role on the determination of grapevine berry number and raise the interest of their validation by complementary approaches.

3.2.2. Berry weight

Berry size is a major component of crop yield and fruit quality, so understanding its genetic basis is crucial. Multiple QTL analyses on biparental progenies indicate that this trait is mainly controlled by the *SdI* genomic region on chromosome 18 (Cabezas et al., 2006; Doligez et al., 2002; Mejia et al., 2007; Doligez et al., 2013). However, this control only occurs in progenies derived from stenospermocarpic varieties, and just reveals the importance of the normal seed development on berry growth. For this reason, stenospermocarpic varieties require the use of gibberelins to increase berry size to produce commercially acceptable fruits. Beyond this specific major *locus*, other genomic regions have been suggested to affect berry weight in a seedless-independent manner (Cabezas et al., 2006; Doligez et al., 2013). In this line, GWAS results have indicated a series of genomic regions (on chromosomes 17, 18 and 19) significantly associated with berry weight phenotypic variation (Guo et al., 2019). Interestingly, the associated *locus* found on chromosome 18 *via* GWAS differed from that of the *SdI locus*, but it was found in the neighboring region of the *VviANT1* (*AINTEGUMENTA 1*) gene. Previous works indicate that this gene might be involved in the regulation of berry dimensions independently of seed content (Chialva et al., 2016). On the contrary, other reported GWAS did not find any significantly associated genomic region for this trait (Laucou et al., 2018; Migicovsky et al., 2017; Liang et al., 2019). As previously discussed (Migicovsky et al., 2017), the high structuration of this trait affects the ability of GWAS to detect significant signals for berry weight and berry weight-related features.

Besides, the association between berry size phenotypic variation and two candidate genes (*VviNAC26* and *VviTFL1A*) has been tested using different sets of cultivars (Fernandez et al., 2014; Tello et al., 2015b). *VviNAC26* was selected as a candidate gene given its role in the berry flesh formation observed in the *flb* somatic variant of the cultivar Ugni Blanc (Fernandez et al., 2006), whilst *VviTFL1A* selection was based on the known involvement of *TFL1* in inflorescence architecture and development (Liu et al., 2013; Prusinkiewicz et al., 2007). The analysis of the *VviNAC26* gene sequence and promoter in 114 cultivars revealed 69 polymorphisms, eight of them significantly associated with berry weight and/or dimensions after MLM testing. Further *in silico* analyses indicated that two of the associated polymorphisms are located in two *cis*-transcriptional regulatory elements, suggesting some regulatory effect of *VviNAC26* on berry size *via* gene expression. The functional role of *VviNAC26* on fruit growth has been recently demonstrated through the study of *VviNAC26*-overexpressing tomato transgenic lines (Zhang et al., 2021). Following this work, VviNAC26 might act regulating

grapevine fruit and seed development by influencing ethylene and ABA pathways, and interacting with *VviPI* (PISTILLATA, also called *Vvi-MADS9*), a MADS box transcription factor needed to achieve normal fleshy fruit development (Fernandez et al., 2013). Regarding *VviTFL1A*, the identification of two sequence polymorphisms associated with berry weight variation in a CGAS suggests the involvement of this gene on this trait (Fernandez et al., 2014), which will be an additional effect of *VviTFL1A* to the one observed in a *VviTFL1A*-overexpressing grapevine somatic variant (Fernandez et al., 2010).

3.3. Resistance traits

Strategies of viticulture adaptation to current biotic and abiotic stresses include the use of new varieties, both for scions and rootstocks. Ideally, new bred plant material should harbor some level of genetic resistance to well-known pests and diseases (phylloxera, powdery mildew, downy mildew), and they should have beneficial traits to adapt to changing environmental conditions (Töpfer and Trapp, 2022; Delrot et al., 2020; Vezzulli et al., 2022). *V. vinifera* L. cultivars are sensitive to the most relevant grapevine pathogens, so non-*vinifera* genetic resources have been used to explore the genetic diversity of direct and indirect traits conferring biotic resistance. On the other hand, the need of adaptation to unfavorable environmental conditions (drought, salinity, cold and heat) contributed to the wide genetic diversity among *V. vinifera* L. cultivars available nowadays (Tortosa et al., 2016). The available commercial rootstocks also present wide genetic diversity to adapt to abiotic stressors (Fort et al., 2017).

