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Breaking Yield Ceiling in Wheat: Progress and Future Prospects

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Abstract

Wheat is one of the most important staple crops that contribute considerably to global food and nutritional security. The future projections of the demand for wheat show significant enhancement owing to the population growth and probable changes in diets. Further, historical yield trends show a reduction in the relative rate of gain for grain yield over time. To maintain future food security, there is a strong need to find ways to further increase the yield potential of wheat. Grain yield is a quantitative trait that is highly influenced by the environment. It is determined by various inter-linked yield component traits. Molecular breeding approaches have already proven useful in improving the grain yield of wheat and recent advances in high-throughput genotyping platforms now have remodelled molecular breeding to genomics-assisted breeding. Hence, here in this chapter, we have discussed various advancements in understanding the genetics of grain yield, its major components, and summarised the various powerful strategies, such as gene cloning, mining superior alleles, transgenic technologies, advanced genome editing techniques, genomic selection, genome-wide association studies-assisted genomic selection, haplotype-based breeding (HBB), which may be/being used for grain yield improvement in wheat and as the new breeding strategies they could also be utilised to break the yield ceiling in wheat.

Keywords: wheat, grain yield, genomics resources, molecular breeding, genomics-assisted breeding

1. Introduction

Wheat (*Triticum aestivum* L.) is the most extensively grown food crop around the world and ranks second after rice [1]. China is the top wheat-growing country which recently in 2020, produced 134,250 thousand tonnes of wheat accounting for approximately 20.66% of the total wheat production around the globe. The top five wheat-growing countries (China, India, Russian Federation, United States of America, and Canada) together account for 63.46% of the world's wheat production (6,499,759 thousand tonnes in 2020) [2]. It accounts for more than 20% of the calorific intake of humans and supplies more protein (approximately 23%) than all animal sources [1]. The progress for the genetic improvement of grain yield in wheat ranged from 0.3% to 1.0% per year during the last century [3]. Nevertheless, it has been decreased in recent years, largely due to the narrow genetic base of the germplasm used for the development of new genotypes and the lack of adoption of novel breeding strategies.

Noticeably, there is a need to increase wheat yield to feed the world population which may be increased from the current 7.5 billion to more than 9 billion by 2050, and this is with the unusual constraints posed by climate change. Under such kind of pressure, wheat breeding programs need to do more to achieve the targeted genetic gain in grain yield ensuring food security in the near future. Many studies have shown that increases in the harvest index (HI), grain weight (GW), grain number per spike (GNPS), and decreases in plant height (PH) are the major traits associated with genetic gain in wheat [4, 5]. Improvement in HI has permitted better partitioning of photosynthetic assimilates to the developing grains, resulting in greater grain yield (GY). The HI of cultivated wheat varieties generally ranges from 0.4 to 0.5 which is already close to the theoretical maximum value of 0.62 [6, 7]. Furthermore, HI values more than 0.5 are very hard to achieve, particularly in unfavourable environmental conditions [8]. This situation again shows that genetic progress in wheat breeding programs may be difficult. Therefore, understanding the changes (either increment or reduction) in yield and related traits is an essential step towards developing new breeding strategies and a further improvement in the grain yield.

Grain yield is the final result of plant growth and development and hence most, if not all, genes are supposed to contribute towards yield either indirectly or directly. Consequently, achieving increased grain yield is a non-trivial task, and the accumulative knowledge from wheat breeding suggests that we would require concurrent improvements of both the 'source' and 'sink' tissues. Traditional breeding largely depends on empirical phenotypic selection, which has already resulted in the development and release of a large number of high-yielding varieties. However, time consumption, labour intensity, environmental dependence, and low efficiency are prime barriers that nowadays hinder conventional/traditional wheat breeding. High-yielding wheat varieties can result from the uncovering of novel genetic variation, better selection techniques, or the identification of superior genotypes with novel or improved characteristics caused by favourable combinations of superior alleles at multiple loci. In recent years, an impressive number of advancements in genetics and genomics have been made in wheat. Owing to the tremendous effort of IWGSC, the 'gold standard' reference genome has become available for wheat cultivar 'Chinese Spring'. The most comprehensive assembly of this reference line has been recently released in 2018 which gave access to a total of 107,891 high-confidence genes [9]. The genome sequences may assist the identification of important genes at an unprecedented level which is a key aspect in wheat breeding. Different types of molecular markers, such as RFLP, AFLP, SCAR, STS, SSR, CAPS, and GBS-SNPs, have been identified and mapped on the different chromosomes of wheat and highly dense genetic maps have also been developed (available at <https://wheat.pw.usda.gov/GG3/>) which are being utilised in various genetic studies in wheat [10, 11]. To date, more than 15 different high-throughput GBS strategies have been developed and utilised in various crops including wheat [12]. Moreover, several SNP arrays/assays have also been developed which are flexible in terms of data point and sample number customization, which contributes to its high-density scanning and robust call rates compared to PCR and NGS-based markers. Several high-density SNP genotyping arrays have been utilised for genetic dissection of different traits and marker-assisted breeding in wheat namely the Illumina Wheat 9 K iSelect SNP array [13], the Illumina Wheat 90 K iSelect SNP genotyping array [14], the Wheat 15 K SNP array [15], the Wheat 55 K SNP array, the Axiom Wheat 660 K SNP array, the Axiom HD Wheat genotyping (820 K) array [16], the Wheat Breeders' 35 K Axiom array [17], and the Wheat 50 K *Triticum* TraitBreed array [18]. These advancements in genomics have

