

# 1 DNA methylation signatures of duplicate gene evolution in angiosperms

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## 6 ABSTRACT

7 Gene duplications have greatly shaped the gene content of plants. Multiple factors, such as the  
8 epigenome, can shape the subsequent evolution of duplicate genes and are the subject of ongoing  
9 study. We analyze genic DNA methylation patterns in 43 angiosperm species and 928  
10 *Arabidopsis thaliana* ecotypes to finding differences in the association of whole-genome and  
11 single-gene duplicates with genic DNA methylation patterns. Whole-genome duplicates were  
12 enriched for patterns associated with higher gene expression and depleted for patterns of non-CG  
13 DNA methylation associated with gene silencing. Single-gene duplicates showed variation in  
14 DNA methylation patterns based on modes of duplication (tandem, proximal, transposed, and  
15 dispersed) and species. Age of gene duplication was a key factor in the DNA methylation of  
16 single-gene duplicates. In single-gene duplicates, non-CG DNA methylation patterns associated  
17 with silencing were younger, less conserved, and enriched for presence-absence variation. In  
18 comparison, DNA methylation patterns associated with constitutive expression were older and  
19 more highly conserved. Surprisingly, across the phylogeny, genes marked by non-CG DNA  
20 methylation were enriched for duplicate pairs with evidence of positive selection. We propose  
21 that DNA methylation has a role in maintaining gene-dosage balance and silencing by non-CG  
22 methylation and may facilitate the evolutionary fate of duplicate genes.

23 **Keywords:** Whole-genome duplication, gene duplication, epigenomics, evolution, DNA  
24 methylation, angiosperms

## 25 Introduction

26 Gene and genome duplication increases organismal gene content, genome size, and generates a  
27 repertoire for functional novelty (Flagel and Wendel 2009; Ohno 1970). Polyploidy or whole-

28 genome duplication (WGD) is much more pervasive in plants than other eukaryotic lineages  
29 (Otto and Whitton 2000). Multiple WGDs over the past 200 million years of angiosperm  
30 evolution has led to higher diversity in plant genomes evident from larger differences in genome  
31 size between closely related plant species than in other eukaryotes (Panchy, Lehti-Shiu, and Shiu  
32 2016). Small-scale or single-gene duplications (SGDs) (Jiang, Bao, et al. 2004; W. Wang et al.  
33 2006; Bailey et al. 2002; Zhang 2003) contribute to this gene repertoire and have been linked to  
34 environmental adaptation and domestication in plants (Michael Freeling 2009; Cuevas et al.  
35 2016; Xiyin Wang et al. 2009; Hanada et al. 2008). Tandem duplicates (TD) are thought to occur  
36 through unequal crossing-over, creating clusters of two or more genes adjacent to each other on  
37 the same chromosome (Zhang 2003). Proximal duplicates (PD) are gene copies separated by  
38 several intervening genes and arose either through the action of local transposition or  
39 interruption of ancient tandem duplication (Zhao et al. 1998; M. Freeling et al. 2008).  
40 Transposed duplication (TRD) creates a paralogous gene copy from the ancestral location to a  
41 novel location either by retrotransposition or DNA-based duplication (Cusack and Wolfe 2007).  
42 Finally, dispersed duplication (DSD) generates copies of genes that are neither adjacent to each  
43 other nor colinear and are produced through mechanisms that are not well understood (Michael  
44 Freeling 2009; Ganko, Meyers, and Vision 2007; Qiao et al. 2019).

45 Following gene duplication, paralogs are retained or lost (e.g., genome fractionation), and this  
46 loss or retention is biased depending on the mode of duplication and gene function (Wendel  
47 2015; Michael Freeling 2009). Products of WGDs are preferentially retained and tend to be  
48 enriched for genes involved in macromolecular complexes such as transcription factors, protein  
49 kinases, ribosomal proteins, and signal transduction. Multiple models have been proposed to  
50 explain the emergence and retention of gene duplicates. Prominent among them, the gene  
51 balance hypothesis posits that the stoichiometric imbalance of macromolecular complexes and  
52 regulatory networks leads to dosage-dependent phenotypic consequences (Veitia, Bottani, and  
53 Birchler 2008). However, comprehensive molecular mechanisms of duplicate gene retention and  
54 determining their functional fate remain largely unexplored (F. Cheng et al. 2018; Panchy, Lehti-  
55 Shiu, and Shiu 2016).

56

57 DNA methylation is an important chromatin modification, altering transcription, and helping to  
58 delineate heterochromatin and euchromatin (Law and Jacobsen 2010). DNA methylation plays a

59 critical role in diverse biological processes such as genome imprinting, X-inactivation, silencing  
60 of transposons (TEs) and repetitive regions, and the regulation of gene expression (A. Bird 2002;  
61 Edwards and Ferguson-Smith 2007; Finnegan, Peacock, and Dennis 1996). Methylation of  
62 cytosines in the CG dinucleotide context can be found throughout plants, animals, and fungi;  
63 while non-CG methylation occurring at trinucleotide CHG and CHH (where H is A, T or C)  
64 contexts is widespread in plants and known to be associated with repression of transposable  
65 elements (Gruenbaum et al. 1981; Meyer, Niedenhof, and ten Lohuis 1994; Zemach et al. 2010).  
66 In plants, maintenance of CG methylation (mCG) is carried out by METHYLTRANSFERASE 1  
67 (MET1), a homolog of the highly conserved mammalian DNA METHYLTRANSFERASE 1  
68 (DNMT1) (Finnegan and Dennis 1993). The establishment and maintenance of non-CG  
69 methylation involve the plant-specific CHROMOMETHYLASE (CMT) family of DNA  
70 methyltransferases and the RNA-directed DNA Methylation (RdDM) pathway (Stroud et al.  
71 2014; Raju et al. 2019).

72  
73 The functional consequence of DNA methylation is dictated by its location and sequence context  
74 and differs for TEs and genes (Law and Jacobsen 2010; Zemach et al. 2010; Sigman and Slotkin  
75 2016). TE repression is an ancient function of DNA methylation (Goll and Bestor 2005;  
76 Henderson and Jacobsen 2007) and transcriptional silencing usually involves ubiquitous  
77 methylation in CG and non-CG contexts (Roudier, Teixeira, and Colot 2009; Zemach et al.  
78 2010). Even though genes and TEs are methylated distinctly, DNA methylation from adjacent  
79 TEs can spread to nearby genes affecting its regulation. Such DNA methylation in gene  
80 promoters is usually associated with transcriptional repression (Suzuki and Bird 2008; Ahmed et  
81 al. 2011), however, there are notable exceptions (Gent et al. 2013; Harris et al. 2018).

82  
83 Patterns of DNA methylation in coding regions of plants show strong associations with gene  
84 expression patterns. Gene body methylated (gbM) genes are characterized by enrichment of  
85 mCG in the transcribed region and depletion at the transcription start site and transcription  
86 termination sites. GbM genes comprise the bulk of methylated genes in many plant species, are  
87 often housekeeping genes with medium to high expression levels, and evolve slowly compared  
88 to unmethylated genes (UM) (Bewick et al. 2016; Takuno and Gaut 2013). UM genes have  
89 insignificant amounts of DNA methylation in coding regions, tend to be shorter in length and

90 number of exons (Takuno and Gaut 2012) and show more variable expression levels (Niederhuth  
91 et al. 2016). TE-like genes with persistent methylation of CHG and CHH nucleotide contexts  
92 within coding sequences, similar to transposons typically have low expression levels, show little  
93 to no conservation in DNA methylation between orthologous genes, and are typically associated  
94 with local TEs (Niederhuth et al. 2016; D. K. Seymour et al. 2014; El Baidouri et al. 2018). It is  
95 possible in some cases that these genes are mis-annotated transposons (Schnable 2019;  
96 Bennetzen et al. 2004), however, TE-like methylation has been observed in many genes of  
97 known function (Niederhuth et al. 2016; Schmitz, He, et al. 2013; Schmitz, Schultz, et al. 2013),  
98 including species-specific genes (Silveira et al. 2013).

99

100 DNA methylation may decrease genetic redundancy through silencing of duplicated gene copies  
101 (El Baidouri et al. 2018). Expression reduction models suggest that heavy DNA methylation  
102 immediately after duplication buffers the expression levels of duplicate genes (Rodin and Riggs  
103 2003; Chang and Liao 2012). Comprehensive analysis of DNA methylation, gene expression,  
104 and chromatin accessibility in humans and mouse have shown that duplicate genes display  
105 stronger signatures of DNA methylation distinguishing younger and older duplicates, and  
106 corresponding functional divergence in chromatin accessibility and gene expression levels  
107 (Keller and Yi 2014; Chang and Liao 2012). Promoters of young duplicates were highly  
108 methylated compared to promoters of older duplicates, and gene duplicates from  
109 retrotransposition displayed more noticeable DNA methylation divergence compared to other  
110 gene pairs (Keller and Yi 2014). However, gene-body methylation did not show a relationship  
111 with evolutionary age as promoter methylation. This was in contrast to studies in rice and  
112 zebrafish that showed an association between gbM and evolutionary age (Keller and Yi 2014; Y.  
113 Wang et al. 2013; Zhong et al. 2016). Recent studies in cassava and soybean showed a strong  
114 correlation between gbM genes and expression of WGD genes (H. Wang et al. 2015; Kim et al.  
115 2015). Moreover, gene duplicates derived from different duplication origins in rice showed  
116 different correlation directions for gbM and expression divergence of duplicates (Y. Wang et al.  
117 2013). Although the role of DNA methylation in differential expression of gene duplicates have  
118 been explored in a few plant taxa (El Baidouri et al. 2018; C. Xu et al. 2018; H. Wang et al.  
119 2015; Y. Wang et al. 2013; Xutong Wang et al. 2017; J. Wang, Marowsky, and Fan 2014), the  
120 complex interaction of the genome and epigenome on duplicate gene evolution remains poorly

121 understood at a broad phylogenetic scale. Here, we examine DNA methylation divergence of  
122 duplicate genes across 43 diverse angiosperm species to identify general trends in the  
123 relationship between DNA methylation and duplicate gene evolution.

