The genomics of local Adaptation in trees: Are we out of the woods yet?

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Abstract

There is substantial interest in uncovering the genetic bases of the traits underlying adaptive responses in tree species, as this information is central to understanding how evolution proceeds in such systems and will aid conservation and industrial endeavors. Here, we synthesize evidence for local adaptation in trees by summarizing 129 common garden experiments across 20 genera of tree species that describe levels of heritability, differentiation of quantitative genetic variation (Q_{ST}), and/or Q_{ST}-F_{ST} comparisons. Given the abundant evidence for local adaptation, we discuss theoretical expectations for adaptive genetic architectures and contextualize progress in trees by synthesizing 52 genotype-phenotype association studies across ten genera. Our survey suggests that most tree traits generally exhibit considerably high heritability ($\overline{h^2}$ = 0.367, $\overline{H^2}$ = 0.430), that underlying genetic variation is often structured across populations ($\overline{Q_{ST}}$ = 0.243) and is significantly greater than F_{ST} in 69% of comparisons across the literature. Despite widespread evidence for local adaptation acting on abundant, heritable genetic variation, we find that single-locus associations explain only a small proportion of the phenotypic variation, often with small estimated per-locus effects ($\overline{r^2}$ = 0.039). Together, these results suggest differential selection across populations often acts on tree phenotypes underlain by polygenic architectures consisting of numerous small to moderate effect loci. We close by addressing hurdles and promising alternatives to fully describing the underlying genetic architecture of quantitative traits in trees, remark upon the current state of tree genomics, and identify future directions for this field.

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Introduction

Trees are plants with an arborescent habit, which is loosely defined as a tall-statured growth form usually producing wood (reviewed by Petit & Hampe 2006). Approximately 15% to 25% of the land plant taxa are classified as being trees (Oldfield *et al.* 1998; Grandtner 2005; Scotland & Wortley 2004), with forested ecosystems accounting for approximately 30% of terrestrial vegetation (Costanza et al. 1997) and providing habitat for terrestrial biodiversity. Indeed, trees play important ecological roles in diverse communities across the globe, such as vertical structural habitat for various taxa, seeds for wildlife forage, forest cover to understory species, the production of oxygen, carbon sequestration, air and water filtration, as well as the reduction of erosion, protracting snowmelt, and desertification. Of these, biological roles are ultimately defined by a set of life history characteristics common to most tree species (Petit & Hampe 2006), despite the polyphyly of the arborescent habit across the phylogeny of land plants. These include predominantly outcrossing mating systems with high levels of gene flow and fecundities, as well as long lifespans and generation times (Loehle 1987; Mitton & Williams 2006; Savolainen et al. 2007). As a result, tree species typically have large effective population sizes, moderate to high levels of genetic diversity, and frequent occurrences of locally adapted ecotypes (see refs in Savolainen et al. 2007; Alberto et al. 2013; Sork et al. 2013; Boshier et al. 2015; Prunier et al. 2015; Holliday et al. 2017). Across species, however, rates of morphological (Stacy et al. 2017) and molecular (Smith 2008, Leitch & Leitch 2012; Buschiazzo et al. 2012; Pavy et al. 2012; Luo et al. 2015) evolution tend to be slow. Additionally, genome size varies enormously across species of trees, ranging from 0.4Gbp to 31Gbp (reviewed in Neale et al. 2017). Recent sequencing efforts in gymnosperms, which dominate the large genome size end of this spectrum, reveal that much of tree genome size variation is due to transposable element dynamics and gene family evolution (Leitch & Leitch 2012; Morse et al. 2009; Nystedt et al. 2013; Prunier et al. 2015; Neale et al. 2017) where duplication events of select gene families

may contribute to the ability of trees to colonize marginalized habitats (Leitch & Leitch 2012; Prunier et al. 2015; Neale et al. 2017).

In trees, the general presence of large geographical ranges and extensive gene flow across these ranges also provides an ideal setting to disentangle neutral from selective evolutionary processes (Neale & Kremer 2011). Indeed, their longevity and wide and heterogeneous geographical distributions lend trees suitable for addressing several key evolutionary questions about the importance of historical climatic fluctuations, and local adaptation involving shifts in allele frequencies (Lotterhos & Whitlock 2014; Savolainen et al. 2007, 2013; Platt et al. 2015). As we detail in subsequent sections, evidence consistent with local adaptation in trees is ubiquitous, even across fine spatial scales where it had been hypothesized that gene flow may overcome selection of locally favored alleles (e.g., Mitton et al. 1989, 1998; Budde et al. 2014; Csilléry et al. 2014; Vizcaíno-Palomar et al. 2014; Eckert et al. 2015; Holliday et al. 2016; Roschanksi et al. 2016; Lind et al. 2017).

Quantitative phenotypes are often used as a proxy for total lifetime fitness, which is composed of two broad components: survival and reproduction. Since most quantitative traits are related to some component of the total lifetime fitness, they are often used to assess potential for local adaptation. For many plant taxa, selection pressures are expected to be strongest for variation in survival during the juvenile stages of development (Donohue et al. 2010), particularly for those taxa with high reproductive output, as is the case for many tree species. As such, juvenile stages in plants have been found to contribute substantially to total lifetime fitness (Postma & Agren 2016). Phenotypic traits associated with juvenile survival have thus received the majority of genetic research focus across tree species, particularly due to the long-lived nature of tree species. Such studies have led to intriguing insights gained through a long history of common garden experimentation (Langlet 1971; Morgenstern 1996). For example, traits such as growth (e.g. height and diameter), form (e.g. specific gravity, straightness), phenology (e.g. bud flush, bud set), juvenile performance (e.g. germination rate,

seed traits) and physiology (e.g. cold hardiness, water-use efficiency) have all been shown to be under moderate to high genetic control (reviewed in Cornelius 1994, Howe *et al*. 2003, Alberto *et al.* 2013; this review). Variation for these traits is also often partitioned among populations (McKay & Latta 2002, Howe 2003, Alberto et al. 2013, Savolainen et al. 2007; Boshier et al. 2015; this review), despite the vast majority of neutral variation remaining within populations (Howe et al. 2003; Neale & Savolainen 2004). With few exceptions (e.g., major gene resistance in the white pine-blister rust pathosystem; Kinloch et al. 1970; Liu et al. 2017), variation for these traits forms a continuum across individuals, thus implying that the underlying genetic architecture of these traits is composed of a large number of small to moderate effect loci (i.e., a polygenic architecture; concept reviewed in Savolainen et al. 2007, 2013; Gagnaire & Gaggiotti 2016; Hoban et al. 2016). There is some uncertainty, however, concerning the properties of the effect size distributions comprising polygenic architectures (*sensu* Fisher 1930, Kimura 1983, and Orr 1998), the relative importance of various forms of gene actions (e.g., dominance, epistasis) in producing trait variation (Crow 2010, Hansen 2013), how these interact to affect the evolution of polygenic architectures in natural populations (Hansen 2006), and how these factors will ultimately influence evolutionary processes and outcomes in forest trees (Savolainen et al. 2007; Sork et al. 2013; Prunier et al. 2015). Considerable strides, made in the past through genotype-phenotype-environment studies (*sensu* Sork et al. 2013), have contributed to intriguing insight into the genomic basis of local adaptation for tree species. However, given the large genome size of many tree species, such methods have been criticized as lacking in power and sufficient coverage needed to detect small effect loci, which is further exacerbated by rapid decay of linkage disequilibrium (LD) in most forest trees (Mackay 2009; Savolainen et al. 2007). Despite these limitations, association studies have been moderately successful in linking genotypes and phenotypes, including providing information for making inferences about local adaptation.

In this review, we highlight the extensive evidence for local adaptation in undomesticated

144 trees by reviewing transplant designs often used in investigations of quantitative genetic
145 differentiation. Using an extensive literature survey across both gymnosperm and angiosperm
146 species, we provide an overview of these transplant methods, give examples of each, and
147 quantify the distribution of narrow sense heritability and Q_{ST} estimates across various trait
148 categories. We further use this survey to establish patterns of comparative quantitative and
149 neutral genetic differentiation (i.e., Q_{ST}-F_{ST} tests). Before we transition into discussing common
150 methods used to uncover loci underlying adaptation, we establish expectations for the genetic
151 architecture of polygenic, fitness-related traits by reviewing the theory available to date. We then
152 provide an extensive review of genotype-phenotype associations in trees and provide the
153 distribution of the percent phenotypic variance explained by empirically associated loci. Using
154 this distribution, we remark on the progress towards uncovering the loci underlying local
155 adaptation in tree species. Given this synthesis, we highlight exemplary genomic resources
156 available in trees to fill knowledge gaps, identify promising avenues of future research, identify
157 key benchmarks and necessary steps towards truly integrating studies of trees into the genomic
158 era, and address our primary question, “Are we out of the woods yet?”.

159 Identifying genetically based phenotypic and heritable variation

160 Trees have evolved numerous adaptations as a result of their vast ecological breadth.
161 As such, it has long been the goal of forest scientists, engaged with industrial and academic
162 pursuits alike, to understand the traits important to viability and persistence within and across
163 tree species. Among the most frequent designs used by forest scientists, common gardens and
164 reciprocal transplants have aimed at describing genetically based differentiation of measured
165 phenotypes among various source populations of varying sizes and across various geographic
166 scales. Across these designs, investigators seek to better understand the phenotypes relevant
167 to local adaptation and the selective pressures influencing these phenotypes. The exact design
168 chosen, however, is generally based on the questions driving the research endeavor and often

169 by the availability of resources (Morgenstern 1996; Blanquart et al. 2013; de Villemereuil et al.
170 2015). In this section, we briefly review these designs, identify relevant questions and
171 inferences, highlight some of the important practical applications of these techniques, and
172 discuss examples of past investigations in various tree species.

173 There is a rich history of forest scientists using the common garden approach dating
174 back hundreds of years (Langlet 1971; Mátyás 1996; Savolainen et al. 2007). In a broad sense,
175 a common garden design is used to test for differentiation among genetically distinct groups in a
176 homogeneous environment. These groups can be clonal replicates or sibships (families) derived
177 from species or hybrids sampled from various populations, provenances, varieties, cultivars, or
178 agricultural accessions (Cheplick 2015). When individuals from various origins are grown
179 together under the same conditions, the observed phenotypic differentiation is expected to
180 reflect underlying genetic variation, especially when maternal effects are assumed or shown to
181 be absent. Common garden and provenance trial designs can also establish evidence that the
182 phenotypes under study are heritable, a prerequisite for an adaptive response to selective
183 agents (Box 1), and that populations exhibit quantitative genetic differentiation (i.e., Q_{ST}; Spitz
184 1993). When driven by questions related to differentiation alone, a single common garden
185 approach can be used to describe levels of quantitative genetic variation within and among
186 genetically distinct groups. In these cases, no environmental variables are manipulated, and
187 thus, unequivocal evidence for trait divergence among groups, and the contributing factors
188 influencing this divergence (e.g., neutral or selective processes), is often limited because
189 conclusions must be based on *post hoc* inferences about source environments for the materials
190 established in the common garden. Even so, single common garden approaches can be a
191 powerful tool to demonstrate evidence congruent with local adaptation. For instance, the white
192 carob tree (*Prosopis alba* Griseb., Leguminosae) growing in Argentina is an ideal multipurpose
193 tree that has potential for use in reforestation and afforestation applications in the region.
194 However, this genus is known to invade other regions, encroach on farmland and waterways,

and has a thorny growth habit that can injure and cause sepsis in livestock. To better understand how forestry applications can balance the benefits of production and forest protection, Bessega et al. (2015) used a single common garden representing eight provenances of *P. alba* to compare estimates of neutral genetic patterns to the quantitative genetic variation of life history traits related to economic importance, leaf morphological traits posited to be influential to heat-tolerance and physiological response, and spine length, a trait of silvicultural significance. They found that for most traits the underlying genetic variation was differentiated across populations ($Q_{ST} \approx 0.000$-0.362, average over all traits = 0.139). Additionally, for most traits, source environments were correlated with measured trait variation in the common garden, suggesting that the observed differentiation was driven by temperature, precipitation, wind speed, and sunshine fraction, with signals of divergent selection corroborated across Q_{ST}-F_{ST} comparisons and tests for selection (e.g., *S* test, *sensu* Ovaskainen et al., 2011). Bessega et al. (2015) concluded that the signal of non-neutral differentiation was indicative of divergent phenotypic optima across populations, and that this variation could be used to direct future breeding programs across the region.

When there is evidence that environmental differences among source populations may be driving adaptive divergence, strong environmental candidates can be manipulated (artificially or via site selection) in a multiple common garden design to further investigate hypotheses of differentiation and adaptation. For instance, the sweet chestnut (*Castanea sativa* Mill., Fagaceae), also known for its edible fruit, is distributed across much of Minor Asia and southern Europe and is an ecologically important component of many Mediterranean systems. *Castanea sativa* exhibits ecological, physiological, morphological, and genetic variability as the range overlays a climatic transition from xeric Mediterranean conditions to wetter Euro-Siberian environments (see refs in Lauteri et al., 2004). Previous common garden experiments carried out by Lauteri and colleagues have indicated that populations across this transition are further

differentiated by water use efficiency (the ratio of plant carbon gain to water loss) and carbon isotope discrimination, Δ. To further explore variability of drought-related traits, Lauteri et al. (2004) used an *ex situ* multiple common garden design using two water and temperature treatments in individual climatic chambers to assess differentiation among six populations across Spain, Italy, and Greece. They found *treatment* and *population x treatment* effects were significant, suggesting variation in drought adaptation across populations. Additionally, populations originating from dry sites generally exhibited higher values of Δ, which was also composed of significant additive genetic variation (h^2 = 0.15-0.52), and suggests that genetic and physiological mechanisms of drought adaptation confer a capacity to colonize a wide arrange of environmental conditions, while strong negative relationships between Δ and growth-related traits is suggestive of strong evolutionary constraints at juvenile stages.

While *ex situ* common gardens approaches (e.g., Lauteri et al. 2004) can provide strong evidence of adaptive divergence among source populations, and in some cases corroborate putative drivers of observed differentiation, these studies can often exclude key environmental factors, possibly leading to confounding signals of adaptation (Kawecki & Ebert 2004). When *in situ* experimentation is feasible, site selection can be used to test for environmental drivers of local adaptation. For example, Evans et al. (2016) investigated traits related to growth and phenology in juvenile narrowleaf cottonwood (*Populus angustifolia* James, Salicaceae) by planting families from nine populations across the native range into three common gardens, one at both the northern and southern range extents and one within the central interior of the range. Phenotypic traits exhibited strong genetic control (H^2 bud flush initiation: 0.11-0.53, bud flush duration: 0.06-0.37, bud set: 0.04-0.73, height: 0.03-0.43, and diameter: 0.20-0.32) and were differentiated across populations (Q_{ST} bud flush initiation: 0.21-0.64, bud flush duration: 0.26-0.57, bud set: 0.70-0.89, height: 0.48-0.90, and diameter: 0.44-0.63). Using Q_{ST}-F_{ST} comparisons and clinal analyses alongside the quantitative genetic analyses, Evans et al.

245 (2016) concluded that climate cues played a major role in structuring adaptive variation across
246 the range of *P. angustifolia*, and that future industrial and conservation applications should
247 utilize this information to inform source environments for optimal outcomes.

