REVIEW

Rice Genomics: over the Past Two Decades and into the Future

Shuhui Song1,2,3,*,a, Dongmei Tian1,b, Zhang Zhang1,2,3,c, Songnian Hu2,3,d Jun Yu2,3,*e

1 BIG Data Center, Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100101, China
2 CAS Key Laboratory of Genome Sciences and Information, Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100101, China
3 University of Chinese Academy of Sciences, Beijing 100049, China

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Abstract Domestic rice (Oryza sativa L.) is one of the most important cereal crops, feeding a large number of worldwide populations. Along with various high-throughput genome sequencing projects, rice genomics has been making great headway toward direct field applications of basic research advances in understanding the molecular mechanisms of agronomical traits and utilizing diverse germplasm resources. Here, we briefly review its achievements over the past two decades and present the potential for its bright future.

Assembling and understanding the rice genomes using different sequencing approaches

Due to its limited genome size and diploidy, rice is an excellent choice among cereals for initiating genomic studies, serving as a model organism for plant biology and agricultural research. In 2002, the first two working draft genomes of the domestic rice (Oryza sativa L.) subspecies, i.e., japonica (cultivar Nipponbare) and indica (cultivar 93-11), were successfully sequenced using whole-genome-shotgun (WGS) sequencing technology [1,2]. The International Rice Genome Sequencing Project (IRGSP) Consortium was launched in September 1997, comprising research groups from Japan, the United States, France, South Korea, India, and China, aimed at delineating the Nipponbare genome using a map-based clone-by-clone (CBC) strategy [3,4]. Meanwhile, there were two other efforts to sequence the same japonica cultivar from two private companies, Syngenta and Monsanto. Their sequencing data were publicly released in a controlled way and integrated into the IRGSP data. On the other hand, the indica genome project...
Harnessing genome sequences to understand the biological basis of heterosis

Heterosis (hybrid vigor) is a phenomenon wherein F1 hybrids bear superiority for multiple agronomic traits attributable to the mix of genetic contributions of its parental inbred lines [16]. This is important in the use of F1 hybrid cultivars that are often elite crop varieties selected by breeders. To meet increasing food demands from population growth, scientists have cultivated hundreds of rice superhybrids in the past few decades. Remarkably, until 2018, a total of 131 rice cultivars had been officially approved as superhybrids with high-yield potential by the Ministry of Agriculture of China (http://www.ricedata.cn/variety/superice.htm). Among them, Liangyou-pei-jiu (LYP9) is one of the representatives developed using a two-line crossing between PA64S and 93-11. The featured high yield, fine grain quality, and strong biotic resistance (bacterial leaf blight and fungal blast diseases) of LYP9 are attributed to its intersubspecific heterosis [17]. In addition, another widely-planted hybrid Shan-you 63 (SY63), was generated using a method named the three-line hybrid system and bred from a cross between the male-sterile Zhen-shan 97A (ZS97A) and the restorer line Ming-hui 63 (MH63). SY63 features superior yield, multiple disease resistance, wide adaptability, and good eating quality, leading to large-scale plantation in southern and central China over the past three decades [18].

Over the past decades, valuable efforts have been devoted to understanding the biological basis of heterosis, including transcriptomic and epigenomic analyses [19–21]. Although several traditional models of heterosis (such as dominance, overdominance, and epistasis) have been suggested to explain the increased yield [22], we still do not understand the molecular mechanisms of heterosis. It is vital to have the high-quality genome sequences of the hybrid parents, which ultimately allows hybrid gene mapping free of sequence gaps and at a single-base resolution. Quality assembly of the parental genomes of hybrids (SY63 and LYP9) have been recently reported [23–25]. A map-based sequencing effort to assemble the parental genomes of SY63, i.e., ZS97 and MH63, yielded 237 contigs for ZS97 and 181 contigs for MH63, covering 90.6% and 93.2% of their estimated genome sizes, respectively [24]. Similarly, with the support of CSRGP, the two parental genomes of LYP9, 93-11 and PA64S, have also been sequenced with high coverage [25]. Consequently, a series of variety-specific genes have been determined through comparative genome studies.

Oryza glaberrima is a domestic rice species in Africa that is reproductively isolated from Asian rice. In the early 2000s, aimed to generate ‘New Rice for Africa’ (NERICA), introgressions were carried out by crossing O. sativa and O. glaberrima cultivars, followed by recurrent back-crossing with the Asian rice parent. In 2017, the genomes of TOG5681 and CG14, parents of two NERICA generations, were sequenced [26]. The complete genome sequences would provide a rich resource, helping to tackle the issue of reproductive isolation for potential hybrid breeding from other distantly-related rice species.

