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Crop breeding – From experience-based selection to precision design

Jie Liu [a,*], Alisdair R. Fernie [b], Jianbing Yan [a,*]

[a] National Key Laboratory of Crop Genetic Improvement, Huazhong Agricultural University, Wuhan, China
[b] Department of Molecular Physiology, Max-Planck-Institute of Molecular Plant Physiology, Am Mühlenberg 1, 14476, Potsdam-Golm, Germany

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ABSTRACT

Crops are the foundation of human society, not only by providing needed nutrition, but also by feeding livestock and serving as raw materials for industry. Cereal crops, which supply most of our calories, have been supporting humans for thousands of years. However food security is facing many challenges nowadays, including growing populations, water shortage, and increased incidence of biotic and abiotic stresses. According to statistical data from the Food and Agriculture Organization of the United Nations (FAO, http://www.fao.org/), the people suffering severe food insecurity increased from 7.9 % in 2015 to 9.7 % in 2019 and the number of people exposed to moderate or severe food insecurity have increased by 400 million over the same time period. Although there are many ways to cope with these challenges, crop breeding remains the most crucial and direct manner. With the development of molecular genetics, the speed of cloning genetic variations underlying corresponding phenotypes of agricultural importance is considerably more rapid. As a consequence breeding methods have evolved from phenotype-based to genome-based selection. In the future, knowledge-driven crop design, which integrates multi-omics data to reveal the connections between genotypes and phenotypes and to build selection models, will undoubtedly become the most efficient way to shape plants, to improve crops, and to ensure food security.

1. A brief history of crop breeding and the evolution of methods of selection

Since human society shifted from hunter-gathering to cultivating crops, humans have depended on a small handful crops to meet the majority of our daily calorie demands (Ross-Ibarra et al., 2007). Among them, maize, rice, and wheat are top three calorie suppliers with all being domesticated 9000~12,000 years ago (Heun et al., 1997; Matsuoka et al., 2002; Doebley et al., 2006; Molina et al., 2011). While the selection method during the initial domestication period and subsequent several thousand years of crop improvement was mainly based on exterior appearance observation (such as color, plant architecture, shattering and so on), in the last two centuries crop breeding has evolved from empirical selection to precisely utilize favorable alleles of target genes (Wallace et al., 2018).

Since the publication of Darwin's *On the Origin of Species* and the rediscovery of Mendel's laws of inheritance, people began to control the mating of plants, to realize the power of heterosis, and to generate elite cultivars through breeding crosses. Maize yield data in the US, which has continuous record from 1866 to 2020, reveals that breeding crosses have led to the increase of maize yield (measured in bushels per acre) from ~25 in 1920s to around180 nowadays (Fig. 1). Another successful example of breeding crosses is the introgression of the "Green Revolution" genes *sd1* (Sasaki et al., 2002; Spielmeyer et al., 2002) and *Rht* (Peng et al., 1999) into elite cultivars, the progeny of which have supported our fast-growing population. In the 1970s, the identification and utilization of cytoplasmic male sterile rice germplasm by Chinese rice scientists made it possible to develop hybrid rice, which took advantage of heterosis, thereby boosting the rice yield, and ensured food security not only in China but also in other Asian countries (Ma and Yuan, 2015).

After a series of breakthroughs in biology, including the construction of linkage maps (Sturtevant, 1913), the discovery of the structure of DNA (Watson and Crick, 1953), and the mapping and cloning of *fw2.2* (Alpert et al., 1995; Alpert and Tanksley, 1996; Frary, 2000), we gained a much more clear understanding as to how the phenotype is controlled by the genotype. This led to considerably greater enthusiasm concerning the mapping of quantitative trait locus (QTL) analysis and its application in breeding programs. Thus, DNA-based molecular markers started to be used to dissect the genetic basis of agronomic traits and to improve crops through genome-based method, including marker-assisted selection (MAS) and genomic selection. Compared with traditional phenotype-based selection, genome-based breeding can directly deploy

* Corresponding authors.
E-mail addresses: jieliu@mail.hzau.edu.cn (J. Liu), yjianbing@mail.hzau.edu.cn (J. Yan).

