Detecting directional epistasis and dominance from cross-line analyses in Alpine populations of *Arabidopsis thaliana*

Running title: Directionality of non-additive genetic effects

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Authors contributions: J.C. initiated the project. M.R and A.W. collected the data. A.L.R. developed the statistical framework and J.C. and A.L.R. analyzed the data. All authors wrote the first draft and edited the manuscript.

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Abstract: The contribution of non-additive genetic effects in general, and to the evolutionary potential of populations in particular, is a topic of long-standing theoretical and empirical interest, which nevertheless remains controversial. As a consequence, the empirical study of these effects in natural populations remains scarce, which is problematic because non-additive effects are expected to modify both the adaptive potential of populations and the way we should measure it. In this study, we explored the contribution of dominance and epistasis in natural Alpine populations of *Arabidopsis thaliana*, for two fitness-related traits, the dry weight and the number of siliques. We first found that, on average, crosses between inbred lines of *A. thaliana* led to heterosis for the dry weight, but outbreeding depression for the number of siliques. We found that heterosis for the dry weight was due to positive directional dominance. For the number of siliques, however, we found that outbreeding depression was due to the breakdown of positive directional epistasis. The implication of these results for the adaptive potential of the studied populations, as well as the use of line-cross analyses to detect directional non-additive genetic effects, are discussed.

Keywords: Non-additive genetic effects, dominance, epistasis, quantitative genetics, self-fertilization, *Arabidopsis*.

INTRODUCTION

The contribution of non-additive genetic effects to the evolutionary potential of populations is a topic of long-standing theoretical and empirical interest, which nevertheless remains controversial (see for example Crow, 2010 and Hansen, 2013 for a debate around epistasis). Non-additive genetic effects are generally describing the dominant relationship of alleles at a given locus, and the epistatic interactions of alleles at different loci, even if other forms of non-additive effects exist (Banta & Richards, 2018). Nevertheless, one consensus derived from theoretical studies is that non-additive genetic effects only influence populations' adaptive potential if individual epistatic or dominant effects do not tend to cancel each other, *i.e.*, if a general pattern emerges (Kelly, 1999; Carter *et al.*, 2005).

Among the different non-additive genetic effects, epistasis has retained much of the attention, as it has the potential of modifying the short- and long-term adaptative potential of a species (Cheverud & Routman, 1995; Carter *et al.*, 2005; Hansen, 2015). In the short-term, directional positive (respectively negative) epistasis tend to increase (respectively decrease) the amount of additive variance of a quantitative trait under directional selection, and, as a result, the adaptive potential of a population (Carter *et al.*, 2005). In the long-term, when epistasis is positive on average, the evolution of a phenotypic trait is easier in the direction of high values, because the additive variance tends to increase with the phenotypic value (Le Rouzic, 2014). On the opposite, negative epistasis favours evolution toward low phenotypic values. Despite its potential major role, estimates of directional epistasis are currently rare in the literature (Le Rouzic, 2014). Pavlicev *et al.* (2010) showed a negative average directionality of epistasis for body-composition traits in *Mus musculus*, while in several plant species, epistasis tend to be positive, on average, for different floral and fitness related traits (Johansen-Morris & Latta, 2006; Monnahan & Kelly, 2015; Oakley *et al.*, 2015; Clo *et al.*, 2021). Theoretical work has

71 repeatedly pointed out that epistasis on fitness (or log-fitness) should drive many diversity-
72 generating mechanisms, including the evolution of sex, recombination, and mutation rates
73 (Phillips *et al.*, 2000), but empirical results remain equivocal (Maisnier-Patin *et al.*, 2005;
74 Kouyos *et al.*, 2007; Bakerlee *et al.*, 2022).

