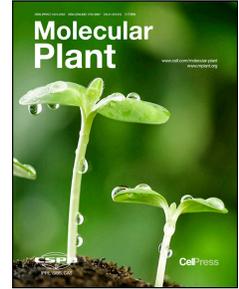


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1 **Orphan crops and their wild relatives in the genomic era**

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10

11 **Short Summary**

12 Orphan crops play important roles in global food and nutrition security and represent
13 a broad gene pool. Here, we provide an overview of genomic studies on orphan crops
14 and their wild relatives (including weeds), and discuss the potential mutual utilization
15 of genomic results among major crops, orphan crops and their wild relatives.

16

17

18 **Abstract**

19 More than half of the calories consumed by humans are provided by three major
20 cereal crops (rice, maize and wheat). Orphan crops are usually well adapted to
21 low-input agricultural conditions, and they not only play vital roles in local areas but
22 can also contribute to food and nutritional needs worldwide. Interestingly, many wild
23 relatives of orphan crops are important weeds of major crops. Although orphan crops
24 and their wild relatives have received little attention from researchers for many years,
25 genomic studies on these plants have recently been performed. Here, we provide an
26 overview of genomic studies on orphan crops, with a focus on orphan cereals and
27 their wild relatives. At least 12 orphan cereals and/or their wild relatives have been
28 genome sequenced. In addition to genomic benefits for orphan crop breeding, we
29 discuss the potential mutual utilization of genomic results among major crops, orphan
30 crops and their wild relatives (including weeds) and provide perspectives on the
31 genetic improvement of both orphan and major crops (including *de novo*
32 domestication of orphan crops) in the coming genomic era.

33

34 **Keywords:** Orphan crop, wild relative, weed, genome, crop diversity

35

36 **Introduction**

37 More than 2,500 species have undergone some extent of domestication, and
38 approximately 300 have been fully domesticated (Dirzo and Raven, 2003; Fernie and
39 Yang, 2019). However, 70% of the calories consumed by humans come from only 15
40 crop species, among which three major crop species (rice, maize and wheat) directly
41 contribute more than half of all the calories consumed (Chang et al., 2019; Dawson et
42 al., 2019). The narrowing of diversity within crop species reduces global food security,
43 and diversifying crop production is critical for sustainable food systems (Dawson et
44 al., 2019; Khoury et al., 2014). Additionally, the growth of the human population
45 requires a sustainable food supply to meet energy and nutritional needs, which is one
46 of the greatest global challenges (Chang et al., 2019). Climate change resulting in
47 increased drought and heat makes current crop production particularly challenging
48 (Mabhaudhi et al., 2019). Environmental degradation and costs resulting from heavy
49 reliance on chemical fertilizers and pesticides lead to unsustainable productivity
50 (Fernie and Yang, 2019). One of the possible solutions for these challenges is the use
51 of orphan crops, which can diversify crop production, provide more sources for food
52 and contribute genetic resources. It has been recognized that orphan crops play
53 important roles in global food and nutrition security and represent a broad gene pool
54 for future crop improvement (Mabhaudhi et al., 2019).

55 Orphan crops are often defined as staple crops that are grown in limited regions, have
56 relatively good adaptation to low-input conditions, are not extensively traded and
57 have received little attention from researchers (Dawson et al., 2019; Ribaut and
58 Ragot, 2019; Varshney et al., 2012b). Orphan crops are also known as underutilized,
59 lost, minor, or neglected crops and as crops for the future (Tadele, 2019). Although
60 orphan crops have limited economic value worldwide, they are often highly important
61 at the local level, especially in developing countries (Chiurugwi et al., 2019).

62 Since the publication of the Arabidopsis genome in 2000, more than 400 flowering
63 plant species have been sequenced as of August 2020
64 (<https://www.plabipd.de/index.ep>). Advances in genome sequencing have promoted

65 genome-based breeding techniques, including genome-wide association studies,
66 genomic selection and design breeding. Due to technological breakthroughs in
67 genome sequencing and reduced costs, orphan crops have also entered their genomic
68 era, accelerating the identification of genes underlying important agronomic traits,
69 breeding processes and the understanding of the evolution of those species. In this
70 article, we focus on orphan cereals and their relatives (referred to here as species
71 within the same genus) whose genome sequence is available. In addition to an
72 overview of genomic studies on orphan crops and their wild relatives, we provide
73 perspectives on how to promote the breeding of both orphan and major crops by
74 utilizing their genomic resources, aiming to face agricultural challenges in the 21st
75 century.

76

77 **Orphan crops and their wild relatives**

78 *Overview of orphan crops*

79 Orphan crops mainly include cereals, pseudocereals, legumes and root crops. Their
80 cultivation area and the major countries in which they are grown were reviewed by
81 Tadele et al. (2019). Select orphan crops (with a focus on cereals) are briefly
82 described below.

83 In addition to the three major crops (rice, maize and wheat), the grass family (Poaceae
84 or Gramineae) also includes many orphan crops. The tribe Paniceae (subfamily
85 Panicoideae) includes foxtail millet (*Setaria italica*), pearl millet (*Pennisetum*
86 *glaucum*, syn. *Cenchrus americanus*), broomcorn millet (also known as common
87 millet, proso millet and hog millet; *Panicum miliaceum*), barnyard millet
88 (*Echinochloa* spp.), and fonio millet (*Digitaria exilis*), etc. (Figure 1). Foxtail millet
89 and broomcorn millet are among the most ancient domesticated crops (Lu et al., 2009).
90 They were initially domesticated in northern China, where they eventually became the
91 dominant food crops (they are members of the ‘Five Grains of China’; the Chinese
92 name is ‘Sù’ (‘粟’) for foxtail millet and ‘Shǔ’ (‘黍’) or ‘Jì’ (‘稷’) for broomcorn millet).