124

125

## 126 **Results:**

### 127 **Patterns and distribution of genic DNA methylation**

128 Annotated gene models from 43 angiosperm species were classified based on their genic DNA  
129 methylation patterns (Niederhuth et al. 2016; Takuno and Gaut 2012) as gene body methylated  
130 (gbM), transposable element-like (TE-like), or unmethylated (UM) (Table S1). We then explored  
131 the genomic distributions of each genic DNA methylation class for each species. It has been  
132 shown that DNA methylation tends to be higher in the centromere and pericentromeric regions  
133 (Cokus et al. 2008; Lister et al. 2008) and non-CG methylation of genes is associated with local  
134 TE content and genome size (Niederhuth et al. 2016; Takuno, Ran, and Gaut 2016). Previously,  
135 El Baidouri et al. took advantage of high-resolution genetic maps in soybean to delineate  
136 pericentromeric regions to show that TE-like genes are enriched in the TE-rich pericentromeric  
137 regions (El Baidouri et al. 2018). Lacking such detail for most species, we used the number  
138 genes, TEs, and TE-base pairs in sliding windows as a proxy for regions of euchromatin and  
139 heterochromatin (Figure 1, Figure S1). Chromosomal plots of the distributions of methylated  
140 genes and TEs, helped visualize these distributions (Figure S2) It should be noted that this  
141 analysis does not capture TE content in the immediate vicinity of genes, but instead reflects large  
142 distribution patterns of both genes and TEs across chromosomes. All three classes of genic  
143 methylation classifications (gbM, TE-like, and UM genes) showed positive correlation with the  
144 distribution of genes in all species (Table-S2), except for TE-like genes in *Arabidopsis thaliana*,  
145 that showed a negative correlation with gene distribution (Pearson's  $r = -0.31$ ,  $p < .001$ ). The  
146 distribution of gbM and UM genes was negatively correlated with TE content across the majority  
147 of species (gbM: 34/43 species; UM: 30/43 species). Those species which showed a positive  
148 correlation between gbM/UM genes and TE content also showed a positive correlation between  
149 TE content and gene distribution. TE-like genes were positively correlated with TE distribution  
150 in *A. thaliana* (Figure 1A, Figure S1,S2) and most other species (28/43). Surprisingly, a number  
151 of species did not show this expected pattern (Figure 1B-F, Figure S1,S2).

152 We observed that many of the species deviating from this expected pattern were located in the  
153 legumes and grasses, which could suggest that there may be lineage-specific effects on the  
154 distributions. We used Pagel's lambda ( $\lambda$ ) to test for phylogenetic signals under a 'Brownian

155 Motion' model of trait evolution (Münkemüller et al. 2012; Pagel 1999). The correlation  
156 between TE-like genes and TEs showed a strong phylogenetic signal (Pagel's lambda ( $\lambda$ ) = 0.61,  
157  $p = .01$ ). Similarly, correlation between gbM genes and TEs also showed evidence of  
158 phylogenetic signal (Pagel's lambda ( $\lambda$ ) = 0.82,  $p = .02$ ; Table-S3). For gbM genes, it was  
159 previously shown that there is a lineage-specific reduction of gbM in the Brassicaceae, which  
160 could explain the observed signal for gbM. To test this, we reanalyzed the data by excluding  
161 *Eutrema salsugineum*, *Brassica rapa*, and *Brassica oleracea* from the analysis and still found  
162 significant evidence of phylogenetic signal for gbM genes and TEs (Pagel's lambda ( $\lambda$ ) = 0.76,  $p$   
163 =  $.04$ ). As genome size correlates with genic non-CG methylation (Niederhuth et al. 2016;  
164 Takuno and Gaut 2012), we analyzed genome size data from the Plant DNA C-values database  
165 (release 7.1; (Pellicer and Leitch 2020)) for all the species used in our study and did not find a  
166 phylogenetic signal for genome size (Pagel's lambda ( $\lambda$ ) = 0.21,  $p = .52$ ). The lack of  
167 phylogenetic signal for genome size in these species suggests that the lineage-specific changes in  
168 distribution of gbM and TE-like genes are unlikely to be derived from genome size variation.

#### 169 **Associations of genic DNA methylation with mode of gene duplication**

170 To understand the relationship between genic DNA methylation and gene duplication we  
171 identified and classified duplicate genes based on their mode of duplication (Table-S4) using  
172 *DupGen\_finder-unique* (Qiao et al. 2019). We then performed a two-sided Fisher's exact test to  
173 obtain an odds ratio for each mode of gene duplication with each DNA methylation classification  
174 (Figure 2, Table-S5). WGDs are depleted of TE-like genes across all species and enriched for  
175 gbM genes in most species, except *B. rapa* (odds.ratio = 0.53,  $p < .001$ ). Several other species  
176 showed under-representation of gbM genes at a lower p-value cutoffs ( $0.001 < p < 0.05$ ), *E.*  
177 *salsugineum* (odds.ratio = 0.29,  $p = .009$ ), *Cucumis sativus* (odds.ratio = 0.91,  $p = .03$ ) and  
178 *Citrullus lanatus* (odds.ratio = 0.88,  $p = .008$ ) (Table-S5). WGDs showed enrichment for  
179 unmethylated genes in 26 out of 43 species. Of the remaining species, *Gossypium raimondii*  
180 (odds.ratio = 0.92,  $p = .003$ ), *Populus trichocarpa* (odds.ratio = 0.73,  $p < .001$ ) and *Glycine max*  
181 (odds.ratio = 0.63,  $p < .001$ ) showed significant depletion of UM genes in WGDs.

182 For single-gene duplications (SGDs), association with genic DNA methylation differed  
183 significantly from WGD and between modes of SGD. Tandem and proximal duplicates were  
184 depleted of gbM genes and often enriched in TE-like and UM genes (Figure 2). There were

185 exceptions, with members of Fabaceae (except *Phaseolus vulgaris*) and Poaceae (except  
186 *Sorghum bicolor*) showing depletion of TE-like genes in tandem duplicates (Table-S5).  
187 Dispersed genes showed clear depletion of UM genes and enrichment of TE-like genes. Patterns  
188 of gbM in dispersed genes were mixed. While members of Poaceae (except *Zea mays* and  
189 *Panicum virgatum*) showed enrichment of gbM genes, Fabaceae (except *P. vulgaris*) showed  
190 depletion of gbM genes (Table-S5). Transposed genes were depleted in UM and TE-like genes  
191 while showing enrichment for gbM genes. Exceptions are *Z. mays*, *Malus domestica*, *Fragaria x*  
192 *ananassa* and *G. max*, which showed depletion of gbM genes and enrichment of TE-like genes.  
193 Singletons are depleted in gbM genes and enriched in UM genes (Figure 2). These findings  
194 enable us to determine the contributions of genic DNA methylation patterns on the evolutionary  
195 fates of gene duplicates.

#### 196 **Stasis and switching in genic DNA methylation states**

197 Duplicate gene pairs may have different methylation profiles. Multiple factors can influence  
198 these differences, such as methylation of parent-of-origin gene, evolutionary constraints, and  
199 chromatin environment of the new duplicate copy. We first compared duplicate pairs where each  
200 gene in the pair could be conclusively classified into one of the three genic methylation classes  
201 (Figure 3A, Table-S6). WGD pairs tend to resemble each other, with ~63% to 96% gene pairs  
202 (median - 87%) having the same methylation profiles. Similarly, tandem (~71%-94%, median –  
203 82%), proximal (~63%-95%, median – 76%), and dispersed (~66-95%, median – 82%)  
204 duplicates also showed a higher proportion of gene pairs with similar methylation profiles.  
205 Transposed duplicates had the broadest range, from 54% gene pairs showing similar methylation  
206 profiles in *Z. mays* to 90% in *E. salisugineum* (median – 77%). This suggests that regardless of  
207 the mode of duplication, most duplicate copies retain similar DNA methylation profiles,  
208 however, switching is not infrequent. For most modes of duplication, the original and derived  
209 copies cannot be determined, so we cannot determine the directionality of switching. For  
210 transposed duplicates, however, it is possible to identify a parental and transposed copy  
211 indicating the direction of switching. A higher proportion of transposed copies were TE-like  
212 genes compared to their parental gene in all species except *C. lanatus* (Table-S7, Figure 3B).  
213 Transposed copies also showed a lower proportion of gbM (40/43 species) and UM genes  
214 (32/43 species) compared to their parent gene in most species (Table-S7, Figure 3B). While the



215 majority of transposed duplicates retain the same genic DNA methylation status as their parental  
216 copy, TE-like transposed copies showed a higher frequency of having switched from their  
217 original methylation status, with higher proportions of the parental copies being either gbM or  
218 UM (Figure 3C).

### 219 **Genic DNA methylation patterns associate with gene age**

220 We hypothesized that there may be a relationship between the age of gene duplication and  
221 patterns of genic DNA methylation and so used two different approaches to address this  
222 question. In the first approach, we examined the distribution of synonymous mutations (Ks)  
223 based on both the mode of gene duplication and the class of genic DNA methylation (Figure  
224 4A,B,D,E, Figure S3). Ks distributions have been widely used to date gene duplication events, as  
225 synonymous mutations are expected to have less of an impact on gene function and so can  
226 accumulate with evolutionary age. A lower Ks, therefore suggests a more recent duplication  
227 event (Lynch and Conery 2000). We find distinct associations between WGDs and SGDs, their  
228 genic DNA methylation profiles, and the age of gene duplication (Figure 4A,B,D,E; Figure S3;  
229 Table S8). TE-like SGDs were clearly younger, while gbM SGDs were older. For WGDs, the  
230 situation is more complex. In some species, WGD gbM genes were younger, while in others,  
231 they were older. These differences likely reflect differences since the last WGD and/or a history  
232 of nested WGDs.

233 In the second approach, we used *MCSanX-transposed* to detect transposed gene duplication  
234 events that occurred at different periods (epochs) in the phylogenetic tree since species  
235 divergence (Table-S9) based on sequential exclusion of the closest outgroup (Y. Wang, Li, and  
236 Paterson 2013). This approach is independent of the Ks-based approach used above. We then  
237 tested transposed genes in each epoch for enrichment or depletion of genic DNA methylation  
238 (Figure 4C,F; Figure S4, Table S10). Younger transposed duplicates were depleted in gbM genes  
239 and enriched for TE-like genes, while more ancient transposed duplicates were depleted of TE-  
240 like genes and enriched for gbM genes. The trend in UM genes was unclear. *B. oleracea* and *P.*  
241 *virgatum* did not show a significant depletion in gbM genes in younger transposed genes, while  
242 *B. rapa* (odds.ratio = 2.45,  $p < .001$ ), and *E. salsugineum* (odds.ratio = 13.08,  $p = 0.004$ ) showed  
243 significant enrichment of gbM genes in younger transposed genes (Table-S10). This deviation  
244 from the depletion of gbM genes in younger transposed genes for Brassicaceae is likely due to

245 the known low number of gbM in these species (Bewick et al. 2016; Niederhuth et al. 2016),  
246 while we cannot explain this effect in *P. virgatum*.

