

Across-population genomic prediction in grapevine opens up promising prospects for breeding

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Abstract

Crop breeding involves two selection steps: choosing progenitors and selecting offspring within progenies. Genomic prediction, based on genome-wide marker estimation of genetic values, could facilitate these steps. However, its potential usefulness in grapevine (*Vitis vinifera* L.) has only been evaluated in non-breeding contexts mainly through cross-validation within a single population. We tested across-population genomic prediction in a more realistic breeding configuration, from a diversity panel to ten bi-parental crosses connected within a half-diallel mating design. Prediction quality was evaluated over 15 traits of interest (related to yield, berry composition, phenology and vigour), for both the average genetic value of each cross (cross mean) and the genetic values of individuals within each cross (individual values). Genomic prediction in these conditions was found useful: for cross mean, average per-trait predictive ability was 0.6, while per-cross predictive ability was halved on average, but reached a maximum of 0.7. Mean predictive ability for individual values within crosses was 0.26, about half the within-half-diallel value taken as a reference. For some traits and/or crosses, these across-population predictive ability values are promising for implementing genomic selection in grapevine breeding. This study also provided key insights on variables affecting predictive ability. Per-cross predictive ability was well predicted by genetic distance between parents and when this predictive ability was below 0.6, it was improved by training set optimization. For individual values, predictive ability mostly depended on trait-related variables (magnitude of the cross effect and heritability). These results will greatly help designing grapevine breeding programs assisted by genomic prediction.

Keywords: *genomic prediction, grapevine, half-diallel, multi-parental population, diversity panel, across-population*

Introduction

1 Breeding for perennial species is mostly based on phenotypic selection and is hindered by cumbersome field
2 trials and the long generation time. Genomic prediction (GP), based on genome-wide prediction of genetic
3 values ¹, has been widely adopted in modern plant and animal breeding programs, for its superiority in terms of
4 cost and time saved compared to traditional phenotypic selection, but also because it allows handling traits with
5 complex genetic determinism. GP requires a model training step within a reference population, prior to model
6 application to a target population of selection candidates ². In perennial crops, a universal population
7 encompassing most of the species' genetic diversity could be particularly interesting as a training population to
8 reduce phenotyping effort, since breeding cycle and juvenile phase are long.

9 Breeding schemes typically involve first the choice of parents (individuals to be crossed) and then the selection
10 of offspring within crosses. GP is adapted both for predicting cross mean and for ranking genotypes within a
11 cross (Mendelian sampling). These steps correspond to the components of the predictive ability (PA) of GP. It is
12 indeed defined as the sum of cross mean and Mendelian sampling terms, as detailed in Werner et al. ³.

13 Under an additive framework, cross mean is expected to be the sum of the breeding values of parents, but
14 some deviation may result from dominance or epistasis ⁴. So far, a few studies only have investigated cross
15 mean PA ^{5, 6, 7, 8}, although none of them clearly investigated its influencing parameters.

16 In contrast, the prediction of genetic values within a cross (Mendelian sampling), has been widely studied, both
17 with simulated and real data. Various parameters affecting PA have been pointed out, including the statistical
18 method used ⁹, the composition and size of training and validation populations ^{10, 11}, the trait genetic
19 architecture and heritability ^{12, 13} and marker density ¹⁴. Genetic relationship between the training and validation
20 sets is known to strongly affect PA ¹⁵, with low or even sometimes negative accuracies for across-breed GP in
21 animals ¹⁶. This can be explained by the loss of linkage phase between the marker and QTL or by differences in
22 linkage disequilibrium among populations ¹⁷. Another explanation is the presence of specific allelic effects and
23 allele frequencies, due to the genetic background ¹⁸. All these effects are linked to genetic relationship. Some
24 studies specifically derived deterministic equations to predict PA for across-population GP, based on genetic
25 relationship and heritability (e.g., [19](#), [20](#), [21](#)).

26 In grapevine (*Vitis vinifera* subsp. *vinifera*), very few authors have assessed the potential interest of GP. Viana et
27 al. ²² investigated GP within a bi-parental population from a cross between an interspecific hybrid and a seedless
28 table grape. Later, Migicovsky et al. ²³ used a panel of 580 *V. vinifera* accessions to perform both GP and
29 genome-wide association study (GWAS) for 33 phenotypes. More recently, Brault et al. ²⁴ investigated GP within
30 a bi-parental population from a cross between Syrah and Grenache. In a related study, Fodor et al. ²⁵ had
31 simulated a structured and highly diverse grapevine panel and bi-parental populations with parents originating
32 from the panel. They applied GP and found little difference between PA values estimated within the panel or
33 across populations. Finally, Flutre et al. ²⁶ studied 127 traits with GWAS and GP within a diversity panel; they
34 also applied across-population GP, but with 23 test offspring and for one trait only. Before genomic selection
35 can be deployed in grapevine, evaluating PA across populations is thus crucially needed. In particular, PA should
36 be evaluated with a diversity panel and a bi-parental progeny as training and validation sets, respectively, a

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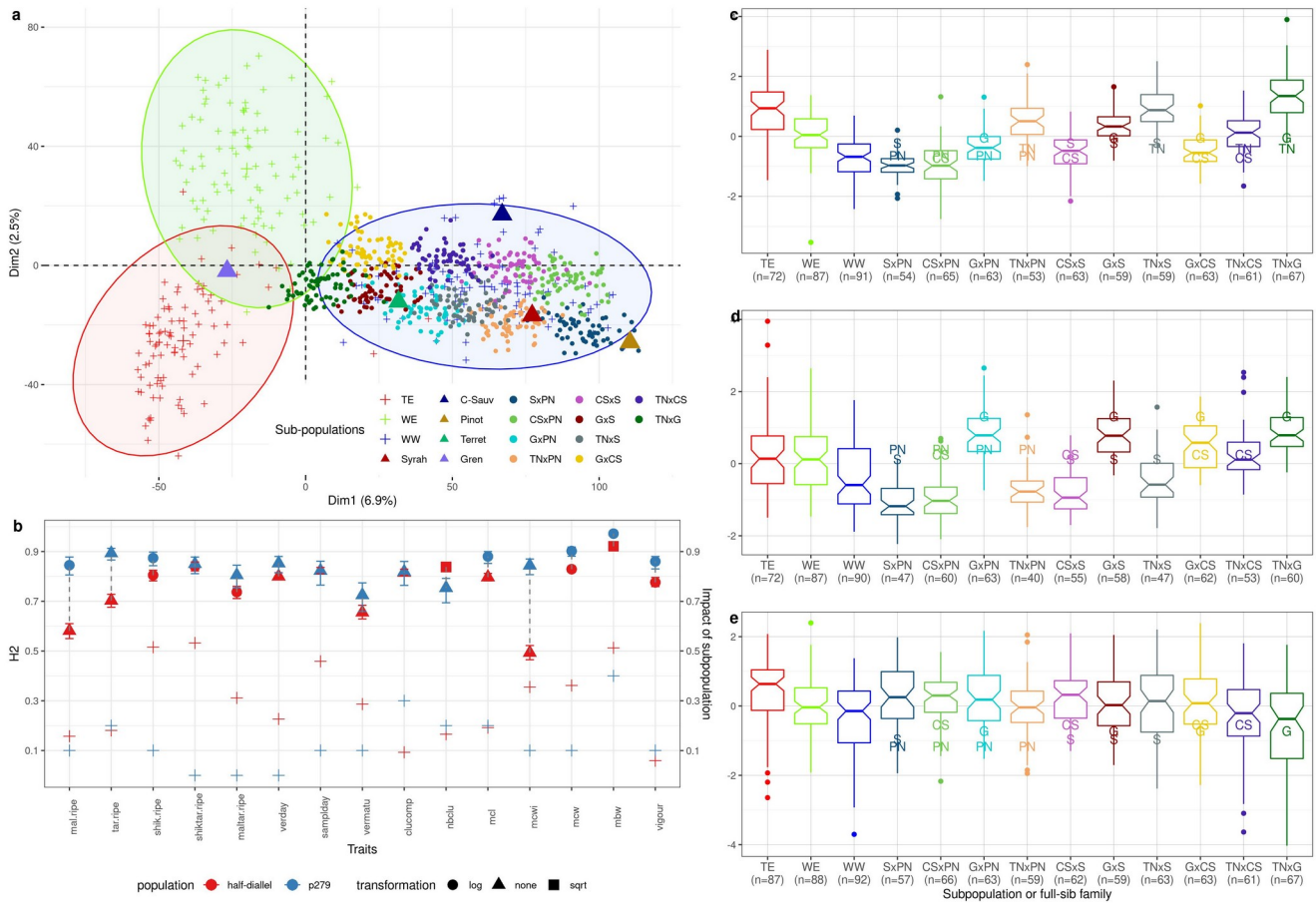
37 configuration much more likely to occur in actual breeding schemes than GP within the same population. As in
 38 grape, studies investigating across-population GP are also lacking in most clonally propagated crops.

39 The aim of this study was to assess across-population genomic PA and to provide a more thorough
 40 understanding of parameters affecting PA in a situation close to the one typically encountered in a breeding
 41 context, i.e. across populations, for a clonally propagated crop such as grapevine. Our study was based on
 42 phenotypic data for 15 traits, related to yield, berry composition, phenology and vigour, measured both in a
 43 diversity panel ²⁷, and in a half-diallel with 10 bi-parental crosses. We assessed PA under three scenarios, first
 44 for cross mean, and then for Mendelian sampling term; the results provided keys to understand PA
 45 determinants in both cases. Finally, we implemented training population optimization to investigate under
 46 which conditions PA can be improved.

47 Results

48 Extent of genetic diversity within the half-diallel 49 population

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52 Figure 1: Description of the half-diallel, relative to the diversity panel. a: PCA of the diversity panel based on 32,894 SNPs with the 3 sub-
53 populations distinguished by different colors, on which half-diallel progenies (dots) and parents (triangles) were projected. b: Broad-sense
54 heritability estimates in the whole half-diallel (red) and in the diversity panel (blue) for the 15 traits studied (left axis), with shape
55 corresponding to the transformation applied to raw data; the relative variance due to the cross effect and the R^2 of the subpopulation effect, for
56 the half-diallel (red) and the diversity panel (blue), respectively, are also reported with '+' (right axis). c, d, e: genotypic value BLUP distribution
57 in each subpopulation or progeny, for mean berry weight, mean cluster width and vigour, respectively; BLUPs for parents are indicated by their
58 initial letters (Table S4). Number of genotypes per subpopulation/progeny is indicated below the subpopulation/progeny name. These traits
59 were chosen to represent various levels of H^2 and relative importance of cross effect. BLUP distributions for all traits are presented in Figure S3.

60 We first evaluated the genetic variability of half-diallel crosses with respect to the diversity panel, through their
61 projection on the first plane of a PCA based on genotypic data at 32,894 SNPs within the diversity panel. The
62 half-diallel crosses were genetically close to the wine west (WW) subpopulation from the diversity panel (Figure
63 1a), which was expected, given that all half-diallel parents except Grenache are wine varieties from western
64 Europe (Figure 1a, Figure S1). The half-diallel diversity covered the whole range of WW diversity, and progenies,
65 all located exactly between their respective parents, were well separated from each other along the first two
66 PCA axes (Figure 1a).

67 We then investigated broad-sense heritability values (H^2) for 15 traits related to yield, berry composition,
68 phenology and vigour. Overall H^2 values were medium to high, ranging from 0.49 for **mcwi** in the half-diallel to
69 0.92 for **mbw** in the panel (Figure 1b; Table S1). Correlation between half-diallel and diversity panel heritability
70 values was 0.31. Per-cross H^2 values for each trait varied among half-diallel crosses (Figure S2), which might
71 result from the fairly small number of offspring per cross (from 64 to 70). Nevertheless, we observed a 0.68
72 correlation between overall and per-cross H^2 . Mean cluster width displayed extreme variation in H^2 per cross
73 (from 0.02 to 0.67). This might be due to the difficulty to phenotype this specific trait because of the presence
74 of lateral wings in some individuals.

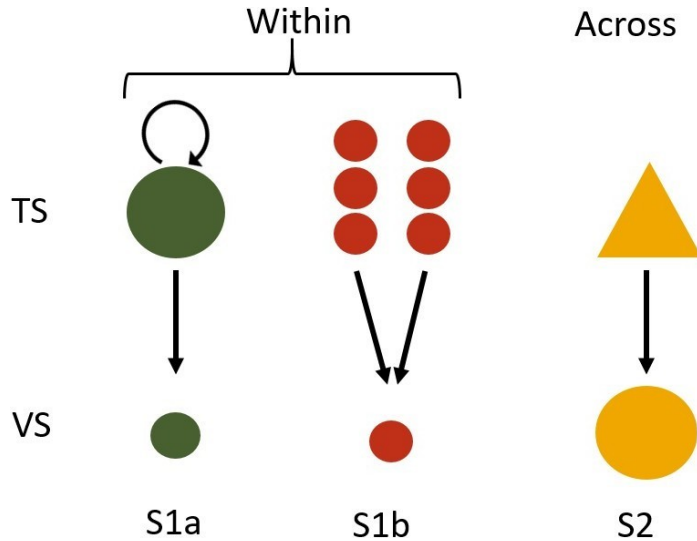
75 Within the half-diallel and for all traits, the *cross* effect was retained in the mixed model for genetic value
76 estimation, but its magnitude with respect to the total genetic variance varied depending on the trait, ranging
77 from less than 10% to ca. 50% (Figure 1b; Table S1). Depending on the trait or cross, the distribution of
78 genotypic BLUPs varied widely (Figure 1c-e; Figure S3), some traits such as **vigour** being quite comparable
79 among crosses, while others such as **mbw** or **mcwi** varied greatly. We also observed transgressive segregation
80 within the half-diallel progenies (Figure 1c-e; Figure S3) for most traits and subpopulations. The 15 traits studied
81 represented a large phenotypic diversity, structured among crosses (Figure S4).