248 As both *in situ* and *ex situ* common garden trials can include multiple environmental
249 influences in their design, reciprocally transplanting to all source environments is not necessarily
250 a requirement to decompose genetic variation underlying adaptive traits or to provide evidence
251 for, or the drivers of, differentiation among populations. Thus, these designs may preclude
252 inferences regarding local adaptation *sensu stricto*. To produce such evidence, source
253 populations can be planted in a (full- or incomplete-factorial) reciprocal transplant design and
254 allow for traits related to fitness to be assessed across native ('home') and non-native ('away')
255 environments. If a population is locally adapted, individuals exposed to their native
256 environments should show increased growth, survival, and reproduction relative to non-native
257 genotypes (Kawecki & Ebert 2004; Leimu & Fischer 2008; Hereford 2009; Savolainen et al.
258 2013). For example, with the goal of delineating conservation units based on molecular and
259 quantitative trait differentiation, Rodríguez-Quilón et al. (2016) used four reciprocally-
260 transplanted common gardens to assess height and survival of samples from 35 natural
261 populations of maritime pine (*Pinus pinaster* Aiton, Pinaceae). For both traits, Q_{ST} was
262 consistently larger than F_{ST} across the four sites, a pattern suggestive of divergent selection. Six
263 distinct gene pools based on evolutionary history of neutral markers were identified, and
264 because high quantitative differentiation (Q_{ST}) was found within these pools, hierarchical
265 analyses were used to further identify ten adaptive population groups for use in conservation
266 and breeding approaches.

267 Available evidence suggests that many populations of tree species have substantial
268 heritable genetic variation, and that the quantitative traits under study often show signals of
269 divergent selection across both broad and fine spatial scales. But how broadly can we apply this
270 statement? Are there overall patterns of heritability and quantitative genetic structure across

271 tree species? Because estimates of heritability and Q_{ST} are often only applicable to a specific
272 set of populations, for a specific set of environments, at any specific point in time, a large
273 sample of these estimates is therefore necessary to synthesize the current literature with regard
274 to patterns across taxa. To accomplish this aim, we synthesized estimates from 129 published
275 studies with estimates of narrow sense heritability (n = 114) and/or estimates of quantitative
276 genetic differentiation (Q_{ST}; n = 37). However, we excluded papers that have been cited for
277 estimates of Q_{ST} or heritability that were calculated *post hoc* from variance components (i.e., we
278 only recorded estimates that were explicitly reported in the original publication). We also
279 exclude from our presentation any estimates of heritability that were greater than 1.0. While
280 some of the articles report individual-tree heritabilities, we focus on estimates of family
281 heritability. For comparison, we further grouped measured traits into 14 broad categories: cold
282 hardiness, disease resistance, drought hardiness, form, growth, herbivore and insect resistance,
283 leaf and needle properties, phenology, plant secondary metabolites, reproduction, resource
284 allocation, seed and early germination properties, survival, and wood properties. Because
285 sample size can influence the estimation of both heritability and Q_{ST}, for each trait category we
286 used a weighted average where weights were equal to the number of families used to estimate
287 variance components and thus h^2 and Q_{ST}.

288 In 1994, Cornelius presented a summary of narrow sense heritability estimates across
289 various form, growth, and wood property traits for *Pinus, Eucalyptus*, as well as other conifers
290 and broadleaf tree species. For many of the distributions underlying their survey, heritability
291 estimates were generally within the range of 0.10-0.30. In comparison, our survey of 1878
292 estimates revealed relatively elevated estimates for these trait groupings (Supplemental Table
293 S1; Supplemental File F1). In general, the average h^2 was within the range of 0.20-0.50, with
294 seed and seedling properties (covering various germination, seed weight, and cotyledon
295 properties) near 0.73 (Figure 1) with tendencies towards values below 0.5 for most traits (Figure
296 S1). Except for disease resistance, herbivore and insect resistance, leaf and needle properties,

297 and plant secondary metabolites, there were more estimates from gymnosperms than from
298 angiosperms, which were generally contributed from species of *Pinus* than from either *Populus*
299 or *Eucalyptus* (Supplemental Table S1). Grouping heritability estimates across all trait
300 categories and species, there was no indication of a decrease in heritability across age groups
301 (Figure S2). There was also a general lack of a trend when heritabilities were compared within
302 trait groups, except for cold hardiness, and perhaps either form or leaf and needle properties
303 (Figure S3). While the (lack of) trends are likely better suited for analysis within individual traits
304 for a given population within a species, as opposed to our groupings here, these patterns
305 provide insight into interspecific patterns. Additionally, our survey of heritability estimates reveal
306 substantial additive genetic variation across traits that have both ecological and economic
307 importance suggesting abundant sources upon which selection can act in future natural and
308 breeding endeavors.

309 In general, most of Q_{ST} estimates from our survey was from gymnosperm species,
310 except for form, herbivore and insect resistance, leaf and needle properties, phenology, plant
311 secondary metabolites, and wood properties, where estimates from angiosperms were greatest
312 (Supplemental Table S2; Supplemental File F1). The mean weighted Q_{ST} across traits groups
313 from our survey was generally between 0.10-0.28, except for drought hardiness (0.06) and
314 disease resistance (0.04), with median values from the unweighted distribution generally falling
315 below the weighted average for each trait group (Figure 2). This suggests that over various
316 geographic distances, population histories, and species, there is a general pattern of substantial
317 genetic variation among populations underlying measured traits. Given our synthesis of Q_{ST}
318 estimates in trees, we were curious of the evidence for adaptive divergence among populations
319 ($Q_{ST} > F_{ST}$). Of the 37 papers reporting Q_{ST} estimates in our review, 23 compared Q_{ST} with F_{ST}
320 or G_{ST} estimated from the same populations under study (however, we excluded studies that
321 used F_{ST} measurements taken from the literature, e.g., Bower & Aitken 2008). Of these, 18
322 studies compared Q_{ST} and F_{ST} in a statistical framework while the remaining five studies

compared Q_{ST} and F_{ST} numerically. Across numerical and statistical comparisons combined, 67% (254 of 381 traits) exhibited higher Q_{ST} than F_{ST}, with 69% (170 of 246 traits) exhibiting significantly higher Q_{ST} than F_{ST}. Although we did not tally instances where Q_{ST} was reported to be less than F_{ST} (statistically or otherwise), there were some instances in which this was the case. For instance, Lamy et al. (2011) found such patterns when quantifying population genetic differentiation of cavitation resistance across the species range of maritime pine (*Pinus pinaster* Aiton, Pinaceae), while Mahalovich et al. (2011) also found that $Q_{ST} < F_{ST}$ for traits related to white pine-blister rust resistance in inoculated seedlings of whitebark pine (*Pinus albicaulis* Engelm., Pinaceae). While various explanations for such patterns were outlined by Lamy et al. (2011), canalization was argued as the most likely process driving the observed patterns, while Mahahlovich et al. (2011) offered similar arguments for selection favoring the same genotype in different environments.

Despite neutral genetic differentiation partitioned primarily within populations, adaptive genetic variation seems to be structured to a greater degree across populations, more often than not, for the various fitness-related traits reviewed here. Such a pattern is indeed consistent with local adaptation, assuming that (among other considerations such as the recency of selection) mutation rates are considerably lower than migration rates in these populations (Whitlock 1999; Hendry 2002; Leinonen et al 2013). In any case, given an extensive literature supporting the local adaptation hypothesis in trees, our results appear consistent with these patterns of selective forces acting on abundant, heritable genetic variation across populations, even in the face of gene flow (discussed further in the next section).

Expectations for the loci underlying quantitative traits

The homogenous environments of the common garden and reciprocal transplant designs are ideally suited to test hypotheses of local adaptation in trees (Sork et al. 2013). However, uncovering the genetic basis and contributory influence of specific loci underlying

348 these adaptive traits is a sizable endeavor on its own, and the success of such pursuits will be
349 determined, in part, by the genetic architecture (i.e., the number, effect size, type, and
350 interaction of loci) that underlies the trait in question, which is generally not known *a priori*
351 (Stinchcombe & Hoekstra 2008; Rellstab et al. 2013; Savolainen et al. 2013; Hoban et al. 2016;
352 Burghardt et al. 2017; Wadgymar et al. 2017). Much of our early understanding of the
353 architectures of complex traits came shortly after Nilsson-Ehle (1909) and East (1910)
354 independently demonstrated evidence for multiple-factor inheritance, where Fisher (1918) laid
355 the groundwork for quantitative genetics by incorporating the additive properties of variance to
356 partition phenotypic variation into components tractable to a model of Mendelian inheritance. It
357 was this work, and that of Fisher's geometric model (1930), which founded the basis for
358 attributing continuous variation of phenotypes to a polygenic model of many underlying heritable
359 components of mainly small effect. From this model, Fisher (1930) concluded that mutations of
360 small effect were the main drivers of adaptation, suggesting large-effect substitutions to
361 contribute little to adaptation due to negative pleiotropic effects constraining effect size.
362 Therefore, the fate of a given locus would be conditioned on its average, marginal effect on
363 fitness calculated across the species, with non-additive deviations from this linear model of
364 inconsequential influence. This micro-mutationist view, to a large extent, remained the dominant
365 thought for nearly half a century (Orr 2005). It was then that Kimura (1983) established that for
366 an allele to contribute to adaptation, it would need to survive the stochastic nature of drift. Thus,
367 new mutations of low frequency and effect were less likely to contribute substantially to adaptive
368 evolution, and considering the adaptive contribution probability of large and small effect loci,
369 Kimura concluded that mutations of moderate effect would be the most plausible. Years later,
370 Orr (1998) showed that over the entire bout of selection via an adaptive walk, the distribution of
371 fixed substitutions resembles an exponential distribution, with effect size decreasing with the
372 proximity to the phenotypic optimum (i.e., decreasing in an approximate geometric sequence).
373 In addition, the distribution of fitness effects of beneficial mutations is also expected to be

374 exponential (Orr 2003; for more discussion on this aspect, see also Orr 2006; Eyre-Walker &
375 Keightley 2007; Martin & Lenormand 2008, Kopp & Hermisson 2009b; Keightly & Eyre-Walker
376 2010, Dittmar et al. 2016, and references therein). Despite major advances in theory and
377 technology, there still remains substantial uncertainty regarding the exact number of loci
378 underlying many adaptive traits, the effect size distribution of these loci, and how the number of
379 underlying loci and effect distribution may change under various evolutionary regimes (Orr
380 2001; Slate 2005; Hansen 2006; Mackay et al. 2009). In this section, we describe how various
381 factors can contribute to the (perhaps, effective) number of causative loci, and the distribution of
382 effects underlying continuously distributed adaptive traits, beginning first with aspects of the
383 architecture itself (gene action), and concluding with explanations of how various processes
384 (e.g., selection) play an influential role in the evolution of underlying genetic architectures. We
385 then compare these expectations with results from genotype-phenotype associations in trees.
386 While we discuss these examples in isolation, we highlight the fact that the underlying biological
387 processes are often not independent.

388 ***Gene action***

389 The classical genotype-phenotype map is largely one of additive effects, and is
390 represented by a statistical regression of the phenotype on genetic content, as developed by
391 Fisher (1918) and extended by others (e.g., Cockerham 1954; Kempthorne 1954). Indeed,
392 much of the work done in trees has relied on such additive effects to describe heritable and
393 quantitative genetic variation (see previous section). In this model, the phenotypic variance is
394 partitioned into orthogonal (i.e., independent) contributions from the genetic variance (V_G),
395 environmental variance (V_E), and the variance due to interaction between genotype and
396 environment (V_{GxE}; see Box 1). Further, V_G is also the sum of orthogonal variance components,
397 each term representing a different form of gene action. The additive term designates the
398 associated variance contribution of independent alleles, with the dominance term designating

399 the non-additive contribution to variance of interactions among alleles at the same locus, and
400 the epistatic term designating the contribution to variance of non-additive interactions among
401 alleles at different loci (which can take one of many forms such as additive by additive, additive
402 by dominance, etc.; Lynch & Walsh 1998). As a result, non-additive gene action is minimized as
403 non-linear contributions to the overall phenotype (Moreno 1994; Whitlock et al. 1995) that
404 contributes little to the distinction of the different forms of dominance and epistasis (Cheverud &
405 Routman 1995; Hansen & Wagner 2001; Hermisson et al. 2003; Hansen 2006; Mackay 2014)
406 nor towards the inference of aspects of the underlying genetic architecture in general (Nelson et
407 al. 2013; Huang & Mackay 2016).

408 These statistical conveniences afforded by Fisher and others led to the notion that such
409 non-additive effects were transient (i.e., are due to LD, which will decay with the relaxation of
410 selection), or that trends of statistical epistasis were representative of functional epistasis in
411 general, and therefore epistasis was unimportant to evolutionary dynamics (e.g., Bulmer 1980;
412 Crow 2008, 2010; Hill et al. 2008). While minimized in a statistical regression, this does not
413 necessarily mean that epistasis and dominance will not have a profound impact on the genetic
414 architecture, or towards a given population or species' long-term evolutionary trajectory, even if
415 statistical epistatic variance is minimal (Goodnight 1988; Chevrud & Routman 1995; Hansen &
416 Wagner 2001; Hansen 2013; Nelson et al. 2013; Griswold 2015; Paixão & Barton 2016).
417 Indeed, parameterizing a model in which the type I sums of squares is determined by non-
418 additive parameters, as opposed to additive variance in the conventional regression model, the
419 majority of genetic variation is still captured by the primary effect in the model regardless of the
420 underlying architecture (Huang & Mackay 2016). Given the prevalence of evidence for non-
421 additive contributions (e.g., Phillips 2008; de Visser et al. 2011; see also refs in Hansen 2013), it
422 is likely that non-additive effects will play a role in evolutionary outcomes. Indeed, Carter et al.
423 (2005) show that, relative to a purely additive trait (or with non-directional epistasis) under
424 directional selection, positive and negative epistasis can respectfully increase or decrease the

additive genetic variance, and thus increase or decrease the rate of phenotypic response to selection (see also Le Rouzic & Álvarez-Castro 2016). As Jones et al. (2014) show, for a two-trait phenotype controlled by pleiotropic and epistatic effects, epistasis in the presence of selection can also affect the mutational architecture of complex traits, where the average allelic effect evolves to be negatively correlated with the average epistatic coefficient, the strength of which is greater in larger population sizes. Yet, as described by Barton et al. (2016), and further discussed by Barton (2017) and Paixão & Barton (2016), the infinitesimal model can be generalized to include epistatic effects, particularly when the number of underlying loci is large and selection on individual loci is weak. In the case of non-systematic, weak pairwise epistasis, and without mutation or environmental noise, the infinitesimal model holds to a good approximation (Barton et al. 2016). In the case of sparse epistasis with selection and a large number of loci, the change in the mean trait over 100 generations is greater than that under a purely additive architecture, and the decrease in additive genetic variance exceeds, to an extent, that of the neutral case after about 30 generations (which is exacerbated with simpler architectures), with a reduction of the frequency of segregating alleles with positive effect on the trait (Barton et al. 2016; Barton 2017). Despite an ongoing debate within the literature (Wright 1932; Whitlock 1995; Crow 2008, 2010; Gibson 2012; Zuk et al. 2012; Hansen 2013; Hemani et al. 2013; Nelson et al. 2013; Mäki-Tanila & Hill 2014; Ávila et al. 2014; Paixão & Barton 2016), and given that there seems to be no general prevalence of either positive or negative epistatic interactions (Mackay 2014), the infinitesimal model is likely to continue to contribute to our understanding of the evolution of complex traits, as exemplified in its application towards breeding applications (Turelli & Barton 1994) and specifically those successfully applied to trees (Savolainen et al. 2007; Thavamanikumar et al. 2013; Isik et al. 2015). Ultimately, the success of such models will be conditioned on the context, as well as the distinction between physiological and statistical epistasis. Here, (higher order) non-additive contributions to phenotypic variance will likely have minimal deviations from the limit of the infinitesimal model in

the short-term, particularly if epistasis is primarily due to independent, low-order interactions, and should thus be applied with this in mind. As such, while short-term evolutionary processes are likely to hold in this limit, identifying the non-additive loci which underlie the trait, and their respective gene action, may still need further inquiry. Indeed, it is often argued that epistasis is too often neglected in studies of complex traits (e.g., Carlborg & Haley 2004), possibly due to the large sample sizes required to detect significant interactions, and lack of statistical power incurred due to multiple hypothesis testing (Mackay 2014). Given the recent reduced cost of sequencing technology and availability of novel computational and laboratory tools, future studies incorporating investigations of epistasis and dominance (where appropriate and feasible) would contribute to our understanding of genetic architectures and quantitative trait evolution and breeding applications in trees (e.g., Tan et al. 2017, Vitezica et al. 2017). Even so, the additive model is still a powerful tool to describe the loci underlying adaptive traits.