greatly enhanced our understanding of structural and functional aspects of the wheat genome and contributed to wheat improvement in two ways. First, they provided a better understanding of the various biological mechanisms that have led to new or improved screening methods for identifying and selecting superior genotypes more efficiently. Secondly, this new information improved the decision-making process for more efficient breeding strategies. With these advancements, the focus of wheat breeding has gradually switched from phenotype-based to genotype-based selection. Marker-assisted selection (MAS) has improved wheat breeding efficiency to some extent and predominated in breeding programs for decades. Several MAS strategies have been developed—marker-assisted backcrossing (MABC) or introgression of QTL or major genes, selection of complex quantitative traits using molecular markers, and enrichment of favourable alleles in early generations [19]. Availability of high-throughput genotyping platforms and genomics resources now rapidly remodelling marker-assisted breeding to genomics-assisted breeding.

Here in this chapter, we summarise the recent progress in understanding the genetics of grain yield and other related traits together with the new strategies, such as gene cloning and mining of superior alleles, transgenic technologies, genome editing technologies, genomic selection (GS), genome-wide association studies (GWAS)-assisted GS, and haplotype-based breeding (including haplotype-based GWAS and haplotype-based GS), which altogether make it available for genomics-assisted breeding (GAB) in crop improvement and to break the yield ceiling in wheat.

2. Genetics of grain yield and its related traits

Grain yield is a complex polygenic trait, significantly associated with grain number per spike, grain weight, harvest index, number of productive tillers, plant height, days to heading/flowering, etc. The trait is also influenced by the environment and shows a significant level of genotype \times environment interaction with low heritability. Previous studies showed that increased yield potential in the major wheat-growing countries was largely associated with increased grains per square meter, harvest index, and biomass, and reduced plant height [4, 5]. Moreover, it has been revealed that the use of dwarfing genes (*Rht1*, *Rht2*, *Rht8*, and *Rht24*), the 1BL.1RS translocation lines [20–23], and positive selection of desirable alleles of major genes including grain size (for instances, *TaGS3-A1*, *TaTGW6*, *TaSus1*, *TaGW2*, *TaGW8*, and so on), vernalization requirements (*Vrn* genes), photoperiod response (*Ppd-1*), etc. resulted into the enormous improvement in wheat grain yield [24, 25]. It is now believed that further improvement in grain yield can be attained only by exploiting untapped genetic variation and depth understanding of its genetic architecture combined with the use of advanced genomics-assisted breeding techniques. QTL mapping has been one of the innovative approaches for understanding the genetic architecture of grain yield and its component traits in wheat. Advancements in molecular marker systems have revolutionised the field of QTL mapping, as hundreds of QTLs for different yield-related traits have been mapped using different bi-parental and multi-parental mapping populations in several countries [26–31]. The QTL regions identified by the standard interval mapping procedure frequently extend to several centimorgans (cM) on linkage map (on the physical map, it may be equivalent to the several Mbp) which may encompass a large number of genes [31]. Therefore, it becomes very hard to pinpoint the causative locus/candidate gene responsible for a specific trait. Furthermore, the introgression of such large QTL regions based on linked or flanking

markers might carry several unwanted genes due to linkage drag, thereby negatively affecting the performance of generated cultivars encompassing the introgressed genomic segments. Therefore, the genetic resolution of the mapping procedures must be increased to allow QTL placement within the shortest possible genomic region using advanced strategies. Fine mapping is an important strategy that can be used for refining the QTL region. Three major factors, such as phenotyping, population size, and the number of markers, mainly regulate the success of QTL dissection, fine mapping, and further cloning of desired QTLs. Advances in NGS technologies have dramatically reduced per sample genotyping cost and offered increased throughput. Moreover, with the latest SNP genotyping platforms such as SNP chips or arrays in place, it is now quite possible to genotype tens of thousands of samples in a short period [32]. Moreover, QTL fine mapping occasionally reveals surprises, for instance, the presence of distinct genes whose combined effects contribute to the QTL identified using standard mapping procedures, distinct upstream non-coding enhancer/modifier sequences that contribute to phenotypic effects of a QTL, and substantial genetic differences between the alleles in the QTL region. Identification of the genes or sequence variants that underlie QTL may help in investigating the contribution of specific genes or structural variants to the overall genetic architecture of grain yield and related traits [26, 33].