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83 Prediction of cross mean and Mendelian sampling
84 within- and across-populations

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86 Prediction of cross mean

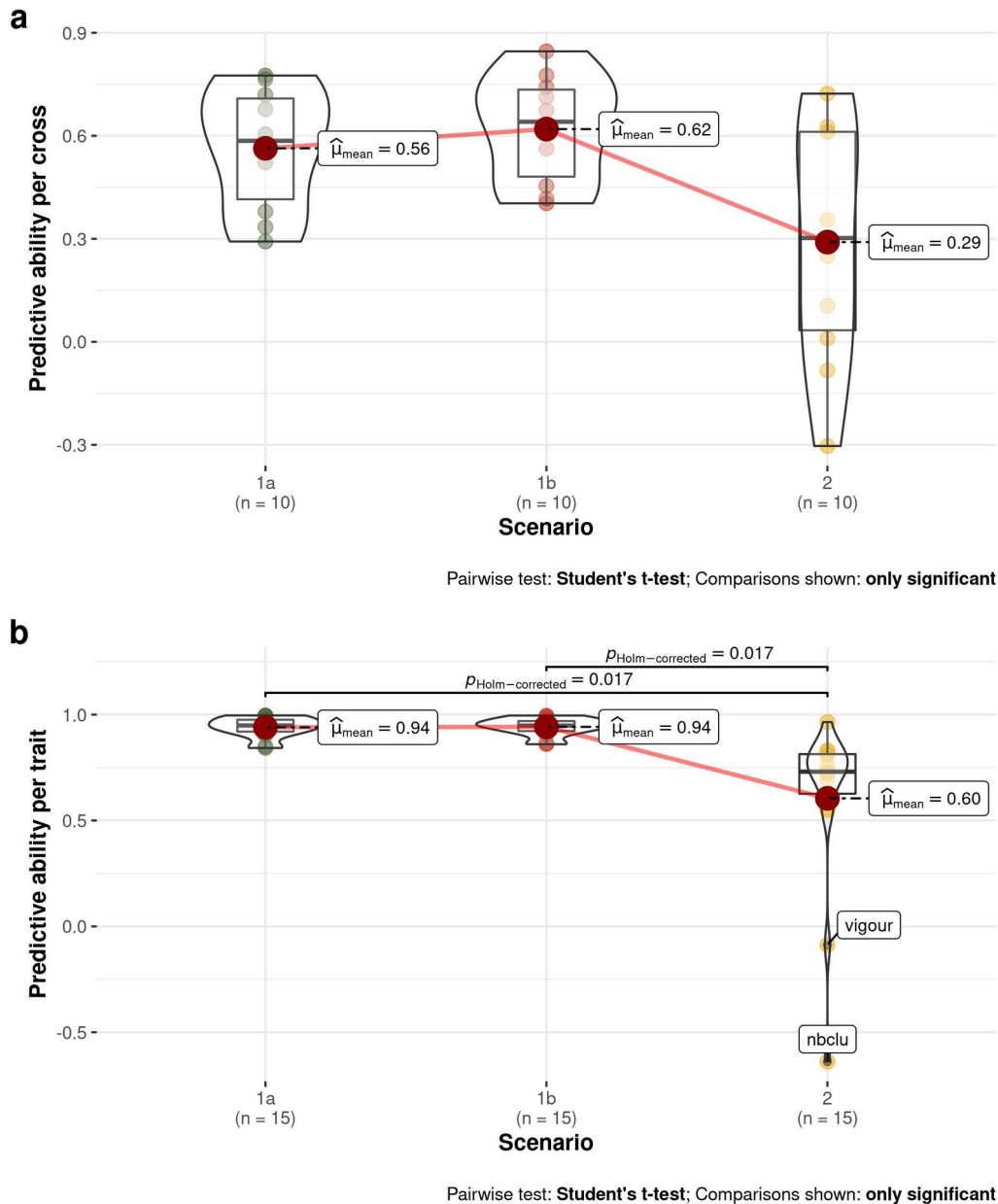


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88 Figure 2: Schematic description of the three scenarios tested. TS: training set, VS: validation set. In scenario 1a, GP was applied within the half-
89 diallel population with 10-fold cross-validation repeated 10 times. In scenario 1b, half-sib families from each parent were used separately as TS.
90 In scenario 2, TS was the diversity panel. See details in Table S5.

91 We first implemented cross mean prediction, as if aiming to select parents for future crosses, selecting the
92 method best adapted to genetic architecture between RR and LASSO (see Material and Methods). Predictive
93 ability (PA) was assessed as Pearson's correlation between the observed mean genotypic value per half-diallel
94 cross and the one predicted based on parental average genotypes (Table S2). Three scenarios were tested
95 (Material and Methods, Figure 2): allelic effects estimated within the whole half-diallel (scenario 1a), in families
96 with one parent in common (scenario 1b), or within the whole diversity panel (scenario 2).

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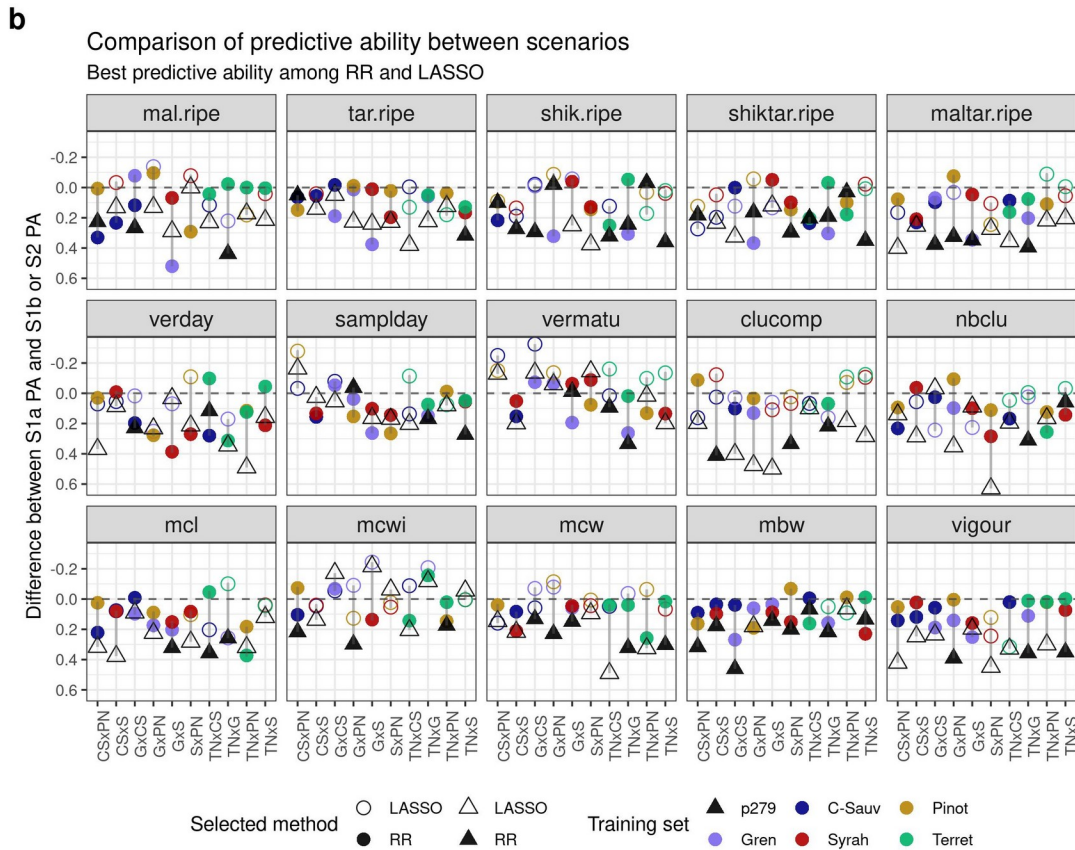
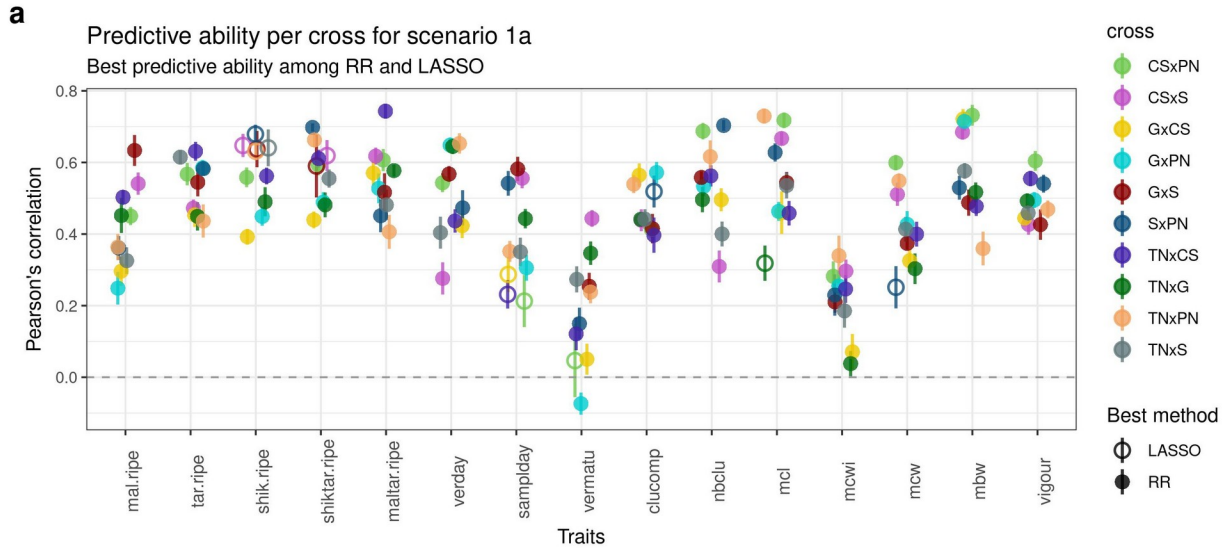
98 Figure 3: Boxplots of PA values for the three scenarios (1a: within whole half-diallel prediction; 1b: half-sib prediction within half-diallel; 2:
 99 across-population prediction with diversity panel as training set and each half-diallel cross as validation set). Each PA value was the best one
 100 obtained between RR and LASSO methods. Average PA is indicated next to each boxplot.
 101 a: per-cross PA, b: per-trait PA.

102 In scenario 2, per-trait and per-cross predictive ability was lower and more variable than in scenarios 1a and 1b
 103 (Figure 3). Average per-cross PA was 0.56, 0.62 and 0.29 in scenarios 1a, 1b and 2, respectively (Figure 3a).
 104 Average per-trait PA was close to 1 for most traits in scenarios 1a and 1b (Figure 3b), and still high (around 0.75)
 105 in scenario 2, when excluding **nbclu** and **vigour** (Table S3). Overall PA (over the 150 cross x trait combinations)
 106 was 0.32. There was upward or downward bias for some traits, scenarios or methods, and in scenario 1a, LASSO
 107 resulted in larger bias (Figure S5).

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108 Prediction of Mendelian sampling

109 We then measured PA for individual offspring within each half-diallel cross, thus considering separately the
 110 Mendelian sampling component. For each cross and trait, we compared the observed and predicted genotypic
 111 values in the three scenarios (Figure 2; Figure S6)



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113 Figure 4: a: Mendelian sampling PA per trait and cross for scenario 1a with the best method between RR and LASSO. Vertical bars represent the
114 standard error around the mean (95 % of the confidence interval), based on the outer cross-validation replicates. PA corresponds to the
115 Pearson's correlation between the BLUPs of the genotypic value and the predicted genotypic values.
116 b: Difference between PA of scenario 1a and of the other scenarios. S2 is displayed with a triangle, and S1b by circles, colored according to the
117 parental training set and filled if the best method was RR and empty otherwise.

118 In scenario 1a (Figure 4a), average PA per trait ranged from 0.18 for **vermatu** to 0.58 for **mbw**, with a 0.47
119 overall average (Figure S7a). The extent of PA variation among crosses depended on the trait and could be very
120 large, as for **vermatu** (from -0.074 to 0.443). Unlike for traits, no cross had constantly high or low PA (Figure
121 S7b). RR method yielded the highest PA values in most cases (91% of the 150 trait x cross combinations).

122 In scenario 1b (Figure 4b), there were two PA values per cross, one for each parental training set (TS). The
123 difference between these two values varied widely, depending on the cross and trait (up to about 0.5 for
124 **mal.ripe** in GxS), with an overall average of 0.39. Most often, PA was lower in scenario 1b than in scenario 1a,
125 likely because no full-sibs were included in the training set. However, there were several cases with PA values
126 similar or higher in scenario 1b for one parental TS compared to scenario 1a. RR method produced the best PA
127 in 61% of the 300 combinations (2 parents x 15 traits x 10 crosses).

128 In scenario 2 (Figure 4b), overall average PA (0.26) was nearly halved compared to scenario 1a, with trait
129 dependent differences in PA between both scenarios. Some traits such as **vigour**, **clucomp** and **maltar.ripe**
130 displayed a particularly marked decrease. On the opposite, **mcwi** and **vermatu** reached equivalent PA values in
131 both scenarios. RR provided the best PA in 61% of the 150 combinations.

