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REVIEW

Recent advances on genome-wide association studies (GWAS) and genomic selection (GS); prospects for Fusarium head blight research in Durum wheat

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Abstract

Purpose Wheat is an important cereal crop that is cultivated in different parts of the world. The biotic stresses are the major concerns in wheat-growing nations and are responsible for production loss globally. The change in climate dynamics makes the pathogen more virulent in foothills and tropical regions. There is growing concern about FHB in major wheat-growing nations, and until now, there has been no known potential source of resistance identified in wheat germplasm. The plant pathogen interaction activates the cascade of pathways, genes, TFs, and resistance genes. Pathogenesis-related genes' role in disease resistance is functionally validated in different plant systems. Similarly, Genomewide association Studies (GWAS) and Genomic selection (GS) are promising tools and have led to the discovery of resistance genes, genomic regions, and novel markers. *Fusarium graminearum* produces deoxynivalenol (DON) mycotoxins in wheat kernels, affecting wheat productivity globally. Modern technology now allows for detecting and managing DON toxin to reduce the risk to humans and animals. This review offers a comprehensive overview of the roles played by GWAS and Genomic selection (GS) in the identification of new genes, genetic variants, molecular markers and DON toxin management strategies.

Methods The review offers a comprehensive and in-depth analysis of the function of *Fusarium graminearum* virulence factors in Durum wheat. The role of GWAS and GS for Fusarium Head Blight (FHB) resistance has been well described. This paper provides a comprehensive description of the various statistical models that are used in GWAS and GS. In this review, we look at how different detection methods have been used to analyze and manage DON toxin exposure.

Results This review highlights the role of virulent genes in Fusarium disease establishment. The role of genome-based selection offers the identification of novel QTLs in resistant wheat germplasm. The role of GWAS and GS selection has minimized the use of population development through breeding technology. Here, we also emphasized the function of recent technological developments in minimizing the impact of DON toxins and their implications for food safety.

Keywords GWAS · GS · DON toxin · *Triticum durum* · *Fusarium graminearum*

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Introduction

Wheat (*Triticum aestivum* L.) is consumed globally as an essential commodity and an important component of the human diet. Bread wheat being hexaploidy in nature contains three genomes (AABBDD), each derived from three different progenitors, such as (AA) derived from *Triticum urartu*, (BB) from an unknown species and (DD) genome has been derived from wild grass *Aegilops tauschii* (DD). Durum wheat (*Triticum Durum)* is an allotetraploid in nature and contains (AABB) genome. A wide range of food products, such as macroni, pasta and desserts are derived from Durum wheat. The economic significance of Durum wheat makes it as an important player to develop resistant cultivars for Fusarium Head Blight (FHB) resistance. FHB markers and QTLs identified in resistant genotypes of *T. aestivum* is complex to cross with Durum wheat due to the sexual incompatibility. Hence it becomes important to identify resistant genes and genomic regions in diverse *T. durum* lines and to cross with cultivated varieties. It provides more than 20% of nutritional demands for human consumption. It is considered a staple crop, and its demand has increased globally by 35–40% [1]. Ever increasing world population requires more acreage for wheat production [2, 3]. By 2050, it is predicted that there will be approximately 10 billion people on earth, which will increase the demand for wheat production globally. The incidence of fungal diseases in *T. durum* has increased as a result of rising temperatures. The rapid evolution of new pathotypes has also been facilitated by variations in global temperature. Many fungal infections have impeded wheat production, viz., stripe rust, leaf rust, spot blotch, powdery mildew, karnal bunt, loose smut and Fusarium Head Blight (FHB). Fusarium head blight caused by *Fusarium graminearum* is one of the most economically important fungal disease in *T. durum*.

Wheat production is threatened by *F. graminearum*, which is primarily responsible for FHB, scab, or ear blight [4]. Various cultural and agronomic strategies were employed to mitigate the disease's severity, but breeding for stable, long-lasting resistant cultivars is the most effective strategy to manage the illness both before and after harvest. [5]. FHB resistance breeding success depends on finding resistant germplasm that contains a specific resistance genes and markers with associated traits [6]. Several wheat diseases, notably the scab pathogen, have had their whole genetic and genomic information disclosed by recent developments in high-throughput next-generation sequencing (NGS). Genome-wide association studies (GWAS) and genomic selection (GS) in wheat germplasm have led to the identification of potential candidate genes and markers. The genes and markers identified through GWAS will be introgressed into susceptible genotypes to increase resistance against broad-spectrum fungal pathogens [7]. This article uncovers and summarises recent literature on association mapping, genome-wide association mapping, and genomic selection associated with Fusarium resistance in wheat to understand resistance mechanisms using Indian wheat germplasm and its integration into association studies to better comprehend disease severity, pathogenesis, toxic effects, and sustainable approaches for the generation of resistant genotypes.