75 On its side, the directionality of dominance received less attention, because its
76 consequence on the evolutionary potential of a species is less general (Walsh & Lynch, 2018).
77 Directional dominance can modifies the way we quantify the adaptive potential of a trait in
78 presence of inbreeding (Kelly, 1999), such that non-additive effects can contribute to the
79 covariance between parents and offspring, which does not occur under random mating
80 (Falconer, 1996; Lynch & Walsh, 1998). In such a case, the adaptive potential of inbred
81 populations is not only described by the additive variance anymore (Cockerham & Weir, 1984;
82 Wright & Cockerham, 1985), and new dominance variances contribute to the evolvability of a
83 trait, only if dominance is directional on average (Clo & Opedal, 2021). Directional (negative)
84 dominance is routinely observed in fitness traits, as shown by the ubiquity of inbreeding
85 depression (Charlesworth & Willis, 2009), but less is known about the directionality of
86 dominance for morphological traits, which can be either positive or negative, pending on studies
87 and traits measured (Shaw *et al.*, 1998; Kelly & Arathi, 2003; Oakley *et al.*, 2015; Clo *et al.*,
88 2021).

89 It appears that the directionality of non-additive genetics effect remains poorly studied,
90 despite their potential role in the adaptive potential of populations, and that inbreeding species
91 can be key actors to start filling the gap, as both directional dominance and epistasis are
92 expected to modify the heritable variance of populations. Due to its major role as a model
93 species in evolutionary biology and its mating system, *Arabidopsis thaliana* appears as a natural
94 choice to study the directionality of non-additive gene effects in plants. *A. thaliana* (L.) Heyhn.
95 (Brassicaceae) is native to Eurasia and North Africa but is nowadays widely distributed

throughout the Northern hemisphere (Hoffmann, 2002). This species occurs in many mountain ranges, including the Alps, and has been reported along a wide altitudinal range, from sea level up to 2000 m in the central Alps (Hoffmann, 2002). Unlike close relatives, *A. thaliana* is a predominately self-fertilizing, annual species. Average outcrossing rates in natural populations have been reported to vary between 0.3% and 2.5% (Abbott & Gomes, 1989; Bergelson *et al.*, 1998; Picó *et al.*, 2008).

In this study, we explored the directionality of dominance and epistasis in natural Alpine populations of *A. thaliana*, for two fitness related traits, the dry weight and the number of siliques. We first found that, on average, crosses between inbred lines of *A. thaliana* led to heterosis for the dry weight, but outbreeding depression for the number of siliques. We found that heterosis for the dry weight was due to positive directional dominance, likely due to the masking of recessive deleterious mutations segregating in the different inbred lines. For the number of siliques however, we found that outbreeding depression was likely due to the breakdown of positive directional epistasis.

MATERIAL AND METHODS

Study populations

We studied six natural alpine populations located along an altitudinal gradient in the Alps in the Saas Valley (Valais, Switzerland). Focal populations (Table S1) were selected from those studied by Luo *et al.* (2015). Three populations are from low altitude (*i.e.* altitudes ranging from 850 to 1000m) and three from close to the high-elevational range margin of the species in the Alps (*i.e.* altitudes ranging from 1792 to 2012m). Distances among populations ranged from

120 0.8 to 25.8 km, with average distances of 6.3 km among low altitude and 1.9 km among high
121 altitude populations. To characterize population genetic structure, all populations were revisited
122 in 2013 and 2014 and 338 individuals were sampled. For our crossing experiment we used
123 offspring of plants collected in 2007 that were propagated in the greenhouse for three
124 generations by single seed descent to standardize maternal effects.

125

126 **Population genetic structure**

127

128 We sampled on average 28 *A. thaliana* individuals per population in 2013 and 2014 (Table S1).
129 Individuals were genotyped using twenty-two of the twenty-four microsatellite markers
130 previously genotyped by Luo *et al.* (2015) (Table S2), using the same protocol. Genotypes were
131 called with Geneious© version R6.1.6 (Biomatters Ltd).