3.3.1. Resistance to biotic factors

The study of the genetic architecture of grapevine disease resistance against multiple pathogens and pests *via* conventional QTL mapping has received great attention of the scientific community in the last decades (recently reviewed in Merdinoglu et al., 2018, Vezzulli et al., 2019, and Vezzulli et al., 2022). In general, these works have indicated that these resistance traits are under oligogenic controls, which has eased the obtaining of efficient genetic markers for MAS, available in the *Vitis* International Variety Catalogue (*V*IVC) website (https://www.vivc.de/loci).

Given the general sensitivity of *V. vinifera* L. cultivars to biotic stressors, most of the GWAS for biotic resistance have been performed in *Vitis* spp. diversity panels. In this regard, the genetic architecture of grapevine white rot disease resistance (caused by *Coniella diplodiella*) has been explored using 160 genome-wide SSR markers in 81 Asian grapevines of diverse *Vitis* species (Zhang et al., 2017b), and 88,877 SNPs from 386 grapevine genotypes from diverse Asian, North American and European grapevine species, as well as some interspecific hybrids (Zhang et al., 2020). The latter work identified six SNPs located on chromosomes 1, 2, 4, 13, 16 and 17 significantly associated with white rot disease symptoms. Besides, the genetic basis of resistance to ripe rot disease, caused by the fungal pathogens *C. acutatum* and *C. gloeosporioides*, was explored using a collection of 350 genotypes from diverse *Vitis* species and hybrids (Jang et al., 2020). The screening of 77,126 SNPs *via* GWAS highlighted 26 and 44 SNPs significantly associated with *C. acutatum* and *C. gloeosporioides* disease symptoms, respectively. Interestingly, some of these *loci* co-localized with some genes that code for two CC–NBS–LRR proteins, known for their role in recognizing specific pathogen-derived products and initiating a plant resistance response.

The genetic basis of downy mildew resistance in the Eurasian grapevine has been explored *via* GWAS taking advantage of the natural resistance to *P. viticola* found in the *V. vinifera* L. Georgian cultivar 'Mgaloblishvili' (Sargolzaei et al., 2020). Association results were useful to detect three new genomic *loci* associated with grapevine resistance mechanisms, denominated *Rpv29*, *Rpv30*, and *Rpv31* (located in chromosomes 14, 3, and 16, respectively). These three new *Rpv loci* co-localize in genomic regions enriched of genes associated with plant defense mechanisms against biotic stress, like receptors of pathogen effectors, signaling mechanisms mediated by protein ubiquitination, and a cluster of Lr10-like (NB-LRR) effector receptors.

Lastly, the genetic basis of five leaf phenotypic traits that confer indirect defense to herbivores in *V. vinifera* (leaf bristles, leaf hairs, and the size, density, and depth of leaf domatia) has been also explored *via* GWAS (LaPlante et al., 2021). Using a diversity panel of 399 *V. vinifera* cultivars genotyped by the Vitis9kSNP array, authors found one SNP in chromosome 5 associated with domatia density. This significant signal was found near an Importin Alpha Isoform 1 gene (involved in downy mildew resistance in *Vitis*) and a GATA Transcription Factor 8 gene (involved in *Arabidopsis* leaf shape development).