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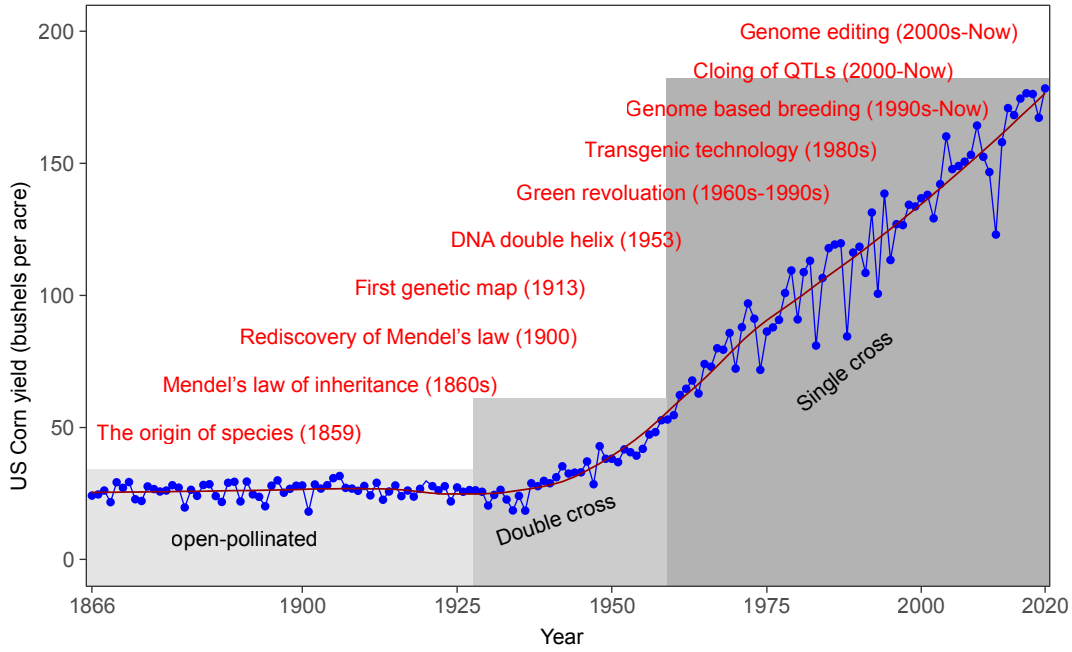

Fig. 1. The evolution of breeding methods in support of US maize yield increases. The key biological findings, which plays important roles in crop breeding, are shown with corresponding time points. The yield data is from United States Department of Agriculture.

favorable alleles underlying the desired traits, and thus leads to precise selection which significantly reduces the time needed to develop new varieties. Marker-based backcrossing of *Sub1A*, which confers rice submergence tolerance through the ethylene response pathway (Xu et al., 2006), into modern high yield varieties took only three generations of backcrossing (Neeraja et al., 2007; Septiningsih et al., 2009). During this time, yield advantages of 1–3 t/ha were observed in naturally occurring zones of submergence (Ismail et al., 2013). While MAS depends on major gene/QTL, genomic selection relies on genetic information of all molecular markers across the entire genome (Meuwissen et al., 2001; Desta and Ortiz, 2014). Both simulation analysis and breeding programs point out that genomic selection is much more effective than MAS (Bernardo and Yu, 2007; Massman et al., 2013). Furthermore, genomic prediction exhibits high predictive ability and accuracy for complex traits such as biomass- and bioenergy- related traits (Riedelsheimer et al., 2012).

The success of *Agrobacterium*-mediated gene transformation in the 1980s enabled the improvement of crops through the introduction of favorable genes via genetic engineering. In 1994, the first genetically modified (GM) food, the FLAVR SAVR tomato, was approved by US Food and Drug Administration (FDA). After this seminal event, more and more GM crops were released and there are now more than 500 approved GM varieties spanning 32 different crops (GM Approval Database: http://www.isaaa.org/gmapprovaldatabase/cropslist/default.asp). The most successful case for application of GM technology is the generation of herbicide tolerant and insect resistance crops by introducing genes encoding 5-*enol*pyruvylshikimate 3-phosphate synthase and Bt toxin into crops (Prado et al., 2014). It has been estimated that GM technology has increased maize production by 230 million tonnes and also brought $116.6 billion of monetary benefit to global farmers during the period 1996–2012 (Brookes and Barfoot, 2014). More recently, genome editing, which we discuss below, has become a massively important breakthrough with Emmanuelle Charpentier and Jennifer Doudna winning the 2020 Nobel Prize for Chemistry for its discovery (https://en.wikipedia.org/wiki/Nobel_Prize_in_Chemistry). The techniques of genome editing display a great potential for crop improvement.

