Theor Appl Genet (2007) 114:723–730
DOI 10.1007/s00122-006-0472-2

ORIGINAL PAPER

Wine grape (*Vitis vinifera* L.) color associates with allelic variation in the domestication gene *VvmybA1*

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Received: 15 May 2006 / Accepted: 17 November 2006 / Published online: 13 January 2007

Abstract During the process of crop domestication and early selection, numerous changes occur in the genetic and physiological make-up of crop plants. In grapevine (*Vitis vinifera*) numerous changes have occurred as a result of human selection, including the emergence of hermaphroditism and greatly increased variation in berry color. This report examines the effect of human selection on variable skin color by examining the variation present in the gene *VvmybA1*, a transcriptional regulator of anthocyanin biosynthesis. In over 200 accessions of *V. vinifera*, the insertion of the retroelement *Gret1* in the promoter region of *VvmybA1* was in strong association with the white-fruited phenotype. This retroelement was inserted at the same location for each individual in which it was present. Additional polymorphisms in the *VvmybA1* gene were also strongly associated with red or pink fruited accessions, including variation that was generated by the excision of *Gret1* from the promoter of *VvmybA1*. Differences in nucleotide diversity were observed between the white and pigmented alleles of *VvmybA1*, suggesting that the white allele arose only once or a limited number of times. Rarely, association of *Gret1* with the white fruited phenotype was not observed, suggesting that the white phenotype can also be obtained through mutation in additional genes. These results provide evidence that variation in one transcriptional regulator has generated an allelic series strongly associated with fruit color variation in cultivated grapevine. These findings provide information about the evolution of grapes since domestication and have direct implications for the regulation of fruit and wine quality of this important crop plant.

Communicated by S. J. Knapp.

Electronic supplementary material The online version of this article (doi:10.1007/s00122-006-0472-2) contains supplementary material, which is available to authorized users.

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Introduction

During the process of crop domestication, numerous changes occur in the genetic and physiological make-up of crop plants (Hancock 1992). Many domestication-related traits have been described, typically: larger seeds/fruit, more uniform ripening, non-dehiscent seeds/fruits, self-pollination, and selection for greater color and flavor diversity. The molecular identity of many of the genes underlying these domestication traits during crop evolution is largely unknown. However, several genes that have been targets of selection during crop domestication have recently been identified. Examples include *fw2.2* for fruit size in tomato, *Waxy* for glutinous rice, *tga1* and *tb1* for kernel and plant architecture in maize, *Y1* (Phytoene synthase) for endosperm color, and the *R-gene* family for anthocyanin synthesis in maize. (Doebley et al. 1997; Frary et al. 2000; Hanson et al. 1996; Olsen and Purugganan 2002; Palaisa et al. 2003a, b; Peng et al. 1999; Purugganan et al. 2000; Wang et al. 2005).

Grapevine (*Vitis vinifera* L.) is one of the oldest domesticated crop plants and economically the most important cultivated fruit crop in the world. The domestication of *V. vinifera* is thought to have occurred approximately 6,000–10,000 B.P. (Levadoux 1956; McGovern 2003; Zohary and Hopf 2000) in a region between the Black and Caspian Seas. There are several morphological and biochemical traits associated with the domestication of *V. vinifera* from the progenitor species *V. vinifera* subsp. *sylvestris* of this important crop. Some of the most striking changes are the emergence of hermaphroditism, greater uniformity of berry maturity within clusters, higher sugar content, and the selection for a wide range of fruit colors (Levadoux 1956; Olmo 1995; Zohary and Spiegel-Roy 1975). The grape ancestor *V. vinifera* subsp. *sylvestris* is believed to bear black-skinned berries with un-pigmented flesh (Olmo 1995; Zohary and Hopf 2000). Cultivated grapes today show substantially greater diversity in fruit color, including: varying shades of black, red, pink, gray, white, and types with pigmented berry flesh. Interestingly, color mutants exist for a great variety of cultivars (Galet 2000a). Diversity in fruit color has led to significant definition of market classes of wine, juice, and table grape cultivars and has cultural significance that extends thousands of years into human history.