132

133 **Experimental design and measured traits**

134

135 Seeds of plants originally collected in 2007 and propagated for three generations by single seed
136 descent in a greenhouse were used as parental lines in the crossing experiment. From each of
137 the six study populations we randomly selected four parental lines with different genotypes
138 based on results reported in Luo *et al.* (2015). All parental lines were submitted to spontaneous
139 self-fertilization and three cross types: (i) outcrossing with pollen from another parental line
140 from the same local population, (ii) outcrossing with a parental line from another population of
141 the same altitude, and (iii) outcrossing with a parental line from another population of the other
142 altitude. For each parental line, self-fertilization and the three cross types were realized on four
143 different plants. Crosses were made using the pollen of plants exclusively grown for pollen
144 production. Parental lines were randomly matched without replacement such that all four

parental lines of each population were included as both seed and pollen parents in all crosses types (Table S3). The F2 generation was produced by spontaneous self-fertilization of one individual from each F1 family (for an overview of the crossing design see Table S3).

Performance and phenotypic variation in all F1 and F2 families was assessed in a single large greenhouse experiment conducted in spring 2014. Seeds were sown on March 4th 2014 and stratified at 4 °C in the dark for six days. Plants were then grown in a greenhouse at ETH Zurich research station Lindau-Eschikon under long-day conditions (*i.e.* 10 kLux light for 16 h, dark for 8 h; 22 °C/18 °C day/night temperatures). For each parental line we grew 24 F1 and 48 F2 offspring. The F1 included six offspring derived from selfing and six offspring derived from each of the three cross types. The F2 generation encompassed six selfed offspring and 14 offspring from each of the three cross types. In total, the experiment encompassed 1728 plants in total (for details see Table S3).

Plants were grown individually in pots randomly arranged in two greenhouse compartments. Within each greenhouse compartment, pots were randomly arranged in 24-pot-trays. To avoid position effects, trays were placed on tables next to each other and surrounded by “border plants” (*i.e.* plants derived by self-pollination from the study populations, sown and grown under the same conditions as the experimental plants). Trays with experimental plants were randomized twice a week until maturation of siliques. All plants were harvested on July 1st, 2014, approximately four months after germination. Plants were first dried for 48h at 45°C. We then measured the dry biomass and estimated the number of siliques per plant. To estimate the number of siliques, we first separated the different branches and isolated the reproductive sections of all branches (*i.e.* the parts of the branches carrying fruits); second, we weighted the reproductive ('reproductive weight') sections of all branches of each individual together to the nearest 0.0001g using a Mettler AE 240 analytical balance. Third, we assessed the number of siliques along three randomly selected and weighted reproductive sections and estimate the

number of siliques per gram ('silique density'); fourth, we estimated the total number of siliques produced per plant ('silique number') as the product of the 'silique density' and the 'reproductive weight'. We performed the following statistical analyses on the 'silique number', which was used as a proxy of individual fitness.

Genetic model

Traditional line cross models consider only two parental lines, and generally define genetic effects from the F2 population, which generally simplifies the mathematical expressions by reducing the number of parameters for the crossed populations (F1, F2, and backcrosses, Lynch & Walsh, 1998). As we aim at analyzing several line crosses at once, we reparametrized this model by taking the grand mean of the parental populations μ as a reference. As a result, the setting resembles a diallel model (Sprague & Tatum, 1942; Falconer & Mackay, 1996), in which the general combining abilities are assimilated to additive effects, and specific combining abilities are dissociated into dominance and epistatic terms. The average phenotypic means of populations P_i and P_j, as well as their intercrosses $F_{1, ij}$ and $F_{2, ij}$ can the expressed as:

$$P_i = \mu + A_i$$

$$P_j = \mu + A_j$$

$$F_{1, ij} = \mu + \tfrac{1}{2} A_i + \tfrac{1}{2} A_j + 2D_{ij} - AA_{ij}$$

$$F_{2, ij} = \mu + \tfrac{1}{2} A_i + \tfrac{1}{2} A_j + D_{ij} - AA_{ij}$$

This setting defines one additive effect A per parental populations, and as many dominance (D) and additive-by-additive (AA) epistasis parameters as independent crosses among populations. In absence of backcrosses, additive-by-dominance epistatic effects cannot be identified and are merged with additive effects. Dominance-by-dominance interactions, as well as higher-order epistatic terms, had to be ignored.