93 In ancient northern China, agriculture was based on the domestication of broomcorn
94 millet and foxtail millet, which then greatly contributed to the development of
95 Chinese civilization (Doust and Diao, 2017). Even today, foxtail millet and
96 broomcorn millet are important crops in the arid and semiarid regions of East Asia
97 (Lu et al., 2009). Pearl millet is widely cultivated as a staple food grain and forage
98 crop in arid and semiarid regions of sub-Saharan Africa, India and South Asia
99 (Varshney et al., 2017b). This species was domesticated more than 4,500 years ago
100 and is considered to have originated in Africa (Hu et al., 2015). Barnyard millet is
101 widely cultivated in Asia, particularly in India, China, Japan and Korea (Renganathan
102 et al., 2020). It comprises at least two different cultivated hexaploid species:
103 *Echinochloa esculenta* in East Asia and *Echinochloa frumentacea* in India
104 (Yamaguchi et al., 2005). In Yunnan Province, China, a cultivated form of tetraploid
105 *Echinochloa* was recognized (Yabuno, 1996), and cultivated hexaploids were also
106 found to be grown for forage purposes according to our survey. Barnyard millet is
107 also an ancient crop, and China is one of its origins, according to Nikolai Vavilov's
108 studies on the centers of origin of cultivated plants (Vavilov, 1951). Based on the
109 evidence of phytolith and starch microfossils, as a major subsistence resource,
110 *Echinochloa* millet was harvested and processed alongside rice during the Shangshan
111 culture period (~10,000 years ago) (Yang et al., 2015). Fonio millet is an orphan
112 cereal in Africa and is also referred to as 'hungry rice', as it is often grown to avoid
113 food shortages during the lean season. Despite its local importance, compared with
114 other cereal species, fonio millet is underexploited and still has many unfavorable
115 characteristics, such as seed shattering and relatively low yields (Abrouk et al., 2020).
116 In the subfamily Panicoideae, there is another orphan crop species, adlay (also known
117 as Job's tears; *Coix lacryma-jobi*), that is closely related to sorghum and belongs to
118 the tribe Andropogoneae (Guo et al., 2020) (Figure 1). *C. lacryma-jobi* is widely
119 grown in Asian countries, including China, Japan and Korea, as a cereal and
120 medicinal crop species (Kang et al., 2020).

121 Finger millet (*Eleusine coracana*) and tef (*Eragrostis tef*) are the only two species that

122 are in the subfamily Chloridoideae that are cultivated as cereals for human
123 consumption (Chanyalew et al., 2019) (Figure 1). Finger millet was domesticated
124 more than 5,000 years ago in the region spanning what is currently Uganda to
125 Ethiopia (Hatakeyama et al., 2018). Finger millet was subsequently introduced to the
126 Western Ghats region of India, which made India the secondary center of diversity for
127 finger millet. Finger millet is considered the fourth most important type of millet after
128 sorghum, pearl millet and foxtail millet (Hittalmani et al., 2017). Tef is the most
129 important cereal in Ethiopia in terms of production, consumption and cash crop value,
130 and its grains yield the best-quality 'injera', a traditional food in Ethiopia (Chanyalew
131 et al., 2019; Girma et al., 2014). Tef is grown primarily by small-scale subsistence
132 farmers, and thousands of locally adapted cultivars have been developed (VanBuren et
133 al., 2020). In addition, weeping lovegrass (*E. curvula*), which belongs to the same
134 genus as tef, is grown for forage purposes (Carballo et al., 2019).

135 Rye (*Secale cereale*) is closely related to wheat (*Triticum aestivum*) and barley
136 (*Hordeum vulgare*), belonging to the Triticeae tribe (subfamily Pooideae). Rye is an
137 important crop for food and feed in Central and Eastern Europe (Bauer et al., 2017).
138 Intermediate wheatgrass (*Thinopyrum intermedium*), native to parts of Eastern Europe
139 and western Asia, has been widely used for forage production in North America and
140 has been domesticated to be perennial grain crop recently (DeHaan et al., 2020;
141 Larson et al., 2019). Another nutritionally important crop of the subfamily Pooideae is
142 oat (*Avena sativa*), grown as a source of food and feed (Maughan et al., 2019).

143 *Zizania* belongs to the same Oryzeae tribe (subfamily Oryzoideae) as rice (Figure 1),
144 and *Zizania latifolia* is a lost ancient cereal crop species according to Chinese history
145 (its Chinese name is 'Gū'). Chinese historical records concerning 'Gū' show that its
146 grains were presented as tributes to the nobles in the Zhou dynasty (1046-256 BC)
147 (Zhao et al., 2019). After the Tang and Song dynasties, 'Gū' gradually disappeared and
148 was replaced with rice (Wang et al., 2013). *Z. latifolia* was also domesticated as a
149 perennial vegetable crop called 'Jiāobái', which is now widely cultivated in China and
150 other Asian countries (Guo et al., 2015). Another annual species (*Zizania palustris*)

151 within this genus is native to North America (where it is referred to as 'wild rice') and
152 has also been domesticated as a cereal (wildrice) in the USA in the last century
153 (Hayes et al., 1989).

154 Other orphan crops include pseudocereals (e.g., Amaranth (*Amaranthus* spp.),
155 buckwheat (*Fagopyrum esculentum*) and quinoa (*Chenopodium quinoa*)), root crops
156 (e.g., cassava (*Manihot esculenta*), sweet potato (*Ipomoea batatas*) and yam
157 (*Dioscorea* spp.)) and legumes. Legumes compose the third largest family of
158 flowering plants that provide important sources of food, fodder, oil and fiber products.
159 Legumes are divided into three subfamilies, among which the subfamily
160 Papilionoideae includes essentially all the major legume crops (Varshney et al., 2009).
161 Among legumes, soybean (*Glycine max*) is undoubtedly considered a major crop, but
162 the others can be classified as orphan crops (some important orphan legumes listed in
163 Supplementary Table 1). For example, groundnut/peanut (*Arachis hypogaea*), which
164 is widely grown worldwide, is among the most important oil and food legumes and
165 has gradually received substantial amounts of scientific research, especially related to
166 the field of genomics (Bertioli et al., 2019; Chen et al., 2019; Zhuang et al., 2019).
167 There are two types of orphan legume species: cool-season grain legumes, such as
168 chickpea (*Cicer arietinum*), pea (*Pisum sativum*) and lentil (*Lens culinaris*), and
169 warm-season grain legumes, such as common bean (*Phaseolus vulgaris*), cowpea
170 (*Vigna unguiculata*) and mung bean (*Vigna radiata*) (Kreplak et al., 2019). Orphan
171 legumes also include forage crops such as alfalfa (*Medicago sativa*) (Chen et al.,
172 2020; Shen et al., 2020) and clover (*Trifolium* spp.) (Hirakawa et al., 2016).

173

174 *Many wild relatives of orphan crops are weeds*

175 Many wild relatives (referred to here as species within the same genus) of orphan
176 crops, particularly orphan cereals, are considered major agricultural weeds that grow
177 together with major crops in the same ecological niche (Figure 1). For example,
178 cultivated foxtail millet was domesticated from wild green foxtail (*Setaria viridis*),

179 which is one of the most widespread weeds worldwide and is typically found in
180 agricultural fields, on roadsides and in open waste areas (Doust and Diao, 2017;
181 Schroder et al., 2017). Green foxtail is one of the major invasive weeds in maize,
182 soybean and wheat fields (Delye et al., 2002).

183 The genus *Echinochloa* includes numerous problematic weed species, among which
184 hexaploid *E. crus-galli* is dominant; this species is distributed in both paddy fields and
185 nonpaddy fields (such as upland crop areas) (Ye et al., 2014). It causes substantial
186 losses in crop yields worldwide, particularly for rice, and is considered one of the
187 most serious weeds in agriculture (Ye et al., 2014). In rice paddy fields, the
188 morphological similarity between rice and *E. crus-galli* at the seedling stage (i.e.,
189 mimicry) makes it hard for farmers to distinguish them and thus remove those weeds
190 from paddies (Ye et al., 2019). Another mimetic weed of this genus in rice paddy
191 fields is the tetraploid *Echinochloa oryzicola* (also called *Echinochloa phyllopogon*),
192 which is the wild counterpart of Mosuo barnyard millet cultivated in Yunnan Province,
193 China (Yabuno, 1996).