132 Exploring factors affecting predictive ability, and 133 training set optimization

134 We sought those variables affecting the PA values observed above, both for prediction of cross mean and
135 Mendelian sampling. We then implemented training set (TS) optimization in an attempt to increase PA.

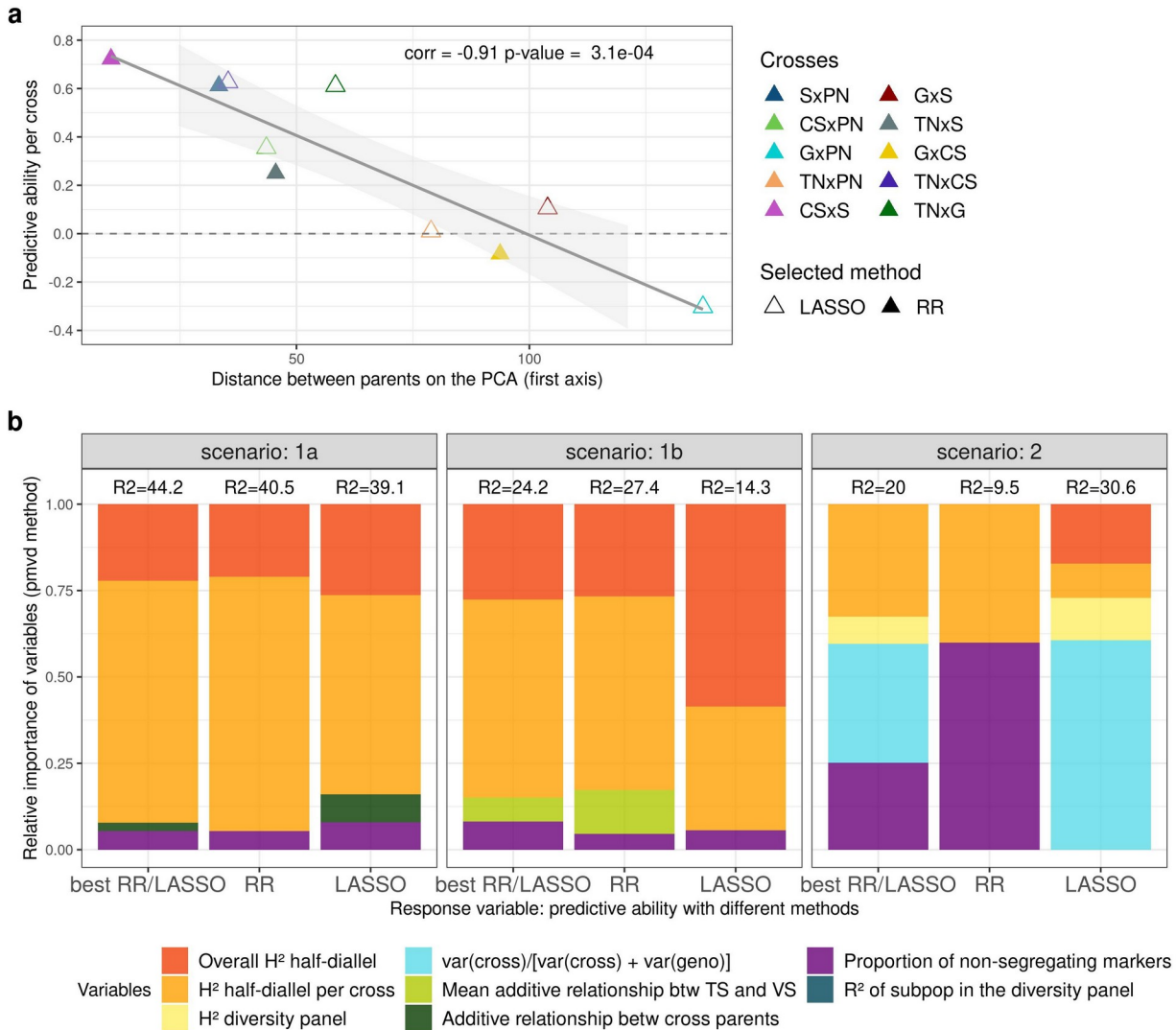
136 Variables affecting the prediction of cross mean

137 In scenario 2, per-cross PA was highly negatively correlated (-0.9) with the cross parents' pairwise distance on
138 the first axis of the diversity panel PCA (Figure 5a, Figure S8a). Correlation with the additive relationship
139 between parents was slightly lower (0.75) and non-significant at 5% (Figure S8a). No such strong correlation was
140 found for per-cross PA in scenarios 1a or 1b (Figure S8a). The proportion of non-segregating markers showed
141 low correlation with per-cross PA in all scenarios (Figure S8a).

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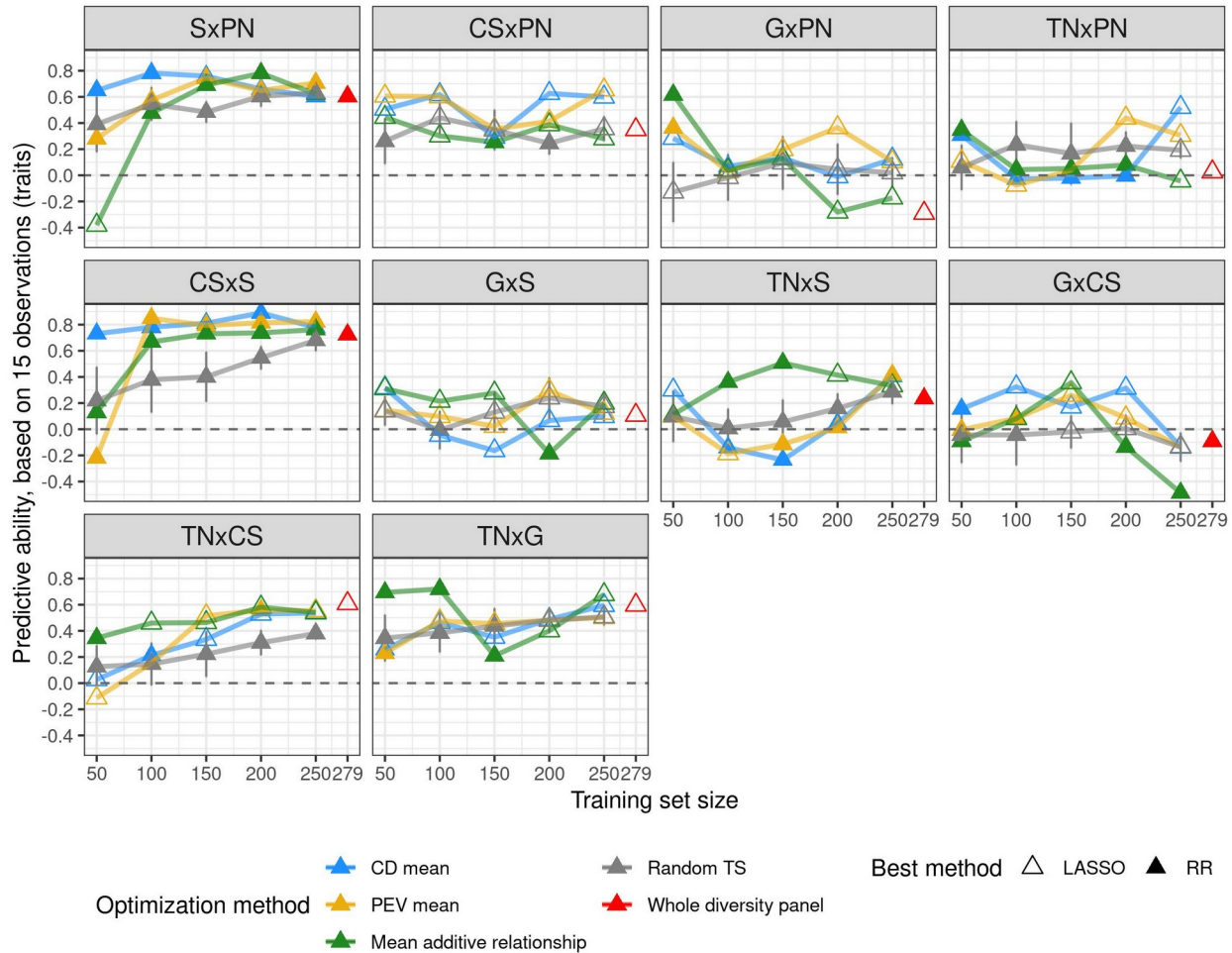


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145 Figure 5: a: Plot of per-cross PA for cross mean in scenario 2, obtained with the best method between RR and LASSO for each cross, against the
 146 distance between cross parents on the first axis of the diversity panel PCA (Figure 1a). Best method is indicated with the triangle filling and cross
 147 with the color. b: Relative importance of variables affecting PA for Mendelian sampling in the three scenarios tested. Variables were selected
 148 from an overall model, after a model selection step. Response individual PA values were obtained either as the best one between RR and
 149 LASSO, with RR or with LASSO. Relative importance was estimated with pmvd method, from relaimpo R-package version 2.2-5.

150 Since variation in per-cross PA for scenario 2 was extremely large, from -0.3 for GxPN to 0.72 for CSxS (Figure
 151 3a), we implemented TS optimization for each cross, to try and increase low PA values. Optimization actually
 152 improved PA for crosses with PA initially below 0.6, for TS sizes between 50 and 150 (Figure 6). The largest
 153 improvement, from -0.29 to 0.62, was observed for GxPN cross.

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155 Figure 6: PA for cross mean prediction after training set optimization and with the best method between RR and LASSO, for each cross. Best
 156 method is indicated with the triangle filling and TS optimization method with the color. For comparison, random selection of TS genotypes (in
 157 grey) was performed and repeated ten times, error bars correspond to 95% of the confidence interval around the mean. We also report per-
 158 cross PA with the whole diversity panel (in red), with a maximum TS size of 279 which may vary depending on traits.

159 The variable that most affected per-trait PA was the $\sigma_C^2 / (\sigma_C^2 + \sigma_G^2)$ ratio (relative variance of cross effect). It was
 160 strongly correlated with PA in scenarios 1a and 1b (0.82 and 0.88, respectively), but not in scenario 2 (Figure
 161 S8b).

162 No other explanatory variable displayed any significant impact despite a fairly high correlation with per-trait or
 163 per-cross PA, which could be due to low sample sizes (15 and 10 for per-trait and per-cross PA, respectively).

164 Factors affecting Mendelian sampling prediction

165 To model Mendelian sampling PA for each scenario and method selected for each trait (RR, LASSO or best), we
 166 applied multiple linear regression on six to nine variables depending on the scenario, as detailed in Material and
 167 Methods. The highest coefficient of determination (44.2%) was obtained in scenario 1a with the best method
 168 (Figure 5b). Coefficients of determination were equivalent, lower and higher for LASSO compared to RR in
 169 scenarios 1a, 1b and 2, respectively. Three variables were found to impact PA in all scenarios: half-diallel overall

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170 H^2 , per-cross H^2 and the proportion of non-segregating markers. Surprisingly, half-diallel overall H^2 was not
171 selected in scenario 2 with either RR or best method, while it had a strong effect in other modalities.

172 The selected variables were quite similar between scenarios 1a and 1b, with a high effect of half-diallel overall
173 and per-cross H^2 , but differed in scenario 2 in which more variables were selected. Overall, most of the relative
174 importance came from variables related to the trait and not to the genetic composition of TS or validation set
175 (VS).

176 We also calculated individual PA with optimized TSs derived from the diversity panel (Figure S9). However, we
177 did not observe any improvement compared to using the whole diversity panel. This is consistent with the fact
178 that genetic relationship seemed not to impact PA (Figure 5b).

179 Discussion

180 Our study allowed us to thoroughly explore GP potential in grapevine breeding, by scanning a large range of
181 potentially useful configurations: (i) with 15 weakly related traits with variable levels of H^2 and phenotypic
182 structure (subpopulation or cross effects on phenotypic data) (Figure S4), (ii) in across-population scenarios with
183 TS ranging from half-sibs (scenario 1b) to a diversity panel (scenario 2), (iii) with 10 balanced VS crosses.
184 Moreover, we decomposed PA into cross mean and Mendelian sampling components, each being useful in
185 breeding to select parental genotypes and offspring within crosses, respectively. All these results allowed us to
186 get insight into main factors affecting PA. We will focus our discussion on prediction with the diversity panel as
187 TS, since this is the most sought-after configuration in perennial species breeding.

188 Range of PA values

189 For the prediction of cross mean, overall PA was 0.32 in scenario 2, equivalent to the average per-cross PA
190 (0.29), while the average per-trait PA was twice as high (0.6) (Figure 3). In other studies concerning other plant
191 crops, the average per-cross PA was not reported ^{5,6,7,8}, probably because, in most cases, there were not
192 enough traits to estimate it. Bernardo et al. ⁵ and Osthusenrich et al. ⁶ also reported a high-average per-trait
193 PA, above 0.9, while Yamamoto et al. ⁸ reported PA values from 0.21 to 0.57 depending on the trait.