The genetic control of anthocyanin biosynthesis, the principal pigments in grape berries, has been extensively studied in several plant species, notably maize, petunia, and *Antirrhinum* (Coe et al. 1988; Quattrocchio et al. 1993). The genetic control and inheritance of fruit color or anthocyanin production in grapevine is poorly understood despite evidence that the primary determination of anthocyanin production in berries appears to be controlled by a single dominant locus in *V. vinifera* (Doligez et al. 2002; Riaz et al. 2004) with white fruit being a recessive character. This observation is supported by numerous reports showing that controlled crosses between white fruited vines universally result in white fruited progeny (Barritt and Einset 1969; Hedrick and Anthony 1915; Madero et al. 1986; Snyder and Harmon 1939, 1952; Wellington 1939).

Recently, it has been shown that the presence of *Gret1*, a Ty3–*gypsy*-type retro-transposon in the promoter region of a *myb*-like regulatory gene showing sequence similarity to previously described anthocyanin regulators from maize and other plants is present in white-fruited cultivars of *V. vinifera* (Kobayashi et al. 2004). The presence of *Gret1* appears to be associated with white-fruited cultivars when present in a homozygous state. Pigmented cultivars possess at least one allele at the *VvmybA1* locus not containing this large insertion (Kobayashi et al. 2004) but otherwise were not differentiated.

In this study we examined allelic variation in *VvmybA1* in over 200 accessions of cultivated grapevine including several well characterized fruit color mutants. Genetic variation in this locus appears to be caused by a combination of transposable element insertion and excision, and by additional mutations. The insertion of a retroelement, *Gret1*, in the promoter region of the gene was in strong association with the white skinned phenotype. Additional polymorphisms in the *VvmybA1* gene were also strongly associated with red or pink fruited phenotype. Our results indicate that the white fruited-allele of *VvmybA1* most likely arose a limited number of times and that variation in this gene is likely responsible for the majority of the fruit color variation present in modern grapevine cultivars.

Materials and methods

Plant material

One hundred and twenty-three grapevine (*Vitis vinifera*) accessions were sampled that represent the majority of phenotypic diversity available within the French national grapevine germplasm collection held at "Domaine de Vassal", France (Barnaud et al. 2005). The core collection retains at least 80% of the microsatellite diversity found within this species (unpublished data). An additional 70 accessions representing many of the known fruit color mutations, or sports, were included for analysis. Identity of the mutants was checked using morphological characters as well as a set of 20 SSR markers sufficient for the distinction of the 2250 cultivars from the Vassal collection. A set of eight additional cultivars which were obtained from the USDA National Clonal Repository Davis, CA were also included in the study since they represented geographical origin underrepresented in the core-collection. Fruit color was defined as the pigmentation of the berry skin according to the Descriptors for Grapevine (IPGRI et al. 1997) and was scored on a 6-point scale: 1 = blanc/white, 2 = rose/pink, 3 = rouge/red, 4 = noir rougeâtre/reddish-black, 5 = gris/gray, and 6 = noir/black.

Amplification and sequencing

Genomic DNA was isolated following the protocol of Lodhi et al. (1995) or using Qiagen Plant Miniprep Kits (Qiagen, Valencia, Calif.). The *VvmybA1* gene and

promoter region were amplified and direct sequenced in 168 accessions. Primers for detecting presence or absence of *Gret1* and for direct sequencing were as previously reported (Kobayashi et al. 2004) with modifications: Bf 5′-GGACGTTAAAAAATGGTTGCACG TG-3′, Cr 5′-GAACCTCCTTTTTGAAGTGGTGAC T-3′, LRT5f 5′-AGAAGGGGATCCTCCTGGTA-3′, and promoF 5′-GTCCCAAGCAACAGATGGAT-3′.

Nucleotide positions referred to in the text correspond to reference sequence GenBank accession # AB111101 submitted by Kobayashi et al. (2004) (Fig. 1). Sequence data for the regions of *VvmybA1* sequenced in this article have been deposited with the EMBL/GenBank data libraries.

Statistics and DNA sequence analysis

Tests for association (Thornsberry et al. 2001) and linkage disequilbrium (LD) (Hill and Roberston 1968) were performed using the software package TASSEL (http://www.maizegenetics.net) (Remington et al. 2001). DNA sequence alignments were generated in Vector-NTI's AlignX module (Invitrogen, Carlsbad, CA), and converted to NEXUS files utilizing DNAsp 3.53 (Rozas and Rozas 1999). The SNPs or indels at a site frequency of 0.05 or greater were evaluated using TASSEL. All association tests were run with population structure included, using logistic regression as described by Thornsberry et al. (2001). Population structure was estimated utilizing Structure 2.1 (Pritchard et al. 2000) utilizing SSR genotype data for 20 microsatellite loci, representing coverage of each linkage group in the haploid *V. vinifera* genome. One thousand permutations of the data were run to account for multiple tests within a gene. Associations were considered statistically significant if the permuted *P*value was <0.01.

