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Twenty years of rice genomics research: From sequencing and functional genomics to quantitative genomics

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ABSTRACT

Since the completion of the rice genome sequencing project in 2005, we have entered the era of rice genomics, which is still in its ascendancy. Rice genomics studies can be classified into three stages: structural genomics, functional genomics, and quantitative genomics. Structural genomics refers primarily to genome sequencing for the construction of a complete map of rice genome sequence. This is fundamental for rice genetics and molecular biology research. Functional genomics aims to decode the functions of rice genes. Quantitative genomics is large-scale sequence- and statistics-based research to define the quantitative traits and genetic features of rice populations. Rice genomics has been a transformative influence on rice biological research and contributes significantly to rice breeding, making rice a good model plant for studying crop sciences.

Key words: rice, *Oryza sativa*, structural genomics, functional genomics, quantitative genomics

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INTRODUCTION

Rice (*Oryza sativa*), an important cereal and model monocot, provides staple food for more than half of the global population. Two remarkable breakthroughs in rice breeding, dwarf breeding and hybrid rice breeding, have not only dramatically enhanced grain yield but also set the trend for rice breeding throughout the world. Nevertheless, the growth in annual rice production has slowed to the point where production is no longer keeping pace with the increasing number of human consumers. Therefore, the breeding of rice varieties with high yields, high quality, and high stress resistance to ensure food security remains an on-going task.

The umbrella term ''genomics'' circumscribes an interdisciplinary study that aims to elucidate the structure, evolution, and function of an organism's complete DNA sequence rather than individual genes. Chronologically speaking, structural genomics produced the complete rice map-based sequence, which laid a foundation for functional genomics and quantitative genomics in rice (Figure 1). Since then, increasing attention has focused on how to efficiently perform gene identification and functional characterization and on which scientific mysteries in rice can be answered by such knowledge of functional genomics and quantitative genomics. In this review, we outline the genetic resources that have provided an enormous amount of information on rice genomics, and we highlight advances in the available approaches for gene identification. We also describe important quantitative trait loci (QTLs) and their molecular regulatory networks underlying important agronomic traits, and we discuss how this information on rice genomics has contributed to our understanding of important scientific questions such as rice domestication, heterosis, and molecular breeding. Finally, we discuss ongoing challenges and future perspectives for rice genomics research.

ASSEMBLING HIGH-QUALITY REFERENCE GENOME SEQUENCES FOR RICE

Rice is considered to be a perfect model plant for plant genomics research because of its relatively small genome size (~400 Mb), well-established and highly efficient transformation system, extensive genetic resources, and synteny with the sequences of other cereal crops. A complete, high-quality rice reference genome sequence serves as the basis for genomic analysis, providing an unprecedented opportunity to systematically characterize the molecular functions of genes.

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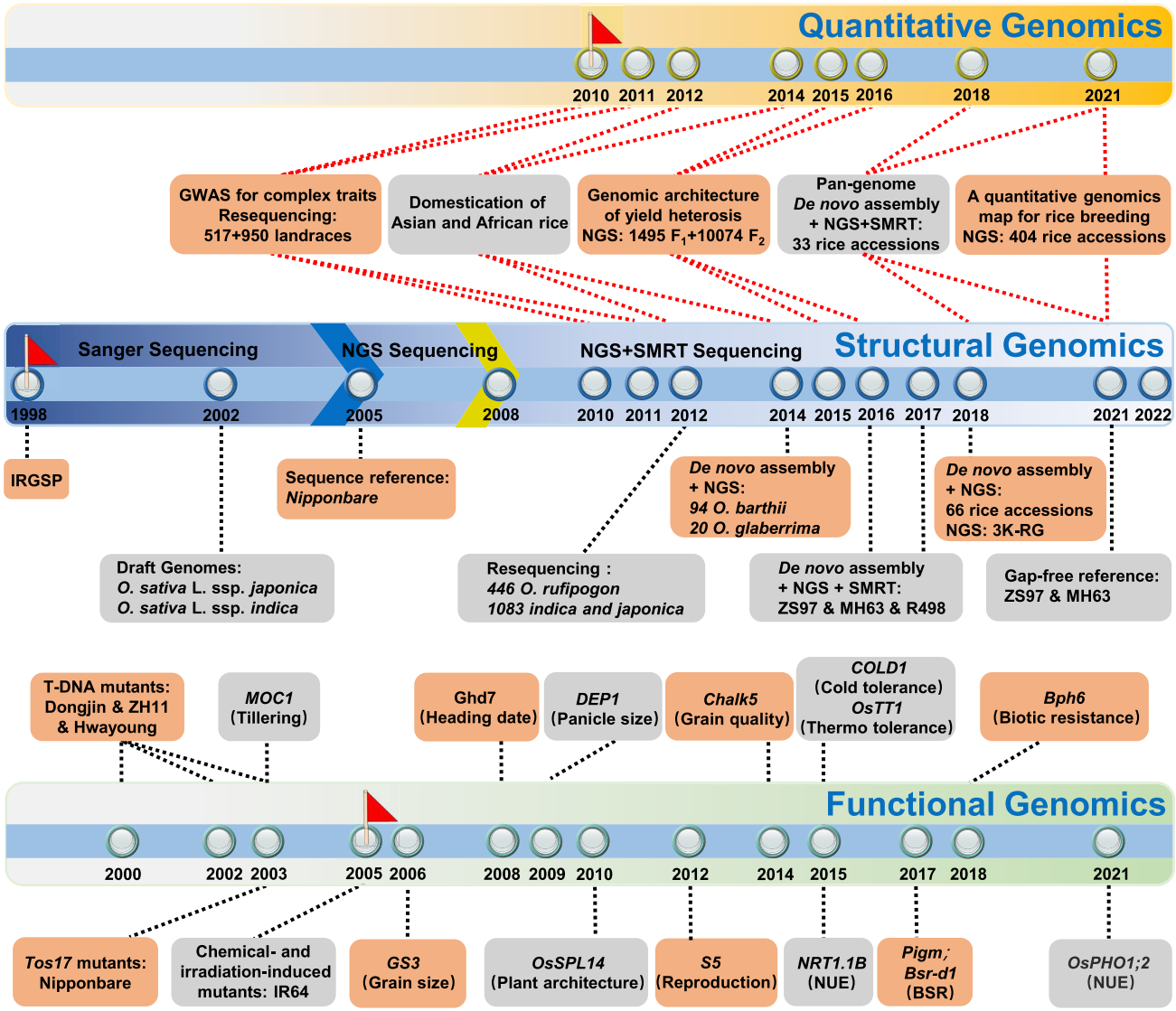

Figure 1. Timeline of rice genomics research.

Rice genomics can be roughly divided into three parts: structural genomics, functional genomics, and quantitative genomics. Structural genomics provides the genome sequences of thousands of rice accessions, which are beneficial for functional genomics (gene identification and functional characterization) and quantitative genomics (quantifying the genetic effects of causal QTLs). The red flag represents the approximate starting time of each part. Representative scientific advances are marked in brown and black boxes. NGS, next-generation sequencing; SMRT sequencing, single-molecule real-time sequencing; NUE, nutrient use efficiency; BSR, broad-spectrum resistance.

In an attempt to obtain a reference sequence, the International Rice Genome Sequencing Project (IRGSP) was established in 1998 to accurately and completely determine the entire genomic sequence of rice by a map-based, clone-by-clone shotgun strategy (Sasaki and Burr, 2000). *O. sativa* L. ssp. *japonica* cv. Nipponbare was chosen as a resource for sequencing, as its genome had been well mapped genetically and physically (Chen et al., 2002; Harushima et al., 1998; Wu et al., 2002). Detailed and informative genetic maps based on polymorphisms within DNA sequences are essential for ascertaining the chromosomal locations of DNA clones and assembling large DNA fragments (Harushima et al., 1998). Thus, marker-dense genetic maps set the stage for the construction and refinement of physical maps. Fingerprinted bacterial artificial chromosome (BAC)/P1-derived artificial chromosome (PAC) libraries were used to construct the rice high-resolution physical map, which helped to identify the minimum tiling path of clones to sequence (Chen et al., 2002; Zhao et al., 2002). In combination with the genetic map of the rice genome, the integrated physical map greatly accelerated the process of whole-genome sequencing of rice. In 2002, two complete sequences of chromosomes 1 and 4 were published (Feng et al., 2002; Sasaki et al., 2002). Meanwhile, the release of two draft sequences of the rice genome (*japonica* cv. Nipponbare and *indica* cv. 9311) obtained by whole-genome shotgun sequencing not only facilitated the preliminary survey of the IRGSP genome sequence but provided a meaningful foundation for crop improvement (Goff et al., 2002; Yu et al.,

2002). After that, a set of state-of-the-art technologies and algorithm analyses were integrated to complete the reference genome; these included cytogenic analysis, the sequence tag connector (STC) approach, high-resolution genetic maps, yeast artificial chromosome (YAC)- and BAC-based physical maps, a transcript map containing expressed sequence tags (EST), and two draft sequences. In 2005, the IRGSP completed a map-based reference genome sequence covering 95% of the Nipponbare genome (International Rice Genome Sequencing, 2005), signifying that rice genome research had officially stepped into the era of functional genomics. In parallel with large-scale sequencing, annotation of the rice genome depended mainly on *ab initio* gene-prediction programs (Feng et al., 2002; Yu et al., 2002), rice full-length (FL) complementary DNA (cDNA) and EST clones (Kikuchi et al., 2003; Rice Annotation et al., 2007), and whole-genome transcriptome data (Li et al., 2006b; Lu et al., 2010). Furthermore, to facilitate genomics-enabled research, the Rice Annotation Project Database (RAP-DB, https://rapdb.dna.affrc.go.jp/) was created to provide new IRGSP genome sequences with literature-based, manually curated annotation, as well as other genomics information (Rice Annotation et al., 2008). Meanwhile, the Rice Genome Annotation Project Database (http://rice.plantbiology.msu.edu/) made parallel efforts toward structural and functional annotation based on pseudomolecules rather than BACs (Ouyang et al., 2007). Together with updated annotation, the Nipponbare genome assembly was also constantly updated by optical map data, resequencing data, and manual curation (Zhou et al., 2007; Kawahara et al., 2013). To date, the RAP-DB has been updated several times (Sakai et al., 2013) and shares an up-to-date and uniform genome reference (Os-Nipponbare-Reference-IRGSP-1.0), accompanied by parallel annotation with the Rice Genome Annotation Project (Release 7).

Thanks to the rapid development of third-generation sequencing technology, some high-quality, chromosome-level reference genomes of rice have also been constructed for the discovery of genes and structural variations. For example, the highly contiguous reference genomes of Zhenshan 97 (ZS97), Minghui 63 (MH63), and Shuhui 498 (R498) were sequenced and assembled to represent the genome sequences of the *indica* subspecies through an integrative strategy of next-generation sequencing (NGS) and single-molecule real-time (SMRT) sequencing (Zhang et al., 2016; Du et al., 2017). In addition, *de novo* genome assemblies of two circum-basmati rice varieties using long-read nanopore sequencing also reached the reference level and provided data for functional and evolutionary genomic analyses (Choi et al., 2020). Notably, the rice pan-genome (see detailed information in the section ''approaches for gene identification'') and gap-free genomes, two milestones in rice structural genomics, have further enriched the reference genomes of rice. For instance, two gap-free reference genome assemblies of the *indica* rice varieties ZS97 and MH63 had higher completeness in gene regions compared with other reported high-quality rice genomes and laid the groundwork for further understanding of genome structure and function (Li et al., 2021b; Song et al., 2021). In short, all the highly reliable rice reference genome assemblies are publicly available for the scientific community, vastly expediting subsequent functional genomic studies.