Pleiotropy is another considerable factor influencing the expectations of the genetic architecture of quantitative traits, its evolution or evolvability, and indeed the genotype-phenotype map (Hansen 2003; Orr 2006; Chevin et al. 2010b; Tenallion 2014). While multiple definitions exist across the literature (see Paaby & Rockman 2013), pleiotropy is generally identified as a single locus influencing multiple phenotypic traits. Other than linkage disequilibrium, pleiotropy is the fundamental cause of genetic covariance among phenotypes (Lande 1980). Given that the number of independent traits under selection is likely limited (Barton 1990), pleiotropy likely plays a substantial role in evolutionary dynamics. It is expected that as the number of traits, n, influenced by a locus increases, the probability of a beneficial mutation will decrease with the effect size of a mutation; where the effect size, r, relative to the distance to the phenotypic optimum, $d \cdot n^{-1/2}$, must be (much) less than d in order to be beneficial (Fisher 1930; the so-called ‘cost of complexity’: Orr 2000). Yet, empirical data seem to contradict this hypothetical cost, as the effect size of mutations often do not scale with pleiotropy in this way, and instead increase with the dimensionality of targeted traits (Wagner et al. 2008;

477 Wang et al. 2010). Additionally, universal pleiotropy, where all mutations affect all phenotypes,
478 and where there is no net directionality of mutations (i.e., mutational isotropy; both aspects as in
479 Fisher 1930), has also been challenged by findings which suggest that only a fraction of
480 phenotypic traits are affected by pleiotropic loci (Wagner et al. 2008; Wang et al. 2010).
481 Relaxation of such assumptions from Fisher's geometric model have shown that the total
482 number of traits affected by pleiotropy has a relatively decreased effect on the rate of evolution
483 in more general models (e.g., Martin & Lenormand 2006; see also Simons et al. 2017, and
484 references in Wagner & Zhang 2011 and Tenaillon 2014). It seems that if model organisms
485 (e.g., Pickrell et al. 2016, Smith 2016) are taken as a bellwether for expectations in trees,
486 pleiotropy is likely a contributing factor for many quantitative traits. Thus, the fraction of
487 beneficial mutations is likely limited when the number of traits influenced is large, suggesting
488 that the cost of complexity (or, more precisely, pleiotropy) may be generally robust (Welch &
489 Waxman 2003), particularly when a population is close to its phenotypic optimum where
490 selection acts against dimensionality of pleiotropic effects (Zhang 2012). Thus, the degree of
491 pleiotropy for underlying loci, distance from phenotypic optima, and covariance among traits
492 under selection can have profound effects on evolutionary outcomes. This is particularly true for
493 the evolvability of architectures and distribution of effect sizes, which further depends on the
494 variational autonomy of the traits affected by pleiotropy and the modularity of mutations, the
495 former of which is ultimately determined by the direction and size of effect among a set of
496 pleiotropic loci across a set of characters (see Arnold 1992; Wagner & Altenberg 1996; Hansen
497 2003, 2006; Wagner et al. 2007; Chevin et al. 2010b; Wagner & Zhang 2011; MacPherson et al.
498 2015).

499 In many investigations of local adaptation, the primary interest is in trait evolution and
500 thus the underlying genetic components. As such, environmental effects and interactions are
501 not often pursued, or perhaps even detected (Yoder & Tiffin 2017), particularly in studies of a
502 single common garden or environment, and are instead treated in much the same way as

503 epistatic interactions discussed above. Nonetheless, genotypic effects can evolve through
504 genotype-by-environment interactions with a changing environment just as is the case for the
505 evolution of non-additive interactions with a changing genetic background (Hansen 2006).
506 Indeed, it is likely that consistent fluctuations in the environment would select for
507 environmentally-perceptive responses, which seems to be the case across many tree species
508 (Li et al. 2017). The contribution to the effect size distribution from GxE interactions will be a
509 function of the variation in selection across the environments experienced by the interacting
510 allele or alleles as well as the level of gene flow between environments and fitness differences
511 among various genetic backgrounds, but to our knowledge such information (to the extent of
512 that for e.g., selective sweeps) is lacking within the literature.

513 ***Negative selection***

514 Negative selection acts against deleterious mutations that arise within populations. It is
515 one, but not the only, mechanism that underlies stabilizing selection, defined at the level of the
516 phenotype where deviations from an optimal value are selected against. Optima in this
517 framework can be thought of either globally (i.e., across all individuals) or locally (i.e., individuals
518 at a certain site or within a certain population), where the latter can have varying optima across
519 populations. The nature of the optima (i.e., being local or global) affects the detectable trait
520 architecture. For example, trait architecture should be composed of rare alleles with a negative
521 relationship between effect size and allele frequency (cf. Eyre-Walker 2010 and references
522 therein), where this relationship can also be confounded with degree of dominance and gene
523 expression network connectivity (Huber et al. 2017), under models of a single global optimum.
524 From a population genetic perspective, the ubiquity of negative selection is encapsulated in the
525 name background selection, which has extensive reviews about its presence in natural systems
526 (Charlesworth 2013), its importance for the neutral and nearly neutral theories of molecular
527 evolution (Ohta 1992, 1996), and its contribution to observable patterns of hitchhiking (Stephan

528 2010). Important for the study of polygenic adaptation and its architecture, however, is that loci
529 identified using GWAS may also include segregating deleterious variation (as argued and hinted
530 at in Eckert et al. 2013b; cf. Yang et al. 2017; Gazal et al. 2017) as this creates trait variance,
531 with little known about their prevalence (including differential prevalence across traits),
532 differentiation in frequencies across populations (but see Holliday et al. 2016), and effects on
533 downstream inferences about divergent selection pressures across populations. It is sets of
534 GWAS loci, though, that are currently analyzed for signatures of local adaptation via spatially
535 divergent (i.e., locally positive) natural selection (e.g., Berg & Coop 2014).

536 Recent exemplary work with expression networks in *Populus tremula* L. (Salicaceae;
537 Mähler et al. 2017) and the herbaceous *Capsella grandiflora* Boiss. (Brassicaceae; Josephs et
538 al. 2015, 2017a) have revealed intriguing insight into the effects of negative selection on the
539 architecture of complex traits in plants, as well as the relationship between network connectivity
540 and the strength of negative selection. In *P. tremula*, genes with expression levels that were
541 significantly associated with sequence variation were found more often in the periphery of the
542 co-expression network (lower network connectivity) than within network module cores (higher
543 connectivity), while expression-associated SNPs were negatively correlated with network
544 connectivity and effect size, a pattern also found between connectivity and expression variance,
545 and minor allele frequency and QTL effect size (Mähler et al. 2017). Genes associated with
546 sequence variation had less skewed site-frequency spectra (i.e., the frequency distribution of
547 allelic variants) and lower estimates of nonsynonymous to synonymous divergence (d_N/d_S) than
548 genes not associated to sequence variation, together suggesting that genes within the periphery
549 of co-expression networks are likely under less selective constraint than those genes with high
550 network connectivity which likely experience greater intensities of purifying selection. These
551 genes thus tend to have more segregating variation and may be those most likely to be
552 detected with current sample sizes utilized in GWAS, which has implications for estimation of
553 trait architecture and its 'degree' of polygenicity. Even so, while there is prevalent evidence of

554 negative selection in trees (e.g., Krutovsky & Neale 2005, Palmé et al. 2009, Eckert et al.
555 2013a,b), more inquiry is needed.

556 ***Positive selection***

557 The temporal and spatial heterogeneity of selection can impact the evolution of genomic
558 architectures underlying adaptation. These impacts are often thought of on a spectrum of trade-
559 offs, with one end being antagonistic pleiotropy where allelic effects vary between positive and
560 negative on fitness across populations, and conditional neutrality where allelic effects on fitness
561 are positive in one or more populations and nearly zero in others (Anderson et al. 2012,
562 Savolainen et al. 2013). For instance, alleles incorporated into a population after a shift in
563 environmental influence can increase from low to high frequency via positive selection. The
564 existence of such a beneficial allele can manifest in several ways: from new mutations,
565 introgression through gene flow, or molecular reorganization through novel recombination,
566 inversion, transposition, copy number variation, or insertion-deletion events. If there is strong
567 selection acting on this allele ($N_e s >> 1$), it will sweep to high frequency creating a signature of
568 reduced polymorphism at neutral sites physically linked to the allele ('genetic hitchhiking',
569 Maynard Haigh & Smith 1974) resulting in a hard 'selective sweep' (Berry et al. 1991). However,
570 in structured populations with limited gene flow, this process can take significantly longer to
571 reach fixation, resulting in incomplete sweeps (Whitlock 2003). Additionally, Pavlidis et al.
572 (2012) found that, in congruence with Chevin & Hospital (2008), a multilocus genotype often
573 prevents the trajectories of individual alleles from sweeping to fixation, with an increasing
574 number of loci leading to decreasing probability of fixation, and as a result, an altered selective
575 signature at such loci (see also Jain & Stephan 2017). As such, hard selective sweeps in a
576 polygenic architecture are expected to be rare (but not completely absent) under most
577 circumstances, particularly when the shift in environment causes a relatively small deviation
578 from the phenotypic optimum. Thus, hard sweeps most likely apply to loci with relatively large

579 effect above a calculated, context-dependent threshold value (Orr 2005; de Vladar & Barton
580 2014; Stephan 2015; see specifically Jain & Stephan 2015, 2017).

581 While early literature (Maynard & Smith 1974; Kaplan et al. 1989) focused on the rapid
582 sweep of an allele incorporated into a population after an environmental shift, research within
583 the last few decades have focused on 'soft sweeps' resulting from neutral or deleterious
584 mutations that are present in the standing genetic variation prior to the change in the selective
585 environment, wherein the selection coefficient changes with the environmental shift such that
586 the allele(s) become evolutionarily advantageous (Innan & Kim 2004, Przeworski et al. 2005,
587 Berg & Coop 2015; Schrider & Kern 2017; reviewed in Hermisson & Pennings 2005, Barret &
588 Schluter 2008, Messer & Petrov 2013, and Hermisson & Pennings 2017; see also Jensen
589 2014). These allele(s) could manifest via a single low-frequency variant, multiple variants
590 caused by parallel recurrent mutation/reorganization on multiple haplotypes, or multiple unique
591 alleles that arise independently within, perhaps multiple, populations. In such cases where
592 selection acts via soft sweeps, the rate of evolution at the phenotypic level is expected to
593 exceed those of hard sweeps because the alleles under selection have escaped the stochastic
594 nature of drift to a greater degree and are segregating within multiple individuals and genetic
595 backgrounds within the population (Innan & Kim 2004). The extent to which soft sweeps alter
596 the effect size distributions underlying the genetic architecture is likely dependent upon both the
597 strength of selection and effect size before and after the environmental change (Messer &
598 Petrov 2013; Matuszewski et al. 2015; Jain & Stephan 2017), while the frequency before
599 selection influences the likelihood of subsequent detection (Innan & Kim 2004). Additionally, if
600 multiple mutations are segregating during the sweep, the probability of fixation for any given
601 locus also decreases (Pennings & Hermisson 2006a, 2006b; Chevin & Hospital 2008; Ralph &
602 Coop 2010). For many species of trees, which often experience high gene flow and strong
603 diversifying selection across populations, adaptive divergence for polygenic traits is expected to
604 result more often from soft sweeps than hard sweeps, affecting phenotypes by subtle allele

605 frequency changes across populations, such that allele frequency differences of individual loci
606 across populations for neutral and selective sites will often be nearly indistinguishable (Latta
607 1998, 2003; Barton 1999; Kremer & Le Corre 2012; Le Corre & Kremer 2012; Stephan 2015;
608 Yeaman 2015**;** Jain & Stephan 2015, 2017). Indeed, the large effective population sizes found
609 in most tree species would permit large effective mutation rates (or reorganization events)
610 necessary for a soft selective sweep from multiple unique variants, particularly when the
611 phenotype is underlain by a large mutational target (i.e., many loci). Even so, and as highlighted
612 by Stephan (2015) and Bailey & Bataillon (2016), the extent to which scientists can detect the
613 influence of demographic processes on soft versus hard sweeps, and vice versa, remains
614 challenging (Jensen et al. 2005; Chevin & Hospital 2008; Hancock et al. 2010; Pritchard et al.
615 2010; Schrider et al. 2015, 2016; Schrider & Kern 2016; Hermisson & Pennings 2017).

616 While discrete directional selection events are likely to be a common evolutionary
617 influence across taxa, fluctuating or sustained directional selection (i.e., moving optima) are also
618 likely to be contributory factors influencing the genetic architecture of quantitative traits
619 (reviewed in Kopp & Matuszewski 2013; see also McCandlish & Stoltzfus 2014). For a
620 sustained moving optimum, the effect size distribution of beneficial alleles is expected to be
621 dependent upon the effect distribution of standing or *de novo* mutations as well as the strength
622 of selection: if the rate of change is dramatic, adaptation from new mutations is expected to
623 occur through intermediate to large-effect loci (Kopp & Hermisson 2009a; Matuszewski et al.
624 2014) or from small-effect loci when adaptation occurs via standing variation (particularly when
625 epistasis is considered, Matuszewski et al. 2015). Under lesser rates of environmental change,
626 adaptation is expected to proceed through mainly alleles of small-effect (Collins et al. 2007;
627 Kopp & Hermisson 2009a, 2009b) where intermediate effects will dominate the long-term
628 distribution of effect sizes of an adaptive walk (Kopp & Hermisson 2009b). In the case of
629 fluctuating environments, outcomes often depend directly on the degree of temporal
630 autocorrelation of the changing environment. In such cases of stochastic fluctuation around a

631 linear trend of environmental change, extinction risk increases relative to that of the strictly
632 linear trend (Bürger & Lynch 1995) where local adaptation lags, to some degree, behind any
633 given contemporaneous scenario. In comparison, and similar in some ways, stochastic
634 fluctuations around a constant mean are expected to resemble the dramatic environmental
635 change scenario described above, characterized by strong selection pressures, maladaptation
636 between generations, and a large lag load (Bürger 1999; Chevin 2012; Kopp & Matuszewski
637 2013). In the case of autocorrelated shifts, the 'predictability' of such fluctuations may decrease
638 the possibility of extinction, increase probability of local adaptation, and lead to similar scenarios
639 as discussed for gradual changes in the environment (Kopp & Matuszewski 2013).