Results

Phenotypic description of sample

Fruit color was recorded for 201 accessions. Among them, 84 exhibited white skin, and 117 exhibited pigmented skin (Supplementary Table 1). Figure 1 presents examples of berries of each type. A subset of 68 accessions consisted of 24 wild type accessions and 44 of their recognized color mutations or sports. Within the wild type accessions 13 were pigmented and 11 were white (Supplementary Table 1).

Presence of Gret1 in VvmybA1

The examination of a large and diverse pool of *V. vinifera* shows that *Gret1* is present in the vast majority of white-skinned grape cultivars tested (Table 1) and that a copy of *VvmybA1* without *Gret1* is not-detectable. However, three of 84 white fruited accessions, 'Avgoulato', 'Gamay Castille mutation blanche', and 'Sultanina-Gora Chirine' contain a copy of *VvmybA1* that does not contain *Gret1* when tested by examining the presence or absence of *Gret1* through the use of allele-specific PCR primers (Table 1). Direct DNA sequencing

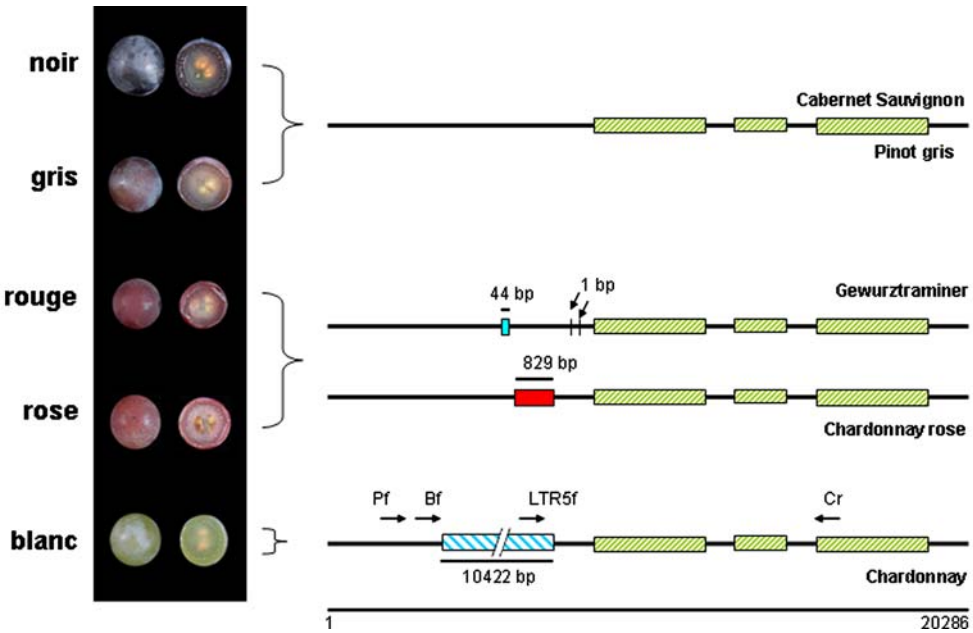

Fig. 1 Range of phenotypic variation in *V. vinifera* berry color and corresponding haplotypes of *VvmybA1*. Relative positions and orientations of primers used to detect presence or absence of *Gret1* and for direct sequencing are indicating by black arrows (Table 2)

Table 1 The association of *Gret1* in *VvmybA1* and visual phenotype of berry skin color.

No.	Phenotype	*Gret1* present	*Gret1* absent
65	Black	65	0
14	Gray	14	0
3	Dark purple/violet	3	0
17	Red	17	0
18	Pink	18	0
84	White	3	81

P value of analysis of variance for presence/absence of Gret1 and presence of pigmentation <0.0001

Table 2 Significant polymorphisms detected by structured association testing and corresponding phenotypes

Site[a]	Polymorphism	Phenotype	*P*-value[b]
7938	44 bp insertion	Red/pink	0.001
	0 bp insertion	Black	
7953	829 bp insertion	Red/pink	0.002
	0 bp insertion	Black	
8812	C	Red/pink	0.008
	T	Black	
8821	G	Red/pink	0.007
	–	Black	

[a] Nucleotide positions of the most significant sites identified by structured association tests. Nucleotide positions are reported relative to GenBank accession AB111101

[b] Permuted *P*-values for structured association testing with SSR-based population structure taken into account

of *VvmybA1* from 68 white fruited accessions revealed insertion of *Gret1* at the same position within the promoter of *VvmybA1* (data not shown).