RESOURCES FOR RICE FUNCTIONAL GENOMICS RESEARCH

Along with the completion of rice reference genome sequences, accumulating genomic resources have also paved the way for subsequent functional genomic research. Genomic resources in rice, including diverse genetic germplasm, mutant libraries, re-sequencing datasets and variation maps, multi-omics data sets, and available databases, not only empower researchers to elucidate the molecular functions of the rice genome but also enable breeders to efficiently develop excellent varieties on a large scale.

Rice genetic germplasm

Rice germplasm accessions are incredibly abundant throughout the world. The genus *Oryza* contains 27 species with 11 genome types, two of which are cultivated (*O. sativa* and *Oryza glaberrima*) and 25 of which are wild, with broad geographic distributions and ecological adaptations (Vaughan et al., 2003; Stein et al., 2018). Wild species of the genus *Oryza* have immense potential to make a meaningful impact on agricultural production of cultivated rice and can widen our understanding of domestication, evolution, polyploidy, and ecological adaptation (Wing et al., 2005; Stein et al., 2018). For instance, a comprehensive map of genome variation from 446 accessions of wild rice (*Oryza rufipogon*) and 1083 rice cultivars (*O. sativa*) revealed the origin of cultivated rice (Huang et al., 2012). In addition, some significant genes derived from wild rice, such as *Xa21* (Song et al., 1995), *Xa23* (Wang et al., 2015a), and *GW5/qSW5/GSE5* (Shomura et al., 2008; Weng et al., 2008; Liu et al., 2017b; Duan et al., 2017), have been cloned successfully and used for rice genetic improvement.

Rice gene banks exist to conserve genetic diversity by collecting large numbers of rice samples, aiming to represent the broad range of diversity within rice species. International efforts have been made to construct rice gene banks in which the extent of genetic variation and its accessibility are of interest to researchers and breeders. A typical case is the International Rice Genebank maintained by the International Rice Research Institute (IRRI, https://www.irri.org/), which holds over 132 000 available rice accessions. In addition, the United States Department of Agriculture Agricultural Research Service (USDA-ARS) and the National Agriculture and Food Research Organization (NARO) Genebank in Japan maintain over 18 000 and 37 000 rice accessions, respectively (Yan et al., 2007; Li et al., 2010; Tanaka et al., 2020). As the origin of Asian cultivated rice, China also has over 60 000 rice accessions (Zhang et al., 2011). Interestingly, Prof. Ying Ting, the famous Chinese rice researcher, collected over 7218 rice accessions from China and other central rice cultivation countries, and all of these accessions are referred to as Ting's collection (Song et al., 2018b).

Whole-genome resequencing of entire collections will make gene banks more informative and efficient (McCouch et al., 2012). Still, such extensive collections are almost impossible to sequence and evaluate in a cost-effective manner. For this reason, the development of a core collection appears to be an effective alternative. A valuable core collection should retain most of the

genetic diversity present in the original collection, thereby enabling better evaluation and management because of its smaller size. For example, a core subset representing approximately 10% of the complete USDA-ARS gene bank was assembled through stratified random sampling and comprehensively assessed using various evaluation criteria (Yan et al., 2007; Agrama et al., 2009). Core collections have been used as association panels for association studies based on various agronomic traits (Song et al., 2018b; Tanaka et al., 2020), and more compact but diverse populations suitable for genome-wide association studies (GWASs) are imperative owing to the need for rigorous and expensive phenotyping. The resultant mini-core panel should capture the maximum possible phenotypic and genotypic variation present in the whole collection, and a smaller subset of the core collection thus mirrors a larger or even complete germplasm panel for genetic analyses. The USDA rice mini-core subset was developed from a core collection representing over 18 000 accessions in its global gene bank. More recently, a mini-core collection representing 3004 accessions in the 3K Rice Genome (3KRG) project was used as an association panel to perform GWAS and population structure analysis (Wang et al., 2018f; Fuentes et al., 2019; Kumar et al., 2020). Collectively, diverse rice germplasm accessions reflecting broad genetic diversity will provide essential building blocks for gene mining and molecular breeding.

Resequencing datasets and variation maps

As mentioned earlier, resequencing large-scale germplasm furnished sufficient genetic variation information for gene identification. In addition, overall genetic variants (GVs) among rice varieties can facilitate biological interpretation for important questions such as crop improvement and domestication (Huang et al., 2012; Wei et al., 2021a). At present, RiceVarMap V2.0 and the gene-coding sequence-haplotype (gcHap) diversity dataset are the two most comprehensive genetic variation maps based on resequencing data (Zhang et al., 2021c; Zhao et al., 2021). Zhao et al. (2021) constructed a functional impact map of GVs by systematically annotating GVs from sequencing data of 4726 rice accessions. In addition to the accurate annotation of coding variants, this map also integrated chromatin accessibility data and a deep convolutional neural network to annotate non-coding regulatory GVs. Thus, this impact map will be a valuable resource for accelerating gene cloning and functional research. As a follow-up to the 3KRG project, Zhang et al. (2021c) characterized the gcHap diversity of 45 963 genes in 3010 rice accessions. Overall GVs in this dataset not only increased the power to detect causal genes, but also provided new insights and evidence for rice breeding and domestication of *O. sativa*.

Mutant libraries

Construction of saturated mutant libraries is very valuable for functional genomics, enabling systematic characterization of the functions of all rice genes. To date, strategies for the production of numerous mutants depend mainly on insertional mutagenesis, chemical/physical mutagenesis, or gene-editing mutagenesis. Insertional mutagenesis based on transfer DNA (T-DNA) insertions and transposon or retrotransposon tagging has been widely used in various rice cultivars, such as Dongjin, Nipponbare, and Zhonghua 11. It is estimated that about 470 000 independent T-DNA insertional lines have been generated, and all these mutants are publicly available online (http://signal.salk.edu/RiceGE/RiceGE_Data_Source.html). In addition, T-DNA insertion combined with transposon tagging can enable convenient large-scale mutant generation and screening. For instance, the *Activator*/*Dissociation* (*Ac*/*Ds*) and Enhancer/Suppressor (*En*/*Spm*) two-component transposon systems in maize have been introduced in rice to generate insertional mutants (Kolesnik et al., 2004; Kumar et al., 2005; Luan et al., 2008). In rice, the transposons *miniature Ping* and *nDart* are also suitable for developing an insertional mutagenesis population (Nakazaki et al., 2003; Nishimura et al., 2008). In addition, Tos17, an endogenous retrotransposon in rice, can be activated by tissue culture and has been exploited to produce about 50 000 mutant lines (Miyao et al., 2003, 2007). Unlike loss of function in T-DNA and transposon or retrotransposon mutants, gene entrapment and gene activation provide two complementary tools for creating dominant gain-of-function mutants and have contributed to the identification of novel genes and regulatory elements (Jeong et al., 2002; Wu et al., 2003; Wan et al., 2009). From all of the above insertion mutants, a large number of flanking sequence tags (FSTs) were isolated, and over half of non-transposable-element-related genes contained insertion tags.

Because the insertions induced by T-DNA and transposons are distributed unevenly across the genome, it is difficult to achieve whole-genome saturation by insertional mutagenesis (Zhang et al., 2007; Wang et al., 2013b). Chemical/physical mutagen-derived mutant lines appear to overcome this drawback of insertional mutagenesis, as genomic deletions induced by chemical and irradiation-based mutagenesis are randomly distributed. Fast neutrons (FNs) and gamma rays generate mainly single base substitutions (SBSs), as well as other structural variations. For example, Li et al. (2017a) identified 91 513 mutations affecting 32 307 genes in an FN-mutagenized population of Kitaake. Among the 91 513 mutations, 48% were SBSs, and deletions accounted for 66% of the non-SBS mutations (Li et al., 2017a). Chemical mutagens such as ethyl methanesulfonate (EMS) and N-methyl-N-nitrosourea (MNU) produce high-density single-nucleotide variations with a random distribution. In the *indica* rice variety IR64, approximately 60 000 chemical and irradiation-induced mutants have aided gene mining and functional characterization (Wu et al., 2005). Taking advantage of targeting induced local lesions in genomes (TILLING), high-throughput mutation discovery in target sites has also become a general tool for functional genomics (Till et al., 2007; Tsai et al., 2011).

Recently, the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 system has emerged as a powerful method for whole-genome mutagenesis in rice (Lu et al., 2017; Meng et al., 2017). The highly specific single guide RNA (sgRNA) library generated by array-based oligonucleotide pool synthesis ensures the targeting specificity of CRISPR/Cas9 and sufficient abundance covering the whole genome, making large-scale targeted mutagenesis possible. Hundreds of thousands of mutant lines have been isolated and evaluated by genotyping and phenotyping. Consequently, abundant mutant libraries with efficient mutant screening systems are essential for functional genomics through forward and reverse genetics.

Multi-omics data sets

With the rapid accumulation of multi-omics data, rice genomic research has stepped into the interactome big data era and can now aim to dissect the genetic complexity of rice from a global and integrated viewpoint (Wu et al., 2021b). In addition to genomics, other omics approaches, such as epigenomics, transcriptomics, proteomics, metabolomics, and phenomics, have produced a massive amount of data for rice functional genomics based on cutting-edge technologies.

An understanding of the transcriptome is essential for deciphering genome structure and function, interpreting the complexity of transcriptional regulation, and identifying the genetic networks that control various agronomic traits. Different hybridization- or sequencing-based approaches, such as massively parallel signature sequencing (MPSS) and microarrays, have been widely used to deduce and quantify the transcriptome during various developmental stages (Rensink and Buell, 2005; Nakano et al., 2006). For example, a rice gene expression atlas based on microarray data revealed some salient features of dynamic gene expression patterns across stages and tissues, providing versatile resources for rice genomic research (Furutani et al., 2006; Wang et al., 2010b). Moreover, RNA-seq has recently emerged as a powerful approach for measuring and quantifying global gene expression in a high-throughput manner, and it is expected to revolutionize the study of transcriptomics (Wang et al., 2009). RNA-seq or microarray profiling coupled with laser microdissection help to uncover transcriptional regulatory networks that underlie different developmental events within various tissues (Jiao et al., 2009; Harrop et al., 2016; Itoh et al., 2016). At present, many gene expression databases for rice have been established, including Transcriptome ENcyclopedia Of Rice (TENOR), Rice Expression Database (RED), and RiceXPro (Sato et al., 2011; Kawahara et al., 2016; Xia et al., 2017). Transcriptomic analysis also affords insights into gene identification and scientific issues, such as expression QTL (eQTL)-guided co-expression analysis and heterosis (Zhai et al., 2013; Wang et al., 2014a; Groen et al., 2020). More recently, the transcriptomic landscape at a single-cell resolution revealed the differentiation trajectories of the rice root, opening new avenues for understanding the molecular mechanism of organ development in plants (Liu et al., 2021a; Zhang et al., 2021g).