While diallel models are designed to estimate genetic variance components (and are thus derived as random-effect statistical models), line-cross models aim to measure individual deviations from additivity, and were thus analyzed with a fixed-effect linear model:

$$z_k = \mu + \tfrac{1}{2} A_{P(k)} + \tfrac{1}{2} A_{Q(k)} + d_k D_{P(k)Q(k)} + aa_k AA_{P(k)Q(k)} + e_k$$

for individual k of phenotype z_k, of parents from population P(k) and Q(k), with $d_k = aa_k = 0$ if $P(k) = Q(k)$, $aa_k = -1$ if $P(k) \neq Q(k)$ (k is from an intercross F_1 or F_2), and $d_k = 2$ (or =1) if k results from an F_1 (or an F_2) intercross. e_k is a Gaussian-distributed residual of variance V_e.

Four models of various complexity were fitted to each dataset: Additive (only the additive terms A_i were considered), Dominance (A_i and D_{ij}), Epistasis (A_i and AA_{ij}), and Full model (A_i, D_{ij}, and AA_{ij}). The four models were compared by a model selection procedure based on the Akaike Information Criterion (Anderson & Burnham, 2004); AIC differences larger than 2 units were considered as substantial differences between models. Models were fit independently on Weight and Silique number; and both genetic differentiation levels (Lineage and Population) were considered.

RESULTS & DISCUSSION

We found that performing the analyses at the scale of the genetic lineages or at the scale of the populations gave similar results, which echoes with recent results arguing that the notion of population is hard to define in predominantly selfing species (Rhode & Cruzan, 2005; Dolgin *et al.*, 2007; Clo *et al.*, 2021, but see Gimond *et al.*, 2013). We decided to presents the results for the genetic lineages in the main text, the results the populations' scale are available in supplementary materials (Table S4, Figure S1).

Consequences of hybridization on dry weight and the production of siliques

Our first question was related to the consequences of hybridization between parental lineages as different effects depending on the trait under study. The raw values of parental lines and within-population crosses are available as supplementary materials (Figure S2). We found that, on average, F_1 hybrids showed a heterosis pattern for the dry weight (Figure 1), with an increase of 9.6% (0.454g in F_1 hybrids), compared to the mean parental value. of 0.414g. This is in line with what is found in other predominantly selfing species (Rhode & Cruzan, 2005; Dolgin *et al.*, 2007; Volis *et al.*, 2011; Gimond *et al.*, 2013; Oakley *et al.*, 2015; Clo *et al.*, 2021). In contrast, F_2 hybrids were close to the parents (0.403g, -2%).

On the opposite, F_1 and F_2 hybrids showed an outbreeding depression pattern for the number of siliques (Figure 1), with respectively a decrease of 5.5% and 11.3% in F_1 and F_2 hybrids, compared to the mean parental value. This is slightly lower than other values found in

238 other predominantly selfing species (Rhode & Cruzan, 2005; Dolgin *et al.*, 2007; Volis *et al.*,
239 2011; Gimond *et al.*, 2013; Oakley *et al.*, 2015; Clo *et al.*, 2021).

240 This opposite patterns for dry weight and fruits number could be considered as a
241 surprising result since both traits are often considered as fitness proxies, and are generally
242 positively correlated (see Younginger *et al.*, 2017 for a review). However, such an observation
243 is not unheard. Studies in natural and laboratory accessions of the highly selfing species
244 *Arabidopsis thaliana* also found a negative relationship between dry mass and a fitness proxy
245 (pollen viability in Nasrallah *et al.*, 2000; seed production in Barth *et al.*, 2003; fruit production
246 Vasseur *et al.*, 2019). In the sister species *A. lyrata*, Li *et al.* (2019) also found that selfing
247 populations exhibit an increase in above- and below-ground biomass, and a slight decrease in
248 fitness (measured as the probability of bolting) in outcrossed progeny of selfing populations.
249 Finally, Clo *et al.* (2021) found that in the predominantly selfing species *Medicago truncatula*,
250 hybridization between inbred lines lead to heterosis for dry mass but outbreeding depression
251 for seed production.