194 The genus *Digitaria*, to which fonio millet belongs, includes the common weed
195 species *Digitaria sanguinalis* (large crabgrass). Large crabgrass is a problematic weed
196 in turfgrass and various crops, including maize, cotton, sorghum, rice and other
197 vegetable crops (Aguyoh and Masiunas, 2003; Li et al., 2017; Turner et al., 2012).

198 The genus *Eleusine*, to which finger millet belongs, includes the weed species
199 goosegrass (*Eleusine indica*), one of the most destructive weeds worldwide (Zhang et
200 al., 2019). It has been reported that a single goosegrass plant can produce up to
201 140,000 seeds, which makes its spread rapidly (Chin, 1979). It is a serious weed in
202 orchards, vegetable farms and many agronomic crops, such as cotton, maize and
203 legume crops (Ma et al., 2015).

204 The weedy form of rye is considered the putative ancestor of modern cultivated rye.
205 Weedy rye grows together with wheat and barley, and they share morphological
206 similarity (i.e., mimicry). When cultivated under more severe conditions, such as

207 colder winters and poor soils, the mimetic weedy rye had better adaptation than wheat
208 and barley and was then domesticated to be a desirable crop (McElroy, 2014). Oat has
209 a similar domestication process to rye, i.e., evolved from weedy oat. This is the theory
210 of 'Vavilovian mimicry', i.e., wild species became a mimetic weed that may have
211 already acquired some domestication traits, and then the weed was fully domesticated
212 to be a crop. These types of crops are called secondary crops (McElroy, 2014;
213 Schreiber et al., 2017).

214

215 *Beneficial traits of orphan crops and their wild relatives*

216 There are many beneficial traits of orphan crops and their wild relatives compared
217 with major crops. Generally, they present high photosynthetic efficiency, are tolerant
218 to various stresses and/or contribute nutritional and/or medicinal compounds. Most
219 orphan cereals, including foxtail millet, pearl millet, broomcorn millet, barnyard
220 millet, fonio millet, adlay, finger millet and tef, utilize the highly efficient C4
221 photosynthesis pathway (Chanyalew et al., 2019; Doust and Diao, 2017; Hittalmani et
222 al., 2017). Accordingly, their wild relatives also adopted the C4 pathway. Compared
223 with C3 photosynthesis, C4 photosynthesis promotes the efficient use of nitrogen and
224 water while reducing photorespiration to a minimum in hot and arid climates (Schuler
225 et al., 2016).

226 Drought is an inevitable outcome of global climate change and poses severe threats to
227 agriculture. It is well known that foxtail millet and its wild progenitor green foxtail
228 are drought tolerant (Doust and Diao, 2017). Pearl millet is well suited to growth
229 under harsh conditions, including low soil fertility, high soil pH, high soil Al^{3+}
230 saturation, low soil moisture, high temperature and high salinity (Varshney et al.,
231 2017b). Broomcorn millet has been reported to be highly drought tolerant (Shi et al.,
232 2019; Zou et al., 2019). Similarly, barnyard millet can grow under adverse
233 environmental conditions with almost no inputs and can withstand various abiotic
234 stresses (Renganathan et al., 2020). Fonio millet is drought tolerant and adapted to

235 nutrient-poor and sandy soils (Abrouk et al., 2020), and tef is tolerant to biotic and
236 abiotic stresses, particularly drought and waterlogging (Cannarozzi et al., 2014;
237 Chanyalew et al., 2019). Rye is tolerant to biotic and abiotic stresses and exhibits high
238 yield potential under marginal conditions (Rabanus-Wallace et al., 2019).

239 Foxtail millet contains a wide range of health-promoting components, including
240 proteins, dietary fibers, vitamins and minerals (Sharma and Niranjana, 2018). The
241 grains of broomcorn millet are highly nutritious and have high contents of proteins,
242 minerals and antioxidants (Zou et al., 2019). Similarly, the grains of barnyard millet
243 and pearl millet contain high contents of protein, fiber and micronutrients such as iron
244 and zinc (Renganathan et al., 2020; Varshney et al., 2017b). Adlay seeds constitute
245 nutritionally balanced food and have a high protein content, and seed extracts have
246 been reported to exert various pharmacological activities, such as anticancer,
247 antioxidant, anti-inflammatory, anti-allergic, antidiabetic and gastroprotective effects
248 (Guo et al., 2020; Kang et al., 2020; Zhu, 2017). Finger millet contains exceptionally
249 high contents of calcium and several valuable amino acids, including lysine, threonine
250 and valine (Ceasar et al., 2018; Saleh et al., 2013), and grains of tef are rich in
251 essential amino acids, particularly alanine, methionine, threonine and tyrosine
252 (Chanyalew et al., 2019). Oat is a nutritionally important crop containing high levels
253 of calcium, β -glucan soluble fiber and high-quality oil and protein (Maughan et al.,
254 2019). Grains of Gu contain dietary fiber and minerals and have a high protein
255 efficiency ratio (Zhai et al., 2001).

256

257 **Genomic studies of orphan crops and their wild relatives**

258 *De novo sequencing of genomes*

259 Efforts in sequencing orphan crop genomes have been made, and several genome
260 sequencing initiatives targeting orphan crops, e.g., the African Orphan Crops
261 Consortium (AOCC; <http://africanorphan crops.org/>), have been established in the last
262 ten years. AOCC aims to sequence the genomes of 101 traditional African food plant

263 species, facilitating their genetic improvement (Hendre et al., 2019; Tadele, 2019).