To further reveal genetic elements of heterosis, low-coverage resequencing efforts have been reported in different...
superhybrid populations. One such effort dissected the immortalized second filial (IMF2) populations derived from the SY63 hybrid, showing the varied contribution of genetic components to yield traits [18]. For instance, overdominance/pseudo-overdominance contributes to a variety of yield-related traits (e.g., the vigor of the yield, number of grains per panicle, and grain weight). In particular, the dominance × dominance interaction is closely associated with tillers per plant and grain weight. To map the heterotic loci at a fine scale, diverse superhybrid varieties and their inbred parental lines were massively resequenced [27,28]. These include the recombinant inbred lines (RILs) of the super hybrid rice LYP9 [29] and the F2 lines from 17 representative hybrid rice crosses [30,31]. The genetic architecture of yield traits and numerous superior alleles that contribute to heterosis were then proposed [27,28]. Collectively, the availability of these parental genome sequences and hybrid population data provide rich resources for deciphering the genetic basis and molecular mechanisms of rice heterosis.

Revealing rice domestication processes by exploiting additional genome sequences of Oryza species

More genome sequences of different Oryza cultivars have been constantly added to the rice knowledge base, including several strains of Asian cultivars and African cultivars (O. glaberrima) with the AA genome in the past few years (Figure 1A, Table 1). The deeply sequenced O. sativa genomes include IR64 (a conventional indica rice variety in China) [32], IR8 (also known as Miracle rice) [33], Swarna (an indica rice cultivar variety with low glycemic index) [34], Shu-hui498 (R498, an indica rice variety cultivar used as a restorer line in a three-line hybrid system) [35], DJ123, and N22 (indica rice with important disease resistance and abiotic tolerance alleles) [32,33]. The African cultivars (O. glaberrima) provide an excellent resource for varietal improvement of O. sativa, as they harbor multiple important agronomic traits, especially for biotic and abiotic resistance. In 2014, CG14 was sequenced and assembled into 12 pseudomolecules with a total size of 316 Mb, and 33,163 gene models were annotated [26,36]. Most of these cultivars were de novo sequenced with high coverage and often through integration of both short and long reads from the NGST platforms, which ensure high sequence coverage and moderate contiguity. For instance, comparative analyses of mutations in three orthologous genes O. sativa Shattering 1 (OsSh1), O. sativa Shattering 4 (OsSh4), and qSh1 (LOC_Os01g62920) from African and Asian rice confirm independent domestication of genes controlling panicle shattering. However, to better identify and compare the orthologous loci, higher contiguity and quality rice genomes are still highly desired for future sequencing.

Wild rice, being adapted to diverse geographical environments and exhibiting tolerance to biotic and abiotic stresses, can be exploited as important genetic resources and gene pools for molecular breeding. To date, there are 22 wild species in the genus Oryza that are distributed throughout the world, which are classified into ten genome types (AA, BB, CC, BBCC, CCDD, EE, FF, GG, HHJJ, and HHKK). Strategies to harness beneficial traits for crop improvement have been exemplified by the introgression of bacterial blight resistance gene Xa21 from the wild rice Oryza longistaminata [37]. In 2003, the International Oryza Map Alignment Project (IOMAP) was initiated, with the aim of providing high-quality wild rice genomic resources for the discovery and utilization of beneficial genes and traits. So far, around 10 new reference genomes have been generated for wild rice species, including O. nivara (AA) and Oryza rufipogon (AA) from Asia; Oryza barthii (AA), O. longistaminata (AA), and Oryza brachyantha (FF) from Africa [36,38]; Oryza glumaepatula (AA) from South America; Oryza meridionalis (AA) from Australia; as well as Oryza punctata (BB) from Africa and Oryza granulata (GG) from China [33,36,39]. In addition, two novel perennial wild rice species from tropical Australia with AA genomes were also sequenced (one is similar to O. rufipogon in plant morphology, and the other is similar to the annual O. meridionalis) [40]. The available genomes of wild progenitors and close relatives provide valuable resources for the identification of candidate genes and chromosome regions selected during domestication [41]. To date, many genes with significantly lower diversity unique to cultivated rice have been identified, representing candidate regions for selective sweeps during domestication [42–44]. Comparative genomic analyses between the wild and the cultivated rice species are essential for mechanistic investigation of genome organization, gene family expansion, segmental duplication, etc.