The epigenomic landscapes sculpted by DNA methylations, histone modifications, non-coding RNAs, and three-dimensional (3D) genome structure involve a complex set of processes that modulate genome activities and determine the diverse profiles of gene expression in distinct cell types or in response to environmental cues (Banerjee and Roychoudhury, 2018). DNA cytosine methylation that occurs at CG, CHG (H = A, C, or T), and CHH is a hallmark of the repression of transposable elements (TEs) and repetitive sequences. Three DNA methyltransferases (OsMET1, OsCMT3, and OsDRM2) and a rice chromatin remodeler (OsDDM1) have been functionally characterized, further enriching our understanding of methylation dynamics during plant growth and development (Tan et al., 2016; Lu et al., 2020b). For instance, genes expressed preferentially in the rice endosperm are hypomethylated, along with increased CHH methylation of small TEs in embryos, suggesting that DNA methylation is a crucial regulator of rice endosperm biogenesis (Zemach et al., 2010). Histone modifications consist mainly of acetylation and methylation and are frequently involved in the control of complex agronomic traits through regulation of gene transcription (Du et al., 2013). A representative example is the antagonistic functions of the H3K27 methyltransferase gene *SDG711* and the H3K4 demethylase gene *JMJ703*, both of which have a role in reprogramming the H3K27me3/H3K4me3 ratio to modulate rice inflorescence meristem activity (Liu et al., 2015). Thus, epigenomic regulation participates in various rice developmental and stress-responsive pathways, especially flowering and reproduction (Shi et al., 2014). In parallel, inheritable and metastable epialleles of functional genes, such as *Epi-d1* (Miura et al., 2009), *Epi-rav6* (Zhang et al., 2015), and *afo* (Wang et al., 2010a), also govern important agronomic traits. Non-coding RNA and 3D genomic structure are reportedly associated with epigenomic regulation. For example, *OsDCL3a* identified by deep sequencing of small RNAs functions in the production of TE-associated 24-nt siRNAs, which may affect the dwarfism phenotype through a conserved epigenetic mechanism (Wei et al., 2014). In addition, chromatin packing and interaction patterns in rice with topologically associated domains have been well defined through high-throughput chromosome conformation capture (Hi-C) analysis (Liu et al., 2017a; Dong et al., 2018). More recently, a comprehensive reference epigenome of 20 rice varieties integrating various datasets has been constructed, helping to delineate the epigenomic landscape and thereby promote understanding of transcriptional regulation (Zhao et al., 2019, 2020).

Proteomics supplements other omics approaches, such as transcriptomics, to determine the identity of overall proteins in a cell, tissue, or organism and to delineate the functions and structures of specific proteins. In general, proteome studies focus mainly on two aspects: protein expression and protein function. Evolving proteomic technologies such as mass spectrometry (MS)-based approaches open the door for the identification and quantification of proteins under defined conditions. For example, numerous small secreted proteins related to rice immunity have been identified through transcriptomics- and proteomics-based screening (Wang et al., 2020a). Furthermore, the proteomic responses of rice to diverse abiotic and biotic stresses have also been well characterized (Zou et al., 2011; Kim et al., 2014). Under PEG-induced drought conditions, 78 differentially expressed proteins were separated by comparative proteomic analysis, and a large percentage of them appeared to be involved in metabolism and bioenergy for better drought adaptation (Agrawal et al., 2016). Compared with other omics approaches, rice proteomics remains in its infancy, but ever-increasing knowledge about protein quantification, modification, localization, and function will propel rice functional genomics to new heights.

Plant metabolites are regarded as readouts of physiological status and are indispensable resources for the plant's own needs and those of humans. Thus, unraveling the genetic basis of the rice metabolome and its natural variation is important for comprehensively understanding gene functions in the post-genomic era. Large-scale metabolite profiling assays based on MS or nuclear magnetic resonance (NMR) spectroscopy provide access to global metabolite data through rapid and accurate detection and quantification (Kumar et al., 2017). For instance, liquid

chromatography (LC)-MS is a promising metabolomic tool that measures non-targeted or targeted metabolites. Based on LC-MS, Chen et al. (2013) adopted a strategy of stepwise multiple ion monitoring enhanced product ions (MIM-EPI) to construct an MS^2 spectral tag (MS2T) library. They obtained a total of 698 non-redundant metabolites, including some phytohormones. Very recently, a rice metabolic regulatory network (RMRN) spanning the entire plant life cycle was constructed by combining metabolomic and transcriptomic data, and this RMRN dataset could be used to identify novel regulatory genes associated with important compounds (Yang et al., 2021). In addition, metabolic QTL (mQTL) mapping and metabolic GWASs (mGWASs) are suitable for unraveling the genetic basis of natural variation in the rice metabolome, as well as understanding the genetic determinants of metabolic pathways (Fang et al., 2019). In artificial populations like recombinant inbred line (RIL) populations, over 2800 mQTLs for 900 metabolites have been detected by genetic analysis of the flag leaf and germinating seed (Gong et al., 2013). In follow-up work with widely targeted metabolic profiling in seeds across three stages, 4681 mQTLs displayed a significant deviation from the random distribution across 12 chromosomes (Li et al., 2019). Further comparative analysis showed that most of the distinct loci were identified among these mQTLs for co-detected metabolites in either different developmental stages or different tissues, suggesting that the majority of mQTLs are under separate genetic regulation. Intriguingly, joint linkage analysis using multiple interconnected biparental populations further strengthened the power for identification of veritable mQTLs (Chen et al., 2018). In unrelated natural accessions, many common variants affecting secondary metabolites were detected by mGWAS using 529 diverse accessions of cultivated rice. Substantial heterogeneity was observed in the natural variation of metabolites and their underlying genetic architectures (Chen et al., 2014). Moreover, either mGWAS or parallel GWAS combined with mGWAS and phenotypic GWAS (pGWAS) have been performed to identify metabolite-related genes underlying complex agronomic traits and decipher the genetic regulation of rice metabolism (Chen et al., 2016; Zhan et al., 2020). Taken together, multi-developmental stage analysis and multidimensional analysis with other omics data have been increasingly used in rice metabolomics to provide clues for dissecting the genetic architecture of rice metabolomes.

High-throughput phenomics generally refers to a multidisciplinary study in which large-scale, multidimensional phenotypic data are acquired and analyzed accurately and rapidly (Yang et al., 2020). On the one hand, plant phenomics meets all the requirements for functional genomics research: it is high throughput, labor saving, time saving, objective, non-destructive, repeatable, and occasionally cost effective. On the other hand, it involves the study of the whole organism, in terms of morphological measurement, physiological processes, stress monitoring, and agronomic trait investigation. To date, high-throughput phenotyping platforms with the above advantages have been used to study functional genomics in rice. Specifically, with advances in a range of technologies such as unmanned aerial vehicles (UAVs) and sophisticated imaging sensors, increasing amounts of phenotypic data derived from controlled environments or field conditions have been used for both forward and reverse genetics. For instance, Yang et al. (2014) developed a high-throughput rice phenotyping facility that could monitor 15 agronomic traits, and 141 associated loci were ultimately identified through GWAS. In addition, 51 image-based traits representing drought responses were extracted to perform GWAS and linkage analysis, and the drought resistance-related gene *OsPP15* was identified and confirmed by genetic transformation experiments (Guo et al., 2018b). Recently, a deep learning-integrated micro-computed tomography imaging system was used to nondestructively quantify lodging resistance, which is also essential for molecular breeding and functional genomics in rice (Wu et al., 2021a).

Available databases and bioinformatics tools in rice

As high-throughput sequencing technologies have been applied broadly in rice genomics research, the amount of resulting data appears to exhibit an exponential growth trend, as seen in the aforementioned multi-omics data. Consequently, numerous well-characterized databases with user-friendly interfaces have been constructed for the rice research community. For example, Information Commons for Rice (IC4R; http://ic4r.org) is a rice knowledgebase that incorporates multi-omics data and gene annotations as well as rice-related literature through community-contributed modules (Consortium et al., 2016). Processing a huge amount of data also requires powerful bioinformatics software and tools. Hence, a number of databases or tools, such as the Rice SNP-Seek Database (http://snp-seek.irri.org) for GWAS and RiceNavi (http://www.xhhuanglab.cn/tool/RiceNavi.html) for quantitative trait nucleotides (QTNs), have been released (Mansueto et al., 2017; Wei et al., 2021a). To provide a glimpse of these available databases and bioinformatic tools, we summarize and categorize them in Table 1 according to several criteria, including access frequency, practicality, functionality, ease of use, and number of citations. Considering the consistency and integrity in rice research, we also summarize some rice germplasm resource databases and practical tools, such as IRRI germplasm (http://irri.org) and CRISPR-P for sgRNA design (http://crispr.hzau.edu.cn).

APPROACHES FOR GENE IDENTIFICATION

Gene cloning is pivotal for understanding the genetic basis of variation in quantitative or complex traits and also plays a prominent role in crop improvement. Gene identification has mainly been performed by conventional forward and reverse genetics approaches, but, owing to recent advances in NGS technology and a well-characterized reference genome, emerging approaches such as genome editing and pan-genome analysis also show great potential for gene identification. Here, as shown in Figure 2, we provide a detailed overview of how these approaches have contributed to gene identification and cloning.

QTL mapping

The premise of QTL mapping is that QTLs can be localized through the statistical genetic linkage between their molecular markers and phenotypes in artificial populations. Recombination frequency is critical for localizing QTLs, and mapping populations, such as F_2 populations and RILs, that harbor genetic

Databases	Description	Resource link
TIGR	genome browser	http://rice.plantbiology.msu.edu/
RAP-DB	genome browser	https://rapdb.dna.affrc.go.jp/index.html
Gramene	comparative genomics	http://www.gramene.org/
Phytozome	comparative genomics	https://phytozome.jgi.doe.gov/pz/portal.html
RiceXPro	expression profile	http://ricexpro.dna.affrc.go.jp/
TENOR	expression profile	https://tenor.dna.affrc.go.jp/
ATTED-II	co-expression analysis	http://atted.jp/
RiceFREND	co-expression analysis	http://ricefrend.dna.affrc.go.jp/publication.html
KEGG_rice	metabolite analysis	https://www.genome.jp/kegg/kegg2.html
IC4R	comprehensive databases	http://ic4r.org/
Rice-data	comprehensive databases	https://www.ricedata.cn/
RIGW	comprehensive databases	http://rice.hzau.edu.cn/
IRRI	rice germplasms	http://irri.org/
RiceGE	rice mutant database	RiceGE: Database Sources, Details and Summary (salk.edu)
NIAS (RTIM)	rice mutant database	https://tos.nias.affrc.go.jp/
RPAN	rice pan-genome database	http://cgm.sjtu.edu.cn/3kricedb/
RicePanGenome	rice pan-genome database	RicePanGenome (ncgr.ac.cn)
Rice Resource Center	rice pan-genome database	http://ricerc.sicau.edu.cn/
RiceVarMap v2.0	GWAS	http://ricevarmap.ncpgr.cn/
Rice SNP-Seek Database	GWAS	https://snp-seek.irri.org/_snp.zul
RiceNavi	molecular breeding	http://www.xhhuanglab.cn/tool/RiceNavi.html
PlantCARE	promoter analysis	http://bioinformatics.psb.ugent.be/webtools/plantcare/html/
CRISPR-P	CRISPR/Cas9 tool	http://crispr.hzau.edu.cn/CRISPR2/

Table 1. Representative bioinformatics databases and tools for rice genomics research.

mosaics derived from parental varieties must contain a sufficient number of recombination events. The most common genetic markers are restriction fragment length polymorphisms (RFLPs), simple sequence repeats (SSRs), polymorphic insertions and deletions (indels), and single nucleotide polymorphisms (SNPs); among them, sequencing-based SNP markers have increasingly been used for the construction of genetic maps. For example, Huang et al. (2009) developed a high-throughput genotyping method based on whole-genome resequencing data to construct a genetic map in rice recombinant populations. They designed a sliding window approach for recombination breakpoint determination and genotype calling by collectively examining genome-wide SNPs. A skeleton bin map derived from recombination maps and rigorous phenotyping values were used to perform composite interval mapping, and 49 QTLs for 14 agronomic traits containing several known genes were localized with relatively high resolution in 150 RILs of rice (Wang et al., 2011). The linkage map constructed with a set of recombination bins, together with exhaustive phenotype data, was subjected to linkage-based analyses, which have long been considered a mainstream and feasible method for QTL mapping.