264 Significant advances in genome sequencing have been achieved in recent years in the
265 grass family (Supplementary Table 1), and at least 11 reference genomes of orphan
266 cereals (including genomes of their relatives) have been published (Figure 1). Foxtail
267 millet was the first orphan cereal to be sequenced, which was performed by two
268 groups (Bennetzen et al., 2012; Zhang et al., 2012). Foxtail millet is diploid ($2n = 2 \times$
269 $= 18$) and has a relatively small genome size (~ 490 Mb) (Zhang et al., 2012). The
270 complete genome sequence of green foxtail is available (Mamidi et al., 2020), and the
271 genome of another highly transformable accession (ME034V) was also recently
272 published (Thielen et al., 2020). Pearl millet is a highly cross-pollinated diploid ($2n =$
273 $2 \times = 14$); this species has a relatively large genome (~ 1.8 Gb) and a high content
274 (77.2%) of repetitive sequences (Varshney et al., 2017b). Broomcorn millet is an
275 allotetraploid ($2n = 4 \times = 36$; genome size of ~ 900 Mb), and its reference genome has
276 been published (Shi et al., 2019; Zou et al., 2019). Reference genomes of barnyard
277 millets are still lacking; however, we have sequenced their wild relatives (two
278 important agricultural weed species: *E. crus-galli* and *E. oryzicola*). The genome
279 assembly of *E. crus-galli* ($2n = 6 \times = 54$; ~ 1.4 Gb) was first completed in 2017 (Guo et
280 al., 2017) and has since been improved substantially through third-generation long
281 reads in 2020 (Ye et al., 2020). The complete genome sequence of *E. oryzicola* ($2n =$
282 $4 \times = 36$; ~ 1.0 Gb), a progenitor of *E. crus-galli*, was made available at the same time
283 (Ye et al., 2020). The genomes of several other orphan cereals, such as fonio millet
284 ($2n = 4 \times = 36$; 893 Mb), adlay ($2n = 2 \times = 20$; 1.8 Gb) and wild *Coix* (*C. aquatica*),
285 were also sequenced in 2020 (Abrouk et al., 2020; Guo et al., 2020; Kang et al., 2020;
286 Liu et al., 2020a).

287 A draft genome sequence of finger millet ($2n = 4 \times = 36$; ~ 1.5 Gb) was published by
288 two groups (Hatakeyama et al., 2018; Hittalmani et al., 2017). A draft assembly of its
289 wild relative, the weed species goosegrass ($2n = 2 \times = 18$; ~ 584 Mb), was also made
290 available recently (Zhang et al., 2019). The genome sequence of tef ($2n = 2 \times = 40$;
291 ~ 622 Mb) was first published in 2014 (Cannarozzi et al., 2014), and a

292 chromosome-scale assembly was recently reported (VanBuren et al., 2020). In
293 addition, weeping lovegrass has also been genome sequenced (Carballo et al., 2019).

294 Rye is diploid with a large genome ($2n = 2\times = 14$; ~ 7.9 Gb), and Bauer et al. (2017)
295 reported its draft genome sequence covering a total length of 2.8 Gb.
296 Rabanus-Wallace et al. (2019) reported a new version of the genome sequence
297 representing 6.7 Gb. Intermediate wheatgrass has a large and complex allohexaploid
298 genome ($2n = 6\times = 42$; ~ 12 Gb) and its genome sequence is available at Phytozome
299 database. Cultivated oat is allohexaploid ($2n = 6\times = 42$), and its genome sequence is
300 not yet available. Genome sequences of two diploid progenitor species (*A. atlantica*
301 and *A. eriantha*) have been released by Maughan et al. (2019). For the extinct cereal
302 'Gū', we reported the genome sequence of wild *Z. latifolia* ($2n = 2\times = 34$; ~ 590 Mb)
303 (Guo et al., 2015).

304 To date, the genomes of at least 16 orphan legume crop species have been sequenced
305 (Supplementary Table 2). Among these species, their genome sizes vary, from 420 Mb
306 (dolichos bean) to 4.45 Gb (pea). Pigeonpea is the first orphan legume whose genome
307 was *de novo* sequenced, which was published in 2012 (Varshney et al., 2012a). The
308 genomes of the pseudocereals amaranth (Clouse et al., 2016), buckwheat (Yasui et al.,
309 2016) and quinoa (Yasui et al., 2016; Jarvis et al., 2017; Zou et al., 2017) and the root
310 crops cassava (Wang et al., 2014), sweet potato (Yang et al., 2017) and yams (Siadjeu
311 et al., 2020; Tamiru et al., 2017) have also been sequenced.

312

313 *Genome resequencing of populations*

314 Similar to major crop species, whole-genome resequencing (WGRS) studies have also
315 been carried out on orphan crop species (Table 1). Among orphan cereals, WGRS was
316 first performed on foxtail millet. Jia et al. (2013) resequenced the genomes of 916
317 diverse foxtail millet varieties and identified 36 selective sweeps that seem to have
318 occurred during modern breeding. Approximately 600 wild green foxtail accessions
319 were recently resequenced with deep-depth coverage (an average of $42.6\times$), and a

320 novel domestication gene involved in seed shattering was identified (Huang et al.,
321 2019; Mamidi et al., 2020).

322 Using a combination of WGRS and reduced-representation sequencing techniques,
323 Varshney et al. (2017) resequenced the genomes of 994 pearl millet lines. Principal
324 component analysis and a phylogenetic tree revealed four main clusters of these lines,
325 including one group containing cultivated germplasm and three groups containing
326 wild accessions, which were geographically separated. The closest of the wild groups
327 to the cultivated samples were from the central part of West Africa, indicating the
328 origin of pearl millet, which is consistent with the results of previous research.

329

330 **Table 1.** Population studies via whole-genome resequencing of orphan cereals and
331 their wild relatives

| Species | Number of samples | Area sampled | Genome coverage (×) | References |
|----------------------|-------------------|---------------|---------------------|--|
| <i>S. italica</i> | 916 | Global | 0.7 | Jia et al., 2013 |
| | 184 | China | 2 | Ni et al., 2017 |
| | 164 | China | 5 | Liu et al., 2020b |
| <i>S. viridis</i> | 605 | North America | 42.6 | Huang et al., 2019; Mamidi et al., 2020 |
| <i>P. glaucum</i> | 414 | Africa, Asia | < 2 | Varshney et al., 2017b |
| <i>E. crus-galli</i> | 328 | China | 15 | Ye et al., 2019 |
| <i>D. exilis</i> | 166 | Africa | 45 | Abrouk et al., 2020 |
| <i>Coix</i> spp. | 27 | China | 12.7 | Liu et al., 2020a |

332 Note that studies with reduced-representation sequencing are not included.

333

334 *E. crus-galli* is dominant in rice paddies and causes substantial rice yield losses. One
335 of the survival strategies employed by *E. crus-galli* is crop mimicry in which the
336 weed has evolved to resemble crop plants, which is thought to be the result of
337 unintentional selection by farmers. We compared mimetic and nonmimetic
338 populations of *E. crus-galli* from the Yangtze River basin on the basis of their
339 phenotype and by genome resequencing (Ye et al., 2019). We demonstrated that the

340 mimetic event occurred as recently as 1,000 years ago, and a genetic bottleneck
 341 during the mimicry process was observed. Genomic regions containing 87 putative
 342 plant architecture-related genes were under selection during the mimicry process.
 343 These data provide genomic evidence for the influence of human selection on crop
 344 mimicry.

345 Genomic resequencing studies have also been conducted on orphan legumes, such as
 346 pigeonpea (Varshney et al., 2017a), chickpea (Varshney et al., 2019), pea (Kreplak et
 347 al., 2019), peanut (Zhuang et al., 2019), common bean (Wu et al., 2020) and alfalfa
 348 (Shen et al., 2020).