As discussed above, several studies have reported hundreds of QTLs in different mapping populations evaluated under different environments. An innovative approach i.e., meta-QTL analysis has emerged which helps in refining the QTL positions by combining the QTL results from independent studies and identifying the most stable and consensus QTLs [34]. The power of this approach lies in detecting regions of the genome that are most often involved in trait variation and reducing the QTL confidence intervals, thus facilitating the identification and characterisation of underlying candidate genes. For the first time in 2010, Zhang and his colleagues [35] conducted a meta-QTL analysis of major QTLs for grain yield and yield-related traits and identified 12 significant MQTLs on chromosomes 1A, 1B, 2A, 2D, 3B, 4A, 4B, 4D, and 5A, few of which also included important known genes, such as *Vrn* and *Rht* [35]. Another study reported 16 MQTLs on chromosomes 1B, 2A, 2D, 3B, 4A, 6A, and 6B, related to grain weight [36]. Most recently in 2021, Saini and his colleagues [37] have identified a total of 141 MQTLs responsible for grain yield and related traits, which included 13 breeder's MQTLs and 24 ortho-MQTLs. This study also identified 1202 high-confidence candidate genes within the physical positions of the MQTL flanking markers [37]. Beside these, recently, various other MQTL studies have been also conducted in wheat [38–41]. DNA markers tightly linked to these meta-QTLs (MQTLs) may be used as molecular tools for MAS in wheat breeding. Association mapping or GWAS offers an alternative route for identifying genomic regions that have effects across a wider range of germplasm if false associations that are caused by population structure and relatedness can be minimised. With the advancements in high-throughput genotyping technologies, haplotypes and SNP-sets (instead of single SNPs) are being utilised for GWAS, thereby reducing the detection of false positives via overcoming the limitations of multiple testing and enhancing the identification of underlying candidate genes which in turn facilitate gene-based association mapping. Several GWAS studies have been conducted in wheat for grain yield and related traits, which have also resulted in the identification of hundreds of high-confidence candidate genes governing yield-related traits [42–46]. Combined linkage analysis and joint linkage association mapping (JLAM) have also been used in wheat for genetic dissection of grain yield-related traits. Unlike meta-QTL analysis, meta-GWAS studies have

been rare in wheat for yield and related traits. For the first time in 2018, Battenfield and his colleagues [47] described this meta-GWAS approach, which combined GWAS analysis from multi-year unbalanced breeding nurseries and identified the consensus and stable marker-trait associations (MTAs) and underlying candidate genes [47]. The markers, as well as candidate genes identified for grain yield and its component traits, provide important genomic resources for wheat breeding. These genomics resources can be immediately implemented to genomics-assisted breeding in wheat for genetic improvement of grain yield.

3. Gene cloning and allele mining: to be used for MAS

MAS allows a more effective selection of target genotypes which further enable certain traits to be 'fast-tracked', resulting in faster line development and variety release. MAS is a more cost-effective approach that can replace phenotyping and thereby allows selection in off-season nurseries as well. Another advantage of using MAS is that the total number of genotypes that need to be tested can be reduced significantly in early generations which allow more efficient use of field or glasshouse space which is generally limited [48]. MAS remains a valid option for major gene or QTL, whereas QTL cloning or gene cloning may become a more routine activity assisted by increased utilisation of high-throughput phenotyping techniques [49], sequencing [50], and identification of high-confidence candidate genes through 'omics' profiling [51]. Cloned QTL/gene may provide new opportunities for a more targeted search for novel alleles in wild wheat germplasm and mutants (**Table 1**).

At present, tremendous sequence information is available in public databases as a result of the sequencing of diverse wheat crop genomes, including reference lines and wild progenitors. This information can be used for mining the novel and superior alleles of agronomically important genes from gene pools to appropriately deploy for the development of high-yielding cultivars. Allele mining also provides insights into the molecular basis of trait variations and identifies the sequence variants associated with superior alleles. Moreover, it helps in the development of allele-specific molecular markers, assisting the introgression of novel alleles via MAS.

4. Transgenic technologies to boost grain yield

Considerable progress has been made in the past for manipulation of genes from diverse sources, including wild relatives and progenitors, and transferring them into wheat to confer increased grain yield, transgenesis can be employed as a powerful alternative for increasing the grain yield through exploiting the genes/traits which does not occur naturally in the wheat species. Transgenic plants refer to plants that contain a gene(s) that has been artificially inserted from an unrelated plant or a completely different species. The increase in grain yield potential through transgenesis involves an ideotypic detail of potential targets for transformation. In 2017, Nadolska-Orczyk and his colleagues [79] reported potential targets for transgenesis which can result in the increased grain yield in wheat. These include 'transcription factors, regulating spike development, which mainly affect grain number; genes involved in metabolism or signalling of growth regulators—cytokinins, gibberellins, and brassinosteroids—which control plant architecture and consequently stem hardness and grain yield; genes determining cell division and proliferation mainly impacting grain size; floral