640 ***Gene flow***

641 Gene flow, to the extent that would be appreciable to that found in trees, is also an
642 important component shaping quantitative expectations. Indeed, since the early 1900s we have
643 known that gene flow can disrupt adaptation if selection is not strong enough to overcome the
644 loss of beneficial alleles (Haldane 1930; Wright 1931; Slatkin 1987; reviewed in Felsenstein
645 1976, Lenormand 2002, Savolainen et al. 2007, 2013, Feder et al. 2012a, and Tigano & Friesen
646 2016). Particularly when gene flow is asymmetric between core and peripheral populations,
647 adaptation can be inhibited in marginal habitats (Kirkpatrick & Barton 1997; Kawecki 2008).
648 Even so, there is abundant evidence that gene flow can promote adaptation and maintain
649 polymorphisms within populations, including *Heliconius* butterflies (Joron et al. 2011), white
650 sand lizards (Laurent et al. 2016), stick insects (Comeault et al. 2014, 2015), cichlid fishes
651 (Meier et al. 2017), Darwin's finches (Lamichhaney et al. 2015), as well as lodgepole pine
652 (Yeaman & Jarvis 2006). There is also evidence to suggest that as the number of traits
653 experiencing spatially heterogeneous selection increases, the degree of local adaptation
654 increases, even with considerable gene flow (MacPherson et al. 2015). The magnitude of gene
655 flow between populations can also impact the distribution of effect sizes, for when gene flow

656 falls below a critical threshold, and over many thousands of generations, there is an increase in
657 the probability of establishment and persistence times of large-effect alleles, thus reducing the
658 proportion of the polymorphism due to small-effect loci (Yeaman and Otto 2011; Yeaman and
659 Whitlock 2011). These dynamics are further influenced by the susceptibility of alleles to
660 'swamping' (Slatktin 1975; Bürger & Akerman 2011; Lenormand 2002; Yeaman 2015; *sensu*
661 Haldane 1930). For alleles that are prone to swamping, adaptive phenotypic divergence
662 depends on genetic variation and is driven by allelic covariance among populations particularly
663 when the underlying architecture is highly polygenic, the mutation rate is high, and the number
664 of loci underlying the trait exceeds the number needed to achieve the local optimum phenotype
665 (genetic redundancy, Yeaman 2015; see Goldstein & Holsinger 1992). Conversely, when there
666 is little genetic redundancy underlying the trait, limited divergence is observed unless the effect
667 size of a given swamping-prone allele exceeds the critical migration threshold. In these cases
668 where swamping-prone alleles contribute to adaptive divergence, the genetic architecture is
669 transient and any given locus contributes ephemerally to phenotypic divergence, even for loci of
670 relatively large effect (Yeaman 2015). In the case of swamping-resistant alleles, the evolved
671 architecture is enriched for large-effect loci and adaptive divergence can be maintained with
672 little genetic variation or input from mutation. Yet while the contribution from such loci can last
673 many thousands of generations, the architecture can again become transient as the genetic
674 redundancy or mutation rate increases (Yeaman and Whitlock 2011; Yeaman 2015).

675 Physical linkage and reduction of recombination between adaptive loci can also play a
676 considerable role in adaptive processes in the face of gene flow (Feder & Nosil 2010; Feder et
677 al. 2012a,b; Yeaman 2013; references therein). In such cases, loci that are tightly linked to other
678 loci already under selection will have an increased probability of contributing to local adaptation,
679 both because of physical linkage as well as by reducing the effective recombination among loci
680 within the sequence block. For instance, Yeaman & Whitlock (2011) showed that under
681 divergent selection with gene flow, the number of contributing loci decreases with increasing

682 recombination while small effect loci tend to cluster in groups that act as a single large effect
683 locus (see also Remington 2015), and strong selection can maintain these clusters of linked loci
684 over greater map distances than can weak selection. More recently, Yeaman (2013) employed
685 individual-based simulations to provide evidence that the clustering of alleles throughout a bout
686 of adaptation is unlikely to be driven mainly by divergence hitchhiking alone, and that instead
687 competition between genomic architectures and chromosomal rearrangements occurring
688 throughout adaptive processes under a range of environmental fluctuation scenarios can lead to
689 the evolution of tightly clustered adaptive loci which persist in the event of gene flow, unlike the
690 clusters identified by Yeaman & Whitlock (2011). Yeaman (2013) found that the level of
691 clustering was a function of the temporal fluctuation period, the rate of rearrangement itself is an
692 important determinant on the evolution of clustered architectures, and clusters can in some
693 cases be evolutionarily disadvantageous. Together, these results suggest that genomic
694 rearrangements (reviewed in Ortiz-Barrientos et al. 2016), including inversions (Kirkpatrick &
695 Barton 2006; reviewed in Hoffman & Rieseberg 2008), which decrease the effective rates of
696 gene flow among adaptive sequences can be an essential component of local adaptation, and
697 indeed some cases of speciation, in the face of gene flow.

698 ***Summary***

699 While we provided an overview of the factors that can influence the genetic architecture
700 of local adaptation, we acknowledge that it is far from exhaustive. Because the phenotypes
701 used in studies of local adaptation (particularly those assumed or corroborated to be a
702 component of total lifetime fitness) often have a continuous distribution, and are thus
703 quantitative in nature, the underlying genetic basis for these traits is likely polygenic and is
704 predicted to be underlain by multiple (often many) segregating loci, many of which may confer
705 small phenotypic effects (and are thus unlikely to be detected using single-locus approaches).
706 Even so, a continuum exists, where the true genetic architecture (the number of contributing

707 loci, as well as their relative locations within the genome, phenotypic effects, and interactions)
708 underlying a given complex trait is itself determined by a combination of evolutionary forces that
709 encompass an interplay between the strength, timing, and direction of (background) selection
710 against the homogenizing effects of gene flow and recombination, disruptive effects of drift,
711 linkage, transposition, inversion, and mutation, interactions between underlying loci as well as
712 between these loci and the environment, structural variation, relationship to gene expression
713 networks, as well as other factors related to life history. Consequently, the contemporary genetic
714 architecture is a result of past evolutionary processes, while the adaptive response to future
715 evolutionary dynamics is influenced in part by the contemporary architecture and genetic
716 variance at hand.

717 The genomics of local adaptation in trees

718 *Common approaches used to identify adaptive loci*

719 Across taxa, the predominant association and outlier methods for uncovering sets of loci
720 underlying local adaptation have relied upon single-locus population genetic approaches.
721 Putatively adaptive loci are often identified by elevated allele frequency differences among
722 populations relative to a null model. Because most of the loci in the genome are assumed to be
723 neutral relative to fitness, outlier loci that stand out from this noise are identified as those being
724 putatively under selection. However, outlier tests based on F_{ST} (*sensu* Lewontin & Krakaur
725 1973) do not incorporate information regarding putative phenotypic targets of selection nor
726 environmental drivers of differentiation, often do not correct for neutral population structure (but
727 see Lotterhas & Whitlock 2015), and will inevitably isolate a biased set of candidate loci
728 (Hermisson 2009; Cruickshank & Hahn 2014). In the case of genotype-environment
729 associations (reviewed in Rellstab et al. 2015; see also De Mita et al. 2013), information about
730 possible environmental drivers is incorporated by assessing the association between allele
731 frequencies and environmental heterogeneity, yet without information regarding traits

732 hypothesized to be influenced by selection (Schoville et al. 2012). Single-locus genome wide
733 association studies (see supplemental box SB1) and quantitative trait loci (QTL) experiments
734 (reviewed in Ritland et al. 2011, Hall et al. 2016) have also been used in such investigations,
735 quantifying the differential effects of typed alleles on a given phenotype. In these cases, a
736 common garden or reciprocal transplant design (discussed above) can be utilized to control for,
737 or at least minimize, environmental effects on the studied phenotypes, while a pedigree is used
738 to minimize false associations and to isolate linkage groups, and/or to predict parental
739 phenotypes through regression analysis of progeny. Despite the shortcomings of these
740 methods, such studies provide candidate loci that can be investigated in further detail, which is
741 particularly advantageous when resources are limited. Indeed, as discussed below, these
742 single-locus approaches dominate the methods used to uncover complex traits (adaptive or
743 otherwise) in trees.

744 ***Current progress in trees***

745 The knowledge gained through the descriptions of genetic architectures underlying
746 complex traits has fundamental implications for the success of conservation and breeding
747 strategies. In light of the expectations outlined above for the architecture of quantitative traits
748 under various evolutionary regimes, and the methods commonly used to detect these loci, we
749 reviewed the literature of single-locus genotype-phenotype associations (GPAs, which included
750 associations to gene expression levels) from studies in forest trees. In doing so, we identified 52
751 articles across 10 genera and 25 species with a total of 2121 GPAs (Supplemental Table S3,
752 Supplemental File F2). Because most studies in trees do not report phenotypic effect sizes of
753 individual loci (i.e., regression coefficients), we report r^2 values which can be used to quantify
754 the percent phenotypic variance explained by the associated locus. In cases where multiple
755 SNPs from a given locus (e.g., a gene or scaffold) were associated to a trait, we averaged the r^2
756 values for that locus. As with our review of trait heritability and Q_{ST}, we grouped phenotypic

757 traits used in associations into twelve broad categories (in this case, no phenotypes fell into
758 Survival or Seed and Seedling Properties groups). Across these trait groups, the mean r^2 was
759 0.039, where 80.85% (n = 1715) of recorded estimates had r^2 values less than 0.05, 18.71% (n
760 = 397) of r^2 values falling between [0.05,0.22], and nine values of r^2 greater than 0.22, which
761 were all related to *Cronartium ribicola* resistance in *Pinus monticola* Douglas ex. D. Don (Figure
762 3).

763 Of the twelve trait groups, all but those traits relating to both reproduction and herbivore
764 and insect resistance had r^2 estimates greater than 0.10, with traits relating to disease
765 resistance, growth, leaf and needle properties, phenology, and wood properties each
766 contributing over 10% of these outliers. These small effects tend to also not account for much of
767 the observed heritability, but can explain sizeable fractions in some instances (e.g., primary
768 metabolites in Eckert et al. 2012). Of the loci associated with expression levels, r^2 estimates
769 were between 0.05 and 0.152 in all but one case (n = 54). We also assessed the propensity of
770 individual loci to be associated to more than one phenotype or expression level across our
771 literature review. Without correcting for the multiple associations of a locus to yearly phenotypes
772 (e.g., bud flush 2009, bud flush 2010), we found that the average number of loci associated to
773 multiple phenotypes per study was 6.94, while after correcting for multiple years the average
774 number decreased to 5.59. The median number of SNPs utilized for association per study was
775 195, where 75% (39/52) of studies used less than 1,000 SNPs, eight studies using less than
776 10,000 SNPs, four studies using between 29,000-35,000 SNPs, and one study utilizing
777 2,822,609 SNPs for association (all studies with greater than 10000 SNPs were from either
778 *Pinus* or *Populus* species). Finally, to explore influence of sample size on estimated percent
779 variance explained across studies we examined the relationship between r^2 estimates and the
780 number of maternal families used in estimate calculations and found a positive but non-
781 significant relationship (ρ = 0.0735, P = 0.623).

782 ***Are we out of the woods yet?***

783 From insight gained from the literature review of genotype-phenotype associations it
784 seems that the vast majority of the genetic architecture of local adaptation and complex traits in
785 trees remains largely unexplained using common methods, a consistent pattern across the past
786 decade of research in trees (Neale & Savolainen 2004; Savolainen et al. 2007; Ćalić et al. 2015;
787 Hall et al. 2017). Furthermore, it is likely that the estimates for percent variance explained are
788 inflated due to a combination of QTLs that break down into smaller effect loci (Remington 2015),
789 the Beavis effect (Beavis 1994; Xu 2003), and the Winner's Curse (Görning et al. 2001; Zöllner
790 & Pritchard 2007) where locus effects are inflated by using the same data for both gene
791 identification and phenotypic prediction (see Box 1 in Josephs et al. 2017b for a detailed
792 synopsis of these biases). Such a pattern suggests that, indeed, many of the traits important to
793 evolutionary, breeding, and conservation insight in trees are likely of a polygenic basis and that
794 future studies must take this into account when seeking to identify the underlying loci.

795 For GWAS and QTL studies, even within studies of model organisms, missing heritability
796 is nothing new. Across taxa, missing heritability is less frequent within phenotypes of mono- to
797 oligogenic bases (as seen for the *Cr2* major-gene resistant locus in *Pinus monticola*, Lui et al.
798 2017), as would be expected, and is a recurrent, pervasive shortcoming from genotype-
799 phenotype associations of complex traits, particularly those maintaining single-locus
800 perspectives. A number of explanations have been put forth to explain the missing heritability,
801 such as epistasis (Hemani et al. 2013) and its inflationary effect on heritability estimates (Zuk et
802 al. 2012), environmental or epigenetic interactions (Feldman & Lewontin 1975) as well as their
803 inflationary effect on heritability estimates (Zuk et al. 2012), (unmeasured) low-frequency
804 variants of large effect (Dickson et al. 2010), genetic or variance heterogeneity of individual
805 alleles (Leiserson et al. 2013; *cf*. Box 1 in Nelson et al. 2013), or common variants with effect
806 size below detection thresholds (Yang et al. 2010). As such, here we avoid supporting one

807 causative hypothesis over another, particularly given the ongoing discussion within the
808 literature, for which strengths and weakness for any viewpoint are apparent (e.g., Gibson et al.
809 2010), and because of the progress yet to be made in trees.

810 Indeed, the dissection of the genetic architectures underlying complex traits in trees is
811 still in its nascency compared to the progress of model organisms (for which missing heritability
812 is still an issue), and beyond issues of coverage, genomic saturation, and genomic resources
813 (discussed below in The Path Forward), we must approach this issue with all possibilities in
814 mind. Given the unique properties of the life histories, genome size and organization of many
815 tree species, and the limited numbers of studies with large sets of molecular markers, causative
816 sources of the missing heritability should be ruled out, or supported, as with any other
817 hypothesis, particularly as we gain information from contemporary studies of trees that address
818 shortcomings of those in the past. Further, we must keep in mind differences between functional
819 and statistical epistasis (Álvarez-Castro et al. 2007; Nelson et al. 2013; Huang & Mackay 2016).
820 In any case, it seems that sample sizes will need to be increased (Hall et al. 2016), albeit with
821 diminishing returns (Boyle et al. 2017; Simons et al. 2017), to discover a higher proportion of the
822 underlying loci in trees due to small to moderate additive effects, so incorporating investigations
823 into such aspects of epistasis, GxE effects, and network analyses (when appropriate), may be a
824 worthwhile complement (e.g., Mähler et al. 2017, Mizrachi et al. 2017; Tan et al. 2017).

825 While the infinitesimal model will continue to prove to be immensely useful for breeding
826 programs and for short-term evolutionary predictions, and we may find that the missing
827 heritability in trees is truly due to consequences of the infinitesimal regime (as is often cited to
828 be the majority consensus across taxa for missing heritability), it has been argued that the
829 analysis paradigm for such studies is near its limits in describing the functional genetic
830 architecture of quantitative traits, and that it is therefore necessary to move beyond single-locus
831 perspectives and reconsider common practices (Pritchard & Di Rienzo 2010; Nelson et al. 2013;
832 Sork et al. 2013; Tiffin & Ross-Ibarra 2014; Wadgymar et al. 2017). At this stage, it seems that

we investigators seeking to describe the genetic architecture of quantitative traits in trees have some ways yet to go before we are truly out of the woods. In the next section, we describe the path forward to describing genetic architectures from a polygenic and functional perspective, identify resources available to advance our knowledge and fill knowledge gaps, as well as future directions for this research area.

The Path Forward

As we have outlined, there is still ample room for improvement in our description and understanding of the genomic architecture of quantitative traits in trees. In this section, we orient our path forward by first highlighting utilities available to, and underused within, the forest genetics community to describe the genetic architecture of complex traits. We then outline several suggestions to facilitate further progress and advocate for prospective perspectives in future studies such that information and data may continue to be used easily in subsequent syntheses across pathways, environments, species, and towards insight to identify future needed resources as our understanding progresses. While our recommendations are specific to the tree community, we also acknowledge other valuable recommendations from recent reviews (e.g., Savolainen et al. 2013; Tiffin & Ross-Ibarra 2014; Lotterhos & Whitlock 2015; Gagnaire & Gaggiotti 2016; Hoban et al. 2016; Wellenreuther et al. 2016; Burghardt et al. 2017; Wadgymar et al. 2017).

Stepping off the path – what's in our pack?

The genetic architecture underlying local adaptation and complex traits likely has a polygenic basis composed of many loci of relatively weak effect yet many of the common association or outlier methods will often fail to detect many of the causative loci of small to moderate influence. Such investigations have so far led to an incomplete description of studied architectures, and, in many cases, have limited our understanding of complex traits in trees to a handful of loci. While we do not advocate that such single-locus methods be avoided in future

858 studies (considered further in the next section), here we outline underused and promising
859 approaches to identify and describe underlying loci that explicitly take into account the polygenic
860 basis of such traits and may help advance our understanding in future studies. Multivariate,
861 multiple regression, and machine learning techniques are three such examples, and differ from
862 univariate analyses by analyzing patterns among multiple loci simultaneously.