247 We reasoned that some of the variation in the enrichment of genic DNA methylation classes  
248 amongst SGDs might be due to variation in the age of SGDs. To test this, we plotted the  
249 distribution of Ks for transposed, tandem, and proximal genes, ordered based on their median Ks  
250 (Figure S5). For transposed duplicates, species enriched for TE-like genes tended to be younger,  
251 while species depleted for TE-like genes tended to be older. For tandem and proximal genes,  
252 however, the pattern was not as clear, suggesting a much more complex scenario where other  
253 factors contribute to the enrichment or depletion of TE-like genes amongst these duplicates.

#### 254 **Genic DNA methylation and duplicate gene evolution**

255 There are multiple possible evolutionary fates of duplicate genes (Panchy, Lehti-Shiu, and Shiu  
256 2016). The ratio of nonsynonymous (Ka) to synonymous mutations (Ks) is commonly used to  
257 test for selection (Kreitman 2000). A  $Ka/Ks < 1$  is indicative of purifying selection,  $Ka/Ks \sim 1$   
258 suggests a protein is evolving neutrally, while a  $Ka/Ks > 1$  is suggestive of positive selection.  
259 Comparing the Ka/Ks distributions for duplicate gene pairs (Figure 5A-D, Figure S6, Table-S11)  
260 shows that the vast majority of duplicate pairs have a  $Ka/Ks < 1$ , indicating purifying selection.  
261 However, the distribution of TE-like genes, particularly for single-gene duplicates, is strongly  
262 shifted toward higher values, which suggests relaxed selective constraints on many TE-like  
263 genes. This trend was true of all TE-like gene duplicates, regardless of mode of duplication, but  
264 was particularly pronounced for transposed and dispersed SGDs (Figure S6). Interestingly, the  
265 distribution of TE-like genes in many species also shows a shift toward  $Ka/Ks > 1$  (Figure 5,  
266 Figure-S6). Limiting our analysis to duplicate genes with a  $Ka/Ks > 1.1$ , TE-like genes were  
267 significantly overrepresented in 38/43 species (Figure 5E,F, Table-S12). Of the other five, the  
268 number of only *L. japonicus* appeared to show an opposite pattern, but this was non-significant  
269 given the low number of genes with  $Ka/Ks > 1.1$ . GbM genes, in contrast, were significantly  
270 underrepresented in 39/43 species and of the remaining four, only *E. salsugineum* showed an  
271 opposite pattern (Figure 5E,F, Table-S12). UM genes were significantly overrepresented in 18  
272 species, and significantly underrepresented in 14 species (Figure 5E,F, Table-S12).

273 Larger-impact mutations besides nonsynonymous substitutions can impact genes. For instance,

274 differentially methylated regions in all three sequence contexts (C-DMRs) are enriched amongst  
275 structural variation in *A. thaliana* (Kawakatsu et al. 2016). Presence absence variation (PAV) is a  
276 type of structural variation where entire gene copies may be present or absent between  
277 individuals in a species. We used previously published PAV data from four species (*B. oleracea*,  
278 *Solanum lycopersicum*, *Solanum tuberosum*, and *Z. mays*) to examine whether there was a  
279 relationship between PAV and genic DNA methylation. We initially examined the relationship  
280 between genic DNA methylation for all genes (duplicate and non-duplicate) and PAVs in all four  
281 species (Figure S8; Table-S13). TE-like genes showed a significant enrichment amongst PAVs  
282 ( $p < 0.001$ ) in all species, while gbM genes were significantly depleted ( $p < 0.001$ ) in all but *B.*  
283 *oleracea*. UM genes showed conflicting patterns, being enriched in both *B. oleracea* and *S.*  
284 *lycopersicum* ( $p < 0.001$ ), depleted in *Z. mays* ( $p < 0.001$ ) and no-significant enrichment in *S.*  
285 *tuberosum*. These same observations held up when the analysis was limited to duplicate genes  
286 (Figure S8, Table-S13).

### 287 **Population scale genic DNA methylation of duplicate genes**

288 Within a species DNA methylation can vary across the population (Schmitz, He, et al. 2013;  
289 Kawakatsu et al. 2016; Vaughn et al. 2007; Eichten et al. 2013, 2016). We leveraged methylome  
290 data from the *A. thaliana* 1001 Epigenomes Project (Kawakatsu et al. 2016) to examine the  
291 relationship between gene duplication and DNA methylation at a population level. Genes from  
292 928 *A. thaliana* accessions were classified as before. For each genic methylation classification,  
293 we binned the genes based on the frequency of each classification (0%, <25%, 25%-50%, 50%-  
294 75%, >75%) across all 928 accessions (see methods). Looking at the distribution of synonymous  
295 substitutions (Ks), we see clear differences in the frequency of methylation states and the age of  
296 duplication. GbM genes increase in frequency across the population with increasing age of  
297 duplication, while more recently duplicated genes are less likely to be gbM (Figure 6A). TE-like  
298 and unmethylated genes show the opposite pattern (Figure 6B,C), with increased frequency in  
299 younger duplicates

300 Increasing frequency of gbM across the population corresponds with an increase in Ks, while  
301 increasing frequency of both TE-like and UM corresponds to a decrease in Ks (Figure 6D-F).  
302 This suggests a relationship between the age of duplication and population-level frequencies of  
303 genic DNA methylation. We further explored how each duplication mode affects genic

304 methylation variation across diverse *A. thaliana* accessions. While dispersed duplicates with  
305 gbM in <25% of accession are equally distributed among young and old genes, duplicates with  
306 gbM in more accession tend to be older dispersed duplicates (Figure S9A). In contrast, we see  
307 exactly the opposite trend in TE-like genes where younger dispersed genes have higher  
308 proportion of TE-like methylation across the accessions. We also see a similar pattern in the  
309 transposed duplicates, with older transposed duplicates with TE-like methylation showing <25%  
310 accession with TE-like methylation (Figure S9B). These results suggest that DNA methylation  
311 plays an important role in the evolution of duplicate gene retention through inter- and intra-  
312 species variation in genic methylation patterns.

313

## 314 **Discussion:**

315 We have characterized DNA methylation patterns and modes of gene duplication across 43  
316 Angiosperm species. Our findings show that different patterns of genic methylation are associated  
317 with different modes (WGD vs SGD) and features (e.g. duplicate age) of gene duplication. The  
318 role of the epigenome, in particular, DNA methylation, in the evolution of duplicate genes has  
319 been explored in a handful of taxa (Keller and Yi 2014; Xutong Wang et al. 2017; Kim et al.  
320 2015; C. Xu et al. 2018; Y. Wang et al. 2013; Zhong et al. 2016; Rodin and Riggs 2003; Chang  
321 and Liao 2012; El Baidouri et al. 2018). Lineage-specific differences in DNA methylation  
322 pathways, rates of gene duplication, and how the data are analyzed can all contribute to  
323 differences in the observed associations between DNA methylation and gene duplication. We  
324 focused on DNA methylation within coding regions as these have shown consistent associations  
325 with gene expression and other genic features in plants (Takuno and Gaut 2012; Niederhuth et al.  
326 2016; D. K. Seymour et al. 2014; Takuno, Ran, and Gaut 2016).

327 For most species, TE-like genes are enriched in TE-rich regions, while gbM and UM genes are  
328 depleted. However, we find a number of exceptions to these trends and evidence of phylogenetic  
329 signals for the correlations of TE-like and gbM genes with TE-content. This suggests that there  
330 are lineage-specific differences in how these genes are distributed. The underlying cause(s) of  
331 these differences remains to be determined, but we suspect that it may reflect differences in  
332 chromosomal architecture and the distributions of genes and TEs. For instance, rice is known to  
333 have a high content of MITEs near genes not found in other species (Jiang, Feschotte, et al.  
334 2004). In soybean, we found that TE-like genes were negatively correlated with TE content,  
335 which appears to contradict the enrichment of soybean TE-like genes in pericentromeres found  
336 by El Baidouri et al (2018). This discrepancy could be due to differences in classifying genes and  
337 chromosome binning between the two papers. It must be emphasized that our gene classification  
338 was very conservative, and thus, a large proportion of genes for which methylation data was  
339 ambiguous remained ‘unclassified.’

340 We find distinct patterns between genic DNA methylation and different modes of gene  
341 duplication. WGD genes are consistently depleted in TE-like genes and commonly enriched in  
342 gbM and unmethylated genes. A notable exception of this is *E. salsugineum* and *B. rapa*, where

343 it has been shown that gbM has been lost or reduced due to the evolution of the DNA  
344 methyltransferase *CHROMOMETHYLASE 3* (Bewick et al. 2016). The story is more complicated  
345 for SGDs. El Baidouri et al. (2018) found that in soybean, non-collinear genes, excluding tandem  
346 duplicates (e.g., transposed, dispersed), were enriched for TE-like DNA methylation and that this  
347 was due to translocation to heterochromatin rich regions. We find that when examined across  
348 species, SGDs show high variance in their enrichment or depletion of different types of genic  
349 DNA methylation. Certainly the local context of TEs is a major factor, but contrary to this, even  
350 transposed duplicates showed enrichment of gbM and depletion of TE-like methylation in some  
351 species. Variance in the correlation between TEs and genic DNA methylation patterns all suggest  
352 that there are other factors that contribute to determining DNA methylation in duplicate genes.

353 While we see evidence of switching of genic DNA methylation states between duplicates, the  
354 majority have the same state as its duplicate. While the high degree of correspondence between  
355 duplicates, might be most easily explained by the duplicated copy retaining the methylated state  
356 of its parent, this is not a given. Correspondence of DNA methylation states could arise by  
357 multiple mechanisms. For instance, in the *PAI* genes of Arabidopsis, an inverted tandem  
358 duplicate, *PAI4*, results in silencing in *trans* of all four members of this gene family by the  
359 RdDM pathway (Luff, Pawlowski, and Bender 1999; Melquist, Luff, and Bender 1999). So in  
360 this example, the methylation of all genes is altered but still correspond to each other.  
361 Divergence in duplicate pairs could arise immediately, when a duplicated copy is translocated to  
362 a different chromatin context (El Baidouri et al. 2018), but could also arise much later due to  
363 localized TE insertions. From our comparative analyses, we cannot with confidence determine  
364 the directionality or timing in changes of genic methylation state.