All 117 *V. vinifera* accessions that contain pigmented berry skin, ranging from black to light pink, were observed to have a copy of *VvmybA1* without the presence of *Gret1* (Table 1) although size polymorphisms were frequently detected for many of the red and pink skinned accessions. The pattern of presence or absence of *Gret1* was not observed to differ between the pool of mutant genotypes and the non-mutant pool and the data were therefore combined in Table 1.

Sequence polymorphisms in VvmybA1

Direct DNA sequencing of *VvmybA1* was performed on 168 accessions (68 white-fruited and 100 pigmented). Since PCR amplifications were mostly allele specific we were able to define the haplotypes for the different alleles. Five major haplotypes were observed, four of which were associated with berry color within the accessions analyzed (Fig. 1).

The sequence from 68 white fruited accessions revealed virtually no sequence diversity within the alleles of *VvmybA1* (data not shown) containing *Gret1*. Sequence polymorphisms were, however, observed within the pigmented accessions (Table 2). Forty-six polymorphic sites were identified within 2,196 bp from the 100 pigmented accessions sequenced comprising a portion of the promoter region as well as the exons and introns through the beginning of the third exon of *VvmybA1*. Ten indels (ranging from 1 to 829 nucleotides) and 36 SNPs were identified (Supplementary Table 2).

Linkage Disequilibrium

Estimates of the extent of linkage disequilibrium (LD) within *V. vinifera* have previously been reported in the literature, but at a large scale utilizing SSR markers (Barnaud et al. 2005). To estimate the degree of decay in LD over nucleotide distance, LD was estimated within the sample of *V. vinifera* accessions utilizing the sequence data from *VvmybA1* (Fig. 2). When averaged over sliding windows of 200 bp the square of the correlation of allele frequencies was observed to be approximately 0.2 for a span of approximately 700 bp and then to decay rapidly to very low levels, below 0.05. These values are sufficiently low that an association analysis of *VvmybA1* DNA sequence polymorphisms within this pool of genotypes is likely to have sufficient resolution for candidate gene analysis.

Structured association testing

An association analysis was conducted utilizing DNA sequence polymorphisms within *Gret1* while control-

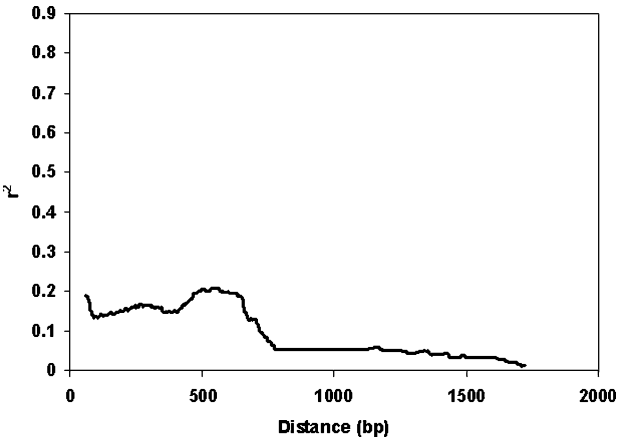

Fig. 2 LD plot of squared correlations of allele frequency (r^2) against distance between polymorphic sites for *VvmybA1*. Measurement was performed by averaging r^2 values over a distance of 200 bp and plotting the values against distance (bp)

ling for potential population structure within the pool of accessions. Population structure was estimated utilizing data for 20 SSR loci, 19 of which were unlinked on separate linkage groups within the *V. vinifera* genome (Adam-Blondon et al. 2004). Permuted *P*-values of 0.01 or less were selected for determining significant association between candidate polymorphic sites and the berry color phenotype. One single nucleotide polymorphisms (SNPs) and three insertion/deletions (indels) were significantly associated with fruit skin color in the structured association analysis of pigmented accessions (Table 2). All four polymorphisms were associated with genetic differences separating black or gray-skinned accessions from red and pink-skinned accessions (Table 2). No significant associations were detected distinguishing black and gray accessions. Among the red and pink accessions, multiple polymorphisms were observed. An 829 bp indel in the promoter was observed in several of the red-fruited accessions examined. One additional 44 bp indel within the promoter of *VvmybA1* was frequently associated with the red and pink skinned accessions as were one SNP and a 1 bp indel, also within the promoter, identified through association testing (Table 2). These three polymorphisms appeared to be in linkage disequilibrium and collectively represent one haplotype associated with red/pink fruited cultivars.