3.3.2. Resistance to abiotic factors

As inferred from genetic mapping studies in biparental progenies, the genetic architecture of grapevine adaptation traits to abiotic factors is thought to be highly complex, with many genomic regions involved in the multiple mechanisms favoring grapevine adaptation to adverse climate conditions (Coupel-Ledru et al., 2016; Torregrosa et al., 2017; Coupel-Ledru et al., 2014). To our knowledge, only two works have linked grapevine allelic variation and abiotic resistance variability *via* AM so far. These two works explore the genetic basis of (i) cold tolerance in a diversity panel of multiple *Vitis* spp (Wang et al., 2021)., and (ii) drought adaptation in a core collection of grapevine rootstocks (Trenti et al., 2021). Thus, grapevine genetic mechanisms to counteract chilling temperature and freezing conditions was explored using 118 genotypes from different *Vitis* species and grapevine hybrids, which were re-sequenced and then mapped to the *V. amurensis* cv. Shanputao genome. This process led to the identification of 1.04 million genome-wide SNPs, which were tested for association *via* MLM with two cold tolerance-related traits: the low temperature exotherm value and the low temperature freezing point. Association results were useful to identify one gene in chromosome 19 coding for a phosphoglycerate kinase (involved in sugar metabolism) as a candidate contributing to the survival of grapevine buds in winter (Wang et al., 2021). On the other hand, the response to drought was explored by AM in a core collection of 100 *Vitis* spp. grape rootstocks genotyped with the GrapeReseq 20 K SNPs chip. For phenotypic data, a thermal-infrared imaging system was used to estimate stomatal conductance values during progressive water deficit (Trenti et al., 2021). GWAS results pointed out five SNPs (located in chromosomes 3, 13, 16, 17 and 18) associated with phenotypic variation after Bonferroni correction, and 19 SNPs using the FDR's less conservative approach. These *loci* were further screened to detect a series of candidate genes likely involved in rootstocks' drought stress response. Within the 13 genes potentially involved in trait variance, authors found one gene coding for a raffinose synthase in chromosome 17 as a candidate gene explaining rootstocks' early response to drought stress. In this regard, raffinose synthases are suggested to mediate the accumulation of raffinose in plant leaves in response to multiple abiotic stresses, including drought (ElSayed et al., 2014).

3.4. Other traits

Other traits explored *via* AM are flower sex, major phenological stages (budburst, flowering, veraison, ripening dates), and different leaf and shoot morphological traits. Consistent with conventional QTL studies in biparental progenies (Dalbó et al., 2000; Marguerit et al., 2009), the well-known grapevine sex-determining region has been identified in chromosome 2 in three independent GWAS (Laucou et al., 2018; Migicovsky et al., 2017; Flutre et al., 2022). On the contrary, no convincing significant signals have been found for most of the major phenological stages explored by GWAS (Laucou et al., 2018; Migicovsky et al., 2017), but for one SNP in chromosome 3 significantly associated to budburst-to-veraison time variation (Laucou et al., 2018). These results contrast with the numerous QTLs found for phenology-related traits in different biparental progenies, with little consensus among

publications (Costantini et al., 2008; Grzeskowiak et al., 2013; Duchene et al., 2012). Some of the reasons explaining the lack of significant associations found for phenological dates in GWAS are (i) the complex genetic basis of this trait, with probably several independent mechanisms determining grapevine phenology at a species level; (ii) the noise linked to data collected across multiple seasons by multiple observers; and (iii) the probable high level of genotype × environment × season interaction underlying phenology traits determination (Laucou et al., 2018; Migicovsky et al., 2017).

Lastly, the genetic basis for leaf shape and venation patterning has been explored in a collection of 961 grapevines genotyped for 6114 genome-wide SNPs (Chitwood et al., 2014). Following this work, leaf morphology seems to be regulated by several *loci* in chromosomes 1 and 6, some of them overlapping with known regulators of leaf development. On the other hand, out of eight ampelographic traits, only the variation observed for the type of petiolar sinus (delineated/non-delineated by veins) was found to be significantly associated with one SNP on chromosome 11 (Migicovsky et al., 2017).

4. Conclusion and perspectives

Developing a new grapevine cultivar using traditional breeding techniques requires about 25 years. Fortunately, this process can be shortened by up to 10 years if meaningful genetic markers linked to the phenotype of interest are used (Töpfer et al., 2011). Decades of conventional QTL mapping research in biparental progenies have provided useful information on the genetic basis of highly relevant traits for table and wine grapes breeding activities (Vezzulli et al., 2019, 2022). Occasionally, these works led to the development of efficient genetic markers now used in MAS-breeding programs to improve traits with a simple genetic architecture (Merkouropoulos et al., 2016; Migliaro et al., 2014; Bergamini et al., 2013). Nonetheless, the information available for other relevant traits with more complex genetic determinism remains limited, including some that might be critical to face current viticulture challenges. Now, the availability of grapevine core collections that pool most of the diversity at a species or genus level whilst with a manageable number of genotypes (Nicolas et al., 2016), together to high capacity sequencing technologies, bioinformatics tools, and efficient modeling solutions foster the analysis of their genetic basis in a broader context by alternative approaches, including AM (Tibbs Cortes et al., 2021).