In general, a larger population size coupled with high-resolution genotype information can considerably improve the resolution and accuracy of QTL mapping, which, mirroring the rice genome, means that candidate genes are located within a smaller genomic interval. Hence, map-based cloning with a larger population size is necessary to narrow down candidate intervals to a single gene. Additional steps toward gene validation, such as transgenic complementation tests and near-isogenic line (NIL) verifications, are also relatively straightforward in rice.

GWAS

GWAS relies on the correlation between nucleotide polymorphisms and phenotypic variance among diverse germplasms. The limitations of QTL mapping associated with low mapping resolution and limited genetic diversity in biparental populations hinder the process of gene isolation, whereas GWASs that make use of genetic diversity and are based on population genetics can simultaneously detect dozens of natural allelic variations that influence complex agronomic traits (Yano et al., 2016). In contrast to tedious linkage mapping, GWAS is considered a powerful and cost-efficient tool for gene identification (the samples in GWAS panels can be genotyped only once but phenotyped for various traits many times), especially low-coverage sequencing approaches that further expedite the cost reduction. For example, Huang et al. (2010) successfully performed GWAS for 14 agronomic traits to identify a substantial number of loci by sequencing 517 rice landraces at approximately 1-fold genome coverage. They constructed a

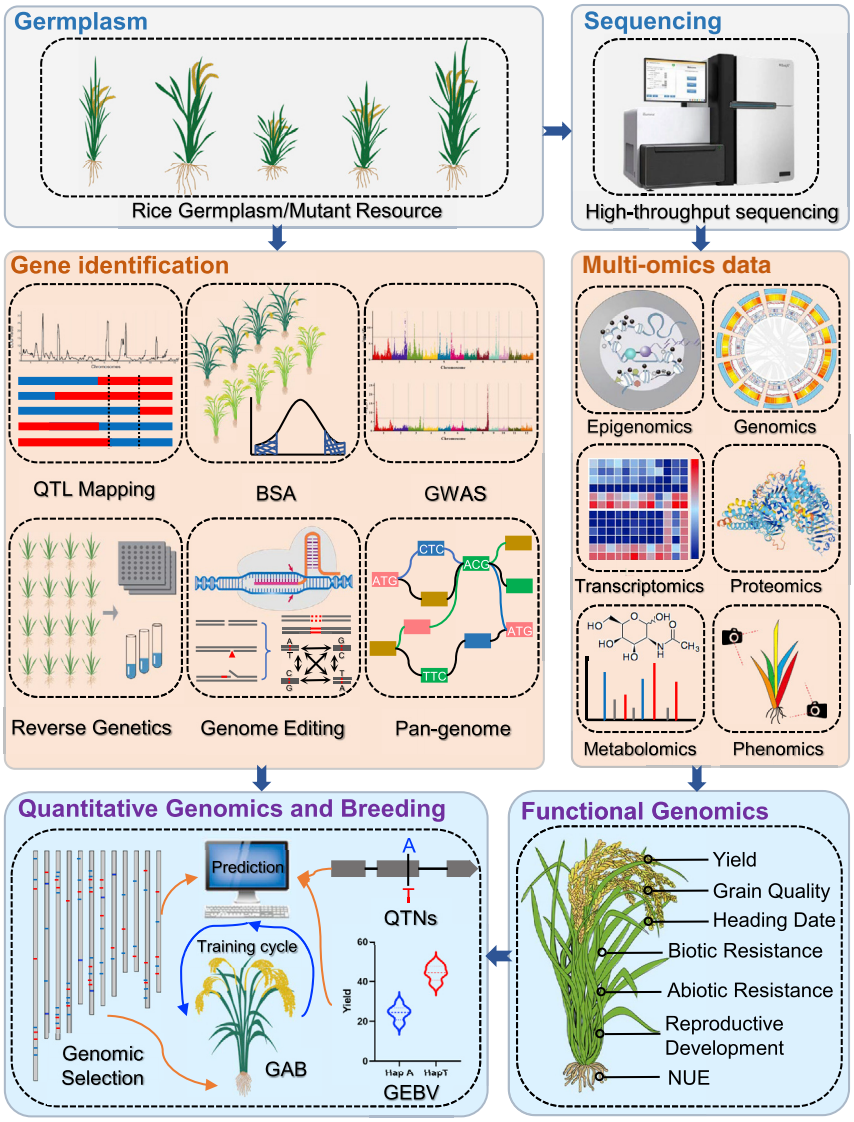

Figure 2. Schematic diagram illustrating the procedure for rice functional genomics research.

QTNs, quantitative trait nucleotides; GAB, genomics-assisted breeding; GEBV, genomic estimated breeding value.

high-density haplotype map of the rice genome through a data-imputation method based on the *k*-nearest neighbor algorithm (KNN). Sample number and sequencing coverage are two key factors to consider in the experimental design (Han and Huang, 2013). A larger sample size generally means higher detection power of the GWAS and a greater number of identified allelic variants. Given this fact, a larger and more diverse sample consisting of 950 worldwide rice varieties was used to perform GWAS, and a total of 32 new loci associated with flowering time and grain-related traits were identified (Huang et al., 2011). Similarly, a number of major and minor effect QTLs as well as subpopulation-specific alleles controlling grain length were identified by GWAS, indicating that an expanded diversity panel considerably improved the power and resolution of GWAS (McCouch et al., 2016). However, GWAS using sequencing data with low sequencing depth (1–2×) has similar power to that using genotypes from high-coverage data, and low-coverage sequencing can detect causal polymorphisms through haplotype-based *de novo* assembly (Huang et al., 2011; Wang et al., 2016). The integration of sequence-based GWAS with other functional analyses, such as expression pattern analysis and knockout lines of candidate genes, has the potential to match traits to their causal polymorphisms in rice. One of many examples is *OsSPL13*, which positively regulates grain length and yield; higher expression of *OsSPL13* with a tandem-repeat sequence in its 5′ UTR is associated with large grain in tropical *japonica* rice (Si et al., 2016). Very recently, a 1D/2D GWAS strategy was used to explore the complex genome-wide interactions underlying the reciprocal adaptation of rice and *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), and quite a number of *Xoo* virulence-related genes and quantitative resistance genes of rice were identified (Zhang et al., 2021b). It is worth noting that the extent of linkage disequilibrium (LD) and population structure in rice is likely to result in spurious associations between genotype and phenotype. Rice is a self-pollinating species that exhibits a large degree of LD and extremely strong population structure owing to its evolutionary and domestication history. To address these problems, reconstruction populations such as nested association mapping (NAM) populations and multi-parent advanced generation intercrossing (MAGIC) populations have been proposed to avoid strong population structure, and the stringent screening of candidate genes based on the estimated effects of causal polymorphisms raises the positive rate of GWASs (Yano et al., 2016). Hence, careful experimental design that considers confounding effects, as well as refined statistical approaches or models, will maximize the power to identify genes in GWAS (Liu et al., 2016; Li et al., 2022b).

Bulked-segregant analysis

Bulked-segregant analysis (BSA) is a simple and cost-saving QTL mapping strategy that involves sampling and bulking via NGS technology (Zou et al., 2016). In BSA, DNA bulks of progeny are created by pooling individuals that show extreme phenotypic values for the trait of interest. If the molecular markers are linked to the trait of interest, there will be distinct allele frequencies between the two bulks. By contrast, unlinked markers will show similar allele frequencies in the two bulks (Nguyen et al., 2019). Several versions of BSA, including QTL sequencing (QTL-seq), MutMap, and GradedPool-seq, have been implemented with biparental populations (F_2 or RILs), natural populations, and multi-parent populations (NAM or

MAGIC), as well as mutant libraries, to identify genes. For example, QTL-seq was successfully applied to a segregating progeny derived from a biparental population to rapidly identify QTLs by resequencing two pooled bulks (each with 20–50 individuals) that showed extreme opposite trait values (Takagi et al., 2013a). Likewise, MutMap based on whole-genome resequencing of pooled DNA is particularly amenable to rice mutant libraries (Abe et al., 2012). In proof-of-concept experiments, genes related to complex traits such as disease resistance, salt tolerance, and semidwarfism were identified by QTL-seq or MutMap (Abe et al., 2012; Takagi et al., 2013a, 2015). Interestingly, MutMap-Gap, which combines *de novo* assembly and alignment within gap regions, was used to isolate the blast-resistance gene *Pii* (Takagi et al., 2013b). Currently, GradedPool-seq has emerged as a powerful QTL mapping method based on BSA through the resequencing of two or more sorted DNA bulks and has been used to identify QTLs underlying important agronomic traits such as the heterosis gene *GW3p6* (Wang et al., 2019b).

Conventional reverse genetic strategies

There is no denying the fact that most genes have been identified and functionally characterized by reverse genetic approaches. Commonly used methods in conventional reverse genetics are RNA interference (RNAi), TILLING, ectopic expression through transgenic approaches, and mutant libraries. For example, TILLING is a general reverse genetic technique for high-throughput mutation discovery (Till et al., 2007), and NGS enables TILLING to be turned into an *in silico* procedure (Wang et al., 2012b). In addition, the full-length cDNA over-expressor gene (FOX) hunting system, which introduces FL-cDNAs of rice into *Arabidopsis* plants for systematic gain-of-function mutations, is a rapid and efficient method for elucidating rice gene functions based on ectopic expression (Sakurai et al., 2011). Comparative analysis of gene function among rice and other plants such as *Arabidopsis* provides new insights for gene identification (Shimamoto and Kyozuka, 2002). For instance, functional analysis of *OsTIR1*/*OsAFB* mutants that were knocked out by the CRISPR/Cas9 system based on homologous auxin receptor TIR1/AFB family members in *Arabidopsis* indicated that *OsTIR1*/*AFB* family members act partially redundantly in the regulation of rice growth and development (Guo et al., 2021).

Genome editing

Gene editing, a powerful reverse-genetics method for targeting and editing genomes, has become a prevalent and indispensable tool for rice functional genomics research. To date, CRISPR/Cas systems have efficiently achieved knockout, knockin, knock-up, knockdown, and base editing to varying degrees (Huang et al., 2018; Lu et al., 2020a, 2021). CRISPR/Cas systems have been widely used to preferentially modify a variety of complex traits in rice, including yield, grain quality, biotic and abiotic resistance, and reproductive development (Gao, 2021). A key characteristic of the CRISPR/Cas system is the presence of CRISPR-induced DNA double-strand breaks (DSBs) at target sites, which can be used to introduce a variety of genome modifications by one of two main DNA repair pathways: nonhomologous end joining (NHEJ) and homology-directed repair (HDR). Genome editing based on NHEJ is a routine way to disrupt genes by creating small insertions or deletions at target sites. For instance, transgenic rice plants that contained small insertions and deletions introduced by CRISPR/Cas9 into the phytoene desaturase gene (*OsPDS*) displayed an albino and dwarf phenotype (Shan et al., 2013). A robust CRISPR/Cas9 vector system for high-efficiency multiplex genome editing has rendered loss-of-function mutations easier in monocot and dicot plants: multiple sites in one or multiple genes can be edited with an extremely high rate of mutation (Ma et al., 2015a). HDR-mediated gene editing can be used either to insert or replace a desired sequence or to introduce specific point mutations. For example, Wei et al. (2021b) inserted $EBE_{AvrXa23}$ (effector binding element) into the promoter of the *xa23* allele in PXO99^{A}-susceptible Nipponbare through HDR-mediated genome editing, changing it into a broad-spectrum resistance variety. Continuous refinements in CRISPR/Cas systems, such as CRISPR/Cas12a (Cpf1) and Cas-NG, have further broadened the scope of genome editing in plants (Tang et al., 2017; Endo et al., 2019). Beyond DSB-mediated genome editing, various newly emerging CRISPR/Cas systems, including base editing (e.g., the cytosine base-editor and adenine base-editor systems) and prime editing, provide simple and powerful tools for engineering nucleotide substitutions at target sites without the formation of DSBs. The base editors are fusions of single-stranded DNA-specific deaminases with catalytically impaired Cas9 (nCas9 D10A) that can achieve C·G to T·A or A·T to G·C transitions (Shimatani et al., 2017; Zong et al., 2017; Wang et al., 2019c). Prime editing comprises an engineered Cas9 nickase-reverse transcriptase fusion protein and a prime editing guide RNA, which allow for the creation of all 12 types of base substitutions (Lin et al., 2020). Consequently, powerful CRISPR/Cas systems not only serve as precise tools for gene identification and functional characterization but also hold promise for crop improvement (Chen et al., 2019b).