365 Our results show a significant relationship between the age of gene duplication and genic DNA  
366 methylation. This is especially evident for SGDs, where TE-like genes were consistently  
367 younger, and gbM genes were older. These patterns differ for WGDs, depending on the species.  
368 The consistency of the patterns observed in SGDs vs WGDs might be explained by lineage-  
369 specific differences in the number of WGDs and time since last WGD for each lineage  
370 (Garsmeur et al. 2014; Van de Peer, Mizrachi, and Marchal 2017). Within a species, there is an  
371 association between the frequency of genic DNA methylation and duplicate gene age across the  
372 population. In the case of TE-like duplicate genes with high-frequency in the population, it

373 seems most likely that such DNA methylation was established very early in the history of *A.*  
374 *thaliana*, rather than being due to multiple independent instances of silencing. This would  
375 suggest then that despite being evolutionarily younger, these genes still duplicated early enough  
376 to be present throughout the population, rather than being limited to specific lineages. In  
377 contrast, those genes with intermediate frequencies of gbM, UM, or TE-like methylation patterns  
378 indicate ongoing switching of genic DNA methylation states in Arabidopsis. Much of this  
379 variance in DNA methylation can be directly explained by local genetic variation such as novel  
380 TE insertions (Schmitz, He, et al. 2013; Kawakatsu et al. 2016; Vaughn et al. 2007; Eichten et al.  
381 2013, 2016).

382 Duplicate gene sequences evolve differently based on their genic DNA methylation class. GbM  
383 duplicate genes are highly expressed in plants and enriched for housekeeping gene functions, and  
384 in comparisons of orthologous genes are more highly conserved ((Niederhuth et al. 2016;  
385 Takuno and Gaut 2012). Consistent with such a role, gbM duplicate genes, had a  $Ka/Ks < 1$ ,  
386 indicative of purifying selection. In contrast, if a gene were transcriptionally silenced in all  
387 tissues, it would be expected to have little impact on phenotype and so might be expected to  
388 evolve neutrally. However, the posits that heavy DNA methylation immediately following  
389 duplication is a means to suppress duplicate gene expression, thereby shielding it from  
390 accumulating deleterious mutations and ‘pseudogenization’(Chang and Liao 2012; Rodin and  
391 Riggs 2003). Similarly, Adams et al. have also proposed that silenced gene duplicates in cotton  
392 are protected from mutational loss (Adams et al. 2003). Our data shows that TE-like genes had a  
393 higher  $Ka/Ks$  than gbM or UM genes, suggestive of relaxed selection, and were enriched  
394 amongst PAVs. This would suggest that in contrast to the ‘expression reduction model’, most  
395 TE-like duplicates are or are on their way to becoming pseudogenes and lost. This also fits with  
396 the observed lack of conservation of TE-like methylation patterns between species(B. Seymour,  
397 Andreosso, and Seymour 2015; Niederhuth et al. 2016). However, we did find that there was an  
398 enrichment of TE-like genes with a  $Ka/Ks > 1$ , suggestive of positive selection. This would  
399 suggest that silencing by DNA methylation could facilitate functional divergence, as suggested  
400 by Rodin and Riggs (2003). SGDs, in particular, have been linked to adaptation to environmental  
401 conditions (Dassanayake et al. 2011; Hanada et al. 2008). Most TE-like genes are of unknown  
402 function or enriched in functions related to defense (e.g., chitinases, proteinases) (Niederhuth et  
403 al. 2016). Interestingly, a previous search for plant genes under positive selection primarily

404 identified gene families with unknown function and many of the same defense-related genes  
405 (Roth and Liberles 2006). Others have observed that genes associated with C-DMRS  
406 (differentially methylated regions in all three sequence contexts) are often specifically expressed  
407 in specific tissues, especially pollen (Schmitz, Schultz, et al. 2013). So while the evidence  
408 strongly suggests most duplicate genes with TE-like methylation are on their way to extinction,  
409 there is some evidence to support models whereby silencing facilitates functional divergence, but  
410 much more extensive study and evidence is needed to support this possibility.

411 DNA methylation outside of coding regions could also affect the fate of gene duplicates. In  
412 animals, promoter DNA methylation divergence increases with evolutionary age and correlates  
413 with tissue-specific expression and chromatin accessibility profiles (Keller and Yi 2014).  
414 Promoter DNA methylation of younger duplicates was also found in zebrafish and was suggested  
415 to offset detrimental mutations and pseudogenization (Chang and Liao 2012; Zhong et al. 2016).  
416 DNA methylation of upstream regions does show some associations with gene expression in  
417 some plants and is typically thought of being repressive. However, the actual effects can be quite  
418 complex, sometimes contradictory, and poorly understood. For instance, methylated CHH-  
419 islands in promoter regions are associated with increased gene expression (Li et al. 2015; Gent et  
420 al. 2013; Niederhuth et al. 2016). The exact impact of DNA methylation on transcription factor  
421 (TF) binding is often unknown; as depending on the TF it may inhibit, have no impact, or even  
422 facilitate TF binding (Medvedeva et al. 2014; O'Malley et al. 2016). Finally, *cis*-regulatory  
423 regions for most genes in most plant species are unknown or poorly defined. To fully understand  
424 how DNA methylation of regulatory regions affects duplicate gene evolution will require  
425 integration of DNA methylation, known TF binding sites, and their target genes.

426 We propose the following model for gene duplication and genic DNA methylation. While WGD  
427 doubles genome size and, in the case of allopolyploidy, can bring distinct genomes and their  
428 *trans* regulatory factors together, the local sequence context (*cis*-regulatory elements,  
429 neighboring TEs, etc.) for most genes does not change. For most WGD genes, it is unlikely that  
430 their genic DNA methylation states will change either. Supporting this is the high  
431 correspondence of DNA methylation between duplicates. In resynthesized allopolyploids, there  
432 has been little evidence of extensive changes to genic DNA methylation, however, generational  
433 changes are observed in flanking regions (Edger et al. 2017; K. A. Bird et al., n.d.). Features of



434 gbM genes, such as enriched functional categories, are consistent with features of retained WGD  
435 pairs. The enrichment of gbM and depletion of TE-like genes in WGDs, therefore, fits with  
436 expectations of the gene balance hypothesis that postulates retained WGD pairs are dosage-  
437 sensitive genes, enriched in specific functions or part of protein complexes (Veitia, Bottani, and  
438 Birchler 2008). SGDs can change the local sequence and chromatin context of a gene, by moving  
439 that gene to regions of euchromatin or heterochromatin, but also increases the dosage of that  
440 gene relative to the whole. There are, therefore, more mechanistic opportunities for silencing  
441 SGDs, and the fitness effects dosage-sensitive genes may further promote this. In most cases,  
442 these genes are destined for the dustbins of evolution. However, in rare circumstances, silencing  
443 of duplicate genes may help facilitate evolutionary novelty (Rodin and Riggs 2003). In both  
444 WGDs and SGDs, we suspect that genic DNA methylation states are typically established  
445 immediately or very soon after duplication, however, ongoing novel TE insertions or selection  
446 for functional novelty can result in DNA methylation shifts at any point in a gene's evolutionary  
447 history.

448 In summary, this study demonstrates that whole-genome duplication and single gene duplications  
449 show distinct patterns of genic DNA methylation suggesting the action of different chromatin-  
450 based mechanisms leading to contrasting evolutionary trajectories for duplicate gene retention  
451 and loss.

452

## 453 **Methods:**

### 454 **Genomes and annotations**

455 We used the public genomes and gene annotations of 43 species with methylome data (Table-  
456 S13) and an additional 11 species duplicate gene identification(Garcia-Mas et al. 2012; Guo et al.  
457 2013; Ming et al. 2008; Wu et al. 2018; Dohm et al. 2014; Parkin et al. 2014; Initiative and The  
458 International Brachypodium Initiative 2010; Amborella Genome Project 2013; Lamesch et al.  
459 2012; C.-Y. Cheng et al. 2017; Bertioli et al. 2016; Hu et al. 2011; Sato et al. 2008; Paterson et  
460 al. 2012; Schmutz et al. 2010; Edger et al. 2019, 2018; Singh et al. 2013; Bartholomé et al. 2015;  
461 Li et al. 2019; Slotte et al. 2013; D’Hont et al. 2012; R. Yang et al. 2013; Daccord et al. 2017;  
462 Bredeson et al. 2016; Hellsten et al. 2013; Tang et al. 2014; Kawahara et al. 2013; Lovell et al.  
463 2018; Verde et al. 2017; Tuskan et al. 2006; Schmutz et al. 2014; Xue et al. 2018; McCormick et  
464 al. 2018; Bennetzen et al. 2012; Hosmani et al., n.d.; Sharma et al. 2013; Mamidi et al., n.d.;  
465 Motamayor et al. 2013; Jiao et al. 2017; Hibrand Saint-Oyant et al. 2018; VanBuren et al. 2018;  
466 Liu et al. 2014; Colle et al. 2019; VanBuren et al. 2015; Harkess et al. 2017; Hulse-Kemp et al.  
467 2018; S. Xu et al. 2017; Bombarely et al. 2016). These were downloaded from multiple  
468 databases (Table-S13). Only the primary transcript for each gene was used. As there were  
469 differences in the availability and quality of transposon annotations, we re-identified TEs *de*  
470 *novo* for each species using the Extensive *de-novo* TE Annotator (EDTA) pipeline (Ou et al.  
471 2019) provided with gene annotations and coding sequences.

### 472 **DNA methylation data and analyses**

473 We used previously published whole-genome bisulfite sequencing from forty-three Angiosperm  
474 species (Amborella Genome Project 2013; D. K. Seymour et al. 2014; Picard and Gehring 2017;  
475 Bertioli et al. 2016; Niederhuth et al. 2016; Bewick et al. 2016; Lü et al. 2018; Ong-Abdullah et  
476 al. 2015; J. Cheng et al. 2018; Kim et al. 2015; Song et al. 2017; Daccord et al. 2017; Secco et al.  
477 2015; Dong et al. 2017; Y. Yang et al. 2019; L. Wang et al. 2018; Turco et al. 2017; Noshay et  
478 al. 2019). To the extent that was possible we chose datasets from leaf tissue, with high-  
479 sequencing coverage, a low non-conversion rate, and from the same accession as the reference  
480 genome (Table-S14). Data were mapped to their respective genomes using methylpy v1.2.9  
481 (Schultz et al. 2015) and the non-conversion rate calculated based on either unmethylated spiked-

482 id phage lambda DNA or endogenous chloroplast genomes (Table-S14). Individual cytosines  
483 were called as methylated or unmethylated by methylpy. The genic DNA methylation of each  
484 gene was then classified using custom python scripts as previously done (Niederhuth et al. 2016).  
485 First a background rate of DNA methylation for coding sequences was determined by calculating  
486 the average number of methylated CG, CHG, and CHH sites for all genes in all species. A  
487 binomial test was then applied to each gene to test for enrichment of CG, CHG, or CHH  
488 methylation against the background DNA methylation rate. GbM genes had a minimum of 20  
489 CG sites covered by three or more reads each, a significant enrichment of methylated CG sites  
490 (FDR corrected p-value < 0.05), and non-significant amounts of non-CG methylation. TE-like  
491 genes had a minimum of 20 CHG sites covered by three or more reads and significantly enriched  
492 for CHG or 20 CHH sites covered by three or more reads and significantly enriched for CHH.  
493 Unmethylated genes had a minimum of 20 cytosines covered by three reads or more each and no  
494 sites called as methylated. All other genes were classified as either ‘unclassified’ or if missing  
495 data, considered NA.