349

350 *Novel genetic resources for environmental adaptations*

351 Orphan cereals and wild relatives provide abundant gene pools. For example, relative
 352 to cultivated rice, more than 20,000 and 8,000 specific genes can be found in *E.*
 353 *crus-galli* and *Z. latifolia*, respectively (<http://ibi.zju.edu.cn/ricerelativesgd/>) (Mao et
 354 al., 2019). As mentioned above, many orphan cereals are C4 plants and are tolerant to
 355 various stresses. Many genes related to C4 photosynthesis and abiotic stress
 356 (including drought) responses are expected to be found in the genomes of many
 357 orphan cereals and their wild relatives (Table 2). These genes are potential candidates
 358 as valuable resources for the improvement of major crops. A famous example is the
 359 use of rye in wheat breeding. It has been shown that genetic recourses from rye
 360 (translocations) can be found in the genomes of many wheat varieties grown
 361 worldwide, which contribute to abiotic and biotic stress tolerance in wheat (Bauer et
 362 al., 2017; Cheng et al., 2019).

363

364 **Table 2.** Number of genes related to photosynthesis and abiotic stress responses in
 365 select orphan cereals and their wild relatives

| Species | C4 pathway-related genes | | | | | Abiotic stress-related transcription factors | | | |
|---------|--------------------------|-----|----|------|------|--|-----|-----|------|
| | CA | MDH | ME | PEPC | PPDK | AP2 | NAC | MYB | WRKY |

| | | | | | | | | | |
|------------------------|---|----|----|----|----|-----|-----|-----|-----|
| <i>S. italica</i> | 4 | 13 | 8 | 6 | 5 | 184 | 137 | 231 | 109 |
| <i>P. glaucum</i> | 5 | 11 | 6 | 7 | 3 | 57 | 122 | 205 | 85 |
| <i>P. miliaceum</i> | 8 | 19 | 14 | 13 | 11 | 303 | 205 | 350 | 150 |
| <i>E. crus-galli</i> | 8 | 39 | 20 | 25 | 11 | 471 | 414 | 639 | 315 |
| <i>C. lacryma-jobi</i> | 5 | 10 | 14 | 7 | 4 | 127 | 131 | 227 | 79 |
| <i>E. tef</i> | 9 | 22 | 13 | 15 | 11 | 146 | 166 | 314 | 116 |

366 Note that the genes were identified via hidden Markov model (HMM) searches in this
 367 study. The HMM profile of each corresponding Pfam domain was searched against
 368 the annotated proteins encoded by corresponding genomes, with an E value < 1e-5.
 369 CA, carbonic anhydrase; MDH, malate dehydrogenase; ME, malic enzyme; PEPC,
 370 phosphoenolpyruvate carboxylase; PPDK, pyruvate phosphate dikinase.

371

372 **Genomic benefits of orphan crop breeding**

373 Crop breeding has entered the biotechnology-based stage, which involves the
 374 application of transgenic and genomic breeding techniques. We are at the beginning of
 375 the fourth generation of breeding technology (so-called breeding 4.0), which involves
 376 genome design, genome editing, big data, etc. (Fernie and Yang, 2019; Wallace et al.,
 377 2018). Similar to major crops, genomic studies not only accelerate the isolation of
 378 functional genes and improve our understanding of orphan crop evolution but also
 379 promote the breeding process (Figure 2).

380 *Marker assistant breeding*

381 Previously, the widely used markers for crop breeding were simple sequence repeats
 382 (SSRs) or microsatellites. When entering the genomic era, SNP markers are becoming
 383 popular with advances in sequencing technologies. Mapping of quantitative trait loci
 384 (QTLs) is an important first step for functional gene isolation and marker-assisted
 385 breeding (Doust and Diao, 2017). Ni et al. (2017) and Zhang et al. (2017) resequenced
 386 a recombinant inbred line (RIL) population generated from a cross between two elites
 387 (Zhanggu and A2); furthermore, a high-resolution bin map was developed, and a total
 388 of 69 QTLs for 21 agronomic traits were identified. Liu et al. (2020b) resequenced the
 389 genomes of 164 RILs and their two parents (Longgu7 and Yugu1), and 47 QTLs for
 390 four traits were identified. Genome-wide association studies (GWAS) are useful for

391 dissecting complex traits and have been conducted on each of the major crops and on
392 other model plant species. Many cases have also been reported for orphan crops. Jia et
393 al. (2013) performed a GWAS on foxtail millet through resequencing and phenotyping
394 916 diverse varieties from five locations involving 47 agronomic traits. Upadhyaya et
395 al. (2015) genotyped a set of 190 foxtail millet germplasm accessions and identified
396 significant marker-trait associations for plant pigmentation and days to flowering.
397 Another GWAS based on genotyping-by-sequencing (GBS) data on foxtail millet was
398 conducted by Jaiswal et al. (2019), who identified 81 marker-trait associations for ten
399 traits. After 994 lines were resequenced, a GWAS was performed, which revealed
400 1,054 highly significant marker-trait associations for 15 traits in pearl millet
401 (Varshney et al., 2017b). Sharma et al. (2018) evaluated 113 diverse global finger
402 millet germplasm accessions involving 14 agromorphological characteristics in two
403 environments, and single-nucleotide polymorphisms (SNPs) generated via GBS were
404 used for an association analysis, which revealed 109 novel SNPs associated with
405 important agromorphological traits. GWASs have also been conducted on cassava
406 (e.g., do Carmo et al., 2020; Kayondo et al., 2018; Rabbi et al., 2017; Zhang et al.,
407 2018) and orphan legume species such as pigeonpea (Varshney et al., 2017a),
408 chickpea (Li et al., 2018b) and common bean (Wu et al., 2020).

409

410 *Genomic selection*

411 Genomic selection has been widely used for major crop species and livestock.
412 Varshney et al. (2017b) applied resequencing data for genomic selection in pearl
413 millet to predict grain yield, and high prediction accuracy was observed. They also
414 predicted hybrid performance using a genomic selection strategy that considers
415 additive and dominance effects. One hundred and seventy promising hybrid
416 combinations were found, of which 11 combinations were already used for producing
417 hybrids with good performance, and the remaining 159 combinations could be
418 potential candidates for developing new hybrids with high yields. Genomic selection
419 has also been applied in other orphan crop species, such as pigeonpea (Bohra et al.,

420 2020), chickpea (Roorkiwal et al., 2020), pea (Annicchiarico et al., 2017), peanut
421 (Pandey et al., 2020), common bean (Keller et al., 2020), alfalfa (Hawkins and Yu,
422 2018) and cassava (Wolfe et al., 2017).