252

253 **Non-additive effects in natural populations of plants**

254

255 We found that non-additive effects contribute to the genetic architecture of both traits.
256 For the dry mass, we found that the best model explaining the data was the one including
257 additive and dominant genetic effects (Table 1), and the observed pattern of heterosis was due
258 to directional positive dominant effect (Figure 2). Oakley *et al.* (2015) found similar results in
259 crosses between south European and Scandinavian lineages of *A. thaliana*. The directional
260 positive dominance likely reflects the positive effects of masking deleterious mutations fixed
261 at different loci in the different selfing lineages (Charlesworth & Willis, 2009).

For the number of siliques, we found that the best model explaining the data was the one including additive and additive-by-additive epistatic genetic effects (Table 1), and the observed pattern of outbreeding depression was due to directional positive additive-by-additive epistatic interactions (Figure 2). The outbreeding depression can be explained by the breakdown of positive additive-by-additive epistatic interactions found in the parental selfing lineages during the hybridization events, as found in other species (Rhode & Cruzan, 2005; Johansen-Morris & Latta, 2006). The finding of directional positive epistasis is in line with what was found in other plant species (Johansen-Morris & Latta, 2006; Monnahan & Kelly, 2015; Oakley *et al.*, 2015; Clo *et al.*, 2021).

Implications for the adaptive potential of Alpine populations of A. thaliana

The distinct genetic architecture among the two fitness traits studied here implies that the ways we can infer the adaptive potential of each trait are very different. For the dry mass, we found that dominance contribute to the genetic architecture, and is directional on average. When directional dominance occurs, the decomposition of the heritable variance is more complicated (Kelly, 1999). In such a case, new dominance components of the genetic variance are necessary for describing the adaptive potential of selfing species (Wright & Cockerham, 1985), these new terms have been shown to contribute theoretically and empirically to the evolvability of predominantly selfing species (Shaw *et al.*, 1998; Clo *et al.*, 2019; Clo & Opedal, 2021). Estimating all these components of the genetic variance are however necessary to predict the short-term adaptive potential of populations (Clo & Opedal, 2021). It is however important to note that the contribution of epistasis to this trait cannot totally be ruled out (Table S4).

For the number of siliques, we found directional positive additive-by-additive epistasis. In the short-term, directional positive epistasis tend to increase the amount of additive variance of a quantitative trait, and, as a result, the adaptive potential of a population (Carter *et al.*, 2005; Monnahan & Kelly, 2015). In the long-term, when epistasis is positive on average, the evolution of a phenotypic trait is easier in the direction of high values, because the additive variance tends to increase with the phenotypic value (Le Rouzic, 2014).

In addition, and for both traits, selfing populations are expected to harbor a lot of cryptic diversity through genetic associations and linkage disequilibrium (Rieseberg *et al.*, 1999, 2003; Lande & Porcher, 2015; Abu Awad & Roze, 2018), and that this diversity can fuel the mid-term evolvability of selfing populations by rare outcrossing events (Clo *et al.*, 2020). The potential contribution of linkage disequilibrium to evolvability can be measured through the patterns of transgressive segregation in the recombinant generations of crosses (F_2, F_3 …), knowing that a fraction of the fraction is environmental, which can be easily measured by the variance within inbred lines, for example.

Limits of the method

Our line cross analysis makes it possible to test for the presence of directional dominance and epistasis, it suffers from technical limitations, and potential biases. First, it allows us to test for directional epistasis, which is primordial for understanding the capacity of populations to respond to selection, but do not allow to dissection the different forms of epistasis (additive-by-additive, additive-by-dominant, and dominant-by-dominant). For inferring all these parameters from cross-line analyses, ones need more generations of crosses than just the F_1 and F_2 individuals (see (Lynch & Walsh, 1998), including reciprocal back-crosses for

example (see Oakley *et al.*, 2015 for a case study). Another major limitation is that our method does not allow to differentiate complex patterns of dominance and epistasis. Clo *et al.* (2021), using a similar crossing scheme in the predominantly selfing species *Medicago truncatula*, theoretically showed that it is impossible to distinguish epistasis components involving dominance (such as dominance-by-additive and dominance-by-dominance) from non-epistatic dominance using cross-line analysis. This means that the directional positive dominance we detected for the dry weight could be a mixture of directional negative dominance and epistasis, or just complex epistasis (beyond additive-by-additive interaction effects).