#### 496 **Genomic distribution and phylogenetic comparisons**

497 To determine the genomic distribution of methylated genes we calculated the total number of  
498 genes, genes belonging to each of the genic DNA methylation classes, the number of TEs, and  
499 number of TE nucleotides in 100 kb sliding windows, sliding every 50 kb. Pearson correlation  
500 coefficients ( $r$ ) were calculated using the ‘*rcorr*’ function in the R package ‘*corrplot*’ (Wei et al.  
501 2017). These correlations were tested for phylogenetic signals using the function *phylosig*  
502 (method="lambda") in the R package *phytools* (Revell 2012). Pagel’s lambda measures  
503 phylogenetic signal under a Brownian motion model of trait evolution where a value of ‘0’  
504 indicates no phylogenetic signal and ‘1’ as a strong phylogenetic signal (Münkemüller et al.  
505 2012; Pagel 1999). The genome size of all species were extracted from the Plant DNA C-value  
506 database as the amount in picograms of DNA contained within a haploid nucleus of the plant  
507 species (Pellicer and Leitch 2020). These were then tested for the phylogenetic signal as above.  
508 The input phylogenetic tree and branch lengths (Dataset-S1) used in *phylosig* was created with  
509 orthofinder (Emms and Kelly 2015) with default parameters.

#### 510 **Gene duplication classification**

511 For each species, DIAMOND (Buchfink, Xie, and Huson 2015) was used to perform a blastp  
512 search of all genes against itself and *A. trichopoda*. A maximum of 5 hits per gene, with a e-  
513 value  $< 1e-10$  were kept. Duplicate genes were identified and classified by *DupGen\_finder-*  
514 *unique* (Qiao et al. 2019). *MCSanX-transposed* (Y. Wang, Li, and Paterson 2013) was used to  
515 detect transposed duplicates occurring within different epochs since species divergence (Table-  
516 S9). Custom R scripts were used to determine the frequencies of each of the different modes of  
517 gene duplication, as well as genic methylation classification (gbM, TE-like, unmethylated, and  
518 unclassified). A two-sided Fisher's exact test was used to determine whether there was any  
519 statistically significant association between modes of duplication and genic methylation  
520 classification. A stringent p-value threshold of  $<.001$  was set for all comparisons, however, we  
521 do report p-value significance between .001 to .05 in the heatmap. Heatmaps were plotted using  
522 the function *heatmap.2* in the R package *gplots*. The Phylogenetic tree in Figure S2 was created  
523 in R using the packages 'V.PhyloMaker' and 'phytools' (Jin and Qian, 2019).

#### 524 **Nucleotide evolution**

525 Nonsynonymous substitutions (Ka), synonymous substitutions (Ks) and the ratio of Ka/Ks for  
526 each duplicate pair was determined using the *calculate\_Ka\_Ks\_pipeline.pl* (Qiao et al. 2019).  
527 Briefly each pair of protein sequences are aligned using MAFFT (v7.402)(Katoh and Standley  
528 2013) and converted into a codon alignment using PAL2NAL (Suyama, Torrents, and Bork  
529 2006). A modified version of the Yang-Nielsen method,  $\gamma$ -MYN was used to calculate Ka and  
530 Ks values using the Tamura-Nei model (D. Wang et al. 2010; Qiao et al. 2019). For a subset of  
531 duplicate genes, multiple possible duplicate pairs are possible. To minimize bias in these cases,  
532 we randomly selected one set of Ka & Ks values to represent that gene. We tested the  
533 distribution of Ks and Ka/Ks for gbM, TE-like, and UM genes for divergence from the  
534 distribution of an equal number of randomly selected genes using the Kolmogorov-Smirnov test  
535 (Massey 1951), a non-parametric test. Gene pairs with a Ka/Ks  $> 1.1$  were considered as  
536 candidates undergoing positive selection and were tested for enrichment or depletion amongst  
537 gbM, TE-like, and UM genes using a two-sided Fisher's exact test (Fisher 1935) and an FDR-  
538 corrected p-value  $< 0.05$ .

#### 539 **Presence absence variation**

540 Previously published PAV variants were downloaded for *B. oleracea* (Golicz et al. 2016), *S.*  
541 *lycopersicum* (Gao et al. 2019), *S. tuberosum* (Hardigan et al. 2016), and *Z. mays* (Hirsch et al.  
542 2014). For both *S. tuberosum* and *Z. mays*, genes with an average read coverage of  $< 0.2$  in at  
543 least one accession were considered to be PAVs. In all species, only genes present in the  
544 reference accession were considered for analyses, as DNA methylation data was not available for  
545 non-reference genes. PAVs were merged with genic DNA methylation data in R and tested for  
546 enrichment or depletion using a two-sided Fisher's Exact test (Fisher 1935) and an FDR-  
547 corrected p-value  $< 0.05$ .

#### 548 **Arabidopsis diversity**

549 Processed WGBS data from the previously published *Arabidopsis thaliana* 1001 Epigenomes  
550 Project (Kawakatsu et al. 2016) was downloaded from the Gene Expression Omnibus (GEO  
551 Accession GSE43857). Of these, 928 accessions had been called using methylpy and were  
552 compatible with our methods. Genes were classified as done above for the 43 species using the  
553 same background methylation rates. These data were imported into R and the frequency of each  
554 genic DNA methylation class for each gene in the population binned into 0%,  $<25\%$ , 25-50%,  
555 50-75%, and  $>75\%$ . Ks & Ka/Ks data were the same as those computed above.

#### 556 **Data availability and research reproducibility**

557 All data used in this study are from publicly available genomes and methylomes (Table-S13).  
558 Classified gene lists, gene DNA methylation levels, Ka/Ks data, and formatted genomes and  
559 annotations suitable for reproducing our results are available at **data dryad**. Conda environments  
560 with exact software versions and all custom scripts are available at both  
561 [https://github.com/niederhuth/DNA-methylation-signatures-of-duplicate-gene-evolution-in-](https://github.com/niederhuth/DNA-methylation-signatures-of-duplicate-gene-evolution-in-angiosperms)  
562 [angiosperms](https://github.com/niederhuth/DNA-methylation-signatures-of-duplicate-gene-evolution-in-angiosperms).

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## 572 **Author contributions:**

573 S.K.K.R and C.E.N conceptualized and designed the work and analysis. S.K.K.R, C.E.N. and  
574 S.M.L performed data analysis. S.K.K.R made figures and wrote the original draft; C.E.N wrote  
575 and edited the manuscript. All authors read and approved the final manuscript.

## 576 **FIGURE LEGENDS**

577 **Figure 1:** Correlations of genomic features with genic DNA methylation classifications.  
578 Pearson's correlation coefficient 'r' was measured to determine the distribution of gbM, TE-like,  
579 and UM genes across the genome using TE content and TE nucleotides as a proxy for  
580 heterochromatin. Shades of blue indicate enrichment, while red indicates depletion. Correlations  
581 not significant at  $p < 0.001$  are marked with 'X'. (A) *Arabidopsis thaliana*, (B) *Glycine max*, (C)  
582 *Medicago truncatula*, (D) *Panicum virgatum*, (E) *Solanum lycopersicum*, and (F) *Zea mays*.

583 **Figure 2:** Patterns of genic DNA methylation across different modes of gene duplication across  
584 43 angiosperms. Heatmap shows enrichment/depletion of each genic DNA methylation class  
585 (gbM, TE-like, and UM) for each mode of gene duplication (WGD, tandem, proximal, dispersed,  
586 transposed). Singletons are single-copy genes (non-duplicates) present in the species and the  
587 outgroup. Unless indicated, all associations are statistically significant at a p-value  $< 0.001$ .  
588 \*significant association at a lower p-value cut-off ( $0.001 < p < 0.05$ ). 'NS' – not significant.  
589 Cyan indicates depletion, while pink denotes enrichment.

590 **Figure 3:** Stasis and switching of genic DNA methylation profiles between duplicate gene pairs.  
591 (A) The number of genes for each mode duplication with the same or different genic DNA  
592 methylation profile in *A. thaliana* and *Z. mays*. (B) Percentage of parental and transposed genes  
593 with gbM, TE-like, and UM classification for *A. thaliana* and *Z. mays* shows enrichment of TE-  
594 like methylation in the transposed copy. (C) Proportion of parental genes in each genic DNA  
595 methylation class based on the genic DNA methylation in *A. thaliana* and *Z. mays*. This indicates

596 the direction of genic DNA methylation switching.

597 **Figure 4:** Relationship between genic DNA methylation class and the age of gene duplication.  
598 Density plots (A,B, D,E) show the distribution of synonymous substitutions (Ks) for each genic  
599 DNA methylation class , while bar plots (C and F) show the percentage of gene copies in each  
600 genic DNA methylation class for transposed genes that have duplicated during that ‘epoch’ since  
601 divergence from the species on the x-axis. For example, in *B. distachyon* transposed genes that  
602 have duplicated since *B. distachyon* diverged from *O. sativa* are shown on the x-axis under *O.*  
603 *sativa*. Those shown for *Z. mays*, duplicated in the period since the common ancestor of *B.*  
604 *distachyon* and *O. sativa* diverged from their common ancestor with *Z. mays*, but before the  
605 divergence of *B. distachyon* and *O. sativa*. Horizontal dotted lines indicate the percentage of  
606 each genic DNA methylation class in the whole genome. (A) *B. distachyon* WGD Ks  
607 distributions (B) *B. distachyon* SGD Ks distributions. (C) Percentage of *B. distachyon*  
608 transposed duplicates in each genic DNA methylation class at each ‘epoch’. (D) *G. raimondii*  
609 WGD Ks distributions (E) *G. raimondii* SGD Ks distributions (F) Percentage of *G. raimondii*  
610 transposed duplicates in each genic DNA methylation class at each ‘epoch’.