| Genes/QTLs | Chromosome | Products/enzymes | Associated yield-related traits | References |
|-------------------|------------|--|---|------------|
| <i>TaSus2</i> | 2A, 2B, 2D | Sucrose synthase | Endosperm development | [52] |
| <i>TaCwi-A1</i> | 2A | Cell wall invertase | Kernel weight | [53] |
| <i>TaCWI-5D</i> | 5D | Cell wall invertase | Kernel weight | [54] |
| <i>TaSAP1-A1</i> | 7A | Zinc-finger protein | Thousand grain weight, number of grains per spike, spike length, peduncle length and spikelet's per spike | [55] |
| <i>TaGS1a</i> | 6D | Glutamine synthetase | Mineral nutrient and grain size | [56] |
| <i>TaTGW-7A</i> | 7A | Indole-3-glycerol-phosphate synthase | Thousand grain weight | [57] |
| <i>TaGASR7-A1</i> | 7A | Snakin/GASA protein | Grain length | [58] |
| <i>TaGS-D1</i> | 7D | Glutamine synthetase | Thousand grain weight, grain length | [59] |
| <i>TaCKX6a02</i> | 3D | Cytokinin oxidase/dehydrogenase | Grain size, grain filling rate, grain weight | [60] |
| <i>Tackx</i> | 3A | Cytokinin oxidase | Grain weight and leaf chlorophyll content | [61] |
| <i>TaTPP-6AL1</i> | 6A | Trehalose 6-phosphate phosphatase | Grain weight | [62] |
| <i>TaFlo2-A1</i> | 2A | FLO2 protein | Thousand grain weight, grain size | [63] |
| <i>TaSnRK2.3</i> | 1A, 1B, 1D | Plant-specific protein kinase | Plant height, length of peduncle, penultimate node, thousand grain weight | [64] |
| <i>TaSnRK2.10</i> | 4A, 4B, 4D | Sucrose non-fermenting 1-related protein kinases | Thousand grain weight, spike length | [65] |
| <i>6-SFT-A2</i> | 4A | Fructan 6-fructosyltransferase | Thousand grain weight | [66] |
| <i>TaGW2-6A</i> | 6A | E3 ubiquitin ligase | Grain weight, grain size | [25] |
| <i>TaCKX6-D1</i> | 3D | Cytokinin oxidase/dehydrogenase | Thousand grain weight | [67] |
| <i>TaGL3-5A</i> | 5A | Putative protein phosphatase | Grain length | [68] |
| <i>TaAPO-A1</i> | 7A | F-box protein of 429 amino acids | Total spikelet number per spike | [69] |
| <i>TaTGW6-A1</i> | 3A | Indole-3-acetic acid-glucose hydrolase | Thousand grain weight | [24] |
| <i>TaGW8-B1a</i> | 7B | E3 ubiquitin ligase | Kernel size | [70] |

| Genes/QTLs | Chromosome | Products/enzymes | Associated yield-related traits | References |
|--------------------|------------|-----------------------------------|---|------------|
| <i>TaTAR2.1-3A</i> | 3A | Tryptophan amino transferase | Plant height, spike number | [71] |
| <i>TaNAC2-5A</i> | 5A | NAC transcription factor | Spike number, grain number per spike, and thousand grain weight | [72] |
| <i>TaGS5-3A</i> | 3A | Serine carboxypeptidases | Grain size, grain weight | [73] |
| <i>TaTEF-7A</i> | 7A | Transcript elongation factor | Grain number | [74] |
| <i>TaPPH-A</i> | 7A | Pheophytin pheophorbide hydrolase | Thousand grain weight, grain filling | [75] |
| <i>TaNf-YB4</i> | 3B | Histone-like transcription factor | Number of spikes per plant | [76] |
| <i>TaNfYA-B1</i> | 6B | Histone-like transcription factor | Number of spikes per plant | [77] |
| <i>TaCYP78A3</i> | 7A, 7B, 7D | Cytochrome P450 CYP78A3 | Seed size | [78] |

Table 1.
Cloned genes/QTLs regulating various yield-related traits in wheat.

regulators influencing inflorescence architecture and consequently seed number, and genes involved in carbohydrate metabolism having an impact on plant architecture and grain yield'. Furthermore, modulated expression of flowering genes, which control vernalization and photoperiod-dependent floral induction, may be good for winter or spring wheat varieties [79, 80]. Besides, augmenting photosynthetic rates of lamina and non-lamina organs and the capability to access and utilise a greater amount of resources, such as nutrients or water, may also be potential targets for transgenesis in wheat for grain yield improvement [81, 82]. Besides, information about specific genotypes as well as climatic and agronomic conditions and consideration of the fact that the majority of the genes are members of multigene families is required for successful implementation of selected potential genes in breeding programs [79].

Transgenic wheat has the capacity to transform agriculture, but progress has been very limited as no transgenic wheat cultivar could be commercially approved so far because of consumers' concerns. Few promising reports are available where newly developed transgenic wheat showed a significant grain yield advantage [72, 83]. Over-expression of a nitrate-inducible transcription factor (NAC TF) in wheat enhanced root growth and the ability to uptake nitrogen, therefore, increased nitrogen accumulation and grain yield by 10% (on a single plant basis) [72]. In another study, Gonzalez and his colleagues [83] reported that transgenic wheat lines carrying a mutated version of the sunflower TF (*HaHB4*) can significantly increase grain yield and water use efficiency across a range of environments [83]. Most recently in 2020, Argentina has become the first country to approve a genetically modified wheat variety (HB4). This is a drought-tolerant high-yielding wheat variety jointly developed by Argentine crop inputs manufacturer 'Bioceres' and 'Trigall Genetics' yielding 20% more than other standard wheat varieties in 10 years trials under drought conditions. The commercial approval of this GMO variety solely depends on approval by Brazil, which imports more than

85% of Argentine wheat [84]. Experts have also raised concerns about the growth and marketing of this GMO wheat variety, citing challenges related to food safety, consumer preferences, environmental effects, and socioeconomic issues. More research is required to determine the true safety of this GMO wheat and to decide, whether they are safe for both the consumers and the environment. At least, most would agree that the possible advantage of producing transgenic wheat, which furnishes the human population with cheaper and more food, makes transgenesis a useful invention.