Pan-genome analysis

Recent advances in single-molecule sequencing and physical mapping technologies have led to high-quality chromosome-scale assemblies of rice with extremely high continuity and completeness. Specifically, Wenger et al. (2019) generated long high-fidelity (HiFi) reads with high accuracy (99.8%) by optimizing circular consensus sequencing (CCS) to improve the accuracy of SMRT sequencing on the Pacific Biosciences (PacBio) platform. With the development of genome assemblers such as CANU (Koren et al., 2017) and FALCON (Carvalho et al., 2016), it is therefore possible to build near-complete or gap-free rice genomes (Michael and VanBuren, 2020). Consequently, some gapless rice genome assemblies have been created by incorporating high-coverage long-read sequence data and diverse assembly methods such as genetic maps, Hi-C, and Bionano optical maps (Li et al., 2021b; Song et al., 2021). Non-TE genes with sequence divergence can be identified through comparative analyses of multiple high-quality genomes; for example, 66 gene alleles differed between Nipponbare and Shuhui498 (Du et al., 2017). Nevertheless, a single reference genome does not represent all the diversity within a species (Bayer et al., 2020). Thus, a pan-genome that consists of a core genome and a dispensable genome can be defined as the non-redundant collection of genomic diversity within a single species (Lei et al., 2021). For instance, high-quality assemblies of three

divergent rice genomes representing the *indica* (IR64), temperate *japonica* (Nipponbare), and *aus* (DJ123) subpopulations revealed numerous genome-specific loci associated with complex traits, such as the hybrid sterility locus *S5* and the submergence tolerance locus *Sub1* (Schatz et al., 2014). Zhao et al. (2018b) constructed a pan-genome dataset comprising *O. sativa* and *O. rufipogon* through *de novo* assembly of 66 divergent accessions, and the sequence variations pinpointed new causal variants underlying complex traits. Notably, the plummeting cost and increasing throughput of long-read sequencing technologies allow assemblies to reach extremely high levels of accuracy and yield, enabling us to capture more variations at the population scale by untangling genomic regions missed by NGS (De Coster et al., 2021). For example, Qin et al. (2021) developed a graph-based pan-genome dataset by assembling high-quality genomes of 33 genetically diverse rice accessions. They also identified hidden structural variations (SVs) to expose phenotypic variation that had previously been missed. Intriguingly, a locus harboring two SVs was shown to be associated with early leaf senescence through GWAS based on the graph-based genome rather than on SNP data (Qin et al., 2021).

GENES AND THEIR REGULATORY NETWORKS UNDERLYING IMPORTANT AGRONOMIC TRAITS IN RICE

In the era of genomics, the number of cloned genes that govern important agronomic traits has increased exponentially, and their molecular regulatory pathways have been clarified to some extent. Here, we briefly summarize critical rice genes underlying the important agronomic traits in Table 2, and we emphasize genes newly coupled with their regulatory pathways that have a profound impact on rice functional genomics and crop improvement.

Yield

Yield is quantitatively inherited, unlike traits that are controlled by a single gene (monogenic) or a few genes (oligogenic). The yield of rice is primarily determined by the number of effective panicles, the number of grains, and grain weight. Panicle number per plant, which mirrors the proportion of tillers bearing panicles, is critical for rice grain yield. Tiller bud initiation and outgrowth are intricately regulated by a variety of phytohormones, including auxin, cytokinins (CKs), brassinosteroids (BRs), and strigolactones (SLs). In general, auxin, SLs, gibberellins (GAs), and abscisic acid (ABA) function to repress bud outgrowth, whereas CKs and BRs promote bud outgrowth in rice (Wang et al., 2018a; Liu et al., 2020). Notably, strong empirical evidence involving the biosynthesis and signaling pathway of SLs suggests that SLs can inhibit bud outgrowth to regulate shoot branching (Umehara et al., 2008; Waters et al., 2017). For instance, the activity of SLs can be abrogated to promote axillary bud outgrowth through SL-dependent degradation of the DWARF53 repressor mediated by the DWARF14 (D14)-DWARF3 (D3) complex (Jiang et al., 2013; Zhou et al., 2013). Surprisingly, *Ideal Plant Architecture 1* (*IPA1*) functions as a direct downstream component of D53 in the regulation of rice tiller number and plays an essential role in the feedback regulation of SL-induced *D53* expression (Song et al., 2017). In addition, *OsSPL14* (*IPA1*/*WFP*) acts as a core transcription factor in the formation of plant architecture (Jiao et al., 2010; Miura et al., 2010). Also, a natural tandem array in the *IPA1* promoter (*qWS8*/*ipa1-2D*) increased *IPA1* expression by attenuating the epigenetic repression of *IPA1* mediated by nearby heterochromatin, greatly enhancing grain yield (Zhang et al., 2017a). In addition, *MONOCULM1* (*MOC1*) encodes a plant-specific GRAS family nuclear protein that plays an important role in initiating axillary buds and promoting bud outgrowth (Li et al., 2003). An array of genes such as *TE* (*Tiller Enhancer*)/*TAD1* (*Tillering and Dwarf 1*) and *SLR1* (*SLENDER RICE 1*) function in mediating the stability of MOC1 protein to regulate rice tillering (Lin et al., 2012; Xu et al., 2012; Liao et al., 2019). Moreover, tiller angle is also vital for grain yield, as it affects plant density and light interception. Some important genes associated with tiller angle, such as *LAZY1*, *PROG1*, and *Tiller Angle Control 1* (*TAC1*), have been well characterized and jointly contribute to shaping the ideal plant architecture in rice (Li et al., 2007; Yu et al., 2007; Jin et al., 2008; Tan et al., 2008).

Panicle size and grain number per plant are the major contributors to grain production in rice. CKs generally have positive effects on the activity and maintenance of the reproductive meristem. Hence, homeostasis of CK levels in the inflorescence meristem is essential for regulating panicle branching and grain number. For instance, *Gn1a*/*OsCKX2* is involved in the degradation of CKs (Ashikari et al., 2005), whereas *LOG* and *GNP1* are associated with the activation of CKs (Kurakawa et al., 2007; Wu et al., 2016). The expression of *OsCKX2* can be directly modulated by the zinc-finger transcription factor *DROUGHT AND SALT TOLERANCE* (*DST*), and the mutant allele DST^{reg1} increases CK levels by reducing *OsCKX2* expression in the reproductive shoot apical meristem (SAM), thus further enhancing panicle branching and consequently increasing grain number (Li et al., 2013). In addition, the *DST-OsCKX2* module may function downstream of the *OsER1-OsMKKK10-OsMKK4-OsMPK6* pathway to shape the inflorescence by regulating cytokinin metabolism (Guo et al., 2020). Recently, it was shown that the R2R3 MYB transcription factor *RGN1* may control lateral grain formation by modulating *LOG* expression and thus regulating grain number (Li et al., 2022a). Some other genes related to panicle architecture and grain number, such as *FZP*, *NOG1*, and *GAD1*, have been empirically shown to have enormous potential for improving grain yield (Jin et al., 2016; Bai et al., 2017; Huo et al., 2017).

Grain size and grain weight are regarded as essential targets during rice breeding, and some key grain size regulators involved in several signaling pathways have been well characterized. For example, a G-protein pathway composed of five subunits of the heterotrimeric G proteins plays a conserved role in the regulation of grain size (Sun et al., 2018). Among them, three Gγ proteins, GS3, DEP1, and GGC2, regulate grain size antagonistically. The major QTL *GS2*/*OsGRF4*/*GL2*, regulated by OsmiR396, exhibited higher expression to enhance grain weight and grain size through the *OsmiR396-OsGRF4-OsGIFs* module (Hu et al., 2015b; Che et al., 2015; Duan et al., 2015). In addition, *qSW5*/*GW5*/*GSE5* was identified as a major QTL that controlled grain width and weight, and a deletion in the promoter of *qSW5*/*GW5*/*GSE5* that influenced gene expression appeared to have undergone artificial selection during rice domestication (Shomura et al., 2008; Weng et al., 2008; Liu et al., 2017b; Duan et al., 2017).

Trait	Gene	Gene ID	Functional annotation	References
Yield	*HTD1/D17*	Os04g0550600	carotenoid cleavage dioxygenase 7	Wang et al., 2020b
	qWS8/ipa1-2D	Os08g0509600	SPL family domain	Zhang et al., 2017a
	OsSHI1	Os09g0531600	transcription factor of SHI family	Duan et al., 2019
	FZP	Os07g0669500	ERF transcription factor	Bai et al., 2017
	NOG1	Os01g0752200	enoyl-CoA hydratase/isomerase	Huo et al., 2017
	qLGY3/GW3p6	Os03g0215400	MADS-box transcription factor	Liu et al., 2018b; Wang et al., 2019b
	TGW3/GL3.3/ OsGSK5	Os03g0841800	GSK3/SHAGGY-like kinase	Hu et al., 2018; Xia et al., 2018; Ying et al., 2018
Grain quality	*Waxy^{lv}*	Os06g0133000	granule-bound starch synthase	Zhang et al., 2019a
	OsGluA2	Os10g0400200	glutelin type-A2 precursor	Yang et al., 2019
Heading date	*DHD4*	Os02g0110100	CONSTANS-like transcription factor	Cai et al., 2021
	OsCIPK3	Os07g0687000	CBL-interacting protein kinase	Peng et al., 2021
	DHD1	Os11g0706200	GRAS protein	Zhang et al., 2019b
Biotic resistance	*PICI1*	Os10g0533900	deubiquitinase	Zhai et al., 2022
	ROD1	Os06g0128800	Ca^{2+} sensor	Gao et al., 2021
	Pigm	KU904633	NLR receptor	Deng et al., 2017
	Bsr-d1	Os03g0437200	C2H2-type transcription factor	Li et al., 2017b
	Ptr	Os12g0285100	atypical protein	Zhao et al., 2018a
	Bph6	Os04g0431700	exocyst-localized protein	Guo et al., 2018a
Abiotic resistance	*CTB4a*	Os04g0132500	LRR receptor-like kinase	Zhang et al., 2017b
	HAN1	Os11g0483000	cytochrome P450	Mao et al., 2019
	bZIP73	Os09g0474000	bZIP transcription factor	Liu et al., 2018a
	TT2	Os03g0407400	Gγ subunit	Kan et al., 2021
	SLG1	Os12g0588900	cytosolic tRNA 2-thiolation protein 2	Xu et al., 2020
	AET1	Os05g0535500	$tRNA^{His}$ guanylyltransferase	Chen et al., 2019a
	PSL1	Os01g0296200	polygalacturonase	Zhang et al., 2021d
	OsCd1	Os03g0114800	MFS domain-containing protein	Yan et al., 2019
NUE	*OsTCP19*	Os06g0226700	class-I TCP transcription factor	Liu et al., 2021b
	ARE1	Os08g0224300	abc1-1 repressor1	Wang et al., 2018d
	OsNGR5	Os05g0389000	AP2-domain transcription factor	Wu et al., 2020
	OsPH O 1;2	Os02g0809800	phosphate transporter 1	Ma et al., 2021
	OsDNR1	Os01g0178000	amino transferase	Zhang et al., 2021f
	OsNRT1.1A/ OsNPF6.3	Os08g0155400	nitrate transporter	Wang et al., 2018e
	OsSPX4	Os03g0827500	SPX family protein	Hu et al., 2019
Reproduction	*qHMS7-ORF2*	LOC9266374	toxic genetic element	Yu et al., 2018
	qHMS7-ORF3	Os07g0646600	antidote	Yu et al., 2018
	Sc	Os03g0247300	DUF1618 domain-containing protein	Shen et al., 2017
	ESA1	Os01g0524100	nuclear-membrane-localized protein	Hou et al., 2019
	TMS10	Os02g0283800	LRR receptor-like kinase	Yu et al., 2017

Table 2. Representative rice genes identified during the past 5 years that control important agronomic traits.
SHI, short internodes; CoA, co-enzyme A; MFS, major facilitator superfamily.