611 **Figure 5:** Differences in sequence evolution correspond to different genic DNA methylation  
612 classes. TE-like methylation genes are under relaxed selection compared to gbM and UM genes  
613 as indicated by density plots showing the ratio of non-synonymous to synonymous mutations  
614 (Ka/Ks) for (A) *B. distachyon* WGDs, (B) *B. distachyon* SGDs, (C) *G. raimondii* WGDs and (D)  
615 *G. raimondii* SGDs. However, TE-like methylated genes are also enriched in genes showing  
616 evidence of positive selection. Bar graphs indicate the proportion of genes for each genic DNA  
617 methylation class with a Ka/Ks > 1.1 for (E) *B. distachyon* and (F) *G. raimondii*. \*\*\*FDR-  
618 corrected p-value < 0.001, \*\*FDR-corrected p-value < 0.01, \*FDR-corrected p-value < 0.05, NS  
619 – not significant .

620 **Figure 6:** The frequency of genic DNA methylation across 928 *A. thaliana* ecotypes differs by  
621 the age of gene duplication. Density plots showing the Ks distribution of genes at different  
622 frequencies (0%, <25%, 25%-50%, 50%-75%, >75%) in the population for (A) gbM, (B) TE-  
623 like, and (C) UM genes. Boxplots of Ks distributions show that Ks increases with increasing  
624 frequency of (D) gbM in the population, but decreases with the increasing frequency of (E) TE-  
625 like and (F) UM genes.

## 626 SUPPLEMENTARY TABLES

627 **Table S1:** Classification of genic DNA methylation of all genes in each species. Genes were  
628 classified as gene body methylated (gbM), transposable element-like (TE-like), unmethylated  
629 (UM), or remained unclassified. 'NA' represents genes with missing methylation data.

630 **Table S2:** Correlations between genic DNA methylation class (gbM, TE-like, UM) and genomic  
631 features (number of genes, TEs, and TE nucleotides) in 100kb sliding windows with a 50kb step  
632 size. Positive correlations are marked in blue, negative correlations in red. P-value significance is  
633 indicated by shades of blue, dark blue for  $p$ -value  $< .001$  and light blue for  $p$ -value  $< .05$ .

634 **Table S3:** Pagel's lambda test for phylogenetic signal of trait correlations in Table S2. A lambda  
635 value of '0' indicates no phylogenetic signal, while '1' indicates a strong phylogenetic signal.  
636 Correlations in blue show a statistically significant phylogenetic signal.

637 **Table S4:** Number of genes derived from different modes of duplications in each species.

638 **Table S5:** Fisher's Exact test results for enrichment and depletion of genic DNA methylation  
639 classifications across different modes of duplication. Odds ratios of enriched associations are  
640 colored green, depleted associations are in orange. P-value  $< .001$  are in dark blue, while p-value  
641  $< .05$  are in light blue.

642 **Table S6:** Number of duplicate pairs with different or the same genic DNA methylation status  
643 for each mode of duplication for each species.

644 **Table S7:** Proportions of each genic DNA methylation class genes for parental genes and  
645 transposed copies for each species.

646 **Table S8:** Kolmogorov-Smirnov test results for differences in the distribution of synonymous  
647 substitution rates ( $K_s$ ) for gbM, TE-like and UM genes compared to a random distribution. Blue  
648 indicates distribution is significantly different at a FDR adjusted  $p$ -value  $< 0.05$ .

649 **Table S9:** Outgroup species used for each epoch as part of MCscanX-transposed.

650 **Table S10:** Fisher's Exact test results for enrichment and depletion of genic DNA methylation  
651 classifications across different epochs of transposed duplicates for all species. Odds ratios of



652 enriched associations are colored green, depleted associations are in orange. Blue indicates  
653 distribution is significantly different at a FDR adjusted p-value  $< 0.05$ .

654 **Table S11:** Kolmogorov-Smirnov test results for differences in the distribution of non-  
655 synonymous substitution to synonymous substitution ratios (Ka/Ks) for gbM, TE-like and UM  
656 genes compared to a random distribution. Blue indicates distribution is significantly different at a  
657 FDR adjusted p-value  $< 0.05$ .

658 **Table S12:** Fisher's Exact Test results for enrichment and depletion of gbM, TE-like, and  
659 unmethylated genes with Ka/Ks ratio  $> 1.1$ . Odds ratios of enriched associations are colored  
660 green, depleted associations are in orange. Blue indicates distribution is significantly different at  
661 a FDR adjusted p-value  $< 0.05$ .

662 **Table S13:** Fisher's Exact Test results for enrichment and depletion of known presence-absence  
663 variants for gbM, TE-like, and unmethylated genes. Odds ratios of enriched associations are  
664 colored green, depleted associations are in orange. Blue indicates distribution is significantly  
665 different at a FDR adjusted p-value  $< 0.05$ .

666 **Table S14:** Data source and mapping statistics for all methylome data used in the study.

## 667 SUPPLEMENTARY FIGURES

668 **Figure S1:** Correlations between genes, transposons (TEs), and different classes of methylated  
669 genes. Increasing blue indicates a positive correlation, increasing red indicates a negative  
670 correlation. Boxes marked with an X are statistically non-significant.

671 **Figure S2:** Distribution of genic methylation classified genes and genomic features across the  
672 largest chromosomes in representative species.

673 **Figure S3:** Distribution of genic methylation classified genes based on synonymous substitution  
674 rates (Ks) across different modes of gene duplication. WGD = whole-genome duplication. SGD  
675 = single-gene duplication and combines data from tandem, proximal, transposed, and dispersed  
676 modes of duplication.

677 **Figure S4:** The percentage of gene copies in each genic DNA methylation class for transposed

678 genes that have duplicated during that ‘epoch’ since divergence from the species on the x-axis.  
679 For example, in *B. distachyon* transposed genes that have duplicated since *B. distachyon*  
680 diverged from *O. sativa* are shown on the x-axis under *O. sativa*. Those shown for *Z. mays*  
681 duplicated in the period since the common ancestor of *B. distachyon* and *O. sativa* diverged from  
682 their common ancestor with *Z. mays*, but before the divergence of *B. distachyon* and *O. sativa*.  
683 Horizontal dotted lines indicate the percentage of each genic DNA methylation class in the  
684 whole genome.

685 **Figure S5:** Synonymous substitution rate (Ks) plots of TE-like genes in 43 species. Species are  
686 ordered by median Ks of TE-like genes for transposed (A), tandem (B), and proximal duplicates  
687 (C). Magenta boxplots = species enriched for TE-like genes, blue = depleted, white = NS.  
688 Significance at p-value < 0.05

689 **Figure S6:** Distribution of genic methylation classified genes based on the ratio of non-  
690 synonymous to synonymous substitutions (Ka/Ks) across different modes of gene duplication.  
691 WGD = whole-genome duplication. SGD = single-gene duplication and combines data from  
692 tandem, proximal, transposed, and dispersed modes of duplication.

693 **Figure S7:** Percentage of genes for each genic DNA Methylation class with a Ka/Ks > 1.1.  
694 \*FDR adjusted p-value < 0.05, \*\*FDR adjusted p-value < 0.01, \*\*\*FDR adjusted p-value <  
695 0.001, NS = Not Significant.

696 **Figure S8:** Percentage of Total (all genes), gbM, TE-like, and unmethylated genes with known  
697 presence absences variation. A two-sided Fisher's Exact test was used to test for depletion or  
698 enrichment of PAVs amongst each category of genic DNA methylation. \*FDR corrected p-value  
699 < 0.05, \*\*FDR corrected p-value < 0.01, \*\*\*FDR corrected p-value < 0.001, NS – Not  
700 significantly different.

701 **Figure S9:** Genic methylation variation across different modes of gene duplication and its  
702 relationship with age (Ks).

703 **Dataset S1:** Rooted species tree with branch lengths.