5. Genome-editing technologies

Targeted genome editing has emerged as a powerful tool for studying gene function, correcting defective genes, or introducing novel functionality. Its mechanism involves sequence-specific double-strand breaks (DSBs) in the target DNA, with edits incorporated during the endogenous repair. In the earlier phase of genome editing, to induce the desired double-strand breaks at the target site, the engineering for zinc-finger nucleases (ZFNs) [85] or meganucleases [86] attracted the attention of the researcher community. These genome-editing systems needed specialised competence to produce artificial proteins consisting of customizable DNA-binding domains (sequence-specific), each linked to a non-specific nuclease for target DNA cleavage, and offered researchers with extraordinary tools to perform genetic manipulation. Later, the identification of a novel class of a *Flavobacterium okeanokoites* catalytic domain (FokI) derived from bacterial proteins termed transcription activator-like effectors (TALEs) further offered new possibilities for precisely targeted genome editing [87]. TALE-based programmable nucleases allowed the cleavage of any DNA sequence of interest with comparatively high frequency. Dimerization of FokI nuclease is needed to make an active nuclease, therefore, every time two modules need to be designed to target closely DNA sequences for generating DSBs at target sites. This dimerization requirement limited the use of these two powerful genomes-editing tools, as designing active nucleases was difficult and very expensive [88].

In 2012, an inexpensive, simple, easy to use, and effective genome-editing system that is clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (CRISPR/Cas9) was introduced which revolutionised the field of genome editing [89]. The use of this powerful tool allows producing genome-edited plants in a very short period. CRISPR technology can be efficiently utilised for both precisely eliminating the negative regulator genes and augmenting the activity of positive-regulator genes that affect the trait of interest. Nevertheless, there are only a couple of reports available for validation of the CRISPR technique in wheat compared to other crops, such as rice [90]. In these reports, different genes were targeted by CRISPR/Cas9 to address the major biotic, and abiotic stresses along with improving a few agronomic traits in wheat [90]. An exciting advantage of using the CRISPR/Cas9 technology is the possibility of simultaneously editing multiple target genes using a single CRISPR construct. For instance, Wang and his colleagues [91] practiced this multiplexed genome editing in hexaploid wheat for targeting three different genes viz. *TaLpx-1*, *TaGW2*, and *TaMLO*. They placed three sgRNAs (each specific to a different gene) in a tRNA polycistronic cassette under the control of a single promoter to produce knockouts. Multiplex genome-editing tools can be efficiently utilised to address more complex traits (such as grain yield) involving multiple genes in a single attempt [91]. Moreover, this CRISPR/Cas9 mediated multiplex genome editing can also be utilised to mimic the domestication process during evolution in a short time frame, with

implications for a convenient and rapid generation of high-yielding wheat varieties. Despite the several advantages of using CRISPR/Cas9, one of the prominently associated challenges is off-target effects, that is undesired mutations at unintended sites induced by genome editing. Various methods have been developed to find off-target mutations both *in vitro* and *in vivo*. These include SITE-seq [92], Digenome-seq [93], CIRCLE-seq [94], GUIDE-seq [95], and DISCOVER-seq [96]. In the same way, the engineering of Cas9 proteins has also been performed to enhance the specificity.

5.1 Base editors and prime editing: opening up new avenues for wheat genome engineering

Many crucial agronomic traits are determined by a few base changes or point mutations in a gene [97–99]. CRISPR/Cas9 mediated gene replacements or gene modifications through homology-directed repair (HDR) has been reported as a practicable approach to correct the point mutations in the target DNA/gene and has the capability for accelerating crop improvement [100, 101]. Yet, the low efficiency of template DNA delivery and the rare occurrence of HDR (endogenous) has always been a difficult task in attaining success in plants. Furthermore, the CRISPR/Cas9 system is amenable for gene knock-in or knock-out, but cannot convert base into another. These challenges highlighted the demand for alternative powerful approaches that can result in precise and stable genome editing in crops. In 2016, a novel approach that is ‘Base editing’ was emerged which allows precise base (nucleotide) substitutions in a programmable manner, without requiring a donor template or disruption of a gene [102]. A base editor is a fusion of catalytically inactive Cas9 domain (Cas9 variants, Cas9 nickase, or dCas9) and an adenosine or cytosine domain that converts one base to another. Nucleotide substitutions or single-base changes may generate elite trait variations in crops which assist in accelerating crop improvement. The base-editing system can revert an SNP or single-base change without gene disruption. In recent years, many adenine and cytosine base editors have emerged as powerful tools for precise genome modifications (A to G or C to T) in eukaryotic genomes [102]. The potential of this approach has been demonstrated in several crops, including wheat [103–106]. As aforementioned, HDR efficiency is comparatively low in plant cells, so knock-ins of DNA fragments to target sites are challenging. Recently in 2019, Anzalone and co-workers developed a more efficient genome-editing technology that is ‘Prime editing’ which consists of CRISPR-Cas9 nickase–reverse transcriptase fusions programmed with pegRNAs (prime-editing guide RNAs) that enable precise genome editing without inducing DSBs or requiring a donor DNA template (mandatory for genome editing via HDR) in mammalian cells [107]. The prime editors have been adapted for use in wheat via optimization of the codon, promoter, and editing conditions [108]. This optimised suite of prime editors enabled InDels and point mutations in wheat and rice at higher frequencies [108]. Development of new technologies and tools, newly discovered CRISPR/Cas systems, are being continuously reported, inferring that the CRISPR toolbox for wheat genome engineering would expand further in the near future. Researchers have also focused on the development of efficient approaches for eliminating transgenes from genome-edited plants, such as (a) transient expression of DNA and RNA [109], (b) use of CRISPR/Cas9 ribonucleoprotein complexes [110], (c) use of CRISPR-S—an active interference element [111], and (d) programmed self-elimination of the CRISPR/Cas9 constructs [112] to generate transgene-free genome-edited plants. The elimination of transgenes offers the following two advantages—(i) elimination of Cas9 construct

from genome-edited plants prevents the induction of genetic changes at undesired loci, (ii) elimination of the transgenes is likely a prerequisite for getting regulatory approval of genome-edited crops for commercial applications. In the future, CRISPR technology may be supposed to accelerate wheat biology research, ultimately facilitating the development of high-yielding wheat varieties.