194 For the prediction of Mendelian sampling, overall average PA was slightly lower than overall PA for cross mean
195 in scenario 2 (0.26 and 0.32, respectively). Yet, Mendelian sampling PA was still quite high, considering that TS
196 was essentially unrelated to VS, i.e., with no first-degree relationship with predicted progenies. The same
197 diversity panel was previously used in Flutre et al. ²⁶ for predicting individual genotypic values of 23 additional
198 Syrah x Grenache offspring. The reported PA for **mbw** was 0.56, whereas in the present study, we obtained 0.35
199 in the Grenache x Syrah progeny (n=59). We further investigated such discrepancy, and found it related to a
200 sampling bias due to the small VS size in Flutre et al. ²⁶ (data not shown).

201 The range of average per-trait Mendelian sampling PA observed in scenario 2 (from 0.15 to 0.38) was consistent
202 with those described on fruit perennial species where individual prediction was performed with a TS not directly
203 related to the VS (neither half-sib nor full-sib). In *Coffea*, Ferrao et al. ²⁸ reported differences in per-trait PA,
204 from slightly negative values up to ca. 0.60. But, in this study, overall PA was calculated for all crosses of the VS,
205 thus encompassing both cross mean and Mendelian sampling predictions, making comparison with our
206 Mendelian sampling results alone impossible. In contrast, some studies in apple yielded within cross individual

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207 PA values. For instance, Muranty et al.²⁹ reported average per-trait PA ranging from -0.14 to 0.37, and Roth et
208 al.³⁰ found PA values from -0.29 to 0.72 for fruit texture, highly dependent on the cross for all traits. Conversely,
209 our PA values were mainly stable over crosses and variable over traits, in the three scenarios (Figure S7). This
210 difference might partly be due to the larger trait diversity we explored as compared to Roth et al.³⁰, as
211 suggested by comparing our Figure S4 with their Figure 1A. A complementary explanation could be that progeny
212 size varied from 15 to 80 in Roth et al.³⁰, while here progeny sizes were very close and thus less likely prone to
213 sampling variability and to upward or downward bias.

214 Several factors may influence Mendelian sampling PA in our study compared to others. Among potential
215 inflating factors, we can mention a slight over-representation of phenotyped individuals from the WW panel
216 subpopulation, to which four out of the five parents of the half-diallel belong, leading to a higher genetic
217 relationship between effective TS and VS. Factors potentially decreasing PA could be differences between TS
218 and VS experimental designs since the diversity panel and the half-diallel were not phenotyped on the same
219 years, had different plant management systems (overgrafting or simple grafting, respectively) and were planted
220 a few kilometers apart. Nevertheless, for most studied traits, two years of phenotyping were used to compute
221 genotypic BLUPs, which could at least compensate for differences between years, usually referred to as the
222 millesime effect.

223 Variables affecting PA in across-population genomic 224 prediction

225 We focused on PA obtained with the best method between RR and LASSO, to take into account the part of
226 variability among traits associated with genetic architecture. Indeed, LASSO is supposed to be better adapted to
227 traits underlined by few QTLs, while RR would yield better PA for highly polygenic traits. However, we showed
228 that for a given trait x cross combination, i.e., for a given genetic architecture, the best method selected
229 changed depending on the scenario: LASSO was more often selected for scenario 2 than for scenario 1a, both
230 for cross mean and individual prediction. This means that the best method choice also depends on the
231 relationship between TS and VS. This was also suggested in cattle breeding by MacLeod et al.³¹, who found that
232 BayesRC method (comparable to LASSO) yielded better results than GBLUP (comparable to RR) for across-
233 population GP.

234 Regarding the other factors affecting PA, for cross mean prediction in scenario 2, no tested variable significantly
235 affected per-trait PA. Conversely, per-cross PA was strongly affected by the genetic distance between parents
236 (Figure 5a, Figure S8a). To our knowledge, such correlation has never been reported before, most probably
237 because previous works investigated too few traits to afford per-cross PA calculation. We could hypothesize
238 that when one parent is farthest from WW -the most represented panel subpopulation in TS- (e.g., Grenache,
239 Figure 1a, Figure S1), marker effects for this parent might reflect different QTLs or allelic frequencies, compared
240 to WW ones, thereby explaining the decrease in PA for crosses related to Grenache. Such differences underlying
241 marker effects were already described in maize³². Simultaneously, some QTLs in this parent might be less
242 genetically linked to causal polymorphisms due to more recombinations. However, this cannot be the only
243 explanation for the large correlation of per-cross PA with pairwise parent distance, because the correlation
244 between PA and genetic distance between TS and VS was much lower (Figure S8a).

245 For the prediction of Mendelian sampling, the variables explaining individual PA in scenario 2 were quite
246 different from those explaining cross mean PA. Trait-related variables had a large impact on individual PA: half-

247 diallel overall and per-cross heritability, but also the relative variance of cross effect (Figure 5b). Surprisingly,
248 genetic relationship between TS and VS had little to no impact on PA, although this factor has often been
249 reported to affect PA ^{17,15}. Most studies reported separately the effects of different variables on individual PA.
250 Riedelsheimer et al. ³³ also performed multiple linear regression of individual PA on several factors to study their
251 impact. They found that TS composition (number of crosses and their relationship with VS) explained most of
252 the variance (41.7 %), followed by trait (27.6%) and VS composition (4.8%). The variance in genetic relationship
253 between TS and VS may be smaller in our study.

254 Practical consequences on breeding programs

255 Across-population GP with model training in a diversity panel appeared to be promising in grapevine breeding
256 for some traits and crosses, particularly for parent choice (Figure 3; Figure 4; Table S3; Figure S7).

257 The usefulness of GP for better selecting parents for future crosses can be at first assessed by the low overall
258 correlation between mean parental genotypic values (BLUPs) and mean offspring BLUPs (0.28; see also Figure
259 S10). This correlation was much lower than overall PA for cross mean in scenario 1b (0.66) and slightly lower
260 than overall PA for cross mean in scenario 2 (0.32). In strawberry, Yamamoto et al. ⁸ also evidenced the interest
261 of GP for predicting cross mean, with no additional benefit from including dominance effects into GP models,
262 even if cross means were not equal to parental means. Moreover, in some cases, GP could provide other
263 advantages over mean parental genetic values, for instance when parents are not phenotyped for some
264 reasons, because too young or without representative phenotypes (e.g., using microvine ³⁴, in a new
265 environment, etc). This was actually the case, in our half-diallel trial, for the Terret Noir parent, which suffered
266 from mortality probably due to rootstock incompatibility and consequently had no phenotypic record for most
267 studied traits.

268 Even though PA was quite high for some traits and crosses in scenario 2, on average it remained moderate both
269 for cross mean and individual prediction. Both PAs were much higher in scenario 1a, due to increased
270 relationship between training and validation sets. Nevertheless, such an extreme configuration is rarely used in
271 plant breeding programs, especially in perennial species, because it requires to partly phenotype the cross to be
272 predicted. An intermediate configuration, scenario 1b, could be implemented in breeding programs when PA
273 from scenario 2 is not sufficient and half-sib families are available, because in this scenario, cross mean PA was
274 similar as in scenario 1a and individual PA intermediate between scenarios 1a and 2.

275 We found TS optimization useful mostly for cross mean prediction for crosses with low PA. The advantage of TS
276 optimization was less clear for individual prediction. This was consistent with the fact that genetic parameters
277 more strongly affected cross mean PA than individual PA. In contrast, Roth et al. ³⁰ observed in apple a
278 systematic increase of individual PA with an optimized TS in the same context (i.e., with a diversity panel as TS
279 and bi-parental families as VS, and common optimization methods). To our knowledge, only a single study
280 tested TS optimization for cross mean prediction, by Heslot and Feoktistov ³⁵, who implemented optimization of
281 parent selection for hybrid crossing in sunflower while selecting individuals to phenotype, but did not calculate
282 cross mean PA.

283 Since our results show that prediction of cross mean can be quite accurate and useful in scenario 2, we decided
284 to go one step further and implemented cross mean prediction for all 38,781 possible crosses between the 279
285 genotypes of the diversity panel, based on parental average genotypes (Table S2) and on marker effects
286 estimated with RR in this population. As predicted cross mean were biased for some traits in the ten half-diallel

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287 crosses (Figure S5), we estimated the bias for each trait from these data to correct the predicted mean in the
288 possible diversity panel crosses. Figure S11 shows the large potential diversity to be explored through crossing
289 in grape, for all the traits considered in the present study, illustrating the finding of Myles et al. ³⁶ that genetic
290 diversity in grapevine was largely unexploited. Such an example opens many prospects for the use of GP to
291 design future crosses. Indeed, we limited here our prediction to the 279 panel genotypes representing the *Vitis*
292 *vinifera* diversity, but potentially any other (unphenotyped) genotype of interest with dense genotypic data
293 could be used for this purpose as exemplified with the half-diallel, since its five parents were not part of the
294 diversity panel.

295 Prospects

296 Based on our results, the following improvements could be tested: i) increase SNP density ^{25, 37} and include
297 structural variants ii) implement non-additive effects in GP models such as dominance or epistatic effects and iii)
298 add crosses from other panel subpopulations as VSs. Indeed, since all our half-diallel crosses had at least one
299 parent belonging to the WW subpopulation, it would be beneficial to include crosses with parents from the WE
300 and TE subpopulations too. Specific GP models that include genetic structure in marker effect estimation ^{38, 39}
301 could also be tested.

302 Predicting cross variance could also prove useful to design the offspring selection step, more specifically for
303 choosing the number of offspring to test or produce for a given cross. Depending on the available funds and
304 breeding program, a breeder may want to select crosses with high genetic variance, in order to maximize the
305 probability to generate top-ranking genotypes. Conversely, choosing a cross with low variance could limit the
306 risk of breeding poor genotypes.

307 Conclusion

308 We implemented GP in grapevine in a breeding context, i.e., across populations, on 15 traits, in ten related
309 crosses, and obtained moderate to high PA values for some crosses and traits, thus showing GP usefulness in
310 grapevine. Never before had genomic prediction been implemented for so many traits and crosses
311 simultaneously in this species. We showed that per-cross PA was strongly correlated with the genetic distance
312 between parents, whereas Mendelian sampling PA was largely determined by trait-related variables, such as
313 heritability and the magnitude of the cross effect.

314 Material and Methods

315 Plant material

316 The half-diallel consists of 10 pseudo- F_1 bi-parental families obtained by crossing five *Vitis vinifera* cultivars:
317 Cabernet-Sauvignon (CS), Pinot Noir (PN), Terret Noir (TN), Grenache (G) and Syrah (S) ⁴⁰. Each family comprised
318 between 64 and 70 offspring, with a total of 676 individuals including parents.

319 The diversity panel consists of 279 cultivars selected as maximizing genetic diversity and minimizing kinship
320 among cultivated grapevine. Grapevine genetic diversity is highly heterozygous and weakly structured into three
321 subpopulations: WW (Wine West), WE (Wine East) and TE (Table East) ²⁷.

322 Field experiments

323 Field design

324 The half-diallel was created in 1998 at INRAE Montpellier, grafted on Richter 110, and planted in 2005, at the
325 Institut Agro experimental vineyard "Le Chapitre" in Villeneuve-lès-Maguelone (Southern France). The progenies
326 were planted in two randomized complete blocks, with plots of two consecutive plants per offspring per block.

327 The field design for the diversity panel was previously described in Flutre et al. ²⁶. Briefly, cultivars were
328 overgrafted on 6-year-old Marselan in 2009, itself originally grafted on Fercal rootstock, a few kilometers away
329 from the diversity panel. They were planted in five randomized complete blocks, with one plant per cultivar per
330 block.

331 Phenotyping

332 We studied 15 traits in both trials: berry composition with malic (**mal.ripe**), tartaric (**tar.ripe**) and shikimic acid
333 (**shik.ripe**) concentrations in $\mu_{eq} \cdot L^{-1}$ measured at ripe stage (20° Brix) (according to Rienth et al. ⁴¹), from which
334 two ratios were derived, shikimic / tartaric acid (**shiktar.ripe**) and malic / tartaric acid (**maltar.ripe**);
335 morphological traits with mean berry weight (**mbw**, in g) measured on 100 random berries, mean cluster weight
336 (**mcw**, in g), mean cluster length (**mcl**, in cm) and mean cluster width (**mcwi**, in cm), measured on 3 clusters,
337 number of clusters (**nbclu**) and cluster compactness (**clucomp**) measured on the OIV semi-quantitative scale;
338 phenology traits with veraison date (onset of ripening; **verday**, in days since January 1st), maturity date
339 corresponding to berries reaching 20° Brix (**samplday**, in days since January 1st) and the interval between
340 veraison and maturity (**vermatu**, in days); vigour (**vigour**, in kg), derived as the ratio between pruning weight
341 and the number of canes. Phenotypic data were collected between 2013 and 2017 for the half-diallel and in
342 2011-2012 for the diversity panel. There was a slight over-representation of phenotypes from the WW
343 subpopulation because of fertility issues in WE and TE subpopulations

344 SNP genotyping

345 For the half-diallel, we used genotyping-by-sequencing (GBS) SNP markers derived by Tello et al. ⁴⁰, 622 of the
346 676 individuals being successfully genotyped, as well as the five parents. Raw GBS data were processed
347 separately for each cross, and then markers from all crosses were merged together (390,722 SNPs), thus
348 generating many missing data (85% of missing data per marker on average), since all markers did not segregate
349 in all progenies. Markers with more than 80% of missing data were removed and remaining markers were
350 imputed with FImpute3 ⁴² (86,017 SNPs). Some parental cultivars were used either as female or male, depending
351 on the cross, a configuration not allowed by FImpute3. We thus declared only a partial pedigree maximizing the
352 number of crosses defined with both parents (Table S4). For the diversity panel, we used the same SNP markers
353 as in Flutre et al. ²⁶, except that we applied a filter on minor allelic frequency (5%) and no filter on linkage
354 disequilibrium, which yielded 83,264 SNPs.