704



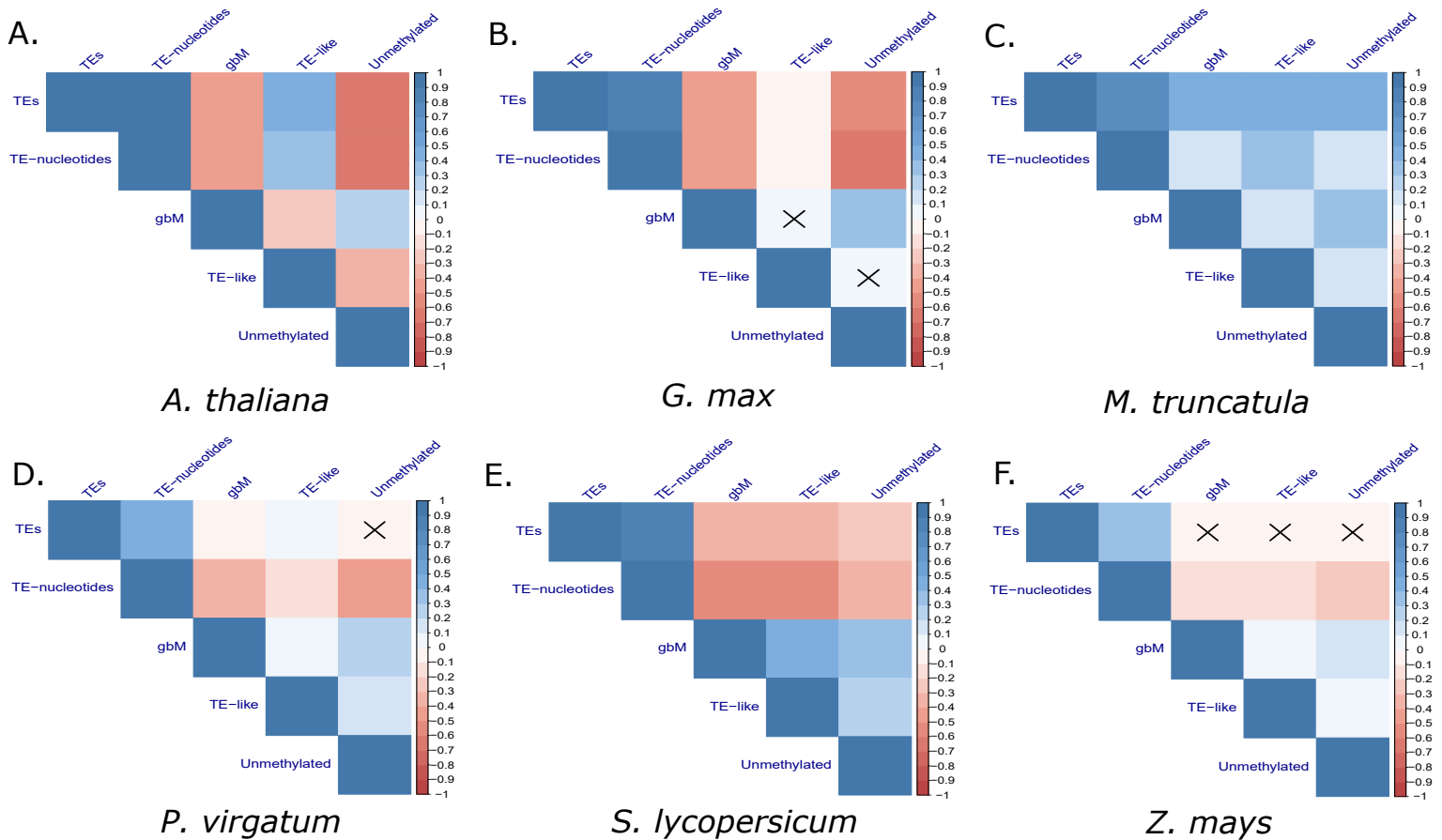


Figure 1: Correlations of genomic features with genic DNA methylation classifications. Pearson's correlation coefficient 'r' was measured to determine the distribution of gbM, TE-like, and UM genes across the genome using TE content and TE nucleotides as a proxy for heterochromatin. Shades of blue indicate enrichment, while red indicates depletion. Correlations not significant at  $p < 0.001$  are marked with 'X'. (A) *Arabidopsis thaliana*, (B) *Glycine max*, (C) *Medicago truncatula*, (D) *Panicum virgatum*, (E) *Solanum lycopersicum*, and (F) *Zea mays*.



Figure 2: Patterns of genic DNA methylation across different modes of gene duplication across 43 angiosperms. Heatmap shows enrichment/depletion of each genic DNA methylation class (gbM, TE-like, and UM) for each mode of gene duplication (WGD, tandem, proximal, dispersed, transposed). Singletons are single-copy genes (non-duplicates) present in the species and the outgroup. Unless indicated, all associations are statistically significant at a p-value < 0.001. \*significant association at a lower p-value cut-off (0.001 < p < 0.05). 'NS' – not significant. Cyan indicates depletion, while pink denotes enrichment.

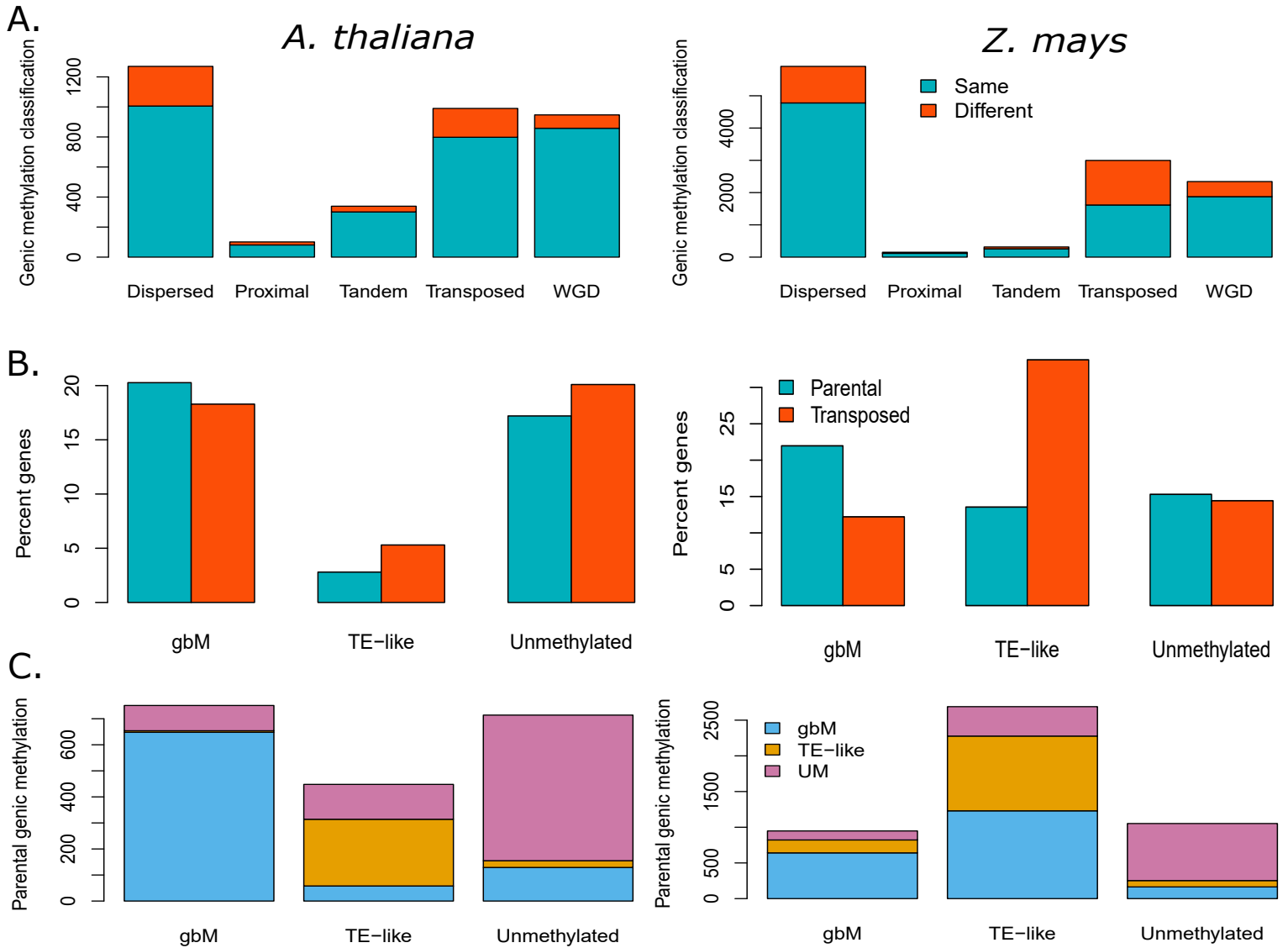


Figure 3: Stasis and switching of genic DNA methylation profiles between duplicate gene pairs. (A) The number of genes for each mode duplication with the same or different genic DNA methylation profile in *A. thaliana* and *Z. mays*. (B) Percentage of parental and transposed genes with gbM, TE-like, and UM classification for *A. thaliana* and *Z. mays* shows enrichment of TE-like methylation in the transposed copy. (C) Proportion of parental genes in each genic DNA methylation class based on the genic DNA methylation in *A. thaliana* and *Z. mays*. This indicates the direction of genic DNA methylation switching.