Two notable polymorphisms were detected that were not significantly associated with the phenotype at the significance thresholds chosen for analysis. A 111 bp indel was observed to be present at position 8,901 (in reference to GenBank accession AB111101) within the promoter of *VvmybA1* in the accessions: 'Kandahar', 'Negra corriente' (syn. 'Criolla Chica'), 'Gora Chirine', 'Sultanina rose', and 'Sultanina rouge'. These five accessions also possessed the 44 bp and two single base polymorphisms observed in several of the red and pink accessions (Table 2). Additionally, a non-synonymous SNP was observed at position 9,437 within exon 3 of *VvmybA1* that was associated with differentiating red/pink accessions from black skinned accessions with a permuted *P*-value of 0.017. The majority of black fruited accessions with a small number of exceptions possess an adenine at this position, while several red/pink accessions possess a guanine (causing a substitution from arginine to glycine), including many red/pink accessions that do not possess any of the previously identified promoter mutations.

Comparison of gene structure between mutants

In order to understand the molecular evolution of *VvmybA1*, a comparison was made between a panel of genotypes and color mutants of those wild type cultivars. The 12 black varieties which have given rise to types with less pigmentation all had similar structure. White-fruited mutations arising from black wild type cultivars universally showed two copies of *VvmybA1* containing *Gret1*, except for 'Gamay Castille Mutation blanche', a white mutation of 'Gamay noir' that did not possess a copy of *VvmybA1* containing *Gret1*. The intermediary phenotype (red/rouge or pink/rose), when present does not present any difference from the black mutant in the structure of *VvmybA1*. The 12 white varieties which have given rise to the pigmented mutants never yielded black berries. Each of the pigmented mutants derived from a white fruited accession possess a *VvmybA1* haplotype showing the presence of the 44 bp indel or the presence of the 829 bp indel. Mutant and wild type accessions were confirmed to be likely sports by the genotyping of 9 SSR loci for each comparison.

Discussion

The results presented here indicate that allelic variation in *VvmybA1* associates with multiple qualitative classes of fruit color in over 200 accessions of cultivated grapevine. Genetic variation in this locus appears to be caused by a combination of transposable element insertion and excision, and by additional mutations. It has been shown previously that approximately 800 bp insertion is present in a few red-skinned varieties that are somatic mutants of white-skinned varieties (Kobayashi et al. 2004). This insertion possesses sequence similarity with the LTR of *Gret1* and it is hypothesized that the excision of *Gret1* during transposition left a footprint within the promoter of these accessions that leads to an alteration in gene regulation and a noticeable phenotypic change. Indeed, gene expression of *VvmybA1* has been detected in red-skinned varieties with this mutation (Kobayashi et al. 2005). Our results indicate that additional mutations are associated with the red or pink fruited phenotypes, one 44 bp indel present in the promoter and two single base pair polymorphisms in the first exon of *VvmybA1*. The functional significance of these additional polymorphisms is unknown.

No significant associations were detected to distinguish black and gray fruited varieties including many gray fruited mutations or sports of black skinned varieties. It has recently been demonstrated that one gray skinned mutation, 'Pinot gris', is chimeric in nature (Hocquigny et al. 2004) in which the mutation leading to the phenotypic change is not sexually transmitted.

Additional gray fruited accessions have been proposed as being chimeras (Galet 2000b). Considering that there is no sequence variation present in *VvmybA1* when comparing gray skinned mutants to their respective wild type black fruited progenitors, it is tempting to speculate that the phenotypic change is due to presence of a single tissue layer showing anthocyanin accumulation juxtaposed on top of a tissue layer with no anthocyanin accumulation, i.e. a white tissue layer. If this hypothesis is correct it should be possible to dissect the tissue layers of a gray skinned variety through somatic embryogenesis and recover pure tissue layer-lines showing only black or white fruited types.