423

424 *Genome editing*

425 Some successful cases of orphan crop breeding and domestication of wild relatives
426 through clustered regularly interspaced short palindromic repeats/CRISPR-associated
427 9 (CRISPR-Cas9) technology have been recently reported. Lemmon et al. (2018)
428 developed genomic resources and efficient transformation methods for the orphan
429 Solanaceae crop groundcherry (*Physalis pruinosa*) and then used CRISPR-Cas9 to
430 mutate orthologs of tomato domestication and improvement genes and to improve
431 productivity-related traits. The target genes involved plant architecture, flower
432 production and fruit size, as undesirable characteristics of groundcherry include its
433 sprawling growth habit and small fruits. Two different groups devised a
434 CRISPR-Cas9 genome-engineering strategy in wild tomato (*Solanum*
435 *pimpinellifolium*); the strategy involved editing six loci that are important for yield
436 and productivity in present-day tomato crop lines (Li et al., 2018a; Zsogon et al.,
437 2018). Both studies were highly successful in terms of the specific traits that were
438 targeted, such as a threefold increase in fruit size, a tenfold increase in fruit number
439 and a twofold increase in fruit lycopene accumulation in engineered *S.*
440 *pimpinellifolium* compared with its wild parent.

441 The CRISPR/Cas9 system has also been successfully used in foxtail millet (Zhao et
442 al., 2020) and green foxtail (Mamidi et al., 2020). Recently, Weiss et al. (2020)
443 developed a protoplast-based assay to rapidly test and optimize the multiplex
444 CRISPR/Cas9 gene-editing system for highly efficient genome editing in green foxtail.
445 In addition, several studies have evaluated the potential of CRISPR/Cas9 in cassava
446 (e.g., Bull et al., 2018; Gomez et al., 2019; Mehta et al., 2019; Odipio et al., 2017).

447

448 *Speed breeding*

449 Speed breeding shortens the breeding cycle and accelerates crop research through
450 rapid generation advancement (Ghosh et al., 2018). Speed breeding protocols for
451 some orphan crops are available, such as peanut (O'Connor et al., 2013), chickpea
452 (Watson et al., 2018) and amaranth (*Amaranthus* spp.) (Stetter et al., 2016).
453 Chiurugwi et al. (2019) recently reviewed the progress of speed breeding in orphan
454 crops. To make foxtail millet more suitable as a model plant, a miniature mutant
455 (*xiaomi*) with a life cycle similar to that of *Arabidopsis* has been identified from a
456 large foxtail millet ethyl methane sulfonate-mutagenized population (Yang et al.,
457 2020). Five to six generations of *xiaomi* can be grown in a year in growth chambers
458 due to its short life cycle and small plant size, similar to *Arabidopsis*. In particular, a
459 reference-grade *xiaomi* genome comprising 429.9 Mb of sequence data along with the
460 speed breeding protocol was provided to the research community.

461

462 **Perspectives**463 *Breeding knowledge from major crops is helpful for orphan crop improvement*

464 The ability to breed major crops has been greatly improved by advances in genomics,
465 and orphan crops would benefit from the knowledge gained from the breeding of
466 major crops, which includes identifying genes that control key agronomic traits and
467 applying advanced breeding methods, etc. (Figure 3).

468 Functional conservation of orthologous genes in crop domestication and improvement
469 has been widely revealed. For example, a stay-green *G* gene from soybean controls
470 seed dormancy and has undergone selection during domestication. Its orthologs also
471 show evidence of selection during domestication in rice and tomato and have
472 conserved functions in controlling seed dormancy in soybean and rice (Wang et al.,
473 2018). Many other cases have also been found for genes that govern plant height in
474 rice and barley (Jia et al., 2009), tiller angle in rice and maize (Dong et al., 2013) and
475 seed size in sorghum, maize and rice (Tao et al., 2017). Cases of conserved functions

476 of genes between major and orphan crops have also been reported. For example,
477 *TEOSINTE BRANCHEDI (TBI)*, a major domestication gene controlling branching in
478 maize, has experienced parallel selection between maize and pearl millet (Remigereau
479 et al., 2011). By targeting the orthologs of tomato domestication and improvement
480 genes, Lemmon et al. (2018) successfully edited these genes in the orphan crop
481 groundcherry, which yielded the expected phenotypes. A number of genes have been
482 functionally characterized in major crop species. For example, more than 3,500 genes
483 in rice have been cloned (<https://funricegenes.github.io/>) (Yao et al., 2018). These
484 genes in major crop species provide valuable information for mining and utilizing
485 genes that play critical roles in the domestication and improvement of orphan crops.

486 Genome-based breeding methods have been widely used in major crops with the
487 advancement of genome sequencing; these methods have shortened the breeding
488 process and have improved selection efficiency (Varshney et al., 2020; Wallace et al.,
489 2018). Theoretically, these genomic breeding methods could also be applied to or
490 benefit orphan crop species. Particularly, precise editing of genes through the
491 CRISPR/Cas9 approach could facilitate the development of improved varieties of
492 orphan crops. However, advanced genomic techniques used in major crops also have
493 challenges when used in some orphan crops. For example, a large LD (linkage
494 disequilibrium) distance makes the use of GWAS difficult in quinoa (Mizuno et al.,
495 2020). When applied to a new plant species, the CRISPR/Cas9 system often requires
496 considerable optimization in terms of vector construction, transgene expression, tissue
497 culture and transformation efficiency (Weiss et al., 2020; Yin et al., 2017). A
498 prerequisite for the application of gene-editing technologies is an effective
499 transformation system, which is not available in most orphan crops (Hua et al., 2019;
500 López-Marqués et al., 2020; Zhang et al., 2020). Therefore, the use of genome editing
501 in orphan crops is still a long way away.

502

503 *Utilization of genomic studies on orphan crops and their wild relatives for*
504 *improvements to major crops*

505 Genome sequences of orphan crops and their wild relatives provide at least three
506 potential benefits for major crop species. First, orphan crops provide valuable genetic
507 resources related to environmental adaptation for major crop improvement (Figures 2
508 and 3). Second, many orphan cereals are C4 plants and thus are potential models for
509 C4 rice. A long-standing goal of the C4 community is to engineer C4 traits into rice to
510 increase rice yields (www.c4rice.org), and maize is currently considered the major
511 model species. Foxtail millet and green foxtail have been proposed to be novel model
512 species for C4 photosynthesis due to their relatively small genomes, ease of gene
513 transformation, and short generation time, etc. (Diao et al., 2014). Considering that *E.*
514 *crus-galli* grows within the same agroecosystem and exhibits morphological
515 characteristics similar to those of rice (i.e., crop mimicry), this species might be an
516 alternative model for the C4 rice project. Third, genomic studies on orphan
517 crop-related agricultural weeds revealed the mechanisms underlying their ability to
518 compete with major crops, which have helped breed crop cultivars with competitive
519 advantages (Figure 3). Crop-weed interactions, such as allelopathic interactions, have
520 long been an important topic in agronomic studies (Guo et al., 2018). Allelopathy, or
521 the ability of one plant to suppress the growth of another nearby plant through the
522 release of chemical compounds (i.e., allelochemicals), is one of the most important
523 features underlying weediness (Guo et al., 2017). Allelopathy has been considered a
524 possible application for weed control; for example, crop varieties with high
525 allelopathic potential toward weeds could be bred (Khanh et al., 2007). The *E.*
526 *crus-galli* genome contains a cluster of genes involved in the biosynthesis of the
527 allelochemical 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA), which
528 plays a critical role in *E. crus-galli* for allelopathic competition with rice in paddy
529 fields (Guo et al., 2017). Thus, breeding DIMBOA-resistant rice cultivars is expected
530 to decrease the application of herbicides in the future.