Dissecting genetic components for complex agronomic traits using genome-wide association studies

Building a comprehensive collection of landraces in terms of morphology, genetic diversity, and geography is fundamental for following genetic studies, such as genome-wide association studies (GWAS) of genotype-to-phenotype relatedness. Totally 773,948 rice accessions are available in various gene banks worldwide, with high genetic diversity [45]. For instance, there are ~101,000 from the International Rice Genebank Collection (IRGC) at the International Rice Research Institute (IRRI), 61,470 from the China National Crop Gene Bank (CCGB) [46], and ~18,000 from the United States Department of Agriculture (USDA) Rice Genebank [47]. Such collections enable population-based genome-wide studies for a broad scope of genetic and biological purposes.

An excellent example that utilizes a large number of rice accessions for GWAS by taking advantage of low-cost sequencing [48,49] was shown by Han and his coworkers. They performed GWAS analyses and identified hundreds of known and new loci associated with 14 agronomic traits, covering two morphological characteristics (leaf angle and tiller number), four grain-related traits (grain width, grain length, grain weight, and spikelet number), three grain quality traits (gelatinization temperature, protein content, and amylose content), three coloration traits (apiculus color, pericarp color, and hull color), and physiological features (heading date, drought tolerance, and degree of seed shattering). Another comprehensive study that involved metabolic profiling and metabolic GWAS (mGWAS) identified hundreds of common variants that exert important influences on the production of secondary metabolites, accordingly revealing the biochemical relevance of gene–metabolite associations in rice [50]. Using the same sequenced materials, many genetic loci were revealed to be related to biochemical traits (e.g., absolute content of chlorophyll), physiological features (e.g., seed germination and degree of seed
shattering), and content of mineral elements [51–55]. A further study reported a mapping effort for major-effect loci at the level of respectively causal SNPs, amylose content, seed length, and pericarp color by combining the diversity of the rice collection with low-coverage sequencing [56]. In short, such methods, by combining low-coverage genome-wide NGS-sequencing and GWAS, represent a complementary strategy for dissecting complex traits. However, there are still many genetic characteristics of important agronomic traits that have not yet been characterized. More studies are certainly required to reveal the genetic mechanisms by combining more phenotypic and genotypic data in natural populations in the near future.

Analyzing genomic diversity through comparative genomic studies and data integration