Grain quality

Rice grain quality consists of appearance, cooking, milling, and nutritional quality, and it is conceivable that better grain quality means higher profits for rice growers. To date, many vital genes underlying grain quality have been harnessed extensively for variety improvement. For example, *Waxy* (*Wx*), encoding granule-bound starch synthase I, is responsible for amylose synthesis that determines eating and cooking quality (ECQ). Natural allelic

variations within the *Wx* locus (e.g., Wx^a, Wx^b, Wx^{lv}, Wx^{mv}, Wx^{in}, and *wx*) are the principal cause of the broad diversity in amylose content (AC) and ECQ (Zhang et al., 2019a, 2021a). Fine-tuning the expression of *Wx* with the CRISPR/Cas9 system can generate new alleles with desirable AC and ECQ (Huang et al., 2020; Zeng et al., 2020). *Chalk5* encodes a vacuolar H^+-translocating pyrophosphatase and is a major QTL that affects grain chalkiness and head rice yield (Li et al., 2014). Interestingly, a few QTLs underlying grain size, such as *GW7*, *OsSPL16/GW8*, and *qLGY3*, play a dual role in improving grain quality and yield (Wang et al., 2012a, 2015b; Liu et al., 2018b).

Heading date

Heading date is an important trait that determines the adaptability of rice varieties to different geographic regions and planting seasons, and it usually affects the grain yield. Rice is a facultative short-day (SD) plant with diverse photoperiod sensitivity (PS) and possesses complicated flowering pathways to regulate heading date. At present, PS flowering in rice is thought to be mainly controlled by the crosstalk of two modules: *OsGI-Hd1-Hd3a/RFT1* under SD conditions and *Ghd7-Ehd1-Hd3a/RFT1* under long-day conditions (Zhou et al., 2021; Zong et al., 2021). *Ehd1* encodes a B-type response regulator that shares no homology with *Arabidopsis genes* and promotes flowering by upregulating the expression of *Hd3a* and *RFT1* under both long-day and SD conditions (Doi et al., 2004; Chen et al., 2022). In addition, the *Ehd1*-centered specific pathway in rice involves multiple upstream genes. Among them, *Hd1*, *Ghd7*, *DTH8/Ghd8*, *OsCOL4*, and *OsCOL10* negatively regulate *Ehd1* (Yano et al., 2000; Xue et al., 2008; Lee et al., 2010; Wei et al., 2010; Nemoto et al., 2016), whereas many flowering promoters, such as *Ehd2/RID1/OsID1*, *OsMADS51*, and *OsMADS50/DTH3*, upregulate the expression of *Ehd1* (Kim et al., 2007; Wu et al., 2008; Bian et al., 2011). In contrast to the repression of *Hd1* under long-day conditions, *Hd1*, an ortholog of the *Arabidopsis* floral activator *CONSTANS*, promotes flowering by elevating *Hd3a/RFT1* expression (Yano et al., 2000; Zong et al., 2021). Collectively, both of the modules function upstream of the florigen genes and are ultimately integrated into florigen. The florigen genes in rice function downstream of the photoperiodic flowering regulatory pathways, and the florigen proteins (Hd3a and RFT1) can form a tri-protein florigen activation complex (FAC) with the bZIP transcription factor OsFD1 and 14-3-3 proteins. Finally, FAC activates floral meristem identity genes such as *OsMADS14/15* to promote the vegetative-to-reproductive transition (Taoka et al., 2011). Recently, *DHD4*, a *CONSTANS*-like transcription factor, was shown to affect the formation of FAC, thus reducing the expression of *OsMADS14/15* to delay flowering (Cai et al., 2021).

Biotic resistance

The yield and quality of rice are severely threatened by pathogens and insect herbivores throughout the growing season (Savary et al., 2019). The most destructive rice diseases include rice blast caused by the hemibiotrophic fungus *Magnaporthe oryzae*, bacterial leaf blight caused by the hemibiotrophic bacterium *Xoo*, bacterial leaf streak caused by *X. oryzae* pv. *oryzicola* (*Xoc*), sheath blight caused by the necrotrophic fungus *Rhizoctonia solani*, and rice false smut caused by the fungal pathogen *Ustilaginoidea virens*. Plants have evolved a two-tiered innate immune system to defend against pathogen infection: pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI) (Jones and Dangl, 2006). To date, several fundamental plasma-membrane-localized pattern recognition receptor (PRR) proteins, such as XA4, XA21, XA3/26, OsCERK1, and OsCEBiP, have been well characterized (Sun et al., 2004; Akamatsu et al., 2013; Pruitt et al., 2015; Hu et al., 2017a). Among them, major resistance (*R*) genes, including *XA21* and *XA4*, confer race-specific durable resistance to *Xoo*. In addition, at least 37 *R* blast genes in rice have been well characterized, and most encode intracellular nucleotide-binding site and leucine-rich repeat (NLR) receptor proteins, suggesting that resistance against blast fungus is governed mainly by ETI immune responses. Despite the existence of *R* genes that confer robust resistance, a large majority of R genes that exhibit race-specific gene-for-gene resistance can be broken down easily (Deng et al., 2020). Hence, QTLs for durable and broad-spectrum resistance (BSR) against diverse pathogen races are favorite resources for rice breeders. For instance, *Pigm*, a cluster of genes encoding NLR receptors, confers BSR and durable resistance to the fungus *M. oryzae* without yield penalty (Deng et al., 2017). Another BSR gene, *bsr-d1*, encodes a C_2H_2-type transcription factor in rice, and a single nucleotide change in the *bsr-d1* promoter reduces its expression through binding of a repressive MYB transcription factor, thereby inhibiting H_2O_2 degradation and augmenting disease resistance (Li et al., 2017b). Notably, *IPA1* promotes both yield and immunity in rice, offering a classic case of balancing immunity and yield (Wang et al., 2018b).

Based on their feeding mode, rice insect pests can be categorized into chewing and piercing-sucking insects. At present, the most in-depth research has been performed on brown planthoppers (BPHs), and 15 BPH *R* genes have been cloned and functionally characterized, including *Bph2*, *Bph6*, *Bph9*, *Bph14*, and *Bph18* (Du et al., 2009; Zhao et al., 2016; Jing et al., 2017; Guo et al., 2018a). *Bph14*, the first cloned planthopper *R* gene in rice, encodes a coiled-coil, nucleotide-binding site, leucine-rich repeat (CC-NB-LRR) protein (Du et al., 2009) whose CC and NB domains activate defense gene expression and the salicylic acid signaling pathway (Hu et al., 2017b). In addition, *Bph9* encodes a rare type of NLR protein and confers both antixenosis and antibiosis to BPH by activating salicylic acid and jasmonic acid signaling pathways (Zhao et al., 2016). *Bph6* confers resistance to planthoppers by increasing exocytosis and participating in cell wall maintenance and reinforcement, and plants that harbor *Bph6* display broad resistance to BPH and white-backed planthoppers without yield penalty (Guo et al., 2018a).

Abiotic resistance

As a sessile organism, rice is able to cope with abiotic stresses such as extreme temperatures, drought, and ionic stress (soil salinity and heavy metals). An interesting phenomenon is that different abiotic stresses share common features in terms of their impacts on plants and the ways in which plants perceive them (Gong et al., 2020). For instance, all abiotic stresses can cause osmotic stress in plant cells. These stresses also trigger a transient rise in the cytosolic free calcium concentration

([Ca^{2+}]), and this in turn serves as a universal second messenger to elicit a resistance response (Zhu, 2016). A good example is *COLD1*, which confers chilling tolerance in *japonica* rice and is considered to encode a cold sensor. COLD1, a G-protein regulator that localizes on the plasma membrane and endoplasmic reticulum, can interact with the Gα subunit to activate a Ca^{2+} channel for sensing low temperature and to enhance G-protein GTPase activity, thus enhancing chilling tolerance (Ma et al., 2015b). Numerous genes underlying chilling tolerance, such as *HAN1*, *bZIP73*, and *CTB2*, have also been identified (Liu et al., 2018a; Mao et al., 2019; Li et al., 2021a), further enriching our understanding of rice adaptation to cold climates. Drought and salt are also major environmental factors that limit rice production and affect its geographic distribution. *Deeper rooting 1* (*DRO1*) is a major QTL that improves drought avoidance by shaping root system architecture, thereby maintaining high yields under drought conditions (Uga et al., 2013). In addition, the maintenance of ion homeostasis, such as the K^+/Na^+ ratio, at a cellular level is critical for plant adaptation under high-salt conditions. For example, *SKC1/OsHKT1;5* encodes an Na^+-selective transporter in rice and protects leaf blades and reproductive tissues from salt toxicity by mediating Na^+ exclusion in the vasculature (Ren et al., 2005; Kobayashi et al., 2017).

Nutrient use efficiency

On the one hand, excessive use of chemical fertilizers composed mainly of the macronutrients nitrogen (N) and phosphorus (P) has made an outstanding contribution to global food security. On the other hand, it has also given rise to ever-growing environmental pollution. Hence, the cultivation of crops with high nutrient use efficiency (NUE) not only guarantees food security but also promotes agricultural sustainability.

To date, a large number of genes that regulate NUE, manifested by the efficiency of nutrient uptake, transport, assimilation, and remobilization, have been cloned and functionally characterized. Among them, almost all the genes that govern NUE are transporters that function in the uptake and transport of nutrients. For instance, the nitrate transporter and sensor gene *OsNRT1.1B-indica* allele improves NUE and grain yield by enhancing nitrate uptake and root-to-shoot transport as well as elevating the expression of nitrate-responsive genes (Hu et al., 2015a). Notably, $OsNRT1.1B^{indica}$ is responsible for recruiting more diverse *indica*-enriched bacterial taxa with N metabolism functions than *japonica*-enriched taxa (Zhang et al., 2019c). Similarly, overexpression of other nitrate transporters, such as *OsNRT1.1A/OsNPF6.3* and *OsNRT2.3b*, also enhanced NUE and grain yield (Fan et al., 2016; Wang et al., 2018e). Very recently, the PHO-type phosphate (Pi) transporter OsPHO1; 2 was shown to maintain Pi reallocation during grain filling, which considerably enhanced grain yield under low-Pi conditions (Ma et al., 2021). In addition, the SULTR-like P distribution transporter (SPDT) also functions as a switch to allocate P preferentially to the grains (Yamaji et al., 2017). Interestingly, the coordinated utilization of N and P plays a pivotal role in achieving maximal yield and maintaining optimal plant growth (Hu and Chu, 2020). For example, the nitrate-NRT1.1B-SPX4 (Pi signaling repressor) cascade can integrate N and P signaling networks to activate P and N responses (Hu et al., 2019).