The integration of QTL and AM findings offer a novel opportunity to resolve previous QTL limitations in grapevine research. Globally, the information provided by GWAS so far indicates that it is possible to find meaningful associations for non-structured traits with a simple genetic architecture (like berry color). On the contrary, because of the confounding effect of population structure in highly structured traits (either oligogenic or polygenic), the use of family-based and structured association models has resulted, in the best case, in the detection of only part of the actual true signals (Laucou et al., 2018; Fodor et al., 2014). This could be solved using a higher number of cultivars (Fodor et al., 2014), but this option is not always feasible for many research institutions. An alternative solution might be testing less structured modeling approaches, which have proved to provide highly useful results to be validated in subsequent studies (Emanuelli et al., 2010; Trenti et al., 2021). For highly complex traits, specific experimental layouts might be essential to validate some of the hypothesis obtained by GWAS (Laucou et al., 2018). It this line, recent works testing the use of genomic prediction models in grapevine indicate that they might be an efficient solution (Migicovsky et al., 2017; Flutre et al., 2022; Brault et al., 2022a, 2021). Likewise, recent insights on the use of phenomic selection indicate that it might be used as a low-cost alternative to genomic selection in grapevine breeding activities, especially when hundreds of individuals need to be screened (Brault et al., 2022b). Regarding CGAS, useful results have been obtained to detect or add evidence into the mutation causing the phenotype of interest. This is the case of the K284N SNP detected in the *VviDXS1* gene sequence (Emanuelli et al., 2010), the presence of the *Gret1* retrotransposon into the *VviMybA1* gene promoter (Fournier-Level et al., 2009a), and the Arg-197Leu missense substitution in *VviAGL11* (Royo et al., 2018), major determinants of muscat flavor, berry color, and seedlessness features, respectively. Results from these and other works have been directly transferred to the breeding sector, where these findings have been exploited for the designing of functional markers for the characterization and prediction of muscat flavor, berry color, and seedlessness (Merkouropoulos et al., 2016; Migliaro et al., 2014; Bergamini et al., 2013).

Some of the works reviewed here lack replications, or they are insufficient in number to obtain robust results. Likewise, few of them have considered genotype × environment interactions. AM involves the analysis of a relatively large number of genotypes, so collecting enough phenotypic data in different environments to ensure statistical robustness is challenging (Zhu et al., 2008). Quantitative phenotyping is time-costly, and although several advances in high-throughput phenotyping have been recently done to reduce the so-called 'phenotyping bottleneck' (Cadle-Davidson et al., 2019), their actual implementation in AM studies is limited (Trenti et al., 2021). Likewise, a common limitation of some of the published works is the use of visual qualitative assessments to rate continuous phenotypic variation (Guo et al., 2019; Liang et al., 2019). The degree of variation that an evaluator can visually quantify (even when trained) is very narrow, and it might not be enough for accurate genetic mapping approaches. Fortunately, high- throughput phenotyping methods provide the precise and objective quantitative data that is preferred to explore the genetic architecture of many traits of interest for grapevine breeding. As exemplified for bunch compactness (Underhill et al., 2020) and berry cuticle-related traits (Herzog et al., 2022), these methods render more accurate quantitative metrics than traditional approaches, which in turn allows the detection of novel genomic regions associated to trait variation.

Lastly, grapevine research has been boosted in the last years by the development and use of multiple *omics* approaches, including, but not limited to, genomics, transcriptomics, proteomics, metabolomics, and epigenomics. In many cases, studies using these approaches have provided essential information to understand how phenotype-genotype interaction works. So, AM results should be combined to those obtained from these *omics* studies to actually understand the functional metabolic pathways involved in trait variation (Alseekh et al., 2021; Scossa et al., 2021). In fact, only through this integration we will be able to expand our knowledge on the genetic basis of the multiple factors causing phenotypic variation (Molendijk and Parker, 2021). Likewise, GWAS-derived approaches like transcriptome-wide and metabolome-wide association studies (TWAS and MWAS, respectively), which test for association between variation in transcript/metabolite abundance and phenotypic variation, can be additionally used to address knowledge gaps about the physiology and genetics of highly complex traits (Wei et al., 2018; Ferguson et al., 2021). This multi-layer approach might be the answer to ultimately understand the genetic basis underlying grapevine phenotypic variation.

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CRediT authorship contribution statement

Javier Tello, Javier Ibáñez: Conceptualized and designed the manuscript. **Javier Tello**: Wrote the manuscript. **Javier Ibáñez**: Critically read and revised the manuscript. **Javier Tello, Javier Ibáñez**: Approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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