More rice genomes with high quality sequences have provided unlimited opportunities for identifying genetic and other molecular markers, e.g., SNPs, or simple sequence repeats (SSRs), which greatly facilitates population-based studies and marker-assisted breeding. To build an open-access information commons for rice genomics (ICRG) would be desirable to host genome assemblies and genome variations in the future and hopefully to integrate other large-scale genome annotations, including information from other omics-level collections. There are several databases available to be integrated, such as Ensembl Genome [57], Gramene [58], RAP-DB [59,60], RGAP [15], dbSNP at NCBI [61], HapRice [62], SNP-Seek [63,64], IC4R [65] in BIG Data Center [66], RiceBase [67], and RiceVarMap [68]. Notably, since 2017, the largest collection of rice SNPs we have organized is deposited in the GVM database (http://bigd.big.ac.cn/gvm/) by collecting and systemically analyzing sequence data of 5152 rice accessions (Figure 1B), in which a total of 18,616,579 SNPs and 9122 manually curated genotype-to-phenotype entries were integrated [69]. Furthermore, more than 10,000 novel, full-length, protein-coding genes and a high number of presence-absence variations (PAVs) were identified by resequencing a core collection of over 3000 Asian cultivated rice accessions from 89 countries, representing another component of species genetic diversity [70–72]. These sequence variations and resources are useful for population structure and diversity analysis. One such example is utilizing a large number of genomic variations for population-based phylogenomic analyses,
| Rice                                      | Genotype | Genome size (Mb) | Sequencing depth (×) | Assembly level | Database                        | Weblink                                      | PMID  |
|-------------------------------------------|----------|-----------------|----------------------|----------------|---------------------------------|----------------------------------------------|-------|
| *O. sativa* L. ssp. japonica* *(cv. Nipponbare)* | AA       | 374.4           | NA                   | Chr            | RAP-DB                          | https://rapdb.dna.affrc.go.jp/               | 23299411 |
| IRGSP1.0                                  | AA       | 374.4           | NA                   | Chr            | RGAP                            | http://rice.plantbiology.msu.edu/           | 24280374 |
| *O. sativa* L. ssp. japonica* *(cv. Nipponbare)* | AA       | 374.4           | NA                   | Chr            | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCF_001433935.1 | 15685292 |
| *O. sativa* L. ssp. japonica* *(cv. Nipponbare)* | AA       | 391.1           | 117                  | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_003865235.1 | 30448535 |
| *O. sativa* L. ssp. japonica* *(cv. Nipponbare)* | AA       | 355.6           | 110                  | Scaffold        | CSHL                            | http://schatzlab.cshl.edu/data/rice          | 25468217 |
| *O. sativa* L. ssp. indica* *(cv. 93-11)*   | AA       | 395.4           | 116                  | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_003865215.1 | 24280374 |
| *O. sativa* L. ssp. indica* *(cv. HR-12)*   | AA       | 426.3           | NA                   | Chr            | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000004655.2 | 11935017 |
| *O. sativa* L. ssp. indica* *(cv. RP Bio-226)* | AA       | 389.8           | 93                   | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_000725085.2 | 26984283 |
| *O. sativa* L. ssp. indica* *(cv. Shuhui498)* | AA       | 391.0           | 120                  | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_002151415.1 | 28469237 |
| *O. sativa* L. ssp. indica* *(cv. Minghui 63)* | AA       | 398.8           | 228                  | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_001618785.1 | 27539398 |
| *O. sativa* L. ssp. indica* *(cv. Zhenshan 97)* | AA       | 387.4           | 120                  | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_001623345.2 | 27622467 |
| *O. sativa* L. ssp. indica* *(cv. IR8)*     | AA       | 389.1           | 70                   | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_001889745.1 | 29358651 |
| *O. sativa* L. ssp. indica* *(cv. IR64)*    | AA       | 345.2           | 110                  | Scaffold        | CSHL                            | http://schatzlab.cshl.edu/data/rice          | 25468217 |
| *O. sativa* L. ssp. indica* *(cv. Swarna)*  | AA       | NA              | 10                   | NA             | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_000817615.1 | 29158416 |
| *O. sativa* L. ssp. indica* *(cv. HEG4)*    | AA       | 342.0           | 220                  | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_000817635.1 | 29158416 |
| *O. sativa* L. ssp. indica* *(cv. Hitomebore)* | AA       | 382.6           | 179                  | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_000817645.1 | 29158416 |
| *O. sativa* L. ssp. indica* *(cv. A123)*    | AA       | 337.7           | 250                  | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_000817655.1 | 29158416 |
| *O. sativa* L. ssp. indica* *(cv. N 22)*    | AA       | 362.3           | 65                   | Chr            | NCBI                            | https://www.ncbi.nlm.nih.gov/assembly/GCA_001952365.1 | 29358651 |
| *O. sativa* L. ssp. indica* *(cv. DJ123)*   | AA       | 345.9           | 110                  | Scaffold        | CSHL                            | http://schatzlab.cshl.edu/data/rice          | 25468217 |
| *O. rufipogon* *(cv.W1943)*                | AA       | 339.2           | 130                  | Scaffold        | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000817225.1 | 29358651 |
| *O. barthii*                               | AA       | 308.3           | 110                  | Chr            | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000818215.1 | 29358651 |
| *O. glaberrima* *(CG14)*                   | AA       | 303.3           | 30                   | Scaffold        | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_001473955.2 | 29358651 |
| *O. glaucacapitata*                        | AA       | 372.9           | 135                  | Chr            | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000576495.1 | 29358651 |
| *O. meridionalis*                          | AA       | 335.7           | 166                  | Chr            | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000338895.2 | 29358651 |
| *O. punctata*                              | BB       | 393.8           | 130                  | Chr            | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000573905.1 | 29358651 |
| *O. brachyantha*                           | FF       | 259.9           | 104                  | Chr            | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000231095.2 | 29358651 |
| *O. nivara*                                | AA       | 338.0           | 102                  | Chr            | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000576065.1 | 29358651 |
| *O. longistaminata*                        | AA       | 326.4           | 52.5                 | Scaffold        | NCBI, Ensembl                   | https://www.ncbi.nlm.nih.gov/assembly/GCA_000789195.1 | 29358651 |
| *O. granulata*                             | GG       | 777.0           | 117                  | Contig          | GWH                             | http://bigd.big.ac.cn/gwh/Assembly/116/show | 30271965 |

Note: ssp, subspecies; cv, cultivar; Chr, chromosome; NA, not applicable; RAP-DB, Rice Annotation Project database; RGAP, Rice Genome Annotation Project; GWH, Genome Warehouse.
providing evidence for the variety of the *O. sativa* gene pool in 5 major different groups — indica, aus/boro, basmati/sadri, tropical japonica, and temperate japonica, and in some unknown subpopulations related to geographic location [70].