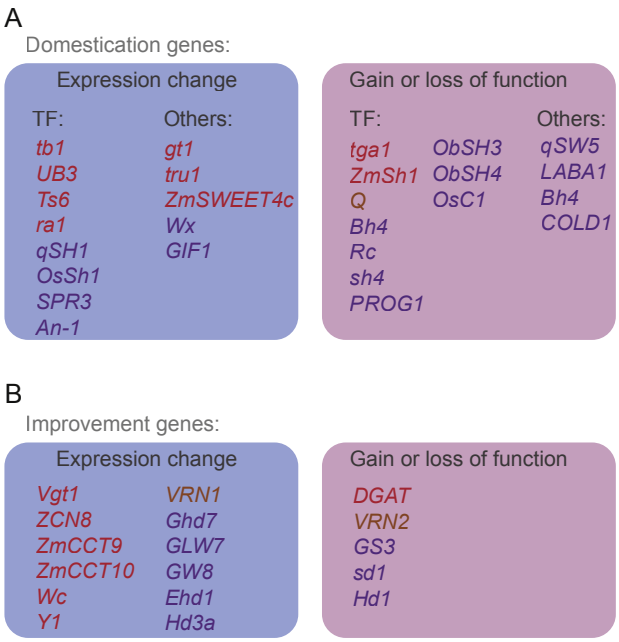

Fig. 2. A short summary of genes selected during domestication (A) and improvement (B) in maize, rice and wheat. The genes are divided into two groups: one represents genes selected for change of expression (left rectangle box), and the other one indicates the genes selected for gain or loss of protein function (right rectangle box). TF is short for transcription factor.

2. The functional genes underlying crop domestication and improvement

Accompanying the advances in molecular genetics, plant scientists now have cloned dozens of genes controlling key agronomic phenotypes, including domestication traits, in many crops. Functions of some of these genes and the pathways in which they are involved have been deeply explored and are nowadays well understood. Of the cloned

domestication genes in maize, rice and wheat, a very large proportion (~65 %) encode transcription factors (Fig. 2A). Some other domestication genes encode enzymes or transporters and regulate seed-related traits, such as grain color (*Bh4* for rice hull color, Zhu et al., 2011), grain quality (*Wx* for rice seed amylose content, Wang et al., 1995; Hirano et al., 1998), grain filling (*GIF1* for rice seed filling, Wang et al., 2008; *ZmSWEET4c* for maize seed filling, Sosso et al., 2015), and awn development (*LABA1*, Hua et al., 2015). In addition, there are two homeobox genes affecting maize plant architecture (*gt1*, Whipple et al., 2011; Wills et al., 2013) and rice seed shattering (*qSH1*, Konishi et al., 2006). Moreover, *COLD1* is a regulator of G-protein signaling in rice and is responsible for the adaption to chilling environment (Ma et al., 2015a, 2015b), whilst *GAD1*, which encodes a secreted peptide affects rice grain number, grain length, and awn development (Jin et al., 2016).Finally, *tru1*, which encodes an ankyrin repeat protein, is a target of *tb1* and regulates plant architecture (Dong et al., 2017). Interestingly, although transcription factors are particularly enriched in the set of domestication genes characterized so far, the ways in which these genes affect domestication traits are not linked to changes in expression level but may also include changes in protein function (Fig. 2A; Liu et al., 2020a, 2020b, 2020c).