Reproductive development

Cross breeding relies on the use of cytoplasmic male sterility (CMS) in three-line systems and photoperiod/thermo-sensitive genic male sterility (P/TGMS) in two-line systems, which are very important for the utilization of heterosis. To date, there are three main mechanistic models for interpreting CMS induction: the premature tapetal programmed cell death (PCD) hypothesis in wild abortive CMS (CMS-WA), the cytoplasmic protein toxicity hypothesis in Boro II CMS (CMS-BT), and the mitochondrial energy deficiency hypothesis in Hong-Lian CMS (CMS-HL). For instance, *WA352*, a causal gene of CMS-WA, encodes a protein that accumulates preferentially in the anther tapetum. WA352 can interact with COX11 (a nucleus-encoded mitochondrial protein) to cause the excessive accumulation of reactive oxygen species (ROS) in the tapetum, which results in premature tapetal PCD and consequent pollen abortion (Luo et al., 2013a). *ORF79* and *ORFH79* are the causal genes of CMS-BT and CMS-HL, respectively (Wang et al., 2006, 2013a). Of course, CMS that is determined by mitochondrial genes and inherited maternally can be suppressed by *restorer of fertility* (*Rf*) genes in the cell nucleus. Most *Rf* genes encode pentatricopeptide repeat (PPR) proteins that disrupt the functions of CMS genes, such as *Rf1a* and *Rf1b* for CMS-BT, *Rf5*/*Rf1a* and *Rf6* for CMS-HL, and *Rf4* for CMS-WA (Chen et al., 2022). In addition to CMS/*Rf* systems, P/TGMS genes, including *Pms1*, *pms3*, *TMS5*, *CSA*, and *TMS10*, have been well characterized in two-line hybrid rice (Zhou et al., 2012b, 2014; Ding et al., 2012; Zhang et al., 2013; Yu et al., 2017). It is evident that inter-subspecies heterosis is generally more robust than intra-subspecies heterosis. However, hybrid sterility (HS) manifested by a severe postzygotic reproductive barrier in inter-(sub)specific hybrid rice hinders the manipulation of distant heterosis. To date, only 11 HS genes have been cloned, including *S1*, *S5*, *Sa*, *Sc*, *qHMS7*, *S27/S28*, and *DPL1/DPL2* (Long et al., 2008; Mizuta et al., 2010; Yamagata et al., 2010; Yang et al., 2012; Shen et al., 2017; Yu et al., 2018; Xie et al., 2019). They are mainly involved in three molecular mechanisms: killer-target systems, killer-protector system, and duplicate gametic lethal system. In the future, more HS genes, as well as their molecular mechanisms, will still need to be revealed in order to overcome the reproductive barrier by exploring or creating hybrid-compatible (neutral) alleles.

FROM FUNCTIONAL GENOMICS TO QUANTITATIVE GENOMICS

Functional genomics focuses on assessing gene function, whereas quantitative genomics, based on functional genomics, aims to fully unravel genomic variation and the genetic basis of complex traits. Quantitative genomics research has also achieved high efficiency in GWAS mapping of QTLs and in quantifying the genetic effects of QTLs on traits. Moreover, post-genomic profiling platforms have enabled the mining and integration of immense amounts of phenotypic and genetic diversity. Hence, a practical pipeline for the analysis of genomic variations and the genetic effects of QTLs can be summarized: (1) sampling and sequencing; (2) genotyping and phenotyping; (3) population genetics analysis; (4) association analysis or linkage analysis; (5) genome assembly, annotation, and variation detection; and (6) quantification of genetic effects. Together, large amounts of

Gene	Gene ID	Functional annotation	Controlled trait	References
An-1	Os04g0350700	helix-loop-helix protein	awn length	Luo et al., 2013b
An-2/LABA1	Os04g0518800	cytokinin-activating enzyme	awn length	Gu et al., 2015; Hua et al., 2015
GAD1/RAE2	Os08g0485500	secretory signal peptide	awn length	Bessho-Uehara et al., 2016; Jin et al., 2016; Yano et al., 2016
qSH1	Os01g0848400	BEL1-type homeobox	shattering	Konishi et al., 2006
sh4	Os04g0670900	transcription factor	shattering	Li et al., 2006a
Bh4	Os04g0460200	amino acid transporter	hull color	Zhu et al., 2011
Rc	Os07g0211500	basic helix-loop-helix protein	pericarp color	Gross et al., 2010
OsG	Os03g0100030	rice ortholog of soybean stay-green gene G	seed dormancy	Wang et al., 2018c
OsLG1	Os04g0656500	SBP-domain protein	panicle shape/ligule development	Ishii et al., 2013
Prog1	Os07g0153600	zinc-finger nuclear transcription factor	tiller angle	Jin et al., 2008; Tan et al., 2008
GW5/qSW5/GSE5	Os05g0187500	plasma membrane-associated protein with IQ domains	grain size	Shomura et al., 2008; Weng et al., 2008; Liu et al., 2017b; Duan et al., 2017

Table 3. Domestication-related genes cloned in rice.

sequencing data derived from thousands of rice accessions expedite the development of population genetics, quantitative genetics, and comparative genomics, which in turn provide fresh insights into long-standing controversies such as domestication and heterosis. Here we review such emerging insights.

Domestication

Crop domestication can be regarded as the genetic modification of a wild species to generate a modern cultivar that has been radically altered to meet human needs. Compared with their progenitors, modern rice cultivars exhibit distinct differences in some agronomic traits (also known as the domestication syndrome), including seed shattering, awn, panicle and plant architecture, hull color, pericarp color, and grain size (Doebley et al., 2006). An array of well-documented domestication loci have been cloned by QTL mapping or GWAS (Table 3) and have contributed to a preliminary understanding of the history of artificial selection. In rice, archaeological and genetic evidence has demonstrated that *O. sativa* was domesticated from *O. rufipogon* (Fuller et al., 2009; Huang et al., 2012). However, the evolutionary origins and domestication process of *O. sativa* have long been debated. Huang et al. (2012) sequenced 446 geographically diverse accessions of *O. rufipogon* and 1083 cultivated varieties and constructed a comprehensive map of rice genome variation to investigate the phylogenetic relationships between cultivated rice and wild rice and to infer signatures of selection in rice domestication. Based on population structure, *O. rufipogon* species can be classified into *Or-I*, *Or-II*, and *Or-III*, and *indica* and *japonica* descend from *Or-I* and wild rice in southern China (sub-clade *Or-IIIa*), respectively. Based on whole-genome screening of selection signatures from domestication (reductions in nucleotide diversity and altered allele frequency at the domestication loci), 55 selective sweeps harboring many well-characterized domestication loci, including *sh4*, *PROG1*, *Bh4*, *qSH1*, *LG1*, *An-1*, and *An-2*, have been identified. Intriguingly, unlike the genome-wide pattern, the two subspecies were clustered together at the domestication loci. Integrating all these data, Huang et al. (2012) proposed a demographic scenario in which *japonica* was first domesticated from *Or-IIIa* around the middle area of the Pearl River in southern China, and *indica* was subsequently developed from crosses between *Or-I* and *japonica*. Eventually, this study answered three puzzles about rice domestication: (1) the geographic origin of cultivated rice, southern China; (2) the direct wild progenitor of cultivated rice, *Or-IIIa*; and (3) the domestication process, a single-origin model with multiple introgressions.

Similarly, population genomics analyses of 20 *O. glaberrima* and 94 *Oryza barthii* accessions demonstrated that African rice (*O. glaberrima*) was domesticated from its progenitor *O. barthii* ~3000 years ago in a single region along the Niger River, providing evidence to support the independent domestication of African rice (Wang et al., 2014b). Notably, a similar but independent 113-kb deletion at the *RAPD* locus in *O. glaberrima* (next to *PROG1*, which controls plant architecture in *O. sativa*) implied the parallel domestication of plant architecture in both Asian and African cultivated rice (Wu et al., 2018).

Heterosis

Heterosis, or hybrid vigor, is economically important for agricultural production, and hybrid rice breeding in particular has made remarkable achievements in grain yield. A century-long history of research on the genetic basis of heterosis suggests that heterosis can be attributed to the orchestrated outcome of several non-mutually exclusive hypotheses (e.g., dominance, overdominance, and epistasis) (Xiao et al., 1995; Li et al., 2008; Zhou et al., 2012a). Moreover, emerging multi-omics perspectives demonstrate that hybrid vigor has arisen from allelic interactions between parental genomes, resulting in altered programming of genes to enhance the agronomic performance of hybrids (Chen, 2013). Indeed, little consensus has yet been reached for the genetic mechanism of heterosis in rice. Taking

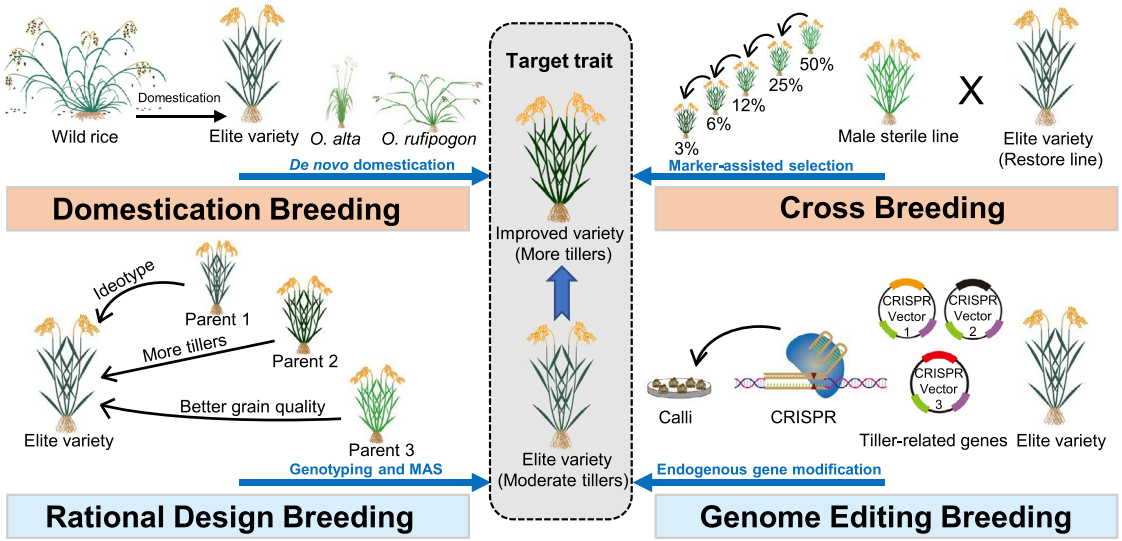

Figure 3. Representative breeding methods used in modern agriculture.
Domestication breeding: improvement of a trait (e.g., tiller number) through *de novo* domestication of wild rice with vigorous tillering ability. Cross breeding: crossing an elite recipient variety with a donor line (e.g., a male sterile line) to select outstanding progeny with the desired trait through marker-assisted selection. Rational design breeding: improvement of traits by pyramiding major genes from multiple donor parents that contribute significantly to desirable traits. Genome editing breeding: improvement of a trait through purposeful modification of target genes.