SSR markers are another class of molecular marker that are widely used in gene mapping and breeding practice. They are also the primary choice for genotyping due to their high density, codominant inheritance, high allelic diversity, and highly reproducible methodology for detection. An excellent example for marker-assisted backcrossing breeding using SSR markers is to integrate rice blast resistance genes into a number of popular rice varieties to improve the blast disease resistance [73,74]. The current genome coverage by both SSR and SNP markers is abundant for marker-assisted selection (MAS) and QTL (quantitative trait loci) mapping.

**Furthering function-centric and trait-centric gene cloning**

The advances in rice genome sequencing projects have greatly boosted functional genomic studies. These studies aimed at exploring genes and regulatory networks of agronomically important traits and their application in varietal improvement, which include but are not limited to, yield, grain quality, reproductive development, and resistance to disease, pests, or abiotic stress. Over the past decades, scientists have used various platforms successfully for functional genomics, such as large-scale mutant libraries [75,76], core germplasm collections, high-density gene expression arrays, and transcriptome sequencing [77]. In doing so, they have defined a number of trait-related genes with agronomic importance. Collectively, a total of 2358 rice functional genes(http://www.ricedata.cn/) were successfully cloned using map-based cloning techniques, including genes related to grain yield, grain size/weight, and grain quality [76,78]. For instance, *GW5*, which regulates cell division during seed development, affects grain width [79,80]; whereas the recently identified plant-specific transcription factor 13 (*OsSPL13*) appears to increase grain length [81].

Another typical example is genes involved in regulating plant architecture by controlling tillering and promoting panicle branching. For instance, *OsSPL14* (also known as ideal plant architecture, *Ipa1*), one of the *Osmir156* targets that interacts with TEOSINTE BRANCHED1, negatively regulates tiller bud outgrowth [82–84]. In addition, *OsSPL14* also regulates the length and grain numbers of panicles by directly interfering with dense and erect panicle 1 (*DEP1*), a key protein determining panicle architecture [84]. The introduction of the *OsSPL14ipa1* allele into Xiushui 11 (XS11) results in approximately an increase of 11% in grain yield [85]. Additional details on achievements of rice functional genomics have been well described in a recent review [86].

**Future perspectives**

As the global human population is projected to reach 9 billion by 2050, rice researchers and breeders, together with those working on the other two major cereal crops — wheat and corn — are pressured to forge ahead to make decisive contributions to the prevention of potential food crises along the way. To fulfill such a challenging achievement, rice genomics and information integration must be conducted continuously, and an all-in effort from the rice research community would be needed to build the ICRG as a platform for the curation and annotation of sharable resources, which are not limited to data and knowledge but also experimental materials (Figure 1).

First, together with the introduction and application of the third-generation sequencers, we envisage that ICRG will contain more high-quality, gap-free genome sequences acquired systematically in the next decade or so from the existing germplasms, which may be expanded to other cereal crops and their wild counterparts. An international effort is in principle the best choice to unite rice scientists around the globe to build a platform upon which to collect data, to exchange information, and to share knowledge. As data accumulate, this platform must be organized to incorporate information from multiple omics levels, such as epigenomics, ribogenomics, proteomics, and metabolomics. Second, a significant effort must focus on gene-level genome annotations based on intensive comparative analyses among cultivars, wild counterparts, and elite hybrids. Most difficulties are expected to come from three basic components: defining all functional genes and their variants, annotating all TEs, and distinguishing orthologous and paralogous genes and their functional distinctions. Specialized databases have to be built and curated by dedicated scientists, in which genome polyploidy and chromosomal level regulatory principles and mechanisms are most likely involved. Third, ICRG dedicated to rice biotechnology must be built by rice genomics and bioinformaticians for end users, such as rice biologists and crop breeders. Because the most likely tools for genetically modified crops now appear to be genome or gene editing in addition to the conventional tools of genetic engineering and hybridization [87], it is a necessity that genome assemblies be of ultimate quality and contiguity. Both are not effortless when working with the current state-of-art technological toolboxes. All possible future milestones are marked in the timeline of rice genomics (Figure 1A).

**Competing interests**

The authors declare no competing interests.

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Song S et al | Rice Genomic Research Past and Future

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