863 The Bayesian sparse linear mixed model (BSLMM), for instance, such as that deployed
864 in the software package GEMMA (Zhou et al. 2013), is developed for both genomic prediction and
865 mapping of complex traits that offers considerable advantages over single-locus genotype-
866 phenotype approaches (Guan & Stephans 2011; Eheret et al. 2012; Zhou et al. 2013; Moser et
867 al. 2015). This analysis has gained in popularity recently, being used across diverse taxa such
868 as stick insects (Comeault et al. 2015, Riesch et al. 2017), butterflies (Gompert et al. 2015),
869 Darwin's finches (Chaves et al. 2016), and trees (Lind et al. 2017). BSLMM is a hybrid of LMM
870 and Baysian variable regression that extends the Lande & Arnold (1983) multiple regression
871 approach in an attempt to address the sparsity of common data sets used in genotype
872 associations, where the number of model parameters (loci) is often much greater than the
873 number of observations (sampled individuals; Zhou et al. 2013; Gompert et al. 2016).
874 Specifically, the model takes into account relatedness among individuals and provides a means
875 to summarize estimates of selection across the genome such as the proportion of phenotypic
876 variation explained (PVE) across genotyped markers by estimating the combined influence of
877 markers with either polygenic (infinitesimal) or measureable (moderate to large) effect, the
878 proportion of PVE explained by genetic loci with measurable effects (PGE), and the number of
879 loci with measurable effects that underlie the trait (for more details see Guan & Stephens 2011;
880 Zhou et al. 2014; Gompert et al. 2016). Additionally, GEMMA returns the posterior inclusion
881 probability for each marker providing evidence for association with the phenotype, and with
882 sufficient genetic sampling PVE should approach the narrow sense heritability if all or most
883 causal sites are in LD with genotyped loci (Gompert et al. 2016), a useful property considering

884 the uncertainties of genomic sampling saturation in trees. While the approach remains
885 promising considering its performance in the context of genomic prediction and inference of
886 PVE (e.g., Zhou et al. 2013, Speed & Balding 2014), there has been no attempts, to our
887 knowledge, to assess the approach under various demographic histories, genetic architectures,
888 and sampling designs. A close approximation to this comes from analyses carried out by
889 Gompert et al. (2016), in which `GEMMA` was evaluated for PVE estimation, estimated effects of
890 causative loci, and the estimated number of underlying SNPs based on various author-specified
891 numbers of causal loci, underlying heritability ranges, and numbers of sampled individuals. In
892 short, the authors convey that `GEMMA` is promising, but that there are important limitations to
893 consider (Gompert et al. 2016). However, because the authors simulated architectures by
894 randomly assigning effects to loci from an empirically-derived sequence data set, and while they
895 were thorough in their data exploration, we encourage these results be replicated *in silico*
896 through full modeling of genomic loci across various demographic, LD, sampling, and
897 architecture scenarios to ensure underlying allele frequencies among populations and LD
898 (within and among populations) reflect realistic patterns which may have an effect on model
899 performance. Such additional analyses will also allow for more specific insight into model
900 performance based on *a priori* biological insight available to investigators, allowing more
901 informed decisions when choosing an appropriate genotype-phenotype association method
902 such as BSLMM.

903 Random Forests (Breiman et al. 2001) is a machine learning algorithm used to identify
904 patterns in highly dimensional data sets to further generate predictive models. Alongside uses
905 outside of evolutionary biology, the Random Forests algorithm has gained popularity in
906 association studies across taxa as well as in trees such as that of genotype-phenotype
907 associations in Sitka spruce (*Picea sitchensis*; Holliday et al. 2012) and genotype-environment
908 associations in white spruce (*P. glauca*; Hornoy et al. 2015). Random Forests is based upon
909 classification (for discrete variables, e.g., soil type) and regression (continuous variables; e.g.,

910 temperature or phenotypic measurements) trees (so-called CART models). During its
911 implementation, Random Forests creates these decision trees using two layers of stochasticity:
912 the first layer is used to grow each tree by using a bootstrap sample of observations
913 (environmental or phenotypic) while the second uses a random subset of predictors (marker
914 loci) to create a node which is then split based on the best split of the observations across
915 permutations of predictors using the residual mean square error (see Figure 2 in Hornoy et al.
916 2015). The observations that were not used as training data to create the model are then used
917 to estimate model accuracy, which can be further used to assess variable importance (Holliday
918 et al. 2012; Hornoy et al. 2015; Forester et al. 2017). While creating a promising alternative to
919 univariate approaches, until recently the Random Forests algorithm has not been fully explored
920 to assess model performance for use in association studies. Forester et al. (2017) provide a
921 thorough analytical assessment using simulated data to remark on performance for use in
922 genotype-environment association studies (GEA). In their analysis, they used published
923 simulations of multilocus selection (Lotterhos & Whitlock 2014, 2015) of various demographic
924 histories and selection intensities across 100 causative (with 9900 neutral) loci to compare the
925 Random Forests algorithm to the multivariate approaches of constrained ordination (redundancy
926 analysis, RDA, and distance-based RDA, dbRDA - both of which are mechanistically described
927 in Legendre & Legendre 2012, but are multivariate analogs of multiple regression on raw or
928 distance-based data) and to the univariate latent factor mixed model (LFMM). In short, Forester
929 et al. (2017) found that LFMM performed better than Random Forests as a GEA, while
930 constrained ordinations resulted in relatively lower false positive and higher true positive rates
931 across levels of selection than both Random Forests and LFMM. Additionally, the authors found
932 that correction for population structure had little influence on true and false positive rates of
933 ordination methods, but considerably reduced true positive rates of Random Forests. They also
934 note that further testing is needed across various evolutionary scenarios. Even so, constrained
935 ordination provides an effective means by which to detect loci under a range of both strong and

weak selection (Forester et al. 2017). While promising under a GEA framework, future analyses may provide evidence that such methods also perform well in genotype-phenotype associations as well. Empirically, it has been used in trees to explore multivariate relationships between phenotypes, genotypes, and environments (e.g., Sork et al. 2016). Additionally, there have been many extensions of the original Random Forests model, such that extensions with purportedly better performance should be assessed alongside other popular association methods in the future.

Once a set of candidate loci have been identified to putatively underlie a phenotype or environment of interest, these loci can be used to further test the hypothesis of polygenic local adaptation. For instance, Berg & Coop (2014) use the significant hits from GWAS data sets to estimate within-population additive genetic values by calculating the frequency-weighted sum of effects across these loci. These values are then compared to a null model of genetic drift that accounts for population structure to test for an excess of variance among populations, ultimately identifying the populations most strongly contributing to this signal. The excess variance statistic (Qx) is analogous to Q_{ST} and is composed of two quantities – an F_{ST}-like component describing allele frequency differentiation across populations and a LD-like component describing coordinated and subtle allele frequency shifts across populations. This method thus allows explicit hypothesis tests related to the expected polygenic architecture of local adaptation across populations of trees. It is also noteworthy in that it combines aspects of the genotype-environment-phenotypic spectrum that underlies local adaptation within a single methodological framework (cf. Sork et al. 2013). Prior attempts take a pairwise approach examining each pairwise combination of the genotype-environment-phenotype spectrum (e.g., Eckert et al. 2015). Despite the promising insight from this method, it has not been used widely outside of model organisms. Future applications in trees should consider the number of causal loci identified to be associated with quantitative phenotypes (driven somewhat by the number of loci used in mapping studies), the number of populations needed to increase power, especially in

962 the correlation of genetic values to environmental data, and the ability to reliably estimate
963 genotypic effects.

964 ***At the trail junction – where to next?***

965 While we have outlined methods above that have not yet realized their full potential in
966 describing genetic architecture of complex traits in trees, there are several matters that we, as a
967 field, must keep in mind such that we can continue to progress our understanding in the most
968 efficient manner. Here we believe the path forward lies in three critical areas which we discuss
969 in further detail below: 1) needed data, 2) standardized data reporting, and 3) empirical studies
970 in trees designed to test theoretical expectations of genetic architectures.

971 ***Needed data***

972 While the common garden approach can facilitate understanding of evolutionary
973 processes without specifically identifying underlying loci (Rausher & Delph 2015), identifying
974 features of the genetic architecture will ultimately inform breeding applications important to
975 management, conservation, and industry, and thus requires knowledge about underlying loci.
976 Consequently, we have not yet had sufficient sampling of both marker densities and studies
977 amenable to replication across systems to truly exhaust the use of single-locus approaches,
978 particularly as the sample size of markers, individuals, and populations increase in the near
979 future. Indeed, Hall et al. (2016) estimated that the number of causative loci underlying
980 quantitative traits in trees is likely in the several hundreds, and to capture 50% of the heritable
981 genetic variation, population sizes of about 200 will be needed for mapping disease traits, and
982 about 25,000 for traits such as growth. Even so, we recommend that such single-locus
983 associations should not be used as the sole method of architecture description as we carry out
984 future studies unless justified *a priori* based on biological principles or knowledge of the
985 expected architecture, and/or for testing specific hypotheses. While the limits of such methods

986 should be considered for a given study, these approaches can be used alongside other lines of
987 evidence to either support or spur further testing of underlying loci (*sensu* Sork et al. 2013). For
988 instance, there is little downside to performing both a single-locus association and a multivariate
989 analysis in the same study, even if some or all of the results for a given technique are excluded
990 to the supplemental section (e.g., Sork et al. 2016). Further, contextualizing genotype-
991 phenotype and genotype-environment relationships with results that describe local adaptation
992 (e.g., phenotype-environment, Q_{ST}-F_{ST} comparisons) can also stimulate further understanding.
993 Specifically, studies which do so within the context of a comparative approach, not only in the
994 sense of Sork et al. (2013), but as well as within the context of comparisons within and across
995 species (e.g., Yeaman et al. 2016) or environments (Holliday et al. 2016), offer unique
996 circumstances under which to advance our understanding of complex traits (Lotterhos &
997 Whitlock 2015; Ćalić et al. 2016; Hoban et al. 2016; Ingvarsson et al. 2016; Mahler et al. 2017).

998 Considering the polygenic and network nature underlying such traits, future studies will
999 benefit from a diverse set of markers that represent both functional proteins (genic regions) as
1000 well as those which control aspects of their expression or post-transcriptional regulation. If one
1001 lesson is to be gained from the recent discussion of the applicability of reduced representation
1002 techniques (Lowry et al. 2016; Catchen et al. 2017; Lowry et al. 2017; McKinney et al. 2017), it
1003 is that genomic resources are paramount to advancement of knowledge, especially when
1004 developed with knowledge of patterns of linkage disequilibrium or, if not with this knowledge,
1005 with goal of quantifying it. However, RADseq remains one of the most cost-effective approaches
1006 available to trees and should thus be assessed in the specific context of tree species,
1007 particularly when strengths and limitations are understood and addressed (as reviewed in
1008 Parchman et al. in review). No matter the approach used for association, some aspect of the
1009 architecture is likely to be missed in trees. For example, RADseq based markers developed
1010 within large genomes are not enriched within genic regions where structural changes to proteins
1011 are expected to affect phenotypes (although choice of enzymes can affect the relative

1012 proportion of genic regions). In contrast, exome based approaches are anchored within coding
1013 regions thus excluding putative regulatory elements outside of the exomic regions used to
1014 develop probes. Recent marker development approaches, such as RAPTURE (Ali et al. 2016),
1015 however, have blurred the lines between RADseq and targeted capture-based approaches and
1016 offer a promising, cost-effective method that can explicitly avoid biased assumptions about the
1017 importance of exomic versus intergenic loci comprising the architecture of local adaptation.

1018 Beyond genetic linkage maps (e.g., Friedline et al. 2015) and reference genomes, which
1019 undoubtedly should be among our top priorities, other techniques outside of traditional
1020 genomics, such as transcriptomics, have the potential to complement genomic studies in many
1021 ways without great need for existing species-specific resources (reviewed in Romero et al.
1022 2012, Strickler et al. 2012; Vialette-Guiraud et al. 2016). For instance, comparative
1023 transcriptomic techniques in trees can be used to identify putatively orthologous sets of markers
1024 (e.g., Wachowiak et al. 2015; Yeaman et al. 2016) that can be used to describe the evolution of
1025 architecture (e.g., shared orthologs versus paralogs across species) or for comparative linkage
1026 mapping (Ritland et al. 2010) across systems. Additionally, with the appropriate study design,
1027 transcriptomics can be implemented in tree species to describe various aspects of differential
1028 expression (Cohen et al. 2010; Carrasco et al. 2017; Cronn et al. 2017), selective constraint
1029 (Mähler et al. 2017), prevailing selective forces (Hodgins et al. 2016), mapping of disease
1030 resistance (Liu et al. 2016; Liu et al. 2017), and regulatory networks (Zinkgraf et al. 2017). The
1031 multilocus paradigm of transcriptomics is amenable to identifying and testing hypotheses of the
1032 genetic architecture of complex traits in a network framework (Jansen et al. 2009; Leiserson et
1033 al. 2013; Civelek & Lusis 2014) and will no doubt provide valuable contributions for tree
1034 evolutionary biologists. Other areas amenable to network description such as metabolomics and
1035 proteomics would also be a complement, particularly if genetic studies contextualize results with
1036 findings from such approaches and vice versa. Ultimately the goal is to use *a priori* knowledge
1037 synthesized across past studies, techniques, and perspectives to guide further hypotheses

about underlying architecture, as exemplified by Mizrachi et al. (2017). Finally, high-throughput phenotyping as well as environmental measures at fine spatial scales below square-kilometers will also facilitate and advance our understanding of complex traits in trees (Sork et al. 2013; Rellstab et al. 2015; Leempoel et al. 2017).

Standardized data reporting

As we continue to accrue genotype-phenotype, genotype-environment, and phenotype-environment associations within and across tree species, authors should consider how their results can most effectively be used in further studies and syntheses, both for the purpose of validation or comparison as well as novel insights yet to be seen. Here we outline a few suggestions that can be broken down into reporting within manuscripts and metadata. For instance, in our survey of common garden studies used to estimate h^2 and Q_{ST}, in many cases the exact design of the study could not be replicated with the information from the manuscript alone. While an abbreviated design may be suitable for the main text, authors can provide much more detail in supplemental materials that can facilitate replication and comparison across studies (e.g., total individuals per garden, family, or block – as opposed to averages or ranges), which will ultimately facilitate syntheses regarding future directions. Further, future studies would benefit from estimating relatedness using marker data which will ultimately improve the precision of h^2, Q_{ST}, and missing heritability estimates (de Villemereuil et al. 2016). For cases in which estimating relatedness from markers is not appropriate or feasible, the field would benefit by authors exploring a range of underlying sibships (e.g., Eckert et al. 2015), which are often assumed to be half-sib relationships. While some studies in our survey assumed a mixed sibship relationship for open-pollinated sources, ultimately such assumptions without data exploration will affect the outcome or conclusions for any given study. A recently released R package by Gilbert and Whitlock (2014) allows for such an exploration of effects of mixed sibships on inference of Q_{ST} and its magnitude relative to F_{ST}. Inclusion of such exploration,

1063 even in the supplement, will help contextualize such studies as they are published. For studies
1064 estimating causality for genotype to phenotype, it would be worthwhile to include the regression
1065 coefficients or other estimates of effect size in addition to PVE (r^2). Importantly, the units of the
1066 effect size must be explicitly reported (e.g., Julian days versus phenotypic standard deviations),
1067 with the standard deviation also reported. For all association studies, supplemental tab- or
1068 comma-delimited text files (outside of a word processing document) easily analyzed with
1069 programming languages would also facilitate synthesis (even if providing redundant information
1070 from the main text), particularly if such files are well described with a README file and
1071 contained data regarding marker position, putative orthogroups, hits to reference genomes,
1072 effect size, PVE, genotypes by individual identifiers, individual population assignments, and if
1073 the sequence or marker was significantly associated to phenotype or environment. Such an
1074 operating procedure may work well in the short term, however in the long term such information
1075 will need to be easily accessible from one or very few repositories.