6. Genomic selection for grain yield improvement

The genetic complexity of grain yield and other yield-related traits limit the power of QTL mapping and association mapping in identifying small effect loci [113]. A powerful breeding strategy that is genomic selection (GS) has been introduced to circumvent this problem which implements whole-genome markers for predictions, and thus can efficiently complement QTL mapping and association analysis in dissecting the complex genetic base of grain yield-related traits in wheat [114, 115]. High-throughput/next-generation genotyping technologies have accelerated the adoption of GS by enabling the development of large sets of DNA marker data at reasonable costs [116]. GS is a potential GAB tool that predicts genomic-estimated breeding values (GEBVs) of individuals (from the breeding population) with genotypic data available via prediction models constructed based on a training population (TP) with available phenotypic and genotypic information [117]. As aforementioned, using the prediction models, the GEBVs of unobserved individuals are predicted, circumventing the omission of the small-effect genomic region (markers) that would fail a threshold (significance) test. Though the effect of each marker is small, a large volume of genotypic information covering the whole genome still has the power to explain all the genetic variance. GS complements conventional breeding approaches and can potentially decrease the requirement of large-scale phenotyping and hasten the rate of genetic gain via shorter breeding cycles [118, 119]. The performance of GS relies mainly on the prediction accuracy, defined as the 'Pearson's correlation between the selection criterion and the true breeding value to select individuals with unknown phenotypes' [120, 121]. Other factors that affect the GS accuracy include gene effects, level of linkage disequilibrium (LD), statistical models, the genetic composition of the TP, relationship between validation population (VP) or selection individuals and TP, and heritability of the target traits [120]. The major objective of GS is to decrease the cost of phenotyping and hasten genetic gains, use of high-throughput phenotyping tools and platforms that enable high-density phenotyping of hundreds to thousands of individuals across time and space using proximal or remote sensing, can increase the intensity and accuracy of selection and, eventually the selection response, as well as reduce phenotyping costs. The main idea of high-throughput phenotyping is to exploit secondary traits, such as canopy temperature, and green normalised difference vegetation index (NDVI) are closely related to grain yield that may be advantageous in early-generation testing of individuals. Data recorded on secondary traits (genetically correlated to grain yield) can be incorporated in multivariate pedigree and GS models, improving indirect selection for GY [122–124]. Moreover, GS can also be applied to gene bank accessions for germplasm enhancement. Accessions stored in germplasm bank represents an under-exploited rich genetic resource for wheat breeders, superior alleles can be extracted from these accessions which may be exploited for grain yield improvement in wheat [125, 126]. In general, lengthy pre-breeding programs are needed to develop lines that possess favourable alleles/genes from the wild accessions with superior agronomic performance and that may be utilised as parents in breeding

| Population type and size* | Number of genotyped markers | Traits | Accuracy of GEBV used | References |
|---|------------------------------|----------------------------|-----------------------|------------|
| Advanced breeding lines from CIMMYT (254) | 41,371 GBS-SNPs | TGW, DTH, and GY | 0.28–0.45 | [128] |
| Two DH populations (165 and 159) | 1975 and 1483 SNPs (90K SNP) | GNPS | 0.10–0.42 | [129] |
| European winter wheat lines (2325) | 12,642 SNPs (9K SNP) | GY | 0.5–0.65 | [130] |
| Winter wheat population (273) | 40,267 SNPs (90K SNP) | GY, TGW, PH and DTH | 0.33–0.67 | [131] |
| Inbred breeding lines (557) | 12,083 GBS-SNPs | DTH and GY | 0.57 | [132] |
| Advanced elite spring wheat lines (287) | 15,000 SNPs (90 K SNP) | GY, TGW and GN | 0.38–0.63 | [133] |
| Lines from multiple families (659) | 9500 DArT-GBS-SNPs | GY | 0.38–0.41 | [134] |
| Winter wheat breeding population from multiple families (861) | 6600 DArT-GBS-SNPs | GY | 0.39–0.48 | [135] |
| Inbred breeding lines (557) | 12,083 GBS-SNPs | GY | 0.65–0.76 | [136] |
| Hybrids obtained by crossing 18 males and 667 females (1888) | 13,005 SNPs (90 K and 15 K) | GY, DTH and PH | 0.5–0.55 | [137] |
| Winter wheat lines (1100) | 27,000 GBS-SNPs | GY | 0.23–0.55 | [138] |
| European winter and spring cultivars (210) | GBS-SNPs | 44 spike morphology traits | 0.2–0.5 | [139] |
| Elite wheat lines (4368) | 2038 GBS-SNPs | DTH, DTM, PH and GY | 0.35–0.44 | [140] |
| Bread wheat lines (10375) | 18,101 GBS-SNPs | GY and TGW | 0.59–0.98 | [141] |
| Double haploid lines (282) | 7426 GBS-SNPs | GY and TGW | 0.47–0.54 | [142] |
| Bread wheat lines (3771) | 8519 GBS-SNPs | DTH, DTM and GY | 0–0.75 | [143] |
| Soft red winter wheat lines (239), Double haploid (100), and Recombinant inbred lines (156) | 2721 SNPs (9 and 90K) | GY, DTH, TGW, GNPS, and PH | – 0.14-0.43 | [144] |
| F4:6 generation and double haploid winter wheat breeding lines (1114) | 7300 DArT-GBS-SNPs | GY | 0.45 | [145] |
| Winter wheat lines (3282) | 18,728 GBS-SNPs | GY | 0.25 | [122] |