355 Finally, we only retained the 32,894 SNPs common to both populations.

356 Phenotypic data analyses

357 Half-diallel

- 358 • Statistical modeling for estimating genotypic values

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359 For each trait, we excluded outlier values by visual inspection of raw phenotypic data and computed a log or
 360 square-root transformation if its distribution looked skewed. Then, we fitted the following linear mixed full
 361 model by Maximum Likelihood:

$$362 \quad y_{ijkl} = \mu + G_i + C_j + B_k + Y_l + (B:Y)_{kl} + (G:Y)_{il} + (C:Y)_{jl} + x + y + x:y + (x:Y)_l + (y:Y)_l + \epsilon_{ijkl}$$

363 with y_{ijkl} the phenotype of genotype i from cross j in block k and year l . Among the fixed terms, μ was the
 364 overall mean, and B_k and Y_l the effects of block k and year l . Among the random terms, G_i and C_j were the
 365 effects of genotype i nested within cross j , and x and y the field coordinates. Interactions are indicated with ":".
 366 ϵ_{ijkl} was the random residual term, assumed to be normally distributed.

367 Sub-model selection was based on Fisher tests for fixed effects and log-likelihood ratio tests for random effects.
 368 It was performed with the step function from lmerTest R-package⁴³. Variance components were estimated after
 369 re-fitting the selected model by Restricted Maximum Likelihood, and diagnostic plots were drawn to visually
 370 check the acceptability of model hypotheses such as homoscedasticity or normality. Best Linear Unbiased
 371 Predictors (BLUPs) of cross (C) and genotype (G) values were computed. For genomic predictions, we used their
 372 sum (C+G) as total genotypic values for both training and validation data. Variance component estimates were
 373 used to compute the proportion of genetic variance due to differences between crosses as: $\sigma_C^2 / (\sigma_C^2 + \sigma_G^2)$.

374 • **Heritability estimation**

375 We estimated overall (for the whole half-diallel) broad-sense heritability for genotype-entry means⁴⁴ as:

$$376 \quad H^2 = \frac{\sigma_C^2 + \sigma_G^2}{\sigma_C^2 + \sigma_G^2 + \frac{\sigma_{C:Y}^2 + \sigma_{G:Y}^2 + \sigma_{x:Y}^2 + \sigma_{y:Y}^2}{n_{year}} + \frac{\sigma_x^2 + \sigma_y^2 + \sigma_{x:y}^2 + \sigma_\epsilon^2}{n_{year} \times n_{rep. year}}}$$

377 with genotype (G) and cross (C) variances at the numerator. Random variance components involving year (Y)
 378 were divided by the mean number of years (n_{year}). Other random variance components involving spatial effects
 379 or residuals were divided by the mean number of years times the mean number of replicates per year ($n_{rep. year}$).

380 We also estimated broad-sense heritability per cross (thereafter used to name half-diallel full-sib family). For
 381 that, we applied the same selected model, but removed all effects involving cross. Then, we estimated variance
 382 components within each cross, and heritability with the same formula, after removing variances involving cross.

383 All information on analyses of phenotypic data and heritability of the half-diallel is detailed in Table S1.

384 **Diversity panel**

385 We used the genotypic values previously estimated in Flutre et al.²⁶ with a similar statistical procedure to the
 386 one described above for the half-diallel. All phenotypic analysis information is provided in Table S3 of Flutre et
 387 al.²⁶.

388 For each of the two populations, genotypic BLUPs were scaled, allowing comparison among traits.

389 Genomic prediction statistical methods

390 Marker effects were estimated using two methods to take into account varying genetic architecture among the
391 traits studied. Ridge regression (RR) ⁴⁵, best adapted to many minor QTLs, shrinks marker effects towards 0.
392 Least Absolute Shrinkage and Selection Operator (LASSO) ⁴⁶, best adapted to a few major QTLs, applies a L1
393 norm on allelic effects, thus forcing some to be exactly 0. Both methods were implemented with R/glmnet
394 package ⁴⁷ and the amount of shrinkage, controlled by λ parameter, was calibrated by five-fold inner cross-
395 validation within each training set, using cv.glmnet function.

396 Genomic prediction scenarios

397 We assessed prediction within half-diallel crosses under three different training scenarios (Figure 2; Table S5):

- 398 • **Scenario 1a:** whole half-diallel prediction. We applied random outer 10-fold cross-validation over the
399 whole half-diallel population. In each fold, 90% of the phenotyped offspring were used as the training
400 set (TS) and the remaining 10% as the validation set (VS). Cross-validation was replicated ten times.
- 401 • **Scenario 1b:** half-sib prediction. For each half-diallel cross used as VS, we trained the model with the
402 three half-sib crosses of each parent in turn, thus predicting each cross twice.
- 403 • **Scenario 2:** across-population prediction. We used the whole diversity panel as TS and each half-diallel
404 cross as VS.

405 Predictive ability assessment

406 In order to account for the effect of genetic architecture, we applied both RR and LASSO methods for each trait
407 and cross and kept the best PA, for both cross mean and within cross individual prediction.

408 Prediction of cross mean

409 Cross mean PA was assessed as Pearson's correlation between the average value of observed total genotypic
410 values (sum of genotype and cross BLUPs for each offspring) for each cross, and the mean predicted genotypic
411 value per cross, calculated in two ways, as:

- 412 • average predicted value over all offspring of the cross. In scenario 1a, each offspring was predicted 10
413 times, thus we also averaged the predicted value over the 10 replicates.
- 414 • predicted value for the parental average genotype, defined at each locus and for each cross as the
415 mean allelic dosage according to the expected segregation pattern based on parents' genotypes (Table
416 S2).
- 417 • genotypic values predicted with these two modalities were highly correlated (above 0.98) in the three
418 scenarios and for the two methods (partly shown in Figure S12). Therefore, in subsequent analyses, we
419 used only prediction with parental average genotypes.

420 Pearson's correlation between observed and predicted values was calculated on all cross x trait combinations
421 (overall PA), for each trait (per-trait PA) and for each cross (per-cross PA).

422 Within-cross individual prediction

423 We measured PA within each cross in each scenario as Pearson's correlation between observed total genotypic
424 values and predicted genotypic values.

425 Test of variables affecting predictive ability

426 We tested the effect of several variables on within-cross individual PA, in each scenario. We built a multiple
427 linear regression model with PA per trait x cross combination as the response variable and as predictors, a set of
428 variables common to all three scenarios plus specific variables for scenarios 1b and 2. Common variables were:
429 the proportion of non-segregating markers in the cross, overall and per-cross broad-sense heritability, the
430 distance between the parents of the cross measured either as the additive relationship or as the distance on the
431 first or first two axes of the panel PCA (Figure 1a) and the proportion of genetic variance due to differences
432 between crosses ($\sigma_C^2 / (\sigma_C^2 + \sigma_G^2)$ ratio). A specific variable for scenarios 1b and 2 was the mean additive
433 relationship between training and validation sets. In scenario 2, it was calculated for each trait only with
434 phenotyped individuals. Specific variables for scenario 2 were: broad-sense heritability in the diversity panel
435 (retrieved from Flutre et al. ²⁶ and Table S1) and the percentage of trait variance explained by the subpopulation
436 factor (see below). After fitting the overall model, we applied a forward-backward stepwise regression, with the
437 AIC criterion to select the best explanatory model. Then, we estimated the relative importance of each variable
438 selected in this model with the pmvd method ⁴⁸, which allows to decompose the R^2 of correlated regressors
439 with the R-package relaimpo ⁴⁹.

440 The percentage of trait variance within the diversity panel explained by subpopulation (WW, WE or TE) was
441 evaluated by fitting for each trait the following linear model: $G = P + \epsilon$, where G is the genotypic (BLUP) value
442 within the diversity panel, P is a fixed subpopulation effect, and ϵ a random residual term. The percentage of
443 variance due to differences between subpopulations was then estimated as the coefficient of determination (R^2)
444 of the model.

445 Training set optimization

446 We tested three methods for optimizing TS in scenario 2, for both cross mean and within-cross individual
447 prediction. We used the STPGA R-package⁵⁰ to implement Prediction Error Variance (*PEVmean*) and *CDmean*
448 (based on the coefficient of determination)¹⁰. Moreover, we computed the mean relationship criterion
449 (*MeanRel*), as the mean additive relationship between each genotype in TS and all genotypes in VS. Each
450 optimized TS was specific to a cross. The realized additive relationship based on marker data was estimated
451 using the rrBLUP R-package⁵¹ with the A.mat function implementing the formula from VanRaden et al. ⁵². For
452 each of these three optimization methods, we tested five TS sizes (50, 100, 150, 200, 250). PA values obtained
453 with each optimized TS were compared with those obtained with a random sample of genotypes of the same
454 size, repeated 10 times.

455 Data availability

456 All analyses were conducted using free and open-source software, mostly R. Phenotypic and genotypic data, R
457 scripts and result tables are available at <https://data.inrae.fr/privateurl.xhtml?token=1925c973-a11b-45ad-b297-69db8ec2c270> .

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463 Author contribution statement

464 VS, AD, PT, TF, JPP and LLC conceived the idea of the study and contributed to funding acquisition; TP, PF, AD
465 and JPP obtained the phenotypic data used in this work; VS, AD, PT, LLC, TF and CB performed and interpreted
466 results; AD conceived the half-diallel population; PT is the PhD supervisor of CB; CB wrote the original draft,
467 which was reviewed and edited by all authors. All authors read and approved the final manuscript.