Similarly, the red and pink fruited accessions show sequence polymorphisms significantly distinguishing the group from black and gray skinned accessions, whereas no distinction was observed between red and pink fruited accessions. Quantitative estimates of anthocyanin concentrations within this group of accessions may help identify significant polymorphisms between the two groups. Also, if chimerism is potentially responsible for phenotypic changes in the gray fruited accessions, it remains possible that some of the lighter pink fruited accessions are chimeras of red fruited accessions.

There is little sequence diversity within the white fruited-allele of *VvmybA1* containing *Gret1*, which is present in almost all white fruited varieties. White fruit is a recessive character and mutations leading to the knock-out of anthocyanin production in berry skin must be in the homozygous state before a phenotypic change will be observed. The lack of sequence diversity suggests that the white fruit allele most likely arose a limited number of times or perhaps only once and that it has spread to be present in the majority of the white fruited varieties in existence today. Further, heterozygous, pigmented varieties that possess the white *VvmybA*1 allele show little sequence diversity for this allele when compared to white-fruited varieties.

Whereas we presume one primary mutation in white-fruited varieties arose and spread to many of the accessions cultivated today and note that the presence of *Gret1* appears highly correlated with white-fruited accessions of *V. vinifer*a, a small number of exceptions were observed. Comparison with the plethora of color mutations in other species leads us to believe that additional mutations capable of eliminating anthocyanin production or accumulation in berry skins must also have arisen(Winkel-Shirley 2001). Thousands of cultivars of *V. vinifera* currently exist. It seems likely that additional somatic mutations not identified here leading to white fruit have arisen over time. The white-fruited accessions identified here that do not contain the *Gret1* insertion in *VvmybA1* may well contain mutations in candidate genes such as *GST*, *UFGT*, *MRP*, and *PAP1/2* that have been identified as causing color mutations in maize and Arabidopsis (Bodeau and Walbot 1992; Goodman et al. 2004; Marrs et al. 1995; Zhang et al. 2003). The germplasm screened in the present study was selected to represent at least 80% of the total found in the French *Vitis* collection as determined by SSR markers. It follows that the variation for the white *VvmybA1* allele observed here, in which 95% of the white genotypes contain a near-monomorphic allele, represents a similar proportion of the total white diversity. We conclude that while there are likely other white mutations present in the total *Vitis* germplasm, these are far rarer or, have not radiated within this species.

Two haplotypes are frequently associated with the red and pink skinned phenotype. However, there are clearly red and pink fruited accessions in which neither of the two red/pink associated *VvmybA1* haplotypes identified here are present. It has been reported that some red/pink accessions possess qualitatively different anthocyanin profiles to black fruited accessions (Galet 2000b). It seems likely that mutations in other points of the anthocyanin biosynthesis pathway have led to the tremendous fruit color diversity present in *V. vinifera* germplasm. Recent evidence suggests that *Gret1* is present in many copies within the genome of *V. vinifera* and it is possible *Gret1* may play a role in altering gene structure and regulation of additional important phenoptypic traits (Pereira et al. 2005).

Interestingly, the extent of LD within *VvmybA1* was shown to be low compared to values reported for other plant species (Brown et al. 2004; Hamblin et al. 2004; Tenaillon et al. 2001). The low levels of LD present in *VvmybA1* suggest that even tightly linked loci will not be in linkage disequilibrium with *VvmybA1*. While the extent of LD needs to be examined at a larger number of loci within *V. vinifera* and additional wild species, our results for *VvmybA1* indicate that the levels of LD may be low in grapevine at the nucleotide level. Grape is a perennial woody crop that typically takes three or more years to begin bearing fruit. The ability to conduct genetic analyses with existing germplasm collections would obviate the need to generate segregating populations in some situations and has the potential to provide better genetic resolution than QTL analysis and linkage mapping.

Anthocyanins and several related flavonoid compounds are extremely important for determining the quality of grapes and grape products, principally wine. The identification and characterization of an important key regulator of grape flavonoid metabolism is an

important early step in increasing our understanding and improving the ability to enhance grape and wine quality.

Acknowledgments We are very grateful to Judith Kolkman for providing helpful suggestions to the manuscript. We would also like to thank Bernie Prins and Malli Aradhya of the USDA National Germplasm repository for providing grape DNA samples.

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