Unlike domestication genes, the functions of genes selected during the crop improvement process are much more diverse. This may be due to the diverse breeding goals,comprising of altering flowering time, plant architecture, seed shape and grain yield. That said, there are still quite some transcription factors that underwent selection during this process including *Vgt1* for maize flowering time (Salvi et al., 2007; Ducrocq et al., 2008), *VRN1* for wheat flowering time (Yan et al., 2003) and *GW8* and *GLW7* for rice seed size and yield (Wang et al., 2012; Si et al., 2016). Furthermore, all the underlying functional variations for these transcription factors lead to expression level changes which subsequently resulted in altered phenotypes (Fig. 2B). In contrast, there is a class of genes containing CCT domain selected in the improvement, which can significantly affect the flowering time of maize and rice (Xue et al., 2008; Yang et al., 2013; Jin et al., 2018). Intriguingly, most of identified improvement genes for maize seed traits encode enzymes. *Wc* and *Y1*, responsible for seed color, encode carotenoid cleavage dioxygenase and phytoene synthase, respectively (Buckner et al., 1990; Tan et al., 2017). *DGAT* for seed oil content encodes an acyl-CoA: diacylglycerol acyltransferase (Zheng et al., 2008). The "green revolution" gene *sd1* also encodes a key enzyme (GA_{20} oxidase) for gibberellin biosynthesis which confers the dwarf phenotype (Sasaki et al., 2002; Spielmeyer et al., 2002). Finally, like *COLD1*, *GS3* is also involved in the G-protein signaling pathway to control rice and maize seed length and yield (Fan et al., 2006, 2009; Li et al., 2009).

From the ways in which these gene were selected, we can infer that the selection strategy differed considerable both between the different selection stage (domestication vs. improvement) and between different crops (maize vs. rice). Regulatory elements, which usually lead to the change of transcript abundance, tended to be selected during both maize domestication and improvement phases. By contrast, selection of gain or loss of protein function was much more prevalent in rice domestication where selection on expression change became more common only in the improvement phase (Fig. 2, red for maize genes and purple for rice genes). One important reason underlying this difference may be the different evolutionary history of these two crops. Maize underwent tetraploidization after divergence from sorghum followed by a subsequent genome rearrangement which finally led to diploidization (Gaut and Doebley, 1997; Gaut et al., 2000), while rice did not undergo such changes. Some maize genes have multiple copies, thus selection on gene expression might be much more efficient then on a protein basis due to the possibility of genetic compensation by other copies. For example, both *ZmSh1-1*, *ZmSh1-5.1*, and *ZmSh1-5.2*, which are orthologs of the sorghum seed shattering gene *Sh1*, have proven to be responsible for seed shattering (Lin et al., 2012). After the domestication of rice, the following improvement phase was focused on fine-tuning in order to gain more desirable traits. In such a situation, expression level changes has a considerable advantage over gain or loss of protein function strategies. This observation provides us the insight that selection on protein function might have been more widely adopted in the initial breeding steps (*de novo* domestication or selection of semidomesticated crops), and that selection on expression might be much more efficient in polyploid species.

Parallel selection is notably highly prevalent during both crop domestication and improvement. Outstanding examples are provided by the selection of *tb1*, seed shattering genes, and the *CCT* domain genes. Selection on *tb1* led to increased apical dominance and reduced branching number in maize (Doebley et al., 1997; Studer et al., 2011). Its ortholog (*INT-C*) in barley can modify the effect of *VRS1*, which is responsible for the domestication of the two-rowed ancestor to generate modern six-rowed cultivars (Komatsuda et al., 2007; Ramsay et al., 2011) and a duplicate gene (*OsTB2*) of *OsTB1* in rice has also been selected and plays an important role in upland rice adaptation (Lyu et al., 2020). Although it is not clear whether the orthologs of this gene were selected in other plant species, their conserved function has been additionally documented in Arabidopsis (Aguilar-Martinez et al., 2007), rice (Takeda et al., 2003) and wheat (Dixon et al., 2018). Lin et al. (2012) have confirmed that in sorghum, maize and rice the non-shattering phenotype was achieved through selection of a set of homologous genes (sorghum: *Sh1*, maize: *ZmSh1-1*, *ZmSh1-5.1*, and *ZmSh1-5.2*, and rice *OsSH1*). Furthermore, the African rice orthologs of *Sh4*, which is the gene underlying the non-shattering phenotype of Asian cultivated rice (Li et al., 2006), also controls the non-shattering phenotype (Wu et al., 2017; Lv et al., 2018). The gene *Ghd7*, which encodes a *CCT* domain protein, plays important roles in rice adaptation by affecting plant height, heading date and yield (Xue et al., 2008; Lu et al., 2012). And its maize ortholog *ZmCCT10*, is also a key gene for maize flowering time and adaptation (Ducrocq et al., 2009; Hung et al., 2012; Yang et al., 2013). Some other *CCT* genes, including *ZmCCT9* in maize (Huang et al., 2018), *Hd1* in rice (Yano et al., 2000), and *VRN2* in wheat (Yan et al., 2004), have also been verified to affect flowering time. This highlights the conserved functions of genes for some important agronomic traits and the capacity of functional genomic approaches to incorporate information from multiple plant species into the breeding programs.