CONCLUSIONS

Our study highlights the need to study the contribution of non-additive genetic effects to the genetic architecture of fitness-related traits. Here, we found that both dominance and epistasis contribute to the genetic architecture of dry weight and silique production, leading to heterosis for the dry mass and outbreeding depression for the number of siliques in F_1 and F_2 hybrids, and suggesting that the adaptive potential of our Alpine populations of *A. thaliana* cannot be described only by the additive genetic variance. The next step could be to determine the contribution of non-additive genetic variance to the evolvability of the fitness traits of our populations.

Data availability: The data and code used to perform the analyses are available at https://github.com/lerouzic/Epicross.

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468 **Table 1.** Summary of the statistical models fitted to data, when analyses are performed at the
469 scale of genetic lines, for the dry weight and the number of siliques. In the table, "a" stands for
470 additive, "d" for dominance, and "aa" for additive-by-additive epistasis.

Trait	Model	Log(likelihood)	d.f.	ΔAIC
Dry weight	a	535.20	28	60.84
	a.d	630.62	93	0.00
	a.aa	625.43	91	6.38
	a.d.aa	683.88	151	9.48
Number of silliques	a	-10729.13	28	98.10
	a.d	-10624.23	93	18.31
	a.aa	-10617.08	91	0.00
	a.d.aa	-10574.11	151	34.06