531

532 *De novo domestication of orphan crops*

533 One strategy for the utilization of wild relatives is *de novo* domestication as a new

534 crop (Pourkheirandish et al., 2020). Domestication of new orphan crops from their
535 wild relatives (including weeds) is helpful for maintaining crop diversity (Figure 3).
536 Among orphan cereals, there are at least two possible cases in which *de novo*
537 domestication can be achieved. The lost cereal Gu (*Z. latifolia*) could be recovered
538 through *de novo* domestication of semiwild (or semidomesticated) *Z. latifolia*. Unlike
539 wild *Z. latifolia*, semiwild *Z. latifolia* has been dedomesticated from Jiaobai
540 (vegetable) and has a compact plant architecture and strong stems (lodging resistance).
541 It does not have enlarged stems, and the seed set of a single plant can reach 20-25%
542 (Wang et al., 2013). These traits would make the recovery of Gu possible with the
543 assistance of recent breeding techniques such as genome editing. Another case of *de*
544 *novo* domestication may involve the mimetic weeds *E. crus-galli* and *E. oryzicola*.
545 These mimetic *Echinochloa* weeds resemble cultivated rice with a small tiller angle, a
546 straight stem node, a green stem base and compact leaves. The major trait that needs
547 to be domesticated is seed shattering; in-depth knowledge about this trait in major
548 crops would be helpful in this process.

549

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554

555 **Author contributions**

556 L. F. designed the framework of the article. C. Y. and L. F. wrote the article.

557

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562

563

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961

962 **Figure legends**

963 **Fig. 1** Examples of orphan cereals and their wild relatives. Only orphan cereals and/or
964 their wild relatives whose *de novo* genome sequence is available are shown. The
965 asterisks (*) indicate important agricultural weeds. References for the genomic studies
966 are listed. Rice, maize and wheat are also shown for understanding the evolutionary
967 relationship between orphan and major cereals.

968 **Fig. 2** Current progress in genomic contributions to the genetics and breeding of
969 orphan crops.

970 **Fig. 3** Potential interaction/exchanges of genomic results among major crops, orphan
971 crops and their wild relatives located in different agricultural ecology regions.