3. The application of genome editing technology in crop improvement

Genome editing (also called gene editing) is one of most powerful tools to study the function of genes and an approach by which is possible to obtain desirable traits in crops. It consists of cutting the genome with a nuclease and then introducing new mutations through DNA repair pathways. Three genome editing systems, namely ZFN (Zinc-Finger Nucleases), TALEN (Transcription Activator-Like Effector Nucleases), and CRISPR-Cas (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein) have been well documented in plants. ZFN has been applied to knock out maize *IPK1* to reduce seed phytate content (Shukla et al., 2009) and to introduce a point mutation in wheat *AHAS* in order to obtain herbicide resistance (Ran et al., 2018). TALEN has also been employed to crop improvement, including editing maize *MTL* for increased haploid induction rates (Kelliher et al., 2017), rice *Os11N3* and *OsBADH2* for disease resistance and fragrance (Li et al., 2012; Shan et al., 2015), and wheat *TaMLO* for resistance to powdery mildew (Wang et al., 2014).

That said, compared to ZFN and TALEN, the CRISPR-Cas system is much more broadly adopted because of its simplicity and efficiency. The largest advantage of the CRISPR/Cas system is that it can edit a handful of genes simultaneously (Ma et al., 2015a, 2015b; Xie et al., 2015; Qi et al., 2016; Zhang et al., 2016; Wang et al., 2017), and can also generate large scale mutant libraries in a high throughput manner (Lu et al., 2017; Meng et al., 2017; Liu et al., 2020a, 2020b, 2020c). Owing to the