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480 **Figure captions:**

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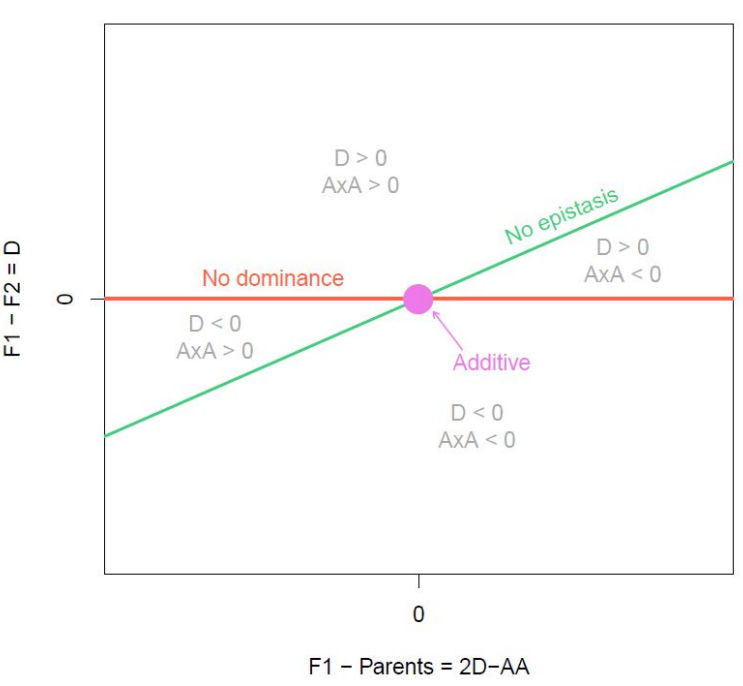
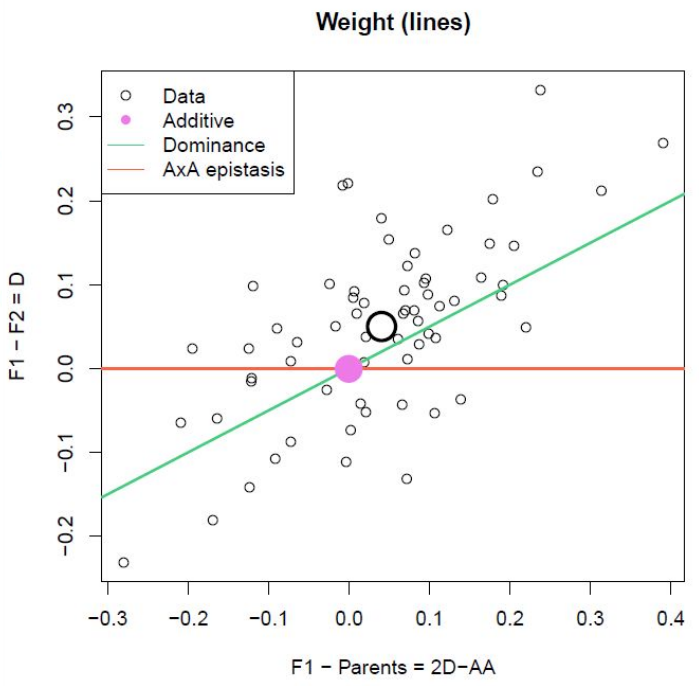
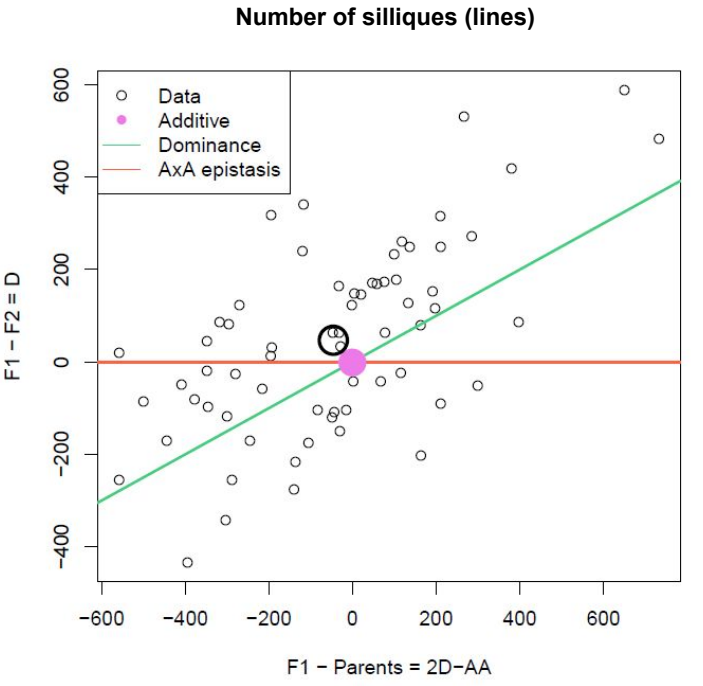
482 **Figure 1.** Graphical representation of the parental, F_1 and F_2 values, when analyses are
483 performed at the scale of the genetic lineages. **Left panel.** Empty representation indicating the
484 directionality of dominance and epistasis as a function of the position of the datapoints. **Middle**
485 **panel.** Distribution of data for the dry weight. **Right panel.** Distribution of data for the number
486 of siliques. The Data circle represent the barycenter of the datapoints.