| Population type and size* | Number of genotyped markers | Traits | Accuracy of GEBV used | References |
|--|-----------------------------|--------|-----------------------|------------|
| >6400 breeding lines | 78,662 GBS-SNPs | GY | 0.41 | [146] |
| Advanced breeding lines (456) | 11,089 GBS-SNPs | GY | 0.33–0.66 | [147] |
| Association mapping panel (456), two F5 populations (61 and 501), two DH populations (447 and 759) | 16,233 GBS-SNPs | GY | 0.21 | [148] |
| Advanced bread wheat lines (4302) | 8443 GBS-SNPs | GY | 0.35–0.43 | [149] |
| Winter wheat lines (1325) | 11,154 SNPs (15 K) | GY | 0.57 | [150] |

GY, GNPS, DTH, DTM, PH, and TGW refer to grain yield, grain number per spike, days to heading, days to maturity, plant height, and thousand grain weight, respectively. Figures in parenthesis are the population size.

Table 2.

Genomic selection studies conducted in wheat for grain yield and related traits.

programs. Using GS, germplasm enhancement breeding programs can be directly started using wild accessions and landraces. In a recent GS-based study, NGS technologies with multi-environment phenotyping were used to study the contribution of exotic genomes to 984 pre-breeding lines. Significant positive contributions of exotic germplasm to pre-breeding lines derived from crosses of CIMMYT's best elite lines with exotics were reported [127]. Genomic selection studies conducted in wheat for grain yield and related traits are presented in **Table 1**. The prediction accuracy of GS for different grain yield-related traits has varied from 0 to 0.98% in wheat (**Table 2**).

6.1 GWAS-assisted GS: making GS more efficient

As discussed above, GWAS estimates marker effects throughout the genome on the target association panel (diverse germplasm) based on prediction models. Based on LD, GWAS may identify new functional variants, including novel MTAs and genes for many agronomically important traits in diverse germplasm. According to a comprehensive simulation study in plants, the use of a few major MTAs/QTLs/genes (each explaining $\geq 10\%$ of the phenotypic variance) as fixed effects in GS models can increase the accuracy of GS for complex quantitative traits [151]. Although, the potential to combine robust and consistent associations identified from GWAS as fixed effects in GS models to increase prediction accuracy for complex traits such as grain yield has not been investigated comprehensively in wheat. The first report of integrating the genetic architecture of GY (revealed through GWAS) into prediction models in wheat has come from the work by Sehgal and co-workers, most recently in 2020 [149]. Firstly, using a haplotype-based genome-wide association study, they identified 58 MTAs for GY. Out of these 58 MTAs, 16 were 'environment-specific' with large effects and eight MTAs were consistent across trials and environments. These consistent MTAs were then used as fixed effects in the prediction models which resulted in a 9–10% increase in prediction accuracy for GY [149]. It is suggested that the utility of GS incorporating GWAS results may be noteworthy for GY when GWAS results detect highly robust and significant genomic regions.

7. Haplotype-based breeding (HBB) for grain yield improvement

Due to low heritability and persistent ‘genotype × environment’ interactions, improving grain yield (GY) is a difficult task for the global plant breeding community, especially under stressful environmental conditions [152–154]. As discussed earlier, GWAS-assisted GS has proven to be an effective method for deciphering the genetic architecture of complex traits, population improvement, and the development of better varieties with a higher yield. However, the problem of ‘missing heritability’, which is widespread in single marker-based GWAS, is not addressed by this approach. The alternative approach to boost the power of GWAS is by constructing haplotypes between neighbouring SNPs on a chromosome. As specific sets of alleles are observed on a single chromosome, haplotypes are inherited jointly with the limited probability of contemporaneous recombination. Haplotypes are implemented in crop improvement in two ways—retrospective and prospective [155]. Plant breeders have to choose the advantageous haplotypes that lead to desirable phenotype(s) for the trait(s) of interest during the long-term selection process. As a result, these advantageous haplotypes in elite crop germplasm can be found utilising the genome resequencing technique to sequence an elite gene pool [156]. Later, molecular markers that characterise these beneficial haplotypes can be produced, and all of these haplotype-defining markers can then be utilised to pick the most ideal combination of haplotypes that govern a certain phenotype. Furthermore, by identifying lines with unique recombination in chromosomal blocks of relevance, these haplotype-related markers can be utilised to distinguish between favourable and unfavourable genetic variation. On the other hand, haplotypes can be employed in a prospective approach, in which a vast collection of ancestral and wild germplasm of specific crop species (not just elite breeding pools) is re-sequenced to find haplotypes with a wider range of genetic variation [153, 155]. The genome-wide haplotypes are employed in this strategy to find novel haplotypes in a wide variety of natural germplasm. For the discovery of QTLs/genes, recent GWA studies based on empirical and simulation data (i.e., better p-values) and allelic effect estimation have demonstrated that haplotype blocks have higher mapping accuracy and power than individual SNPs [153, 155–160]. Haplotype superiority can be explained by a number of factors. Stephens and his colleagues [161] showed that haplotype blocks are more informative than SNP markers because of their multi-allelic character in nature. The scientists found that haplotype variants were more common than SNPs, implying that recombination and recurrent mutation events occurred within and among haplotype genes (**Figure 1**). In addition, as compared to individual SNPs, haplotype-based analysis is predicted to reduce the false positives and shows the intricate mechanism of causal haplotypes [162]. Similarly, the haplotype-assisted GS depicts the complex relationships between genotypic information and phenotypes more accurately than individual SNPs. As a result, this method could eventually aid in improving selection gain per unit of time. Because haplotypes can better capture LD and genomic similarities in various lines and may capture local high-order allelic interactions, they may improve the accuracy of genomic prediction [163]. Furthermore, by depicting population structure in the calibration set, prediction accuracy might be enhanced. The superiority of haplotype-based predictions over SNP-based predictions for all studied traits, including yield, test weight, and protein content, was established in a recent GS study that compared the prediction ability computed from haplotypes and SNPs in a set of 383 advanced lines and cultivars of wheat [164]. Based on evidence revealing higher haplotype-assisted genomic prediction efficiency than SNPs, researchers are increasingly embracing haplotype-assisted genomic prediction in crop development programmes.