972

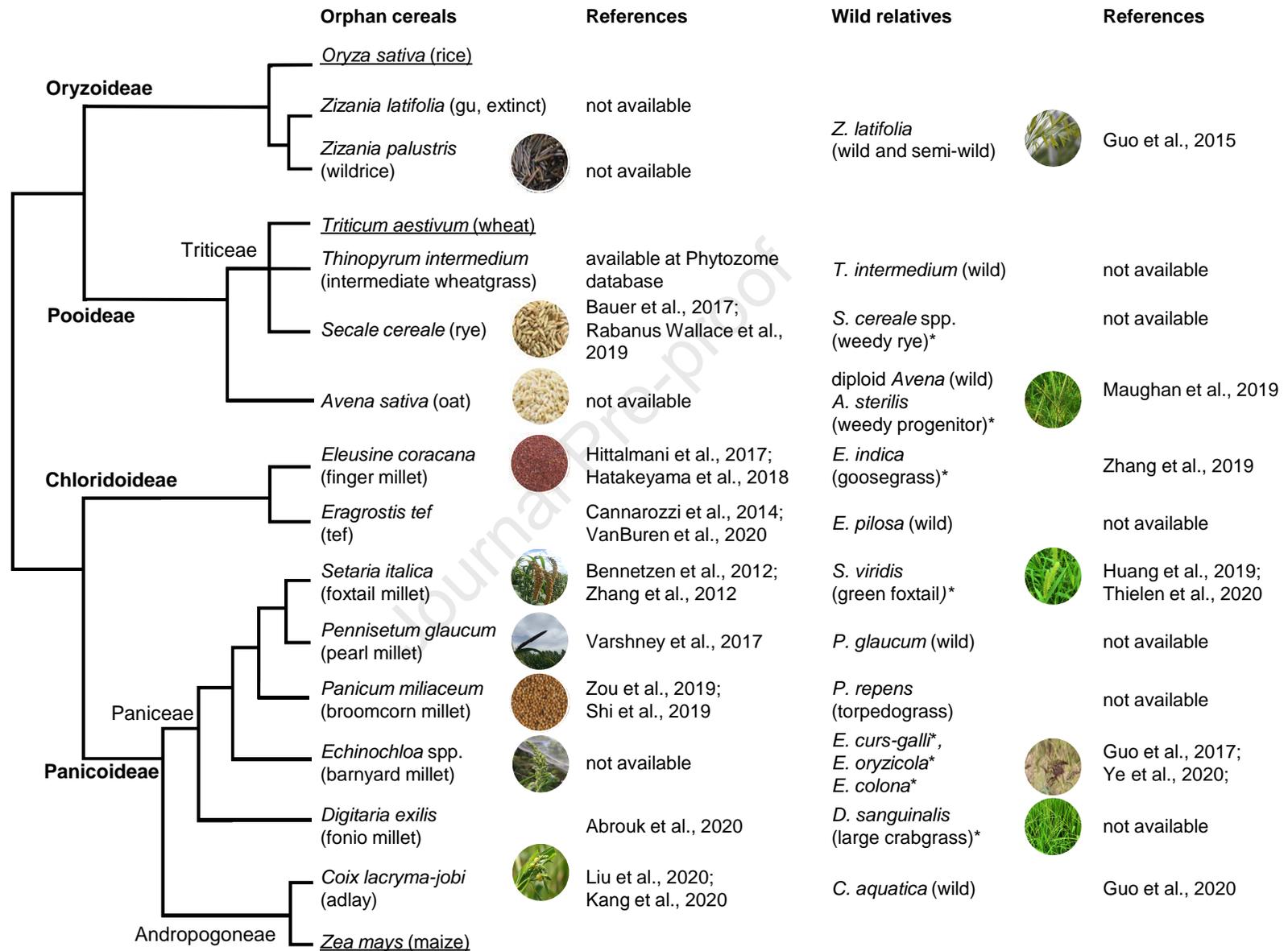


Fig. 1

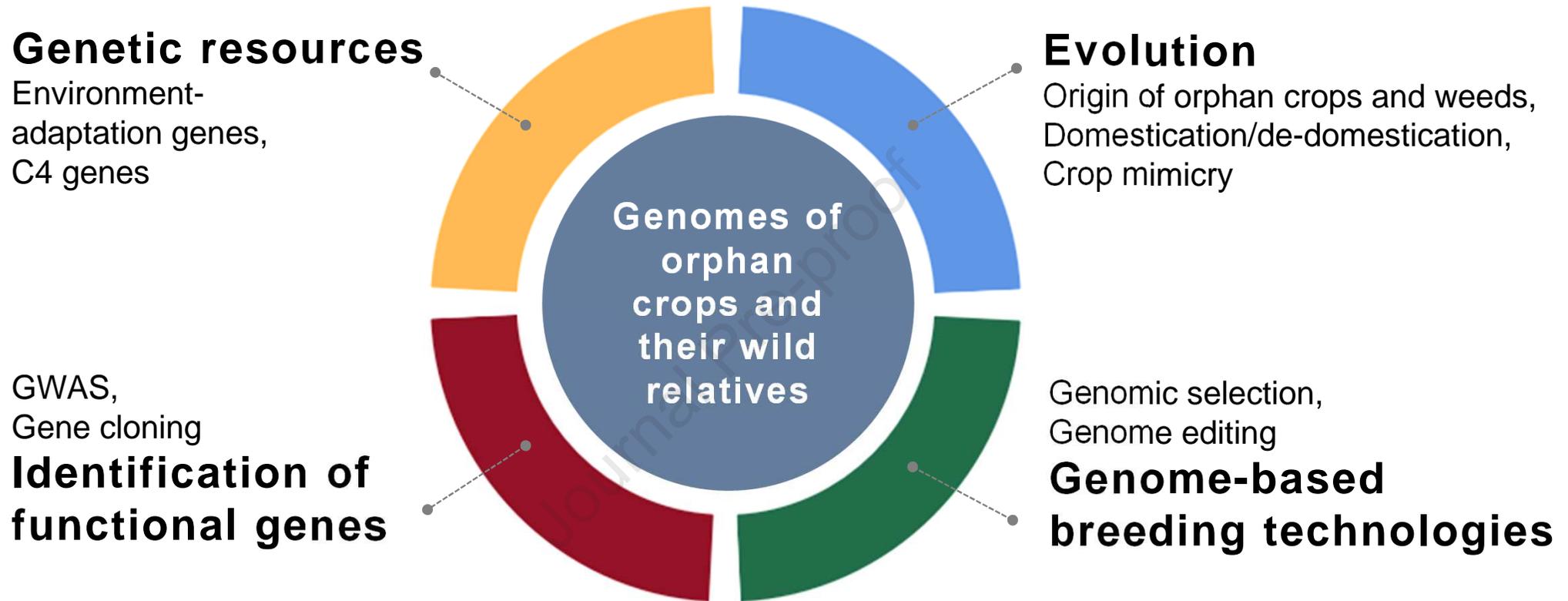
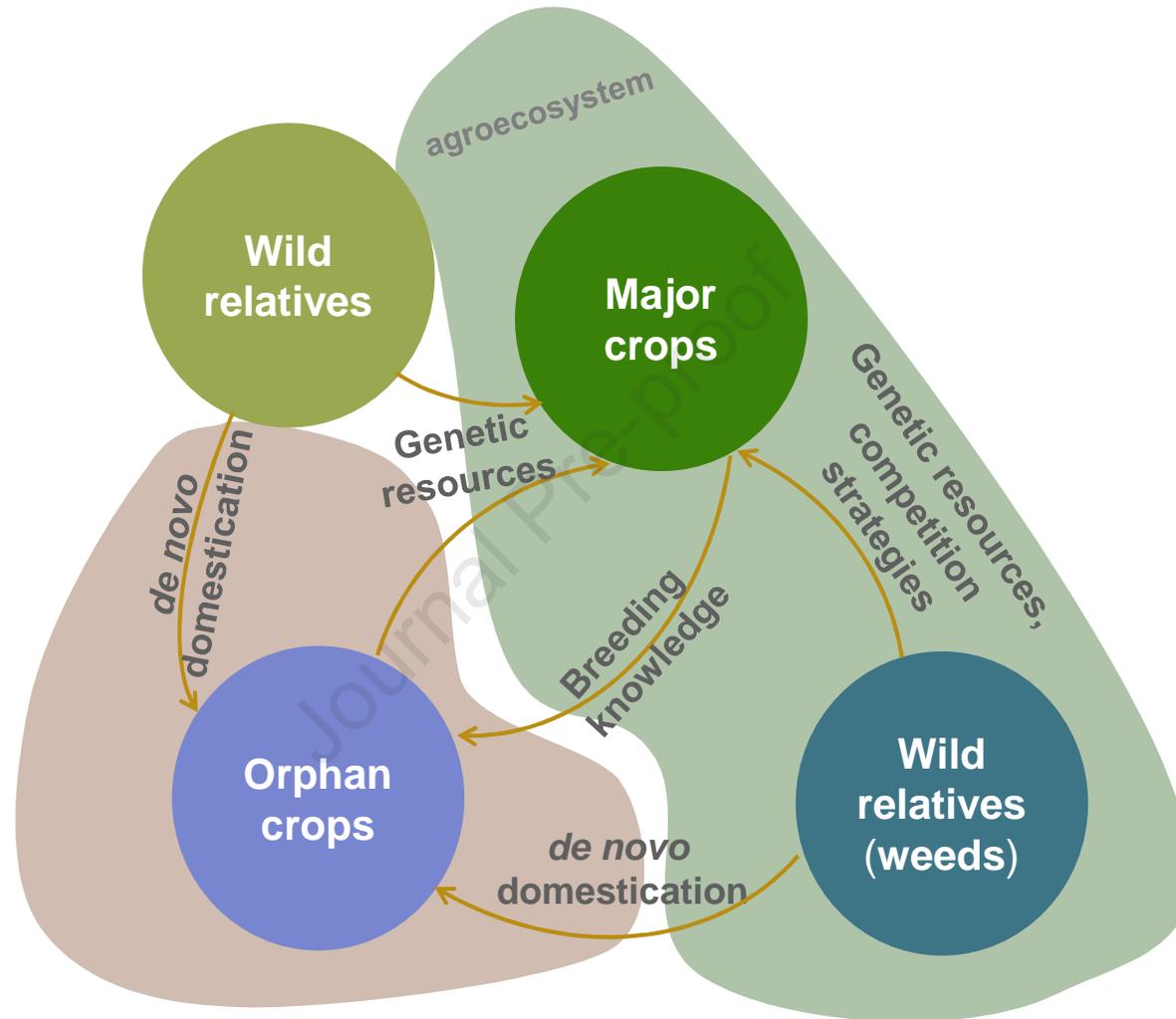


Fig. 2

**Fig. 3**