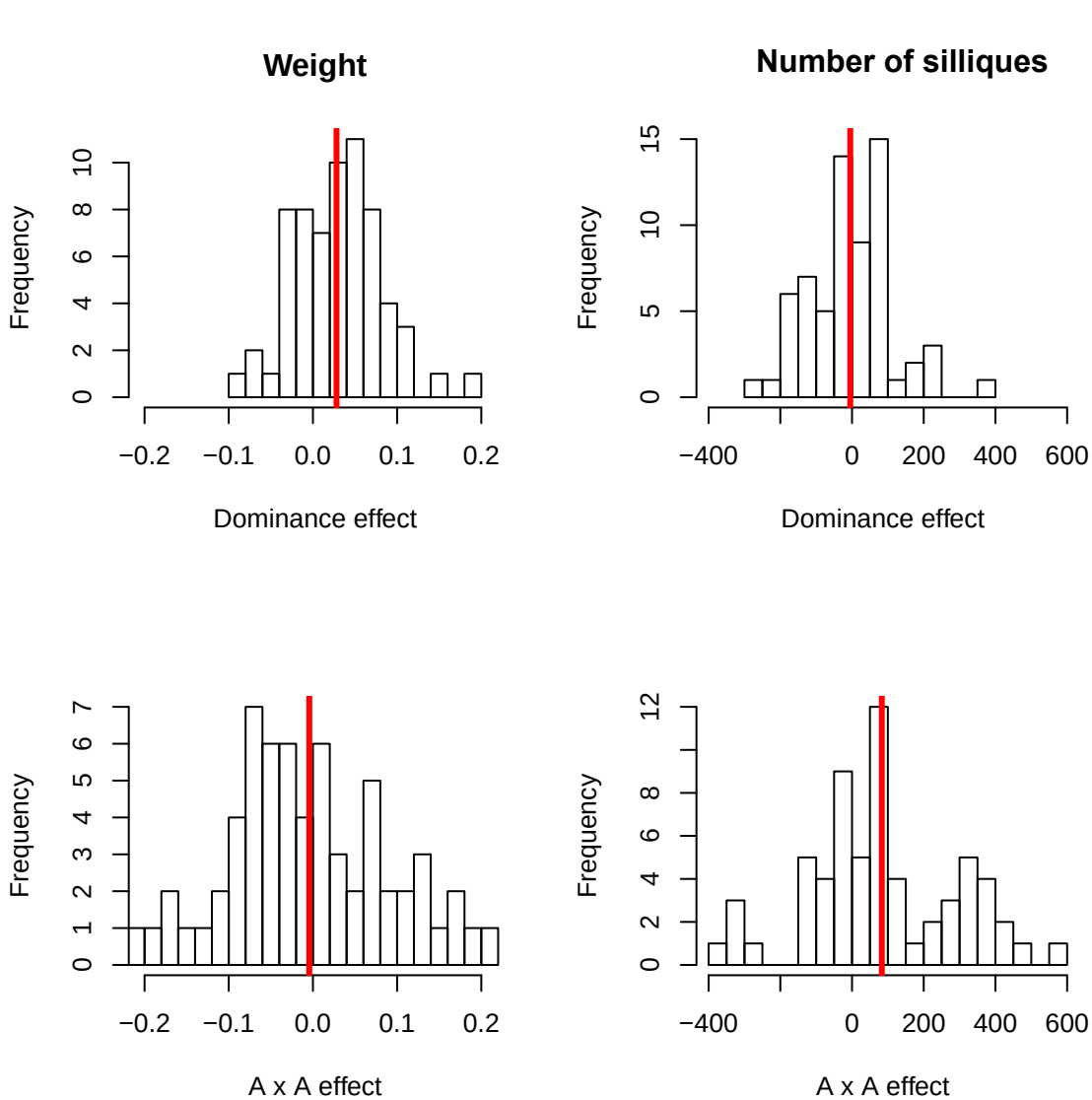
487

488 **Figure 2.** Distribution of the dominance and epistatic genetic effects when analyses are
489 performed at the scale of the genetic lineages, for the dry weight and the number of siliques.
490 The red lines are indicating mean values.


D > 0
AxA > 0
No epistasis
D > 0
AxA < 0
No dominance
D < 0
AxA > 0
Additive
D < 0
AxA < 0
0
0
F1 − F2 = D
F1 − Parents = 2D−AA


Weight (lines)
Data
Additive
Dominance
AxA epistasis
0.3
0.2
0.1
0.0
−0.1
−0.2
−0.3
−0.2
−0.1
0.0
0.1
0.2
0.3
0.4
F1 − F2 = D
F1 − Parents = 2D−AA


Number of silliques (lines)
Data
Additive
Dominance
AxA epistasis
600
400
200
0
−200
−400
−600
−400
−200
0
200
400
600
F1 − F2 = D
F1 − Parents = 2D−AA


Weight
Frequency
0
2
4
6
8
10
−0.2
−0.1
0.0
0.1
0.2
Dominance effect
Number of silliques
Frequency
0
5
10
15
−400
0
200
400
600
Dominance effect
Frequency
0
1
2
3
4
5
6
7
−0.2
−0.1
0.0
0.1
0.2
A x A effect
Frequency
0
2
4
6
8
12
−400
0
200
400
600
A x A effect