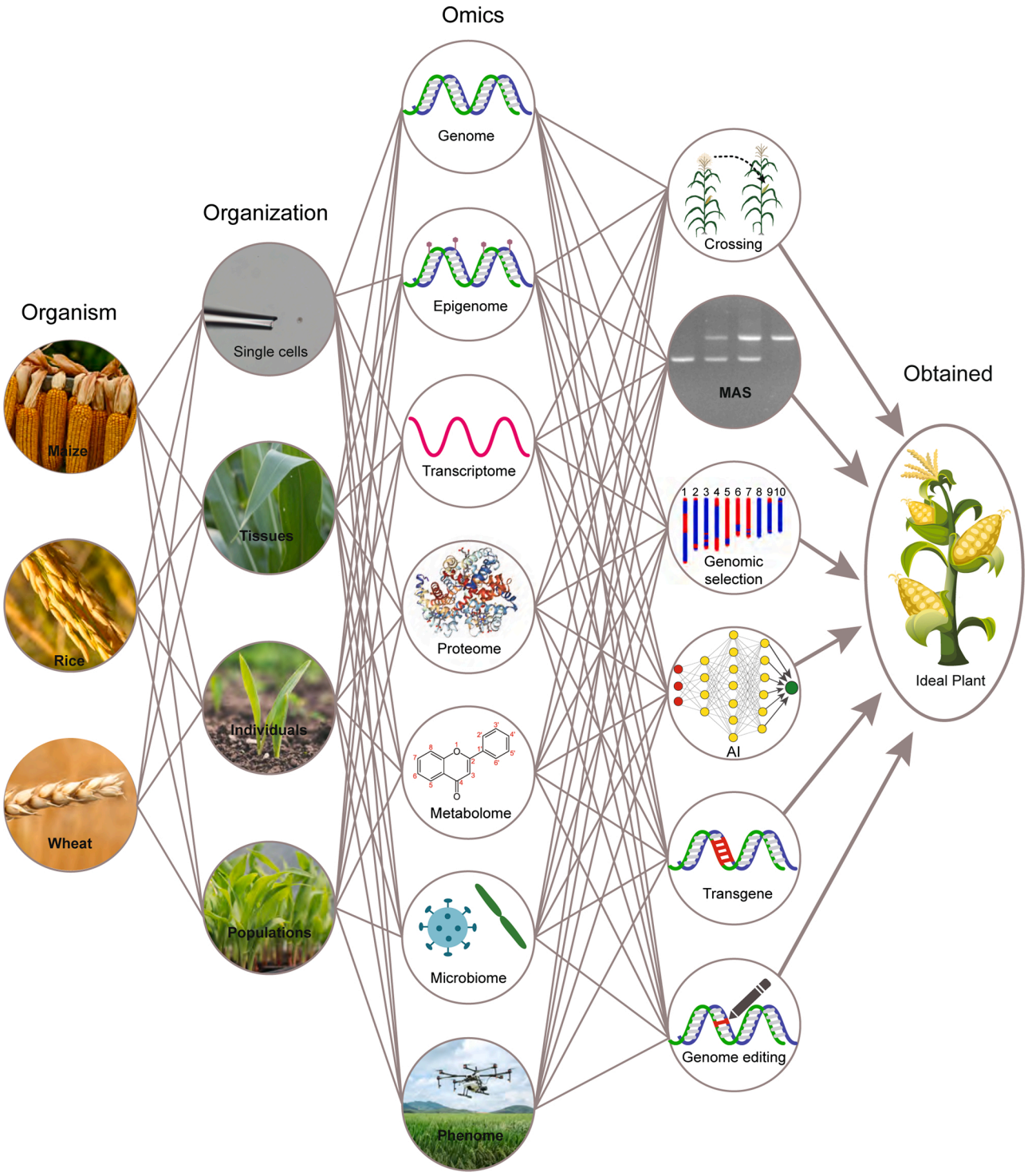

Fig. 3. A 4O (Organism, Organization, Omics, Obained ideal plant) roadmap for knowledge-driven crop design. Plant research has generated and is currently generating tremendous -omics level data among different crops (e.g. maize, rice, and wheat). The combination of -Artificial Intelligence (AI) mediated big data analysis and modern crop selection/modification methods, especially CRISPR-Cas gene editing, will largely accelerate future crop design, *de novo* domestication, and re-domestication.

advantages of CRISPR-Cas system, hundreds of editing events, which are based on this technology, have been published in all major cereal crops (reviewed in Ma et al., 2016; Yin et al., 2017; Char and Yang, 2019; Chen et al., 2019). There are two types of Cas protein, Cas9 and Cas12a (also known as Cpf1), which are widely used. Cas9 prefers G-rich protospacer adjacent motif (PAM) sequences and cleaves upstream of PAM sequences (Sternberg et al., 2014), while Cas12a tends to edit at T-rich PAM sites and cleaves downstream of PAM sequences (Zetsche et al., 2015). Recently, a very small Cas protein, which is named CasΦ (also named Cas12j, ~70 kD; Cas9 and Cas12a, ~160 kD), has been described to edit both human and plant cells (Pausch et al., 2020). There is no doubt that the diverse, distinct, and complementary features of these Cas proteins will ultimately extensively expand the utility of CRISPR-Cas system.

The CRISPR-Cas systems have already shown their superiority in precision breeding through editing coding regions and knocking out a large number of genes of interest (reviewed in Chen et al., 2019). However, the fine-tuning of the expression of target genes, which can be achieved through editing *cis*-regulatory sequence, infusing deactivated Cas9 (dCas9) with transcription factors, and changing the status of epigenetic marks (e.g. DNA methylation and histone acetylation), is also a very promising strategy for future breeding designs. Rodríguez-Leal et al. (2017) provided a classical example of obtaining quantitative variation of important agronomic traits (i.e. fruit size, inflorescence branches, and plant architecture) by editing the promoter sequences of a range of genes of interest in tomtao. Due to the target specificity of Cas9 guided by sgRNA, infusion of Cas9 with a transcription activator or repressor can precisely activate or repress the expression of target genes (Lowder et al., 2015; Li et al., 2017; Lowder et al., 2018). A DNA methylation modification system has also been established through dCas9 mediated SunTag system in plants (Papikian et al., 2019). Targeted gene expression changes have been observed following both locus specific DNA methylation/demethylation and histone acetylation modification (Gallego-Bartolomé et al., 2018; Papikian et al., 2019; Roca Paixão et al., 2019).