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470 declare that they have no conflict of interest. The authors declare that the experiments comply with the current
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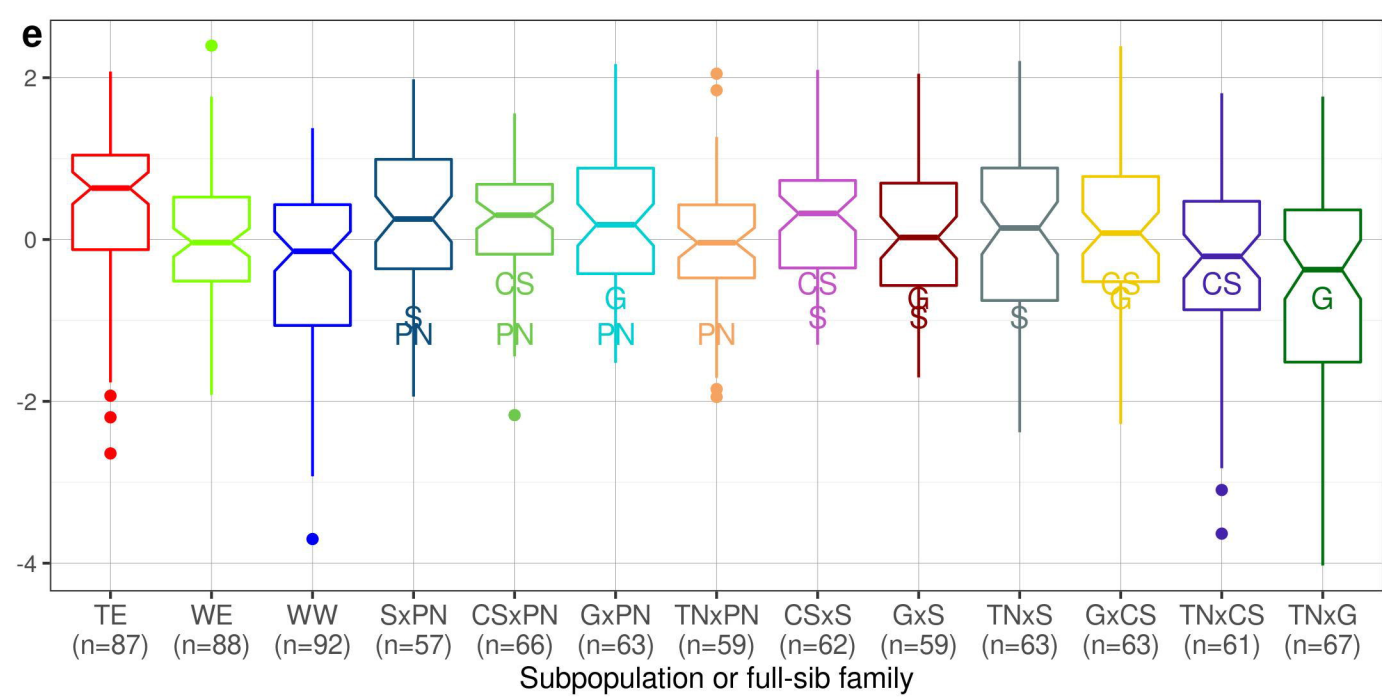
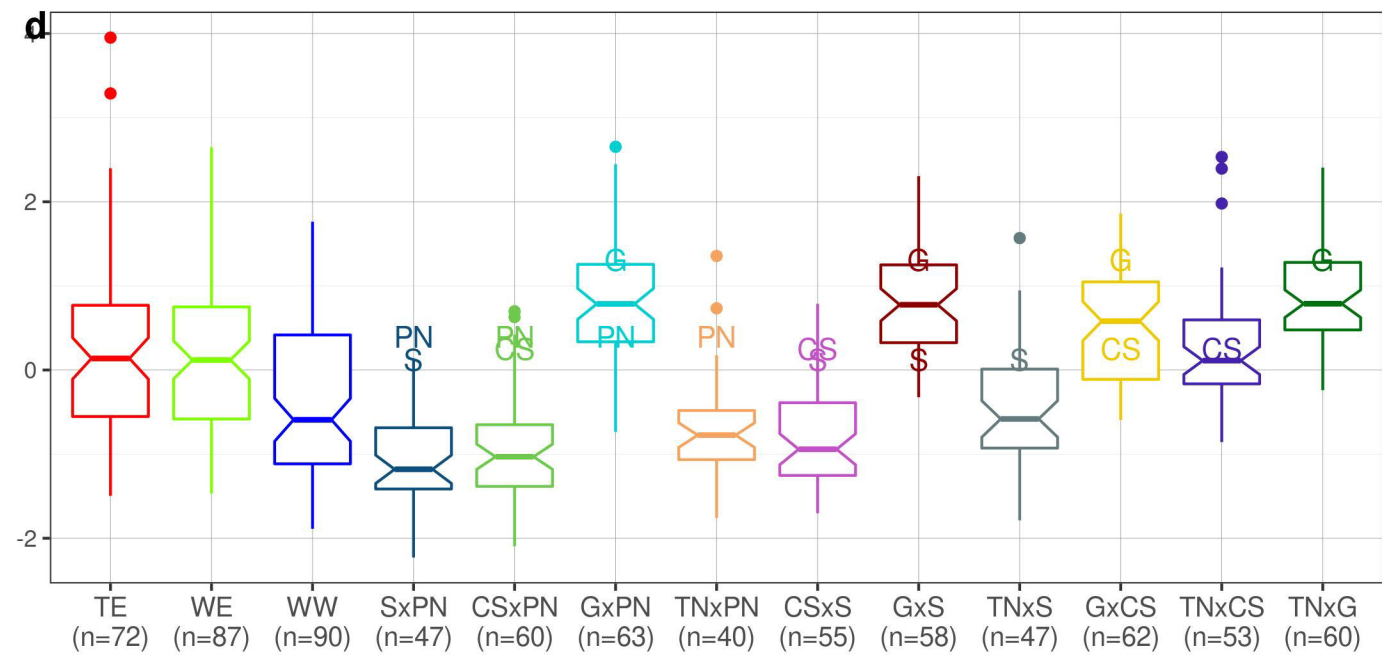
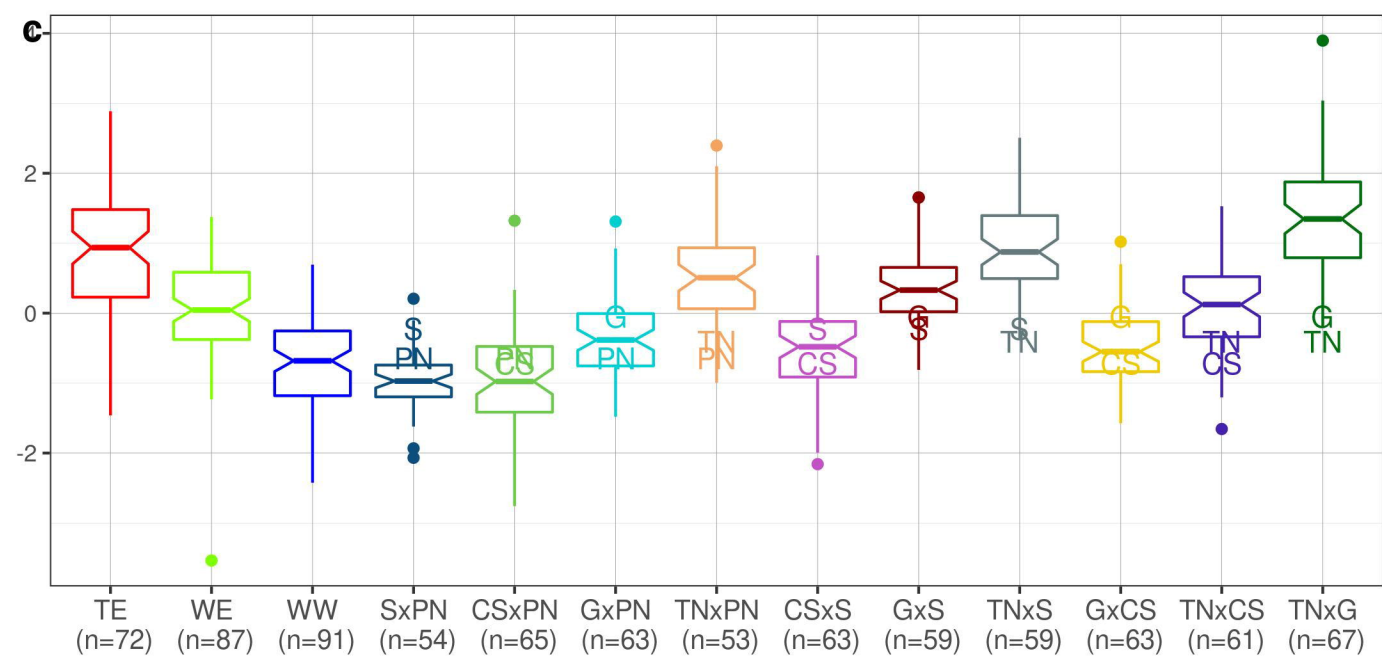
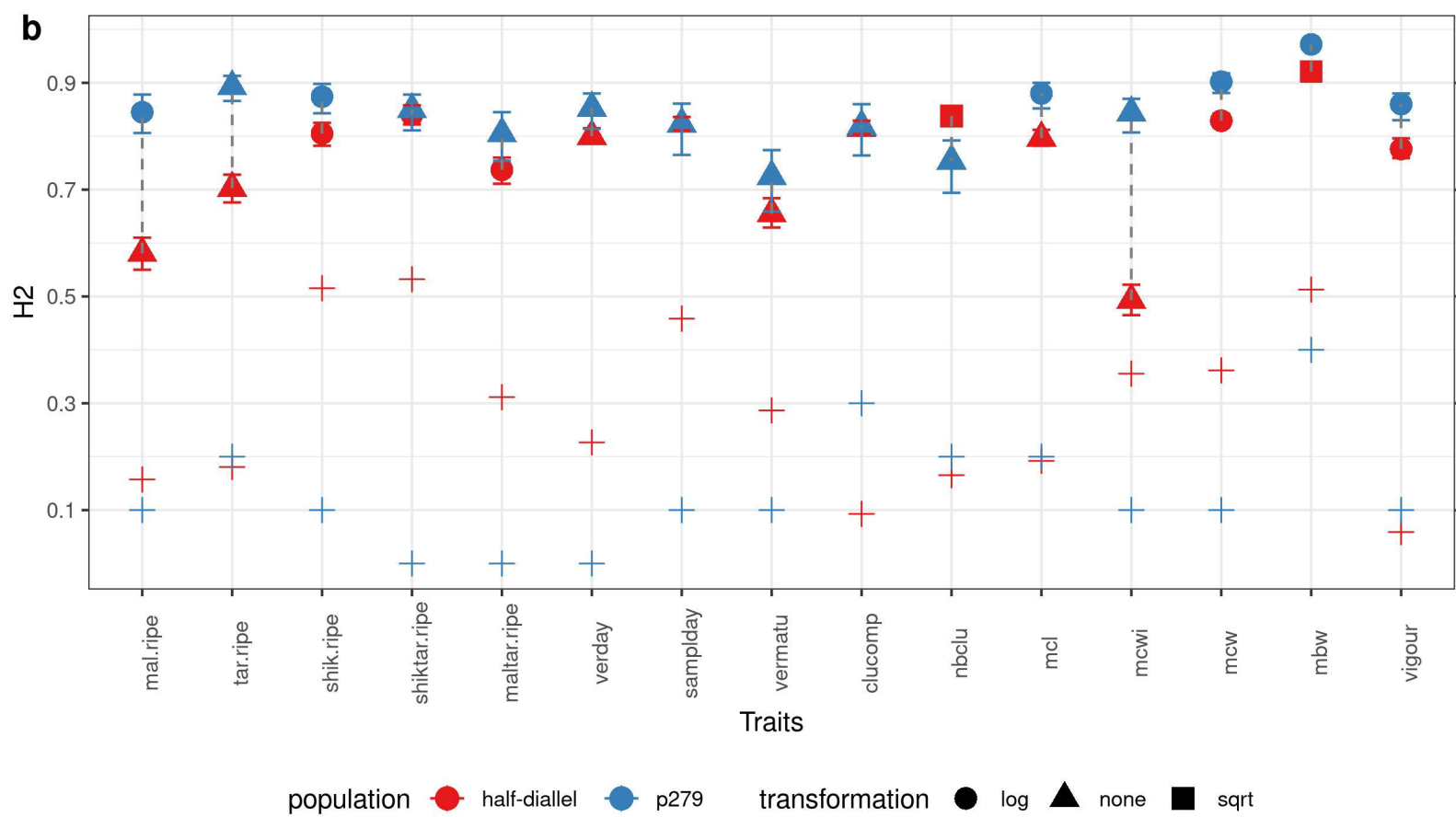