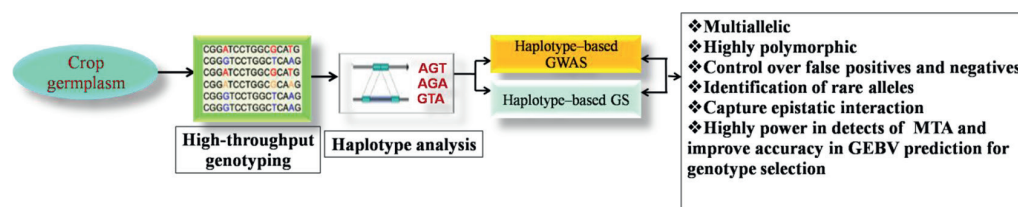


Figure 1. Flow diagram indicating how haplotype-based GWAS and haplotype-based GS, when combined with high-throughput genotyping, have the potential to improve gene identification precision and accuracy (modified from Bhat et al. [162]).

8. Conclusions

Significant progress has been made in wheat in developing various genomics resources, including high-throughput molecular markers, dense genetic maps, and next-generation genotyping platforms. The availability of high-quality wheat genome information has also enabled many next-generation sequencing-based approaches for genetic mapping, allele mining, and identification of candidate genes which have enhanced the precision, pace, and efficiency of trait mapping. At present, trait-associated markers, high-throughput genotyping platforms, and expertise are available for deploying genomics-assisted breeding in wheat. We believe that in the coming years, extensive deployment of genome editing, transgenic technology, genomic selection, haplotype-based breeding in combination or alone would be undertaken for crop improvement and breaking the yield ceiling. Various steps involved in generating high-yielding wheat genotypes using genomics-assisted breeding technologies are represented in **Figure 2**.

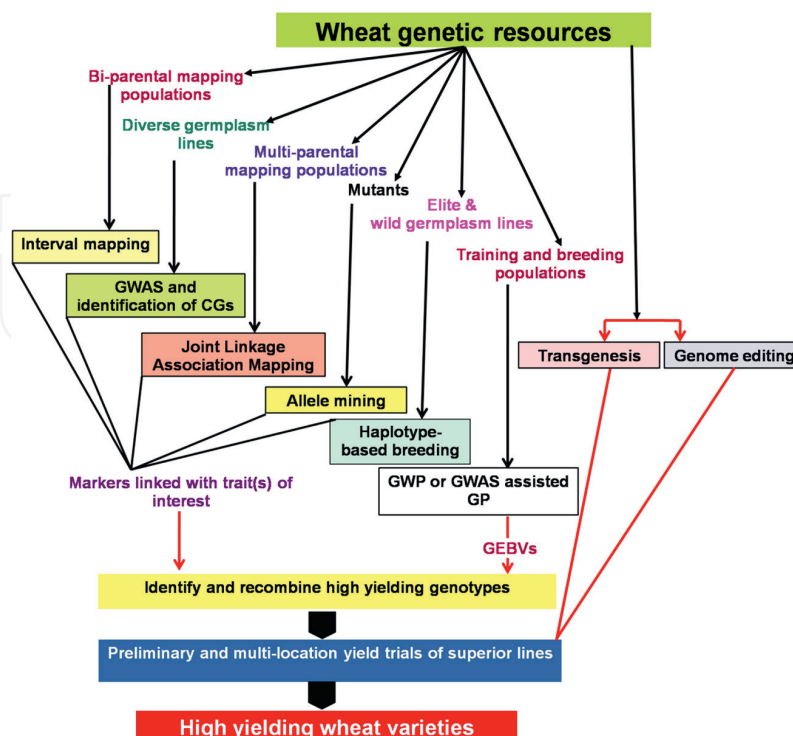


Figure 2. Flowchart demonstrating the steps involved in generating high-yielding wheat genotypes using different genomics-assisted breeding strategies.

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Conflict of interest

The authors declare no conflict of interest.

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