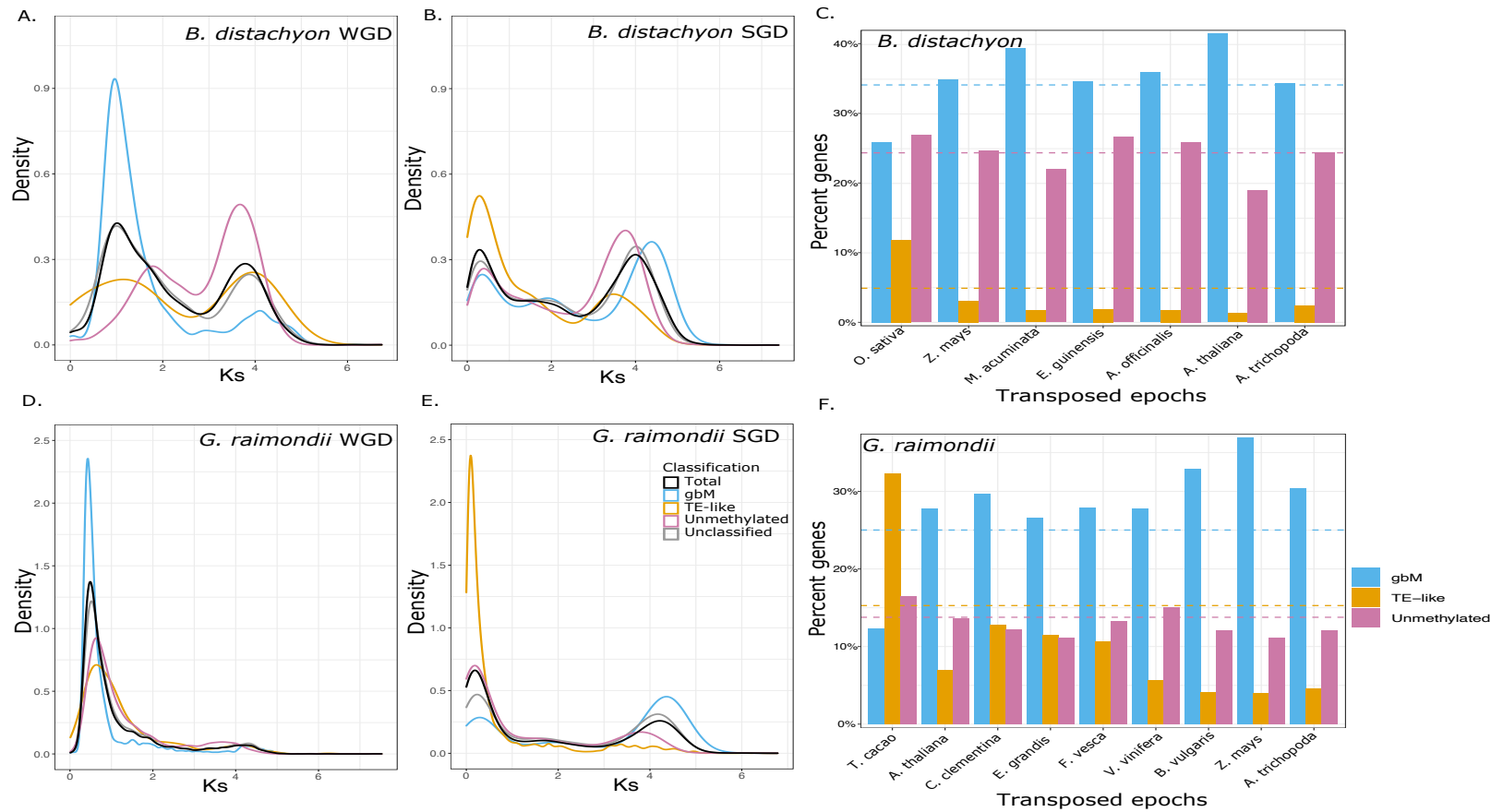


Figure 4: Relationship between genic DNA methylation class and the age of gene duplication. Density plots (A,B, D,E) show the distribution of synonymous substitutions ( $K_s$ ) for each genic DNA methylation class, while bar plots (C and F) show the percentage of gene copies in each genic DNA methylation class for transposed genes that have duplicated during that 'epoch' since divergence from the species genes on the x-axis. For example, in *B. distachyon* transposed genes that have duplicated since *B. distachyon* diverged from *O. sativa* are shown on the x-axis under *O. sativa*. Those shown for *Z. mays* duplicated in the period since the common ancestor of *B. distachyon* and *O. sativa* diverged from their common ancestor with *Z. mays*, but before the divergence of *B. distachyon* and *O. sativa*. Horizontal dotted lines indicate the percentage of each genic DNA methylation class in the whole genome. (A) *B. distachyon* WGD  $K_s$  distributions (B) *B. distachyon* SGD  $K_s$  distributions. (C) Percentage of *B. distachyon* transposed duplicates in each genic DNA methylation class at each 'epoch'. (D) *G. raimondii* WGD  $K_s$  distributions (E) *G. raimondii* SGD  $K_s$  distributions (F) Percentage of *G. raimondii* transposed duplicates in each genic DNA methylation class at each 'epoch'.

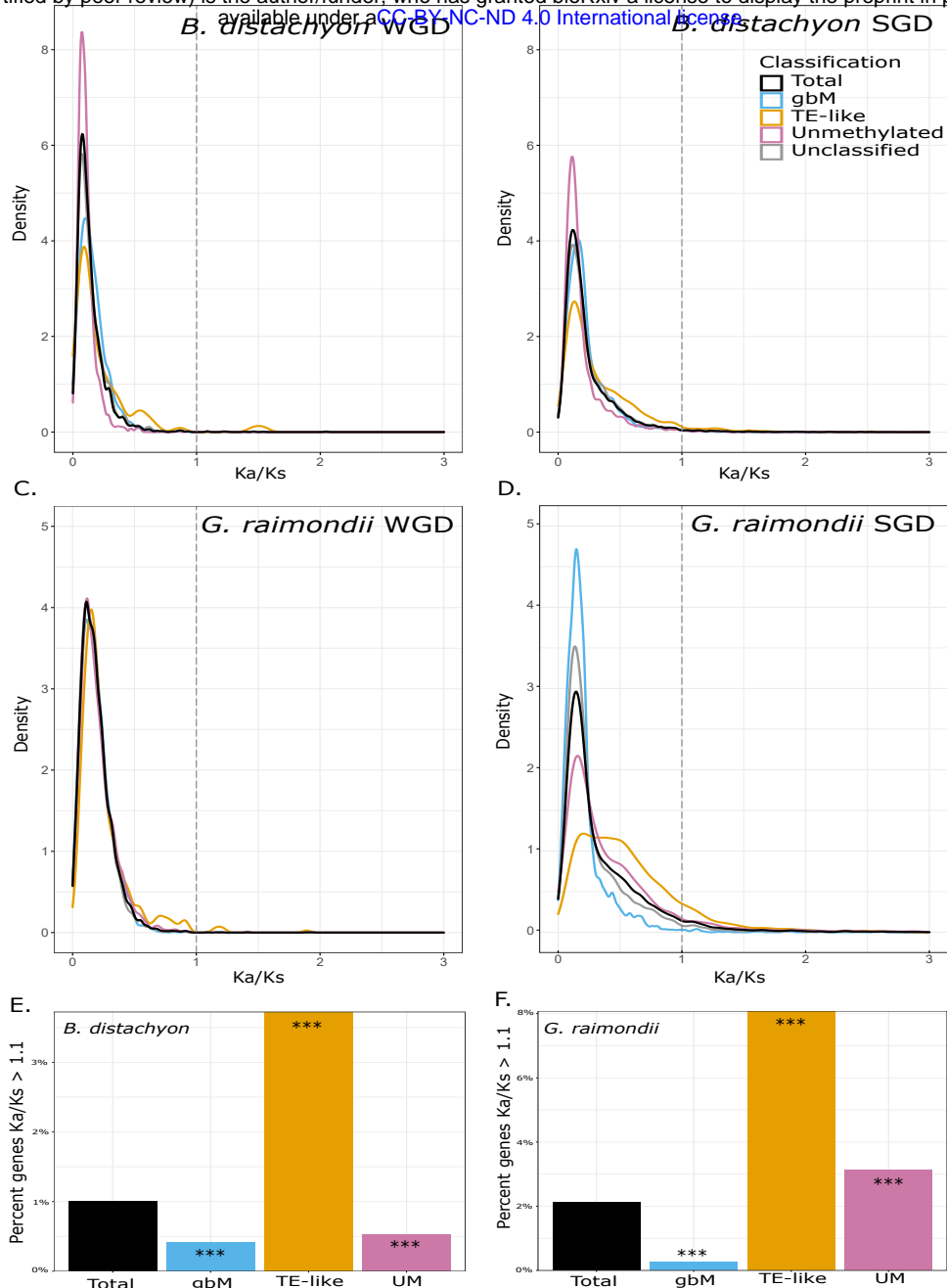


Figure 5: Differences in sequence evolution correspond to different genic DNA methylation classes. TE-like methylation genes are under relaxed selection compared to gbM and UM genes as indicated by density plots showing the ratio of non-synonymous to synonymous mutations (Ka/Ks) for (A) *B. distachyon* WGDs, (B) *B. distachyon* SGDs, (C) *G. raimondii* WGDs and (D) *G. raimondii* SGDs. However, TE-like methylated genes are also enriched in genes showing evidence of positive selection. Bar graphs indicate the proportion of genes for each genic DNA methylation class with a Ka/Ks > 1.1 for (E) *B. distachyon* and (F) *G. raimondii*. \*\*\*FDR-corrected p-value < 0.001, \*\*FDR-corrected p-value < 0.01, \*FDR-corrected p-value < 0.05, NS – not significant .



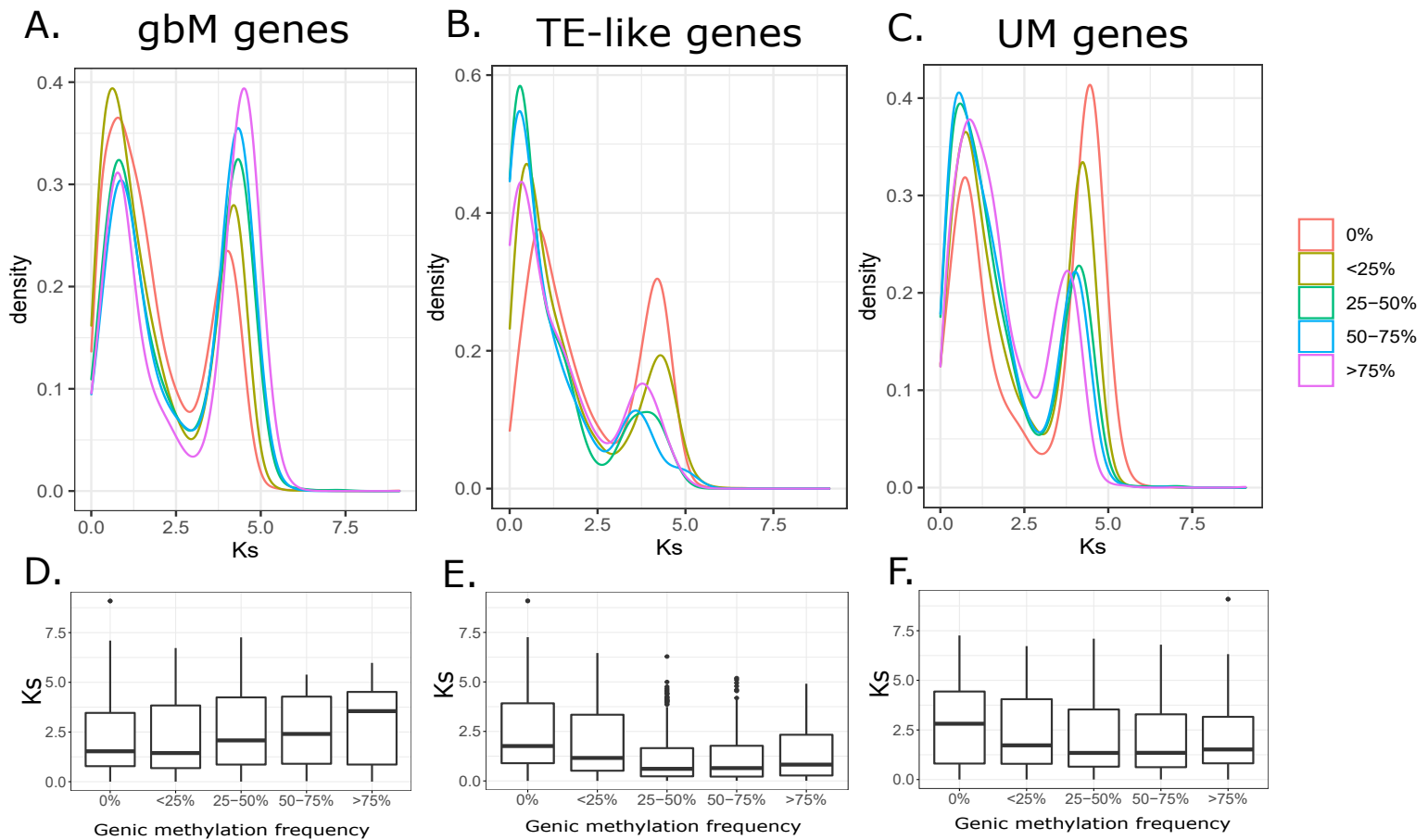


Figure 6: The frequency of genic DNA methylation across 928 *A. thaliana* ecotypes differs by the age of gene duplication. Density plots showing the Ks distribution of genes at different frequencies (0%, <25%, 25%-50%, 50%-75%, >75%) in the population for (A) gbM, (B) TE-like, and (C) UM genes. Boxplots of Ks distributions show that Ks increases with increasing frequency of (D) gbM in the population, but decreases with the increasing frequency of (E) TE-like and (F) UM genes.

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