1076 Data standardization, the inclusion of meta-information, and compilation of these data
1077 specific to trees into a database with common terminology will be crucial to future inquiries with
1078 the purpose of synthesizing evidence for underlying architectures across species and
1079 environmental systems (e.g., as for human GWAS data: https://www.ebi.ac.uk/gwas/). If the
1080 data generated by tree biologists is disparate and housed across databases and journal
1081 supplements this impedes synthesis first by forcing scientists to collate information across
1082 sources, which may be further impeded by data redundancies or inconsistencies in data format
1083 and utilized nomenclature (Wegrzyn et al. 2012). While many journals have required submission
1084 of sequence data to repositories such as NCBI, such databases are lacking with regard to
1085 information pertaining to phenotypic, environmental, and geographic information upon which
1086 much of the foundation of our field is built. Submissions to Dryad somewhat overcome this, but
1087 there is no standardization within the community for content for such submissions and important
1088 information may be lacking. Currently, this information is often appended in supplemental files

1089 that cannot be readily accessed, compared, or queried in an efficient manner. Hierarchical
1090 ontologies can be used to ease this burden. Gene Ontology is likely the most recognizable to
1091 evolutionary biologists, but there also exist Plant Ontologies for organismal structure and
1092 developmental stages, Environmental Ontologies for habitat categorization, and Phenotypic,
1093 Attribute, and Trait Ontologies for the annotation of phenotypes. Such ontologies not only
1094 standardize nomenclature, but also assist in database queries. The utilization of such databases
1095 will no doubt encourage comparative studies and syntheses, as infrastructure and data
1096 accessibility are essential to the comparative approach (Neale et al. 2013; Ingvarsson et al.
1097 2016; Plomion et al. 2016). Luckily, such a database exists for the broader tree genetics
1098 community. The open-source database, called TreeGenes, can be accessed, queried, and
1099 visualized through DiversiTree, a web-based, desktop-style interface (Wegrzyn et al. 2008).
1100 Further, DiversiTree connects to the geographical interface CartograTree (Vasquez-Gross et al.
1101 2013) to encourage comparative synthesis by providing technology to filter and visualize geo-
1102 referenced biotic and abiotic data housed on TreeGenes. As promising as such databases are,
1103 they are only as useful as the data that is deposited to them. While TreeGenes will regularly
1104 import and enhance data from public repositories (through e.g., sequence alignment to
1105 published genomes), often pertinent metadata necessary for comparative synthesis is lacking
1106 (Wegrzn et al. 2008, 2012). Indeed, from our survey of published GPA since the release of the
1107 database in 2008, less than 13% (6/48) of the studies submitted their data directly to
1108 TreeGenes. To better prepare for future synthesis, we advocate that authors submit their data to
1109 the TreeGenes database and that reviewers and editors enforce this habit, as currently
1110 implemented for linkage maps published in *Tree Genetics & Genomes*. Consolidated, open-
1111 source resources will be crucial to the advancement of this field (Neale et al. 2013), and will no
1112 doubt spur knowledge that would not have been recognized otherwise. Prime examples of
1113 advancement to knowledge because of these types of resources and community-wide efforts
1114 come from the human GWAS literature where such resources provide crucial information

1115 necessary to study polygenic adaptation (e.g., Berg & Coop 2014).

1116 ***Empirical tests of theory***

1117 In combination with the development of truly genome-wide public resources, there is
1118 need to use these resources to validate and better characterize foundational ideas and
1119 assumptions in the theory of polygenic adaptation relative to the life history strategies of tree
1120 species. For example, Gagnaire & Gaggiotti (2016) highlight that the degree of polygenicity can
1121 be tested as a function of the number of GWAS hits relative to the length of contigs or
1122 chromosomes containing these markers. Simple models of polygenicity predict that there should
1123 be a positive correlation between these quantities. Thus, rather than assuming some functional
1124 form of a polygenic architecture (i.e., an approximate infinitesimal model) during analysis,
1125 researchers can strive to characterize, or at least exclude some forms of, the underlying genetic
1126 architecture prior to interpretation. In a related fashion, publically available data sets would spur
1127 comparisons across species and study systems to test hypotheses about polygenic
1128 architectures (e.g., genomic organization, effect size distribution) due to the relative timing of
1129 selection, degree of environmental contrast (e.g. diversifying selection and changes to the
1130 strength of negative selection), selection strength, and level of gene flow across diverging
1131 lineages. As an example, much of the theory of polygenic adaptation requires assumptions
1132 about simplistic demographics (where violations have consequences for standing levels of non-
1133 neutral diversity, e.g., Wang et al. 2017) and the equilibration among co-acting evolutionary
1134 forces over a large number of generations (Brandvain & Wright 2016). Indeed, differing
1135 architectures are expected as a function of the timing for the onset of selection (Le Corre &
1136 Kremer 2003; Kremer & Le Corre 2012), with subtle allele frequency shifts across populations
1137 dominating architectures near the onset of selection and larger allele frequency shifts much later
1138 in time. While there is need for empirical validation of this theory, there is also a need to
1139 characterize the prevalence of its predicted patterns across differing clades of tree species. In

other words, researchers could imagine testing the theory itself in natural populations (e.g., as begun by Le Corre & Kremer 2012) or assuming its validity and characterizing the circumstances under which to expect large shifts in allele frequencies across tree species with differing life history strategies. Little of any of this, however, will be possible without development of needed data and its deposition into publically available, standardized databases.

Concluding Remarks

The path forward provides a means by which we can most efficiently describe the underlying genetic architectures of traits important to management, conservation, and industry, and will can ultimately be used to expedite breeding projects. The past evolutionary history will have a profound effect on the underlying genetic architecture of such traits, and thus strengths and weakness of the data and methods used to uncover such architecture should be specifically addressed in future investigations, particularly in how utilized methods perform across various demographic and architecture scenarios. Insights gained from empirically testing theory in trees will also contribute to the advancement of this field and will ultimately quantify the variation in architecture across environments and species and inform effective management. The future is bright, but we are not yet out of the woods. As such, efficient advancement in this field relies on community efforts, standardized reporting, centralized open-access databases, and continual input and review within the community's research.

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Author Contributions

BML and AJE conceived the review, with contributions from MM, CEB, and TMF. BML, MM, CEB, and TMF contributed to the literature search and survey which was analyzed by BML. BML wrote the manuscript with contributions from MM and AJE. AJE created Box 1. All authors contributed to the editing of the manuscript.

FIGURES

Figure 1

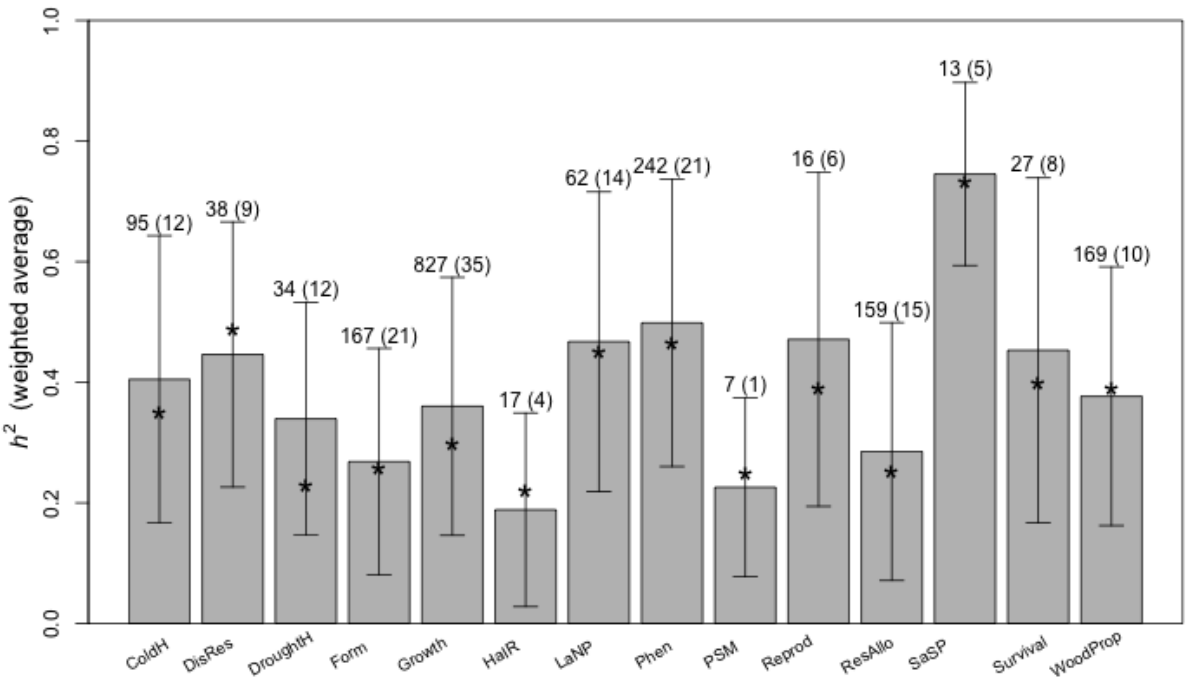
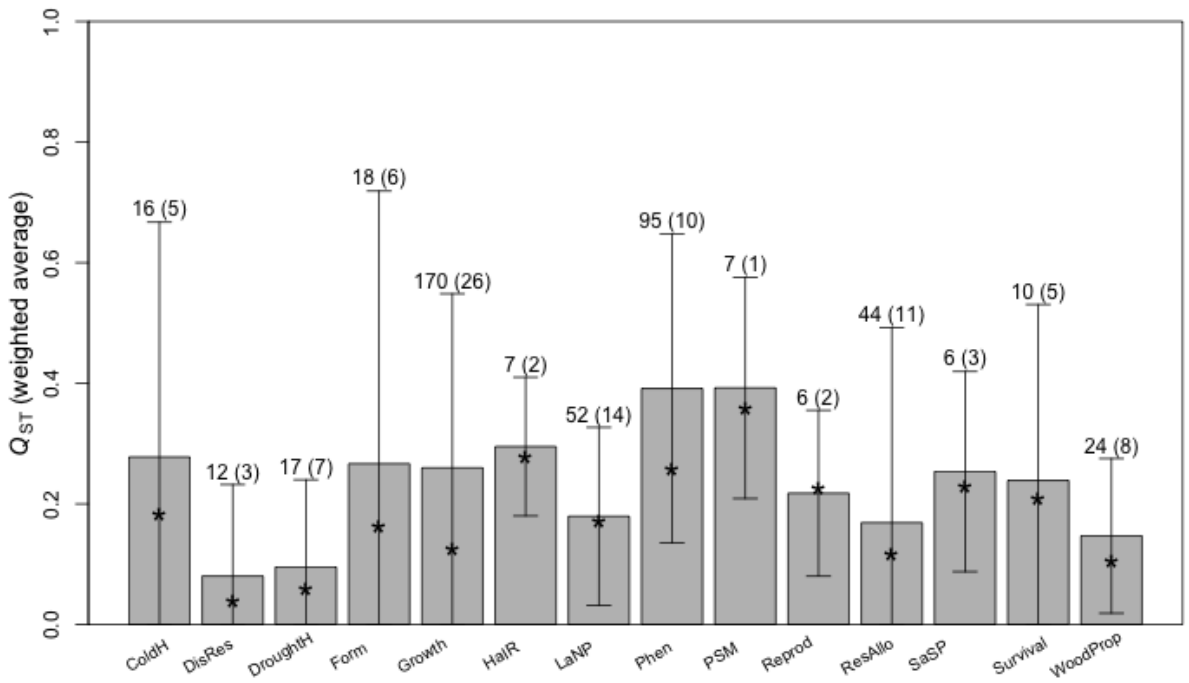


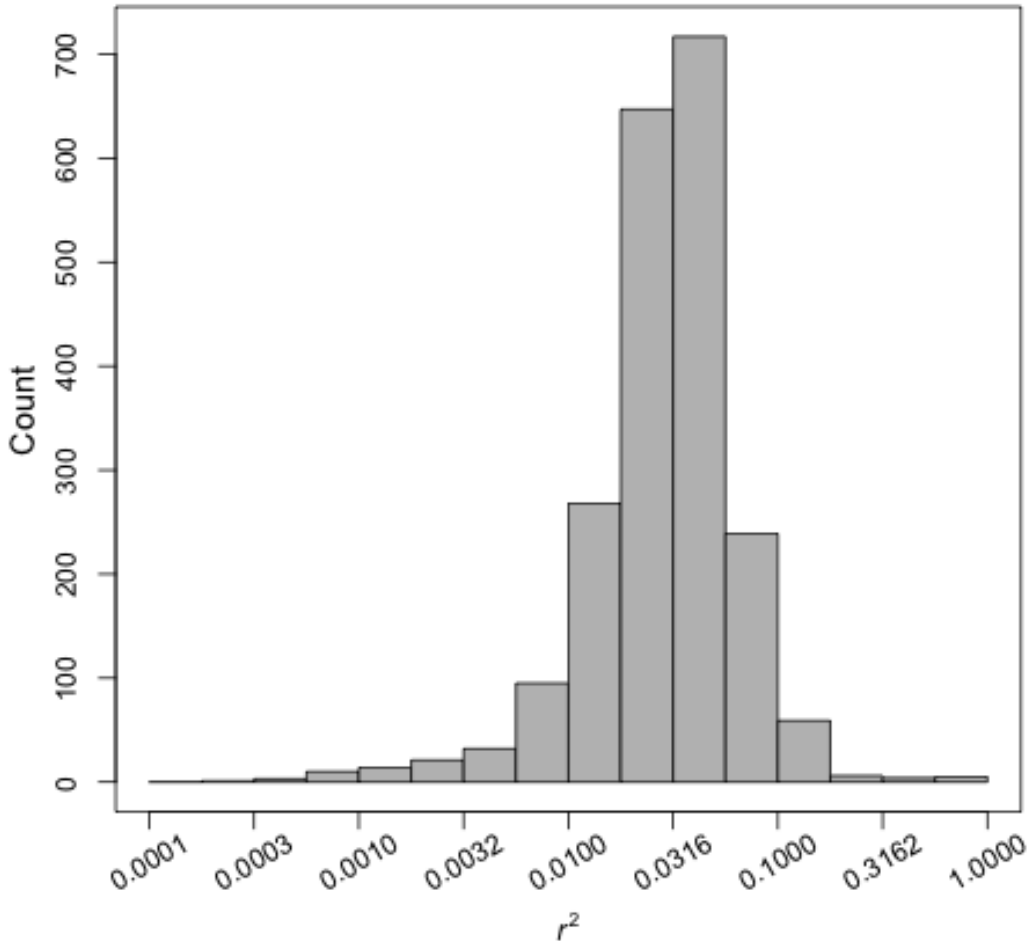
Figure 1. Averages of narrow sense heritability calculated by weighting the number of families used in each estimate of heritability. Error bars represent the standard deviation of the weighted averages. ColdH = cold hardiness, DisRes = disease resistance, DroughtH = drought hardiness, HaIR = herbivore and insect resistance, LaNP = leaf and needle properties, Phen = phenology, PSM = plant secondary metabolites, Reprod = reproduction, ResAllo = resource allocation, SaSP = seed and seedling properties, WoodProp = wood properties. Asterisks indicate median values of the unweighted Q_{ST} distribution.