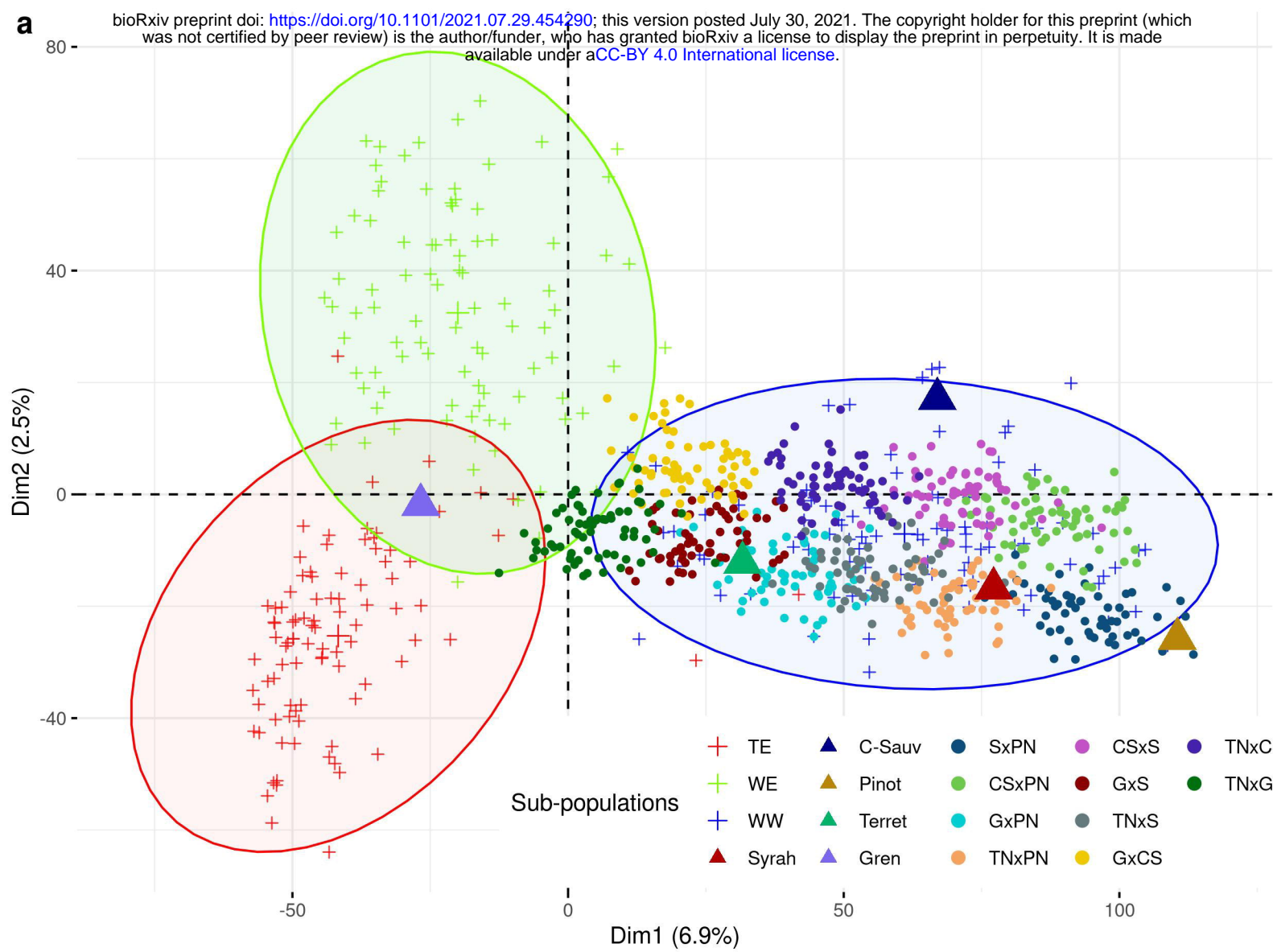
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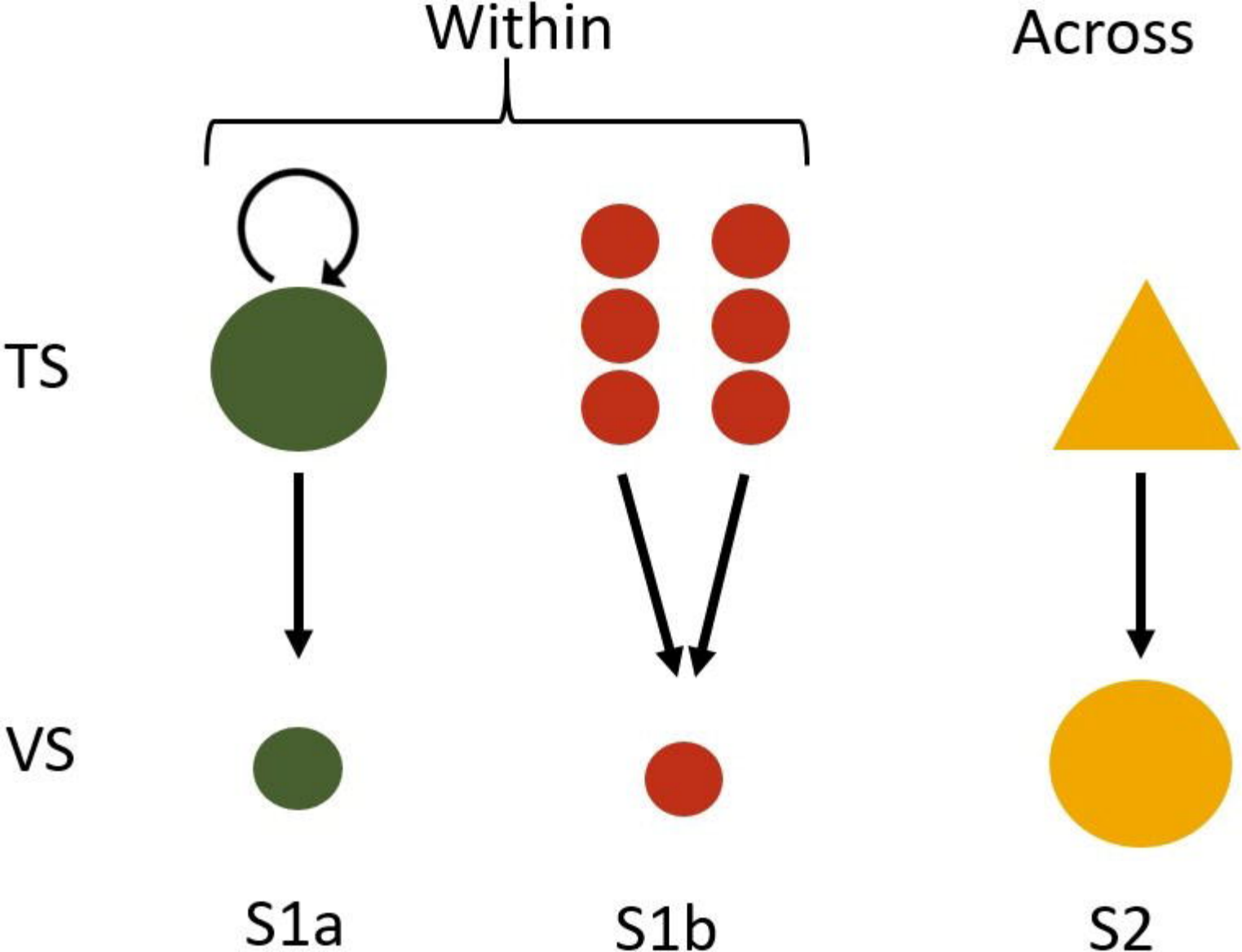
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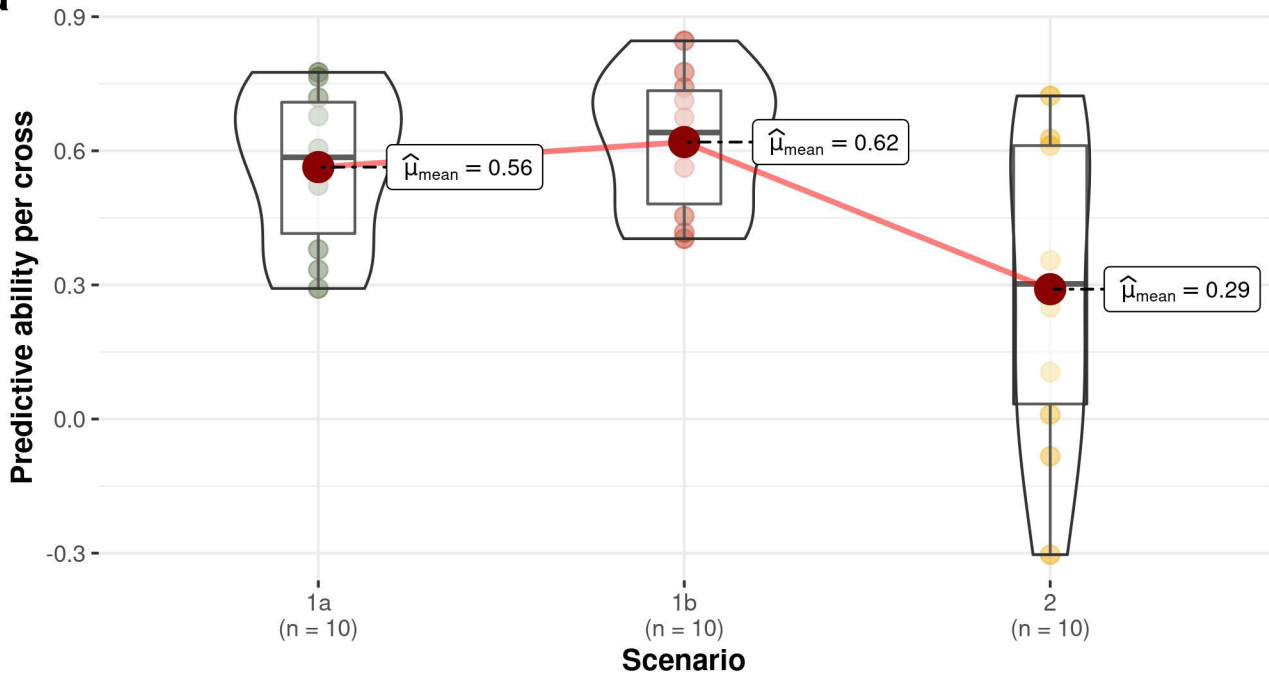
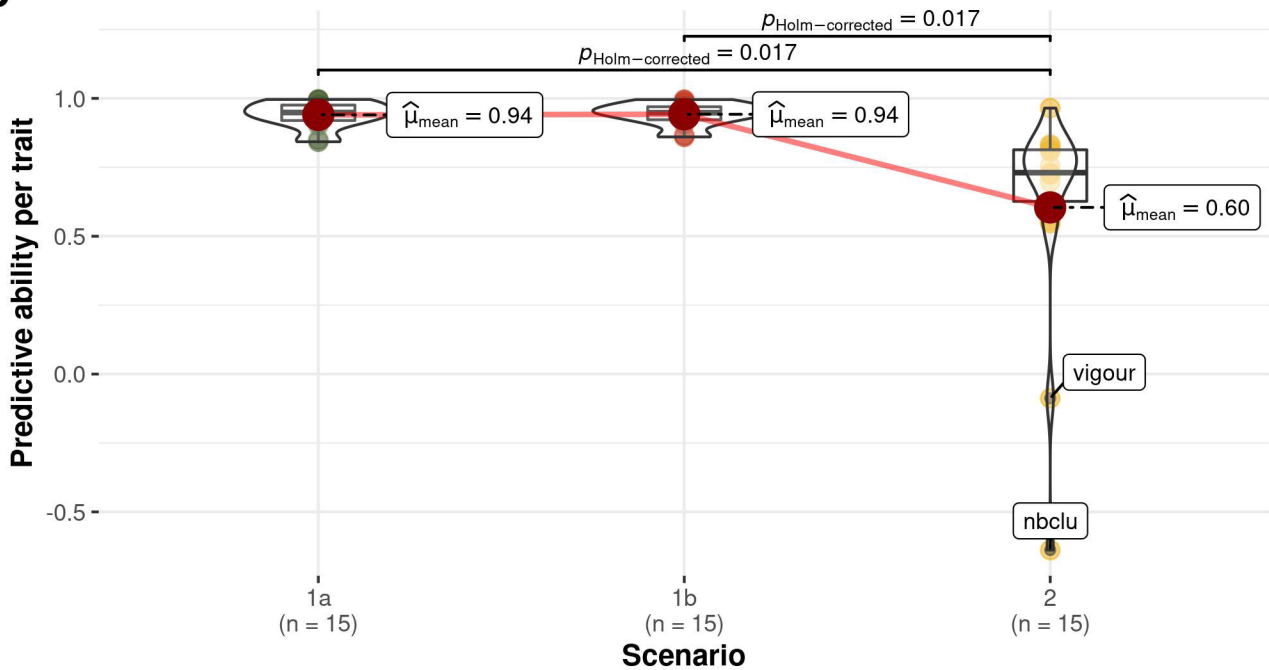
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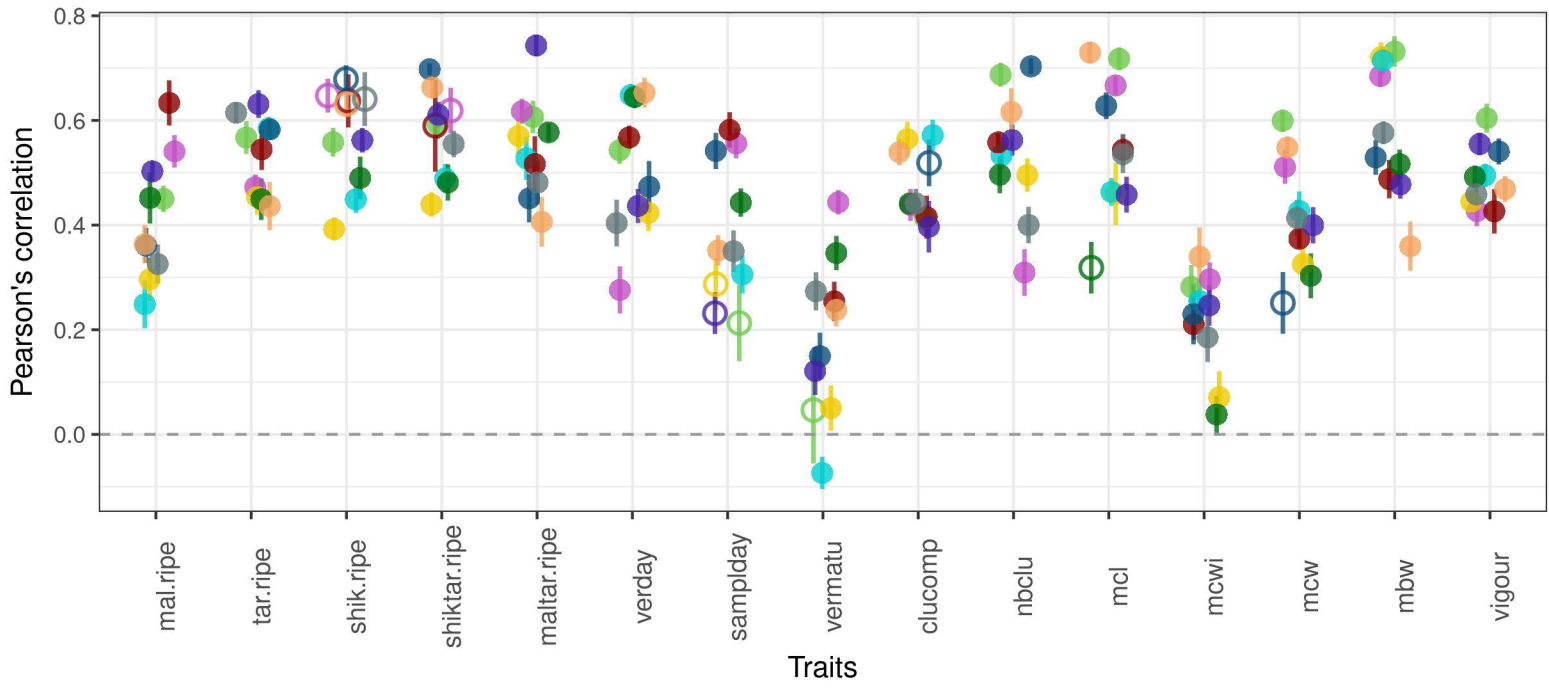
a**b**