Despite the immense interest in these approaches, there are some concerns about the application of CRISPR-Cas system in crop breeding. The biggest one of these being the possibility of deleterious effects caused by the integration of transgenic constructs or off-target mutations. Several studies have documented the off-target effects of the CRISPR-Cas system in plants (Xie and Yang, 2013; Zhang et al., 2014; Endo et al., 2015; Jacobs et al., 2015; Lawrenson et al., 2015; Tang et al., 2018; Zhang et al., 2018; Jin et al., 2019). Jin et al. (2019) reported that cytosine editors, including BE3 and HF1-BE3, could result in genome-wide off-target mutations in rice and that these mutations tended to be enriched in genic regions. There are, however, ways to overcome such side effects. For example, one could remove the deleterious off-target effects by back-crossing with wild types or by choosing differently engineered high-fidelity Cas proteins. But to be honest, unlike in human disease treatment, off- target is not so important in plant applications, because it is easy to remove adverse effects through selection. Another major concern is the regulatory uncertainty of genome editing products. Although there is no difference between genetic changes caused by genome editing and natural mutations, genome editing plants are still considered to be genetically modified organisms (GMO) and are under strict regulation in some contries such as European Union (Jones, 2015). To alleviate this concern, considerable effort has been made to accomplish DNA-free genome editing resulting in no DNA sequence integration into the genome. The key point is to deliver pre-assembled gRNA-Cas9 ribonucleoprotein (RNP) complex into immature plant embryos or zygotes, which has been successfully acheived in maize (Svitashev et al., 2016), wheat (Liang et al., 2017, 2018), and rice (Toda et al., 2019). In parallel, other methods of assessing genome-edited have been proposed. Metabolomics can be used as a method to ensure that unintended effects of the editing can be monitored so that, if these are negligible, genome-edited crops can be regarded as safe (Fraser et al., 2020). Hopefully, a combination of such approaches, alongside the publicity generated by the 2020 Nobel Prize for Chemistry, will allay public skepticism surrounding gene editing.

4. The roadmap to knowledge-driven crop design

Here, we propose a comprehensive knowledge-driven crop breeding strategy called “4O” to **O**btain ideal plant through artificial intelligence (AI) analysis of **O**mics data generated from different **O**rganization levels and from different **O**rganisms (Fig. 3). Plant scientists now can investigate inheritance with multi-omics data (genome, epigenome, transcriptome, proteome, metabolome, microbiome, phenome) from different organization levels, including single cells, tissues, individuals, natural and synthetic populations. With the decreasing cost of sequencing and the acceleration of innovations, especially those allowing the acquisition of high-throughput data, a huge torrent of data has been generated, some of which are recently obtained in single cells (Luo et al., 2020), such as genome sequencing (Li et al., 2015), genome 3D structure identification (Zhou et al., 2019), expression quantification (Nelms and Walbot, 2019) and methylome profiling (Li et al., 2019). However, our capability in data integration and mining seriously lags behind that of data generation, which severely compromises the value of the data. That said the success of AlphaGo (Silver et al., 2016, 2017) is a milestone and indicates the effectiveness and practicability of AI for big data analysis. There are also some prior studies taking advantage of deep learning (Liu et al., 2020a, 2020b, 2020c) to solve large questions in plant biology including high-throughput phenotyping (Singh et al., 2016) and the prediction of gene expression (Sartor et al., 2019; Washburn et al., 2019). However, these is still a big gap between these proof-of-concept studies and the application of AI within crop breeding. New AI tools are urgently needed in order to fully exploit these large datasets, to discover genetic variants contributing to agronomic traits and to build the most effective selection models. Another key component of this strategy is the combination of different crop breeding methods (Fig. 3). Different breeding methods each have their unique advantages and limitations. MAS depends on QTL with large effects, while genomic selection is more effective for traits with complex genetic bases. The CRISPR-Cas system relies on target genes with clearly defined function in influencing target traits and can efficiently target more than 10 genes simultaneously (Zhang et al., 2020). Among these methods, CRISPR-Cas system has met great enthusiasm due to its precision. As demonstrated in a handful of previous studies (Lemmon et al., 2018; Li et al., 2018; Zsögön et al., 2018), the combination of big data based knowledge and the CRISPR-Cas system, has provided plant breeders with the power to *de novo*- or re- domesticate wild plant species which may have superior phenotypic aspects than existing major crops (Fernie and Yan, 2019). This process may reduce the time required for new crop development from the thousands of years of the big three cereals discussed here to a matter of decades.

Declaration of Competing Interest

The authors report no declarations of interest.

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