1980 ***Figure 2***



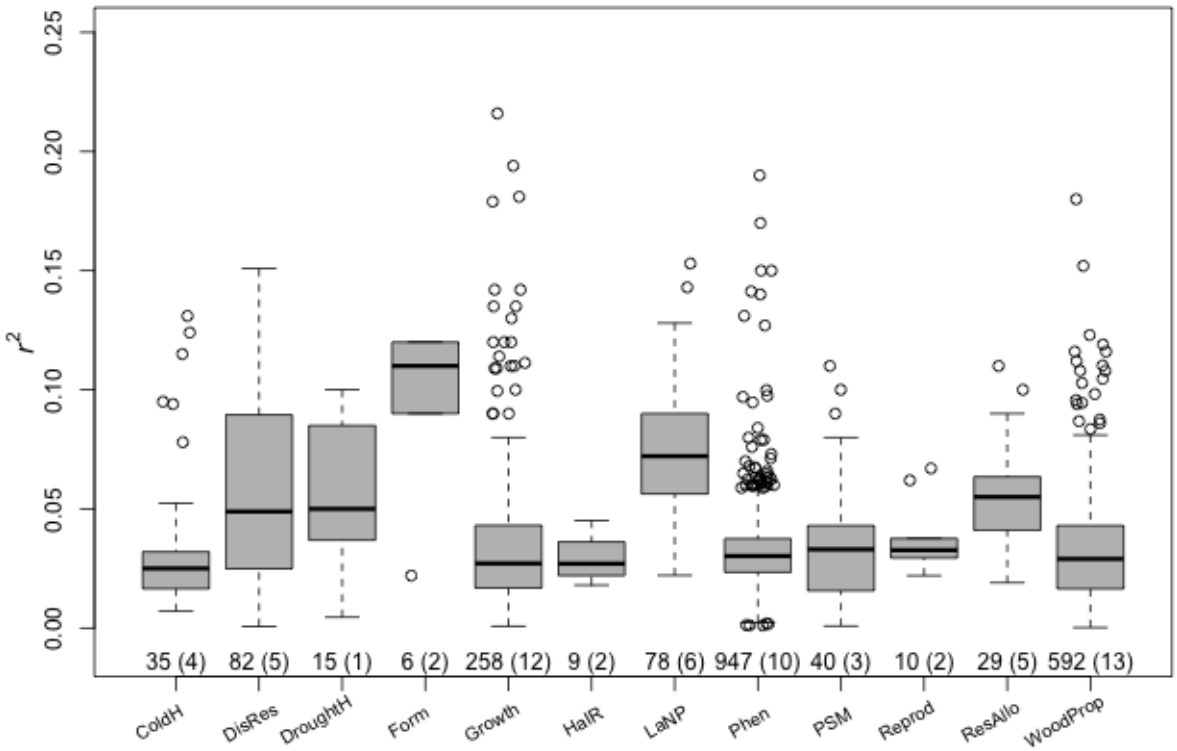
1981
1982 **Figure 2**. Average Q_{ST} for each of 14 traits from literature review calculated by weighting each
1983 estimate by the number of families used in the estimation. Error bars represent the standard
1984 deviation of the weighted averages. Numbers above error bars represent total number of
1985 estimates, with total number of unique species in parentheses. Asterisks indicate median values
1986 of the unweighted Q_{ST} distribution. Abbreviations as in Figure 1.

1987 ***Figure 3A***



1988
1989 **Figure 3A**. Counts of r^2 estimates from single-locus genotype-phenotype associations from
1990 literature review. Note logarithmic x-axis.

1991 ***Figure 3B***



1992
1993 **Figure 3B**. Distribution of r^2 values for trait groups within genotype-phenotype literature review.
1994 Values along x-axis are total number of estimates and number of species across estimates. Not
1995 shown are nine outliers for disease resistance to *Cronartium ribicola* in *Pinus monticola* (range =
1996 [0.402, 1.0]) from Lui et al. 2017. Abbreviations as in Figure 1.

BOXES

Box 1 figure

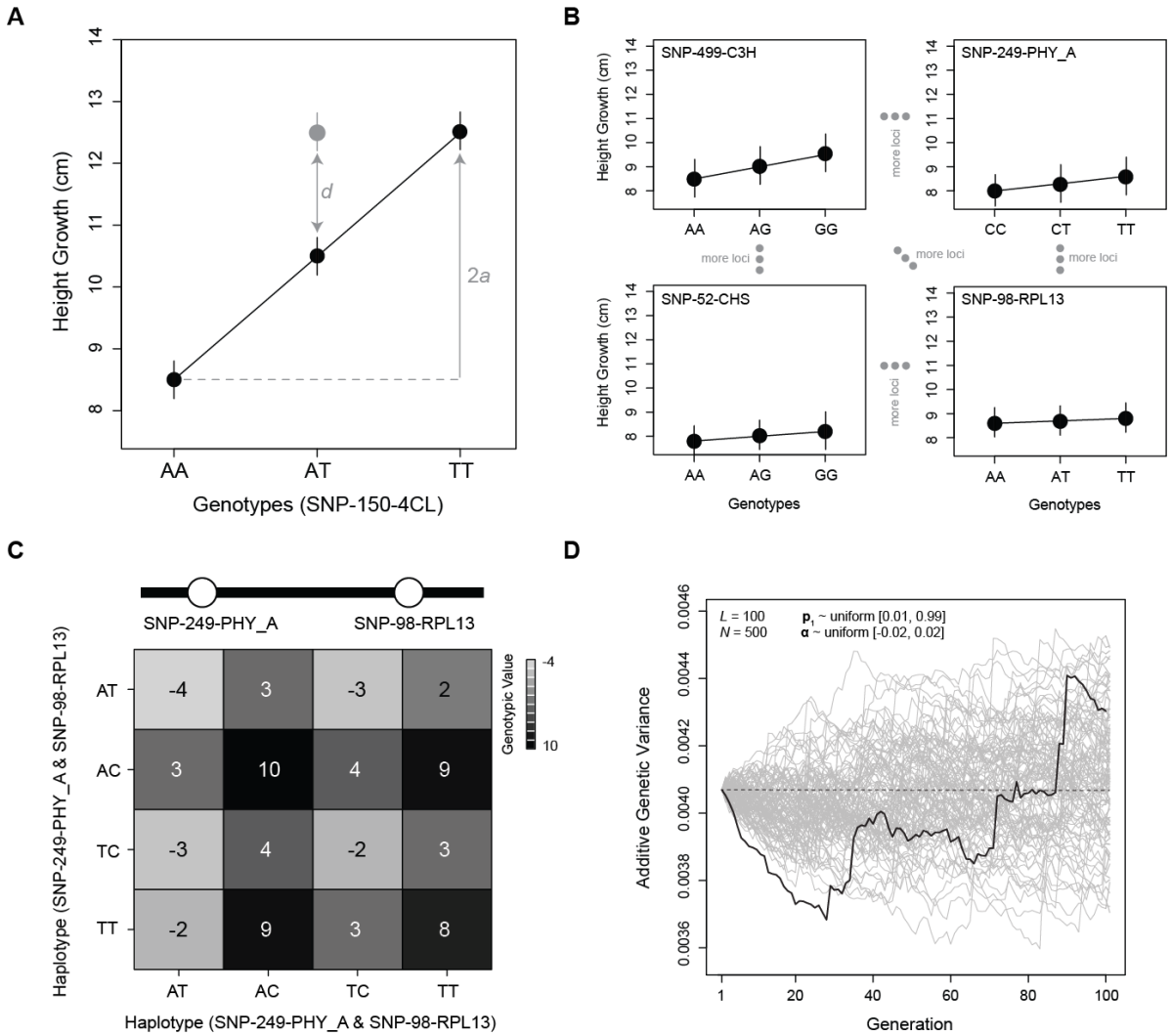


Figure I. Relevant quantitative genetic concepts are needed to understand the evolution of polygenic traits. (A) Additive and nonadditive effects at a single locus, where *a* is defined as the additive effect (also known as the average effect of allelic substitution [α] when there is no dominance) and *d* is defined as the dominance deviation. With dominance, $\alpha = a[1 + k(p - q)]$, where *k* is the degree of dominance (*k* = 0: additive, *k* = 1: dominance, *k* > 1: over-dominance, see Lynch & Walsh 1998). (B) Polygenic traits are determined by multiple genes, each with additive (shown) and non-additive (not shown) effects. The total additive effect is the sum of the additive effects at all causative loci. (C) Additive-by-additive epistasis, where the additive effect of an allele at the PHY_A SNP depends on what allele it is paired with at the RPL13 SNP. In this case, the effects can be thought of as dependent in the following manner using the four possible haplotypes at the PHY_A (A/T SNP) and RPL13 (C/T SNP) SNPs – AC: +5, AT: -2, TC: -1, TT: 4. (D) The effect of genetic drift on the additive genetic variance as determined by 100 independent, causative loci. Each line represents a simulation of genetic drift in a constant sized population (*n* = 500 diploids) conditioned on initial allele frequencies across loci ($\boldsymbol{p_1}$) and effect sizes (**α**). The

expected mean across all 100 simulations is given by the dashed black line. Any given simulation can deviate strongly from this expectation (solid black line). Thus, when the elements of ***p*** change over time, in this case due to genetic drift, so does the additive genetic variance.

Box 1: Basic Concepts from Quantitative Genetics

We follow the traditional decomposition of phenotypes into genetic and environmental components, which forms the basis of quantitative genetics (Fisher 1918, Lynch & Walsh 1998, Charlesworth & Charlesworth 2010, reviewed by Hill 2010). The phenotype of an individual (P) can be decomposed into effects from its genotype (G), its environment (E), and the interaction between its genotype and environment (GxE). Typically, this is thought of as deviations from the population mean, with each causative locus having two alleles. Using this framework, phenotypic variance (σ^2_P) can be decomposed into genotypic variance (σ^2_G), environmental variance (σ^2_E) and the variance due to the interaction between genotypes and environments (σ^2_{GxE}):

$$\sigma^2_P = \sigma^2_G + \sigma^2_E + \sigma^2_{GxE}$$

For a single locus, σ^2_G can be decomposed into variances arising from additive (σ^2_A) and dominance (σ^2_D) effects (Fig. I). For multiple loci, σ^2_G can be decomposed into variances arising from additive, dominance, and epistatic (σ^2_I) effects, with the total additive effect across loci being the summation of the effects at each of the causative loci. Dominance and epistatic effects are jointly termed non-additive effects. Thus, the previous equation can be expanded to the following:

$$\sigma^2_P = \sigma^2_A + \sigma^2_D + \sigma^2_I + \sigma^2_E + \sigma^2_{GxE}$$

The decomposition of σ^2_G into different types of effects provides a way of estimating narrow-sense heritability (h^2), which is defined as the ratio of additive genetic variance (σ^2_A) to total phenotypic variance (σ^2_P). For tree populations, this is often accomplished through variance partitioning techniques (Namkoong 1979) using half-sib designs in common gardens (White *et al.* 2007) or using molecular markers to estimate relatedness in the field (cf. Ritland & Ritland 1996). In the case of half-sib designs, if the assumptions of free recombination and little epistasis among causative loci, random mating, and lack of environmental covariance among sibs are satisfied, σ^2_A is given by (Lynch & Walsh 1998):

$$\sigma^2_A = 4\sigma^2_F$$

where σ^2_F is the variance due to family (e.g., as extracted from a linear mixed model). Hence, for a half-sib design, $h^2 = 4\sigma^2_F/\sigma^2_P$. Other sibling designs are possible, with the 4 in the previous equation replaced by $1/r$, where r is the coefficient of relationship (e.g., Whitlock & Gilbert 2012). Clonal and controlled mating designs are also often used for estimation of heritability, often broad-sense heritability (Namkoong 1979; White *et al.* 2007). When families are nested into populations, and an estimate of the among population variance component is made, these are the components also used to estimate Q_{ST} (Spize 1993; Prout & Barker 1993). When compared against estimates of F_{ST} using a similar variance decomposition procedure (e.g., Yang 1998) and a method suitable to account for the substantial variance associated with these components (e.g., Whitlock & Guillaume 2009) conclusions about local adaptation can be reached.

Heritability estimates are population, environment, and time specific, as evidenced by the relationship between σ^2_A and allele frequencies within populations (Lynch & Walsh 1998; e.g. Berg & Coop 2014):

$$\sigma_A^2 = 2\sum_{i=1}^{L} \alpha_i^2 p_i(1 - p_i)$$

where the summation is over the number of causative loci (L), α is the average effect of allelic substitution at each locus (Fig. I), and p_i is the frequency of one of the alleles at each of the causative loci. Thus, any evolutionary force altering p at some or all of the causative loci will change σ^2_A (cf. Box 3.7 in Charlesworth & Charlesworth 2010). Heritability is also uninformative about the underlying architecture itself, as are the relative magnitudes of the different variance components themselves (Huang & Mackay 2016), and can often be misleading about evolutionary potential (Hansen *et al.* 2011).

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Supplemental Information

The genomics of local Adaptation in trees: Are we out of the woods yet?

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Running Title: Are we out of the woods yet?

Keywords: trees, GWAS, genetic architecture, polygenic local adaptation

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Supplemental Figures

Figure S1

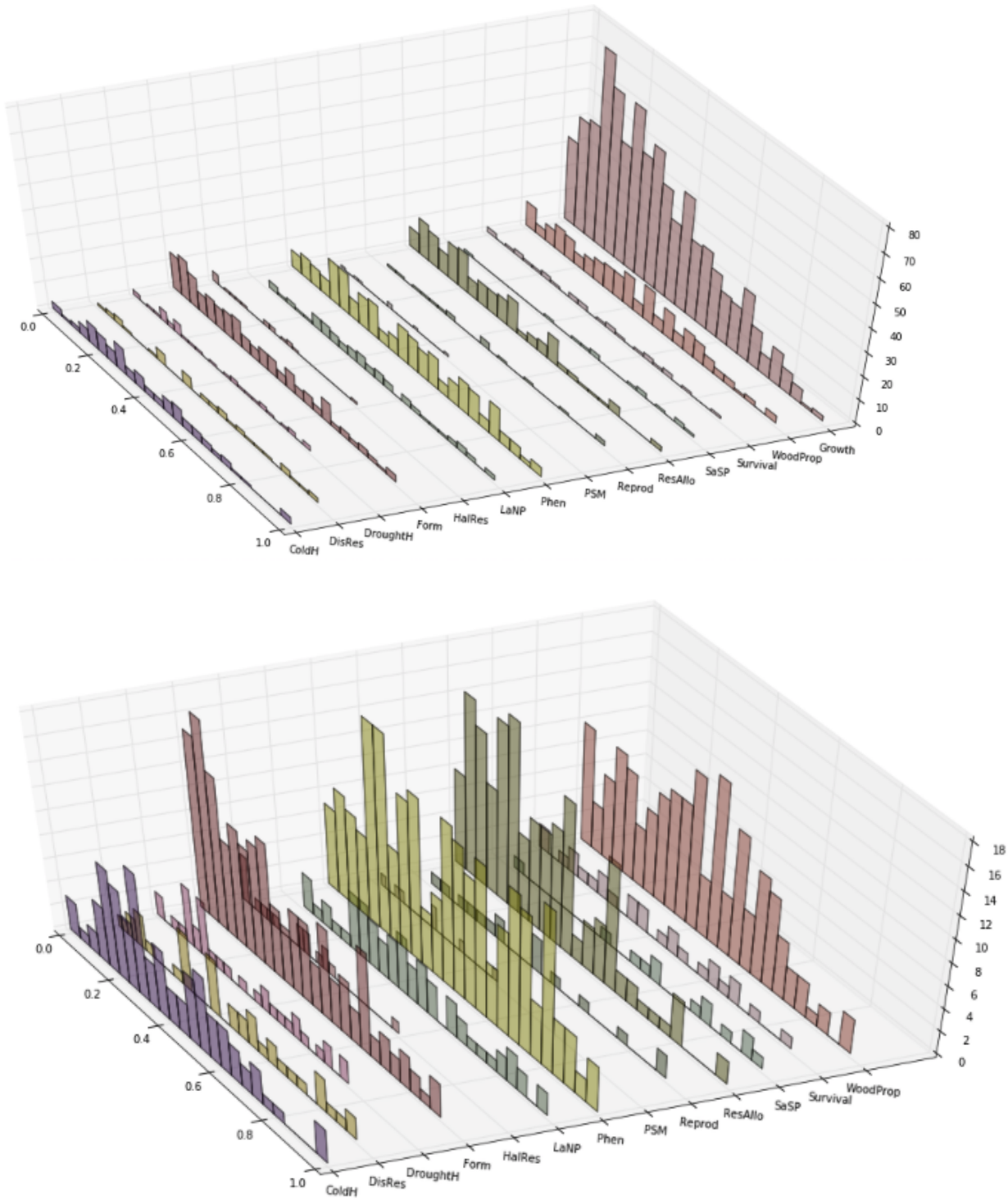
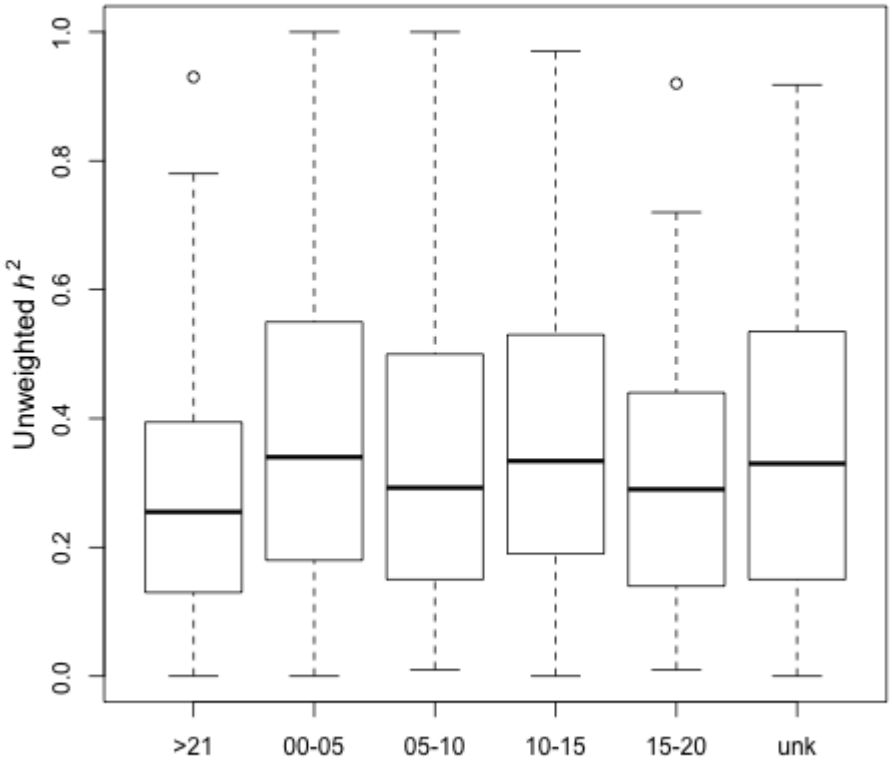