a

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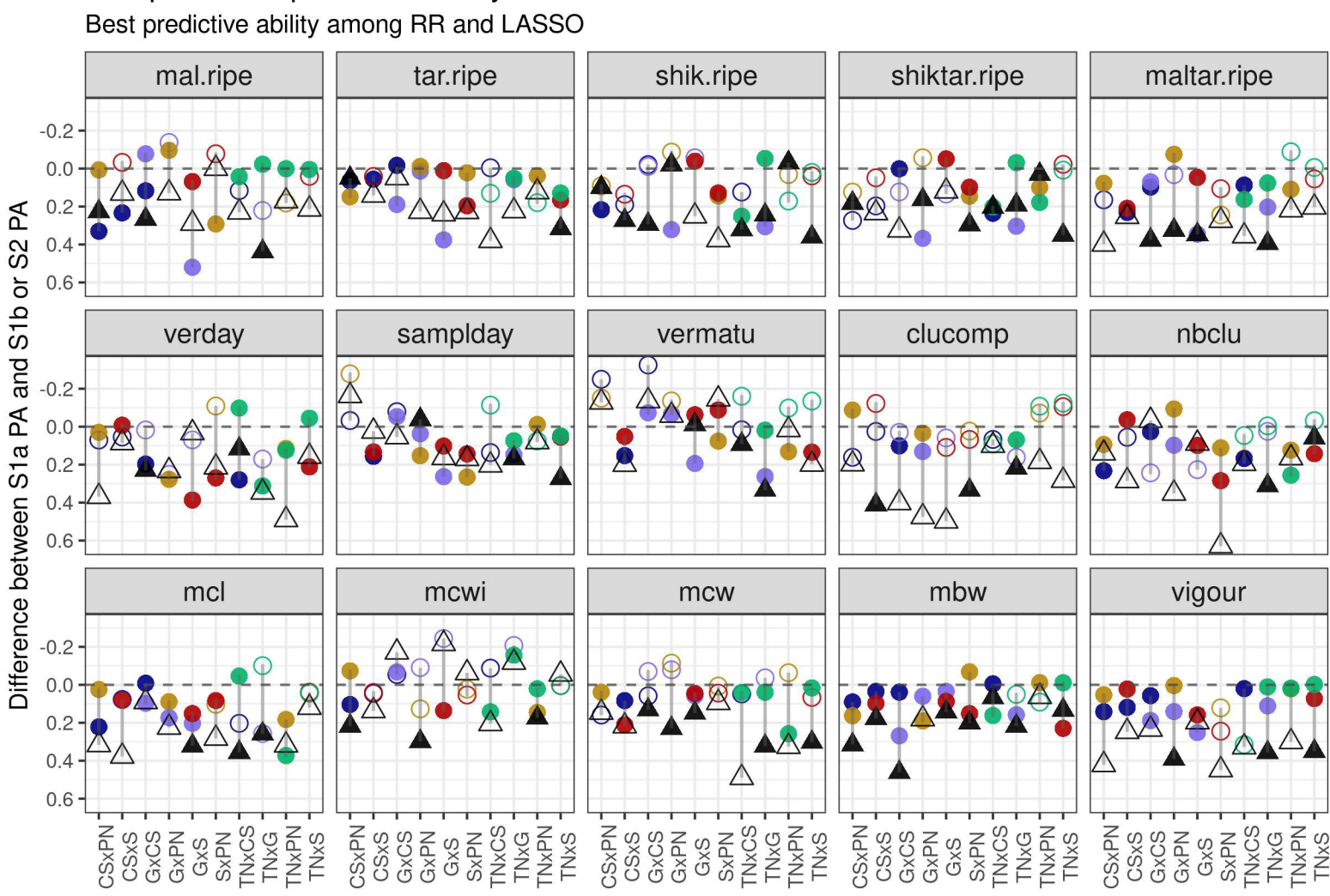
Predictive ability per cross for scenario 1a

Best predictive ability among RR and LASSO

**b**

Comparison of predictive ability between scenarios

Best predictive ability among RR and LASSO

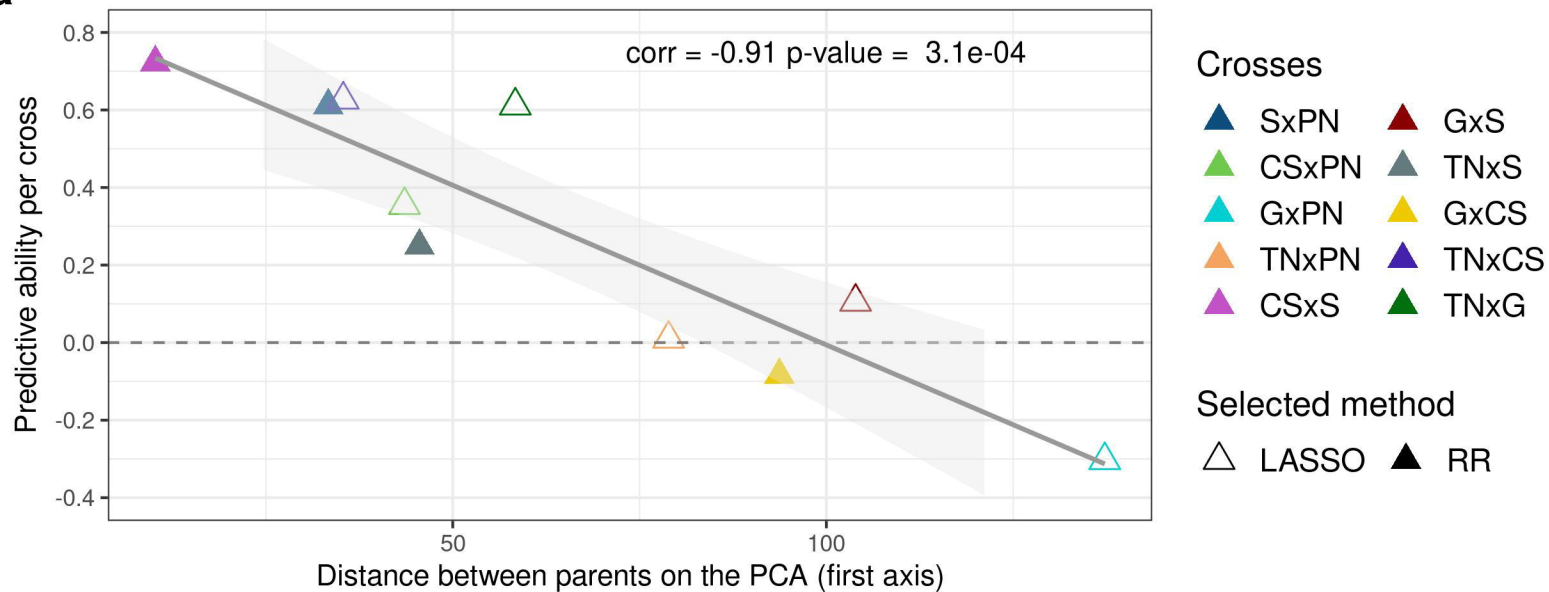
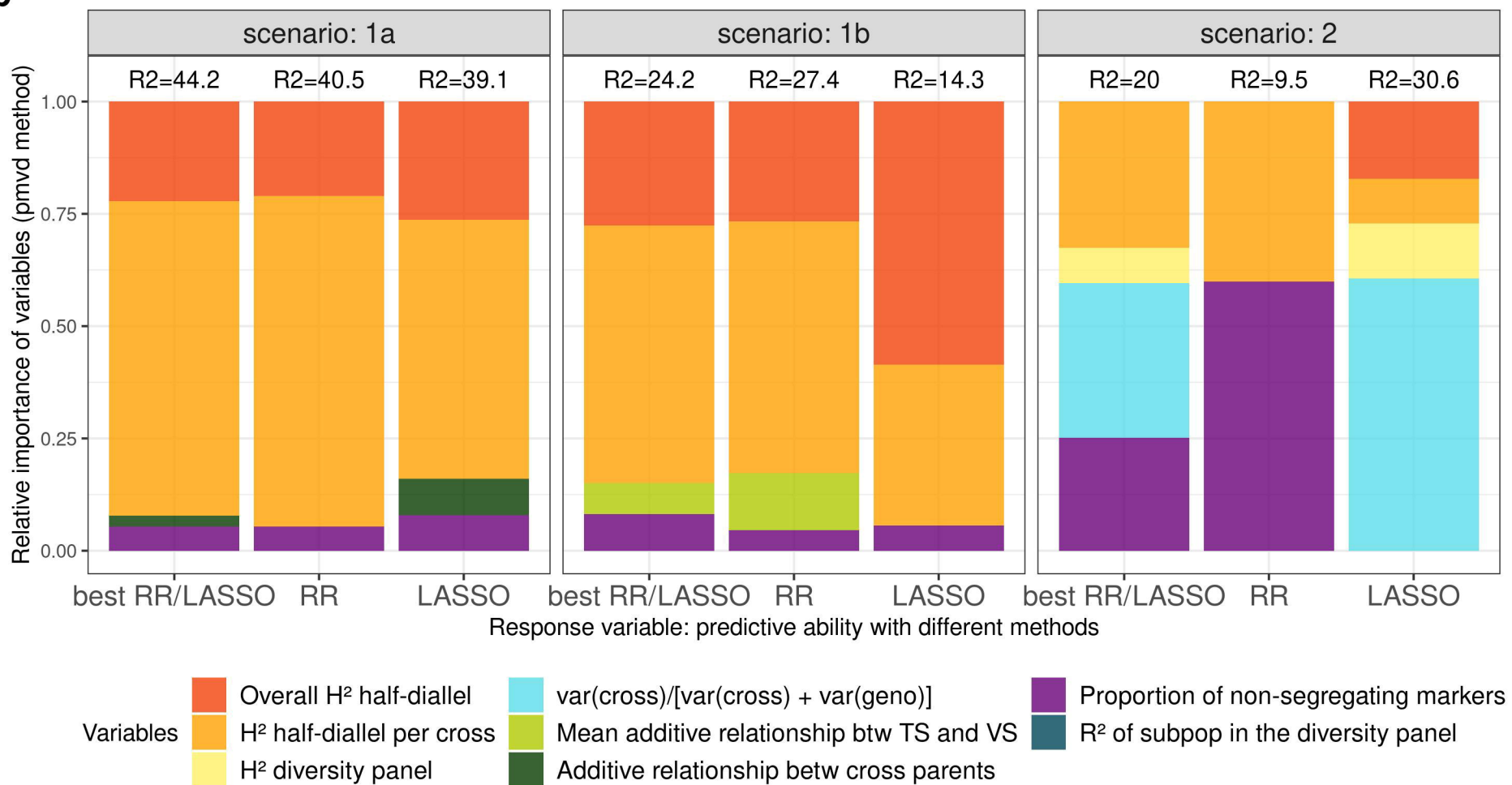


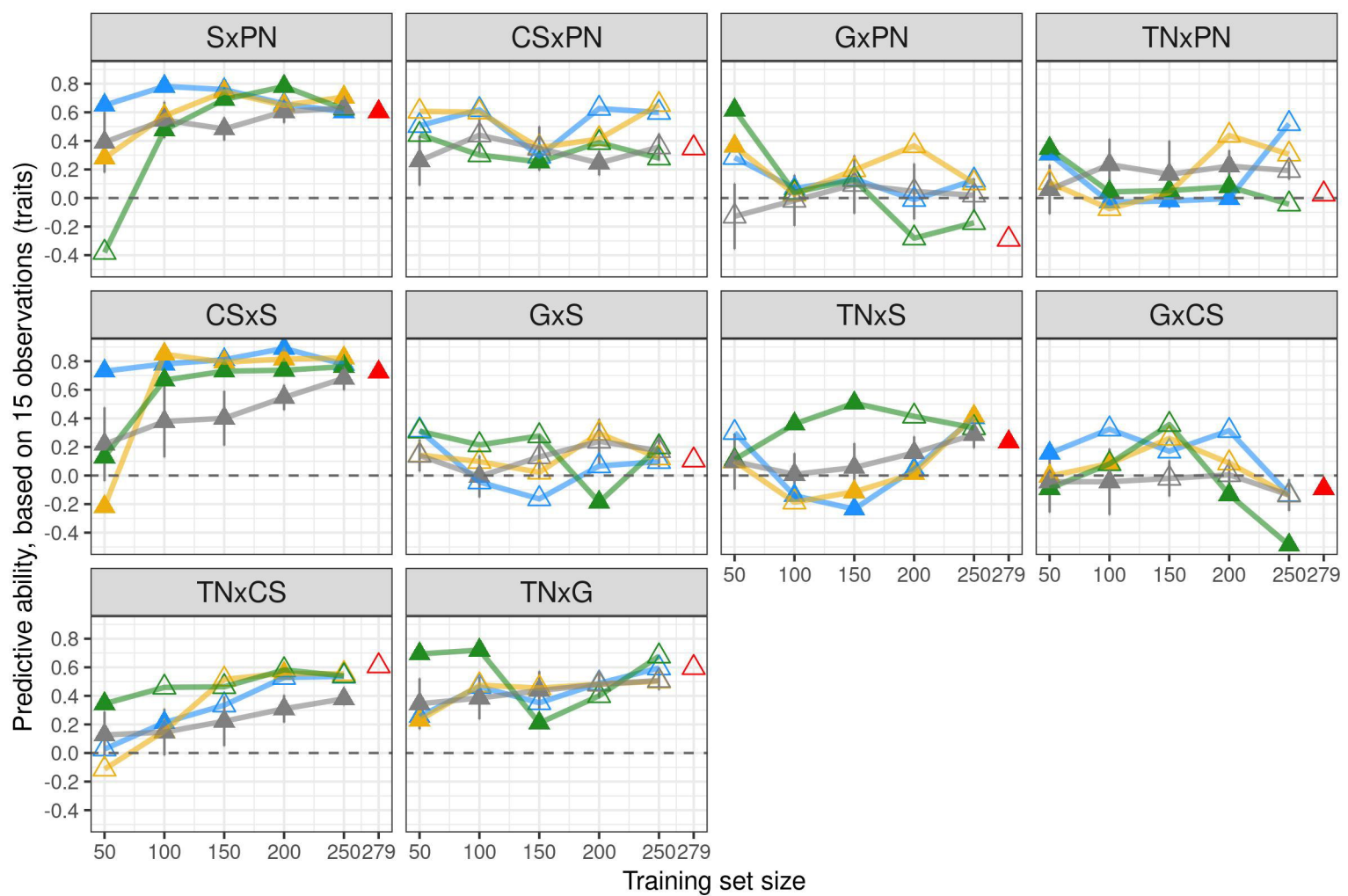
Selected method

○ LASSO △ LASSO
● RR ▲ RR

Training set

▲ p279 ● C-Sauv ● Pinot
● Gren ● Syrah ● Terret

a**b**



CD mean

Random TS

Best method \triangle LASSO \blacktriangle RR

Optimization method PEV mean

Whole diversity panel

Mean additive relationship