advantage of quantitative genomics, the analysis of heterosis QTLs (hQTLs or heterosis genes) is one of the most direct approaches to documenting the relative roles of dominance and overdominance. Given this fact, Huang et al. (2015) developed an integrated genomic approach that exploited population-scale genomic landscapes from 1495 elite hybrid rice varieties and their parental lines to identify hQTLs at fine scales. Ultimately, 130 hQTLs for 38 agronomic traits were identified and analyzed. Among these hQTLs, a strong correlation was observed between the number of superior alleles and grain yield, indicating that effective pyramiding of rare superior alleles with positive dominance is an essential contributor to heterosis. Notably, this study also found evidence of trait-trait dynamics and genotype-environment interactions (G × E), such as heading date genes that were strongly associated with photoperiod and temperature conditions (Huang et al., 2015). For an in-depth investigation of the heterotic effects of hQTLs, 10 074 F_2 individuals derived from 17 representative hybrid rice crosses were sequenced and phenotyped to map hQTLs by a composite interval mapping method (Huang et al., 2016). Based on hybrid breeding systems, 17 hybrid rice crosses were classified into three groups, and no hQTLs were universally shared across all lines within each group. A few heterosis-associated loci from female parents explained a large proportion of the yield advantage of hybrids over their male parents. Overdominance and pseudo-overdominance were observed at only a few heterozygous loci, but most of the heterozygous hQTLs showed partial dominance when all yield-related traits were considered together (Huang et al., 2016). Taken together, these results suggested that dominance underlying functional complementation is an indispensable contributor to yield heterosis. A number of intriguing subsequent studies confirmed this conclusion. For instance, most hQTLs with positive partial or complete dominance were detected in RIL and RILBC populations derived from the two-line hybrid rice Liang-you-pei9 (LYP9), and these hQTLs cumulatively contributed to yield-related heterosis (Li et al., 2016). Very recently, manipulation of several major dominant hQTLs was able to achieve assembly of yield heterosis in the elite hybrid Shanyou63 (Shen et al., 2022).

Molecular breeding

Rice breeding is an on-going task for feeding the ever-increasing population. In fact, rice breeding can be traced back to the dawn of rice domestication. Since then, a series of distinctive breeding methods, such as cross breeding, mutation breeding, polyploidy breeding, and transgenic breeding, have strikingly improved the efficiency of rice breeding. With the rapid accumulation of knowledge on rice genomics, a plethora of innovative technologies have been used for rice improvement, yielding new insights on rice breeding methods (Figure 3). For instance, hybridization (cross breeding) is one of the most efficient and fastest ways to pyramid superior parental genes during rice breeding. However, hybrid breeding that relies on random crosses between diverse varieties and daunting phenotypic selection remains time consuming and labor intensive. As the genomic architecture of heterosis for yield traits has been well characterized (Huang et al., 2016), an updated hybridization strategy has proven to efficiently enhance yield by pyramiding superior genes from female parents (Wang et al., 2019b). Moreover, transgenic breeding, cross breeding, and marker-assisted selection (MAS) breeding require vast amounts of functional genomics information for the selection of candidate genes, especially genes that control invisible agronomic characters such as grain quality, NUE, and biotic and abiotic traits. In the era of functional and quantitative genomics, MAS can act as a bridge between traditional breeding methods and molecular design breeding, owing to its broad applicability. In addition, rational design, which is based on a comprehensive understanding of genes and their regulatory networks that underlie complex agronomic traits, is a

robust and representative molecular design breeding strategy. Zeng et al. (2017) developed new elite varieties by pyramiding multiple significant genes (by MAS and genotyping) underlying grain quality and yield from three parents, and the resulting varieties exhibited higher yield and better grain quality than super-hybrid rice LYP9 and each of their parents. Very recently, a comprehensive map of rice QTNs and related QTN effects estimated from eight GWAS cohorts dramatically expedited the process of rice breeding (Wei et al., 2021a). In addition, RiceNavi, a genome navigation system for QTN pyramiding and breeding route optimization, provides an efficient and easy-to-use platform for rice breeders. More importantly, recent advances in genome editing, such as base editors and prime editors, have remarkably spurred the development of genome editing breeding (Gao, 2021). Programmable targeted mutagenesis based on gene-editing methods is particularly conducive to transferring desired traits into rice and will propel rice breeding toward a more efficient and economical level. For example, rice plants with broad-spectrum tolerance to acetolactate synthase (ALS)-inhibiting herbicides were produced by using a cytosine base editor to create missense mutations in the P171 and/or G628 codons of *ALS* (Zhang et al., 2021e).

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

Unraveling the extensive variation in diverse rice varieties

Extensive allelic variation associated with agronomically important traits has long been held as central to rice breeding. To date, approximately 20 genomes of *Oryza* species and thousands of cultivar varieties have been sequenced, but most genomic data come from *indica* and *japonica*. For this reason, some valuable variations that exist in other *Oryza* species or other subgroups of *O. sativa* are inevitably ignored. For example, *OsTCP19*-H (a haplotype associated with high tillering response to N) with the potential for improving NUE is predominantly found in *aus* and *aromatic* rice, whereas *OsTCP19*-L (low NUE) is enriched in *japonica* and *indica* rice (Liu et al., 2021b). Moreover, we know that *O. glaberrima* carrying tolerance genes to biotic and abiotic stresses is well adapted for cultivation in west Africa. *Thermo-tolerance 1* (*TT1*) and *THERMOTOLERANCE 2* (*TT2*) confer thermotolerance in rice, and these two QTLs come from African rice rather than *O. sativa* (Li et al., 2015; Kan et al., 2021). Hence, to capture all variations, we should also focus on variations in other *Oryza* species and other subgroups of *O. sativa*. For this purpose, we should further consolidate all the pan-genome works to encompass more varieties from different subgroups of *O. sativa* or their progenitors. Meanwhile, we should improve the annotation quality of the rice pan-genome by using more powerful algorithms and integrating more data.

De novo domestication

Rice domestication provides a model system for studying adaptation and is of substantial interest for crop improvement (Chen et al., 2021). On one hand, domestication of rice has enriched its yield-related traits, such as high yield, ideotype, and easy harvest. On the other hand, it has also led to a genetic bottleneck that has reduced genetic diversity and stress resistance. In addition, unlike maize domestication, which frequently featured standing, gain-of-function, regulatory variation, rice domestication tended to display *de novo*, loss-of-function, coding variation (Chen et al., 2021). Hence, *de novo* domestication of wild rice by genome editing appears to be a promising alternative breeding approach for improving rice varieties. A representative example is the *de novo* domestication of wild allotetraploid *Oryza alta* (CCDD), in which six important agronomic traits could be speedily improved through gene editing (Yu et al., 2021). In light of this, an efficient transgenic and genome editing system, as well as a high-quality genome assembly, will be critical for *de novo* domestication.

Quantification of heterosis

Falling sequencing costs, widening availability of bioinformatics tools, and increasing numbers of elite hybrid varieties provide vital opportunities for dissecting the genomic architecture of rice heterosis. However, an integral understanding of the genetic basis of rice heterosis through genetic mapping studies is likely to be confounded by the nonrandom distribution of recombination events and limited population sizes. Hence, larger population sizes and more populations from rice hybrids will be required to elucidate the genetic basis of heterosis. In addition, reports on hQTLs have also varied considerably in their interpretations of whether epistasis plays an essential role in heterosis. It is therefore necessary to estimate the effects of epistasis on heterosis by using sufficient population sizes and multiple populations.

In fact, most hQTLs can be detected by GWAS or QTL mapping of multiple populations (Huang et al., 2015, 2016). Taking population size and number into account, theoretically, more hQTLs will be identified in populations of *indica-japonica* hybrid crosses. This provides an excellent opportunity to quantify yield-related heterosis by estimating hQTL effects. Meanwhile, statistical algorithms and prediction models for statistical genetics should be strengthened, which will be beneficial for the quantification of heterosis or genome-enabled prediction and genomic selection in rice breeding (Wallace et al., 2018; Cui et al., 2020).

Game-changing rice breeding through genome editing

The ability to generate genome-wide, targeted, sequence-defined genetic diversity in rice by genome editing has revolutionized traditional methods of rice breeding. For example, the integration of cross breeding with genome editing has the potential to transform rice breeding. It is estimated to have 15%–30% higher yield potential in inter-(sub)specific hybrid rice than in *indica* intraspecific hybrid rice, but HS hinders the exploitation of distant heterosis. Recently, hybrid-compatible lines (*indica-japonica*) were produced through knockout of the *SaF* and *SaM* alleles in *indica* rice (Xie et al., 2017). Similarly, knockout of any of the *S1* alleles in African rice can eliminate HS (Xie et al., 2019). In addition, genome editing has also been used to induce clonal reproduction, which is important for the clonal maintenance of hybrids (Wang et al., 2019a; Khanday et al., 2019). Moreover, the use of CRISPR-mediated base editors to facilitate directed evolution of plant genes has shown great potential in rice breeding. To this end, two similar methods, saturated targeted endogenous mutagenesis editors (STEMEs)

and base-editing-mediated gene evolution (BEMGE), were developed to create important GVs of target genes for crop improvement (Kuang et al., 2020; Li et al., 2020), and new mutations in *OsALS1* and *OsACC* conferred varying levels of herbicide resistance. Concurrently, the combination of genome editing with speed breeding will further underpin efforts to meet the challenge of feeding the ever-increasing human population (Hickey et al., 2019). Thus, genome editing should be combined with other state-of-the-art technologies and the latest findings in rice genomics to accelerate the breeding process.

Integrated databases for the rice community

The growing wealth of multi-omics data from an increasing number of studies provides an extraordinary opportunity to comprehensively understand the molecular mechanisms of complex traits. Unfortunately, scattered databases and resources that vary in format and quality have hampered effective access and utilization by rice researchers. Hence, efforts should be made to integrate all these available resources and databases, as this will fuel the development of rice systems biology and even rice biology as a whole. Given this goal, basic comprehensive databases such as Rice Information GateWay (RIGW) should include a GBrowse-based view of rice genomic data, multi-omics data, and bioinformatics tools (Song et al., 2018a). However, unlike the useful links to other public databases, the comprehensive databases should also have a powerful ability to search and process integrated information in a unified interface. Integrated databases with easy-to-use and friendly interfaces will further bridge the gap between functional genomics and molecular breeding in rice.

Perspectives on future rice genomics research

As mentioned earlier, rice has been firmly established as a model organism for both basic and applied research on plant genomics. Previous reviews have summarized advances in some aspects of rice genomics (Li et al., 2018; Chen et al., 2022), but this review chronologically and comprehensively summarizes progress in rice genomics over the past 20 years and presents many rich and contemporary views on important scientific problems based on the latest research findings. In the future, the main task of rice genomics is still to dissect the function of every gene in the rice genome and even of every nucleotide in the DNA sequence. Rapid technological advances are making it possible to cut the Gordian knot in rice genomics, providing insight into rice adaptability to the environment, rice plasticity, and rice regeneration. In addition, accumulated multi-omics data have provided fresh and integrated views in rice genomics research. Studies designed to solve genetic mysteries will be further strengthened by the application of more omics technologies. Meanwhile, increasing knowledge from basic research will be conducive to undertaking applied research on rice genomics. For example, understanding the genomic architecture of rice heterosis will hasten the process of hybrid rice breeding through whole-genome genomic selection and hybrid performance prediction. In addition, more new technologies such as genome editing and machine learning approaches will be integrated to revolutionize methods of rice breeding. In the end, we firmly believe that the rapid development of rice genomics will accelerate the process of breeding super rice with high yield, high quality, high stress resistance, and high NUE, so as to cope with the challenges of population growth and climate change.

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