Figure S1. Distributions of unweighted narrow sense heritability with (A) and without (B) inclusion of the Growth distribution. Trait abbreviations as in Figure 1 of the main text.

2088 ***Figure S2***



2089
2090 **Figure S2**. Unweighted narrow sense heritability distributions by age (years). Unk = unknown
2091 age (i.e., not specified by article).

Figure S3

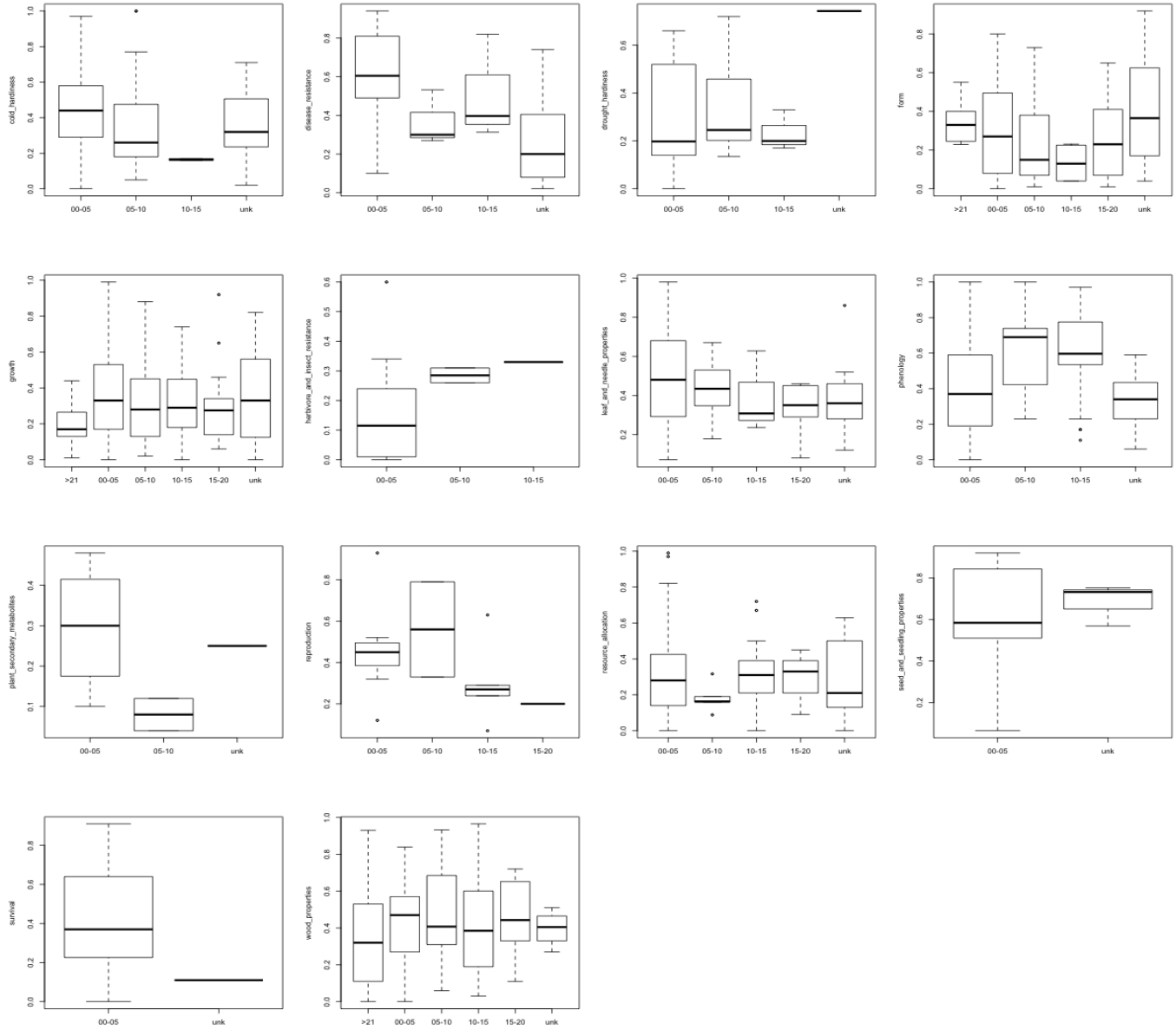


Figure S3. Unweighted narrow sense heritability distributions by age (years) and by trait category. Unk = unknown (i.e., not specified by article)

Figure S4

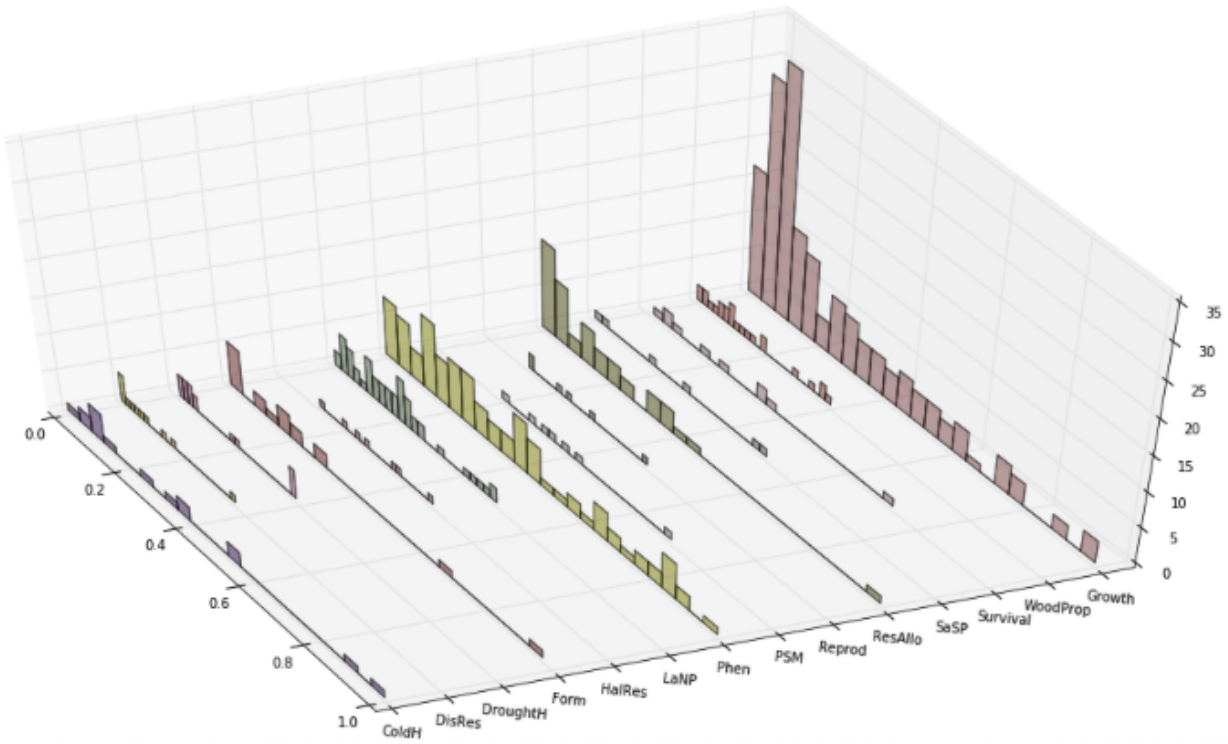


Figure S4. Distributions of unweighted QST estimates from literature survey. Abbreviations as in Figure 1.

2100 ***Supplemental Tables***

2101 ***Table S1***

rait Group	Total species	Total measurements	Angiosperm	Gymnosperm	Eucalypt	Pine	Populus
old hardiness	11	94	35	59	27	6	2
isease resistance	9	38	20	18	1	12	13
rought hardiness	12	36	15	21	4	10	4
orm	15	153	45	108	20	86	3
rowth	41	819	174	645	71	412	21
erbivore and insect resistance	4	17	17	0	8	0	0
eaf and needle properties	16	65	41	24	11	8	20
henology	22	240	92	148	0	50	29
lant secondary metabolites	1	7	7	0	7	0	0
eproduction	12	49	7	42	4	29	2
esource allocation	15	142	29	113	3	58	6
eed and seedling properties	5	13	2	11	0	2	0
urvival	8	27	5	22	1	20	2
/ood properties	10	168	35	133	13	81	22

2102 **Table S1**. Summary of total and per-species measurements used in literature review of narrow
2103 sense heritability.

2104 ***Table S2***

rait Group	Total measurements	Total species	Angiosperm	Gymnosperm	Eucalypt	Pine	Populus
:old hardiness	16	5	3	13	0	10	2
)isease resistance	12	3	3	9	0	9	3
)rought hardiness	17	7	9	8	4	5	4
orm	18	6	15	3	1	3	12
;rowth	170	26	73	97	13	76	44
lerbivore and insect esistance	7	2	7	0	6	0	0
eaf and needle properties	52	14	44	8	11	5	12
'henology	95	10	63	32	0	18	53
lant secondary metabolites	7	1	7	0	7	0	0
:eproduction	6	2	2	4	2	4	0
:esource allocation	44	11	16	28	3	26	10
eed and seedling properties	6	3	2	4	0	0	0
urvival	10	5	2	8	2	8	0
Vood properties	24	8	14	10	8	4	5

2105 **Table S2**. Summary of total and per-species measurements used in literature review of
2106 differentiation of quantitative genetic variation (Q_{ST}).

2107 ***Table S3***

rait Group	Total measurements	Total species	Angiosperm	Gymnosperm	Eucalypt	Pine	Populus
old hardiness	35	4	2	33	0	0	2
isease resistance	82	5	31	51	0	51	30
rought hardiness	15	1	0	15	0	15	0
orm	6	2	0	6	0	5	0
rowth	258	12	205	53	44	17	152
erbivore and insect resistance	9	2	9	0	6	0	3
eaf and needle properties	78	6	58	20	0	5	45
henology	947	10	886	61	0	0	846
lant secondary metabolites	40	3	32	8	29	8	3
eproduction	10	2	0	10	0	9	0
esource allocation	29	5	19	10	4	8	15
/ood properties	592	13	414	178	94	136	316

2108 **Table S3**. Summary of total and per-species measurements used in literature review of percent
2109 phenotypic variance explained by associated markers (r^2).

BOXES

Supplemental Box 1

Brief introduction to methods for single-locus genetic association analysis

Detecting associations between genetic markers and complex trait variation relies on fitting and evaluating linear models, typically of the form:

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\boldsymbol{u} + \mathbf{e},$$

where **y** is a vector of observed or inferred phenotypic values, $\boldsymbol{\beta}$ and **u** are vectors of random and fixed effects, respectively, **X** and **Z** are design matrices associated with $\boldsymbol{\beta}$ and **u**, and **e** is a vector of residuals (Yu *et al.* 2005). In the simplest model, the phenotype (**y**) is modeled as a function of genetic effects at a single locus, represented by marker genotypes for the samples comprising values in **y**, and covariates describing relatedness among sampled trees and the structure among populations from which those trees were sampled. Genetic effects are encoded based on *a priori* assumptions about the underlying architecture of the phenotypic trait under consideration, with the most frequent encoding being that for additive effects (e.g. counts of a reference allele) considered as either fixed or random effects (Goddard *et al.* 2009). Phenotypic values are often estimates derived through analysis of materials established within common gardens, either from clones or sibships, from which estimates of the genetic values of unmeasured trees (e.g. maternal trees for which markers have been genotyped) are made using the theory of Best Linear Unbiased Predictors (BLUPs; Henderson 1975; Searle *et al*. 1992; Piepho *et al.* 2008). Inclusion of only fixed effects results in a General Linear Model (GLM), whereas a mixture of fixed and random effects results in a Mixed Linear Model (MLM or LMM). The use of covariates is necessary to avoid identification of false positive associations arising from the confounding between neutral genetic and phenotypic variation due to demographic history and the analysis of relatives (Devlin & Roeder 1999; Yu *et al.* 2005; Price *et al.* 2006).

Models as described above are typically fitted and evaluated using restricted maximum likelihood (REML, Patterson & Thompson 1971), although Bayesian methods are available and have the advantage of specifying *a priori* assumptions more clearly, remove the distinction between fixed and random effects, and are more applicable to testing biologically realistic models (Stephens & Balding 2009). Output from these models include estimates of effect sizes for markers (e.g. r^2, coefficients for random effects, genotypic trait means) and, when used in a frequentist framework, probability values (*p*-values) of observing test statistics under a null model. Bayesian methods, in contrast, provide strength of evidence measures such as Bayes Factors for the association of each marker to the phenotype of interest. The ability to discover and correctly quantify effect sizes of true positives (i.e. causative markers or indirect associations resulting from linkage to causative markers) is dependent upon experimental design, including design of genotyping assays, and sample sizes (Long & Langley 1999; Zöllner and Pritchard 2007; Spencer *et al.* 2009), as well as genome-wide patterns of linkage disequilibrium relative to the density of markers in the genome, the genetic distance between the indirectly associated maker and the causative locus, and the true underlying genetic architecture of the phenotypic trait under consideration (Platt *et al.* 2010; Prichard *et al.* 2010; Caballero *et al.* 2015).

One model is typically fitted and evaluated per marker-phenotypic trait combination (but see e.g. Wegrzyn *et al.* 2010 for haplotype analysis). Even without the issue of confounding described above, this increases the likelihood of false positives arising solely from performing many statistical tests. A variety of methods exist to deal with multiple testing, with the most popular methods being those based on the false discovery rate (Storey & Tibshirani 2003) and permutation (Hirschhorn & Daly 2005). Additional methods exist for situations where the multiple tests are not independent from one another (e.g. linkage disequilibrium among markers, see Johnson *et al.* 2010) or when permutation analysis is problematic (Joo *et al.* 2016).

2161 **Supplemental References**

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