Pathogenesis and virulence factors of *Fusarium graminearum*

Fusarium graminearum is the most devastating fungal pathogen causing FHB in wheat. The pathogen is more prevalent in the US, Canada and in Asian countries, causing maximum yield loss due to the release of the carcinogen DON toxin [8]. The fungal-pathogen interaction is not fully understood at the molecular level, and there is scant knowledge about Fusarium-wheat pathosystems. Fungal pathogens secrete effectors into the plant cell, and they are recognized by receptors on the cell surface and activate effector-triggered immunity [9]. Effector proteins have well defined role in pathogenicity and help pathogens to evade the host immune system. Similarly, three effector proteins (*FGSG_01831, FGSG_03599*, and *FGSG_12160*) secreted by *F. graminearum* were involved in the fungal infection and bypass the host immune response [10]. Pathogens produce effector proteins for use in host cell membrane invasion and trafficking into the apoplastic,

Table 1 List of key *F. graminearum* effector proteins and their function in the early stages of pathogen invasion and disease development.

Pathogen	Effector Proteins/genes	Function	References
F. graminearum	Trichodiene synthase (*Tri5*)	Regulation of the Tri cluster	[11]
F. graminearum	*Tri6*	Transcription activation of trichothecene biosynthetic	[11]
F. graminearum	*FgSah1*	Fungal development and virulence	[12]
F. graminearum	CAZymes	Plant cell wall degradation (PCWDC) & fungal cell wall modification (FCM)	[13]
F. graminearum	*EIN2*	Ethylene signalling	[14]
F. graminearum	*OSP24*	Important for infectious growth in the rachis tissues in infected wheat heads	[15]

which triggers effector triggered immunity (ETI) in plants that have evolved resistance. (Table 1) summarises the known and predicted effector proteins released by *F. graminearum*.

Pathogens have different modes of interactions with host plants, and Fusarium is a hemibiotrophic fungal pathogen. It establishes itself as a biotroph before switching to necrotrophy. In the case of resistant genotypes, the release of effector molecules initiates the plant immune response and subsequently activates the primary defense mechanism; however, in susceptible hosts, it hijacks the plant's primary defense response and consequently causes disease development [16]. Mycotoxins produced by different fungal pathogens have adverse effects on humans as well as animals. Fungal pathogens secrete host-specific toxins to strengthen their interaction and establish infection in host plants. The primary cause of virulence in host plants is the release of toxins by fungal pathogens.

Plant defense response and disease outcome

Plants have highly developed defense mechanisms to prevent pathogen entry and defend themselves. Due to the absence of adaptive immune responses, the plant immune system relies on innate immunity. Plant resistance to a wide range of microbial pathogens is largely attributed to the innate immune system. The main elements of the plant immune system are resistance (R) genes, reactive oxygen species (ROS) scavenging enzymes, transcription factors, regulatory elements, and pathogenesis related genes (PRs) [17]. Expression of jasmonic acid (JA) marker genes in response to necrotrophic fungal pathogens is well understood, similarly JA-repressor *JAZ* genes (*Bradi3g23190*, *Bradi4g31240*), and the JA biosynthesis lipoxygenase *LOX2* gene *Bradi3g39980* were highly upregulated in response to FHB in the model plant *Brachypodium distachyon* [18]. The pathogen-associated molecular patterns are activated by receptors on the surface of plant cells, which detect the signal through a well-organized plant recognition system [19]. Plants have R genes in their second line of defense, known as effector triggered immunity (ETI), which detects signals through effector proteins (Fig. 1). In higher plants, pathogen entry leads to the activation of ROS scavenging enzymes, i.e. peroxidase (POX) and catalase (CAT). ROS production leads to the release of superoxide anion singlet, H_2O_2 and hydroxide radical production. The hypersensitive response in plants is usually activated by an oxidative burst and protects plants from invading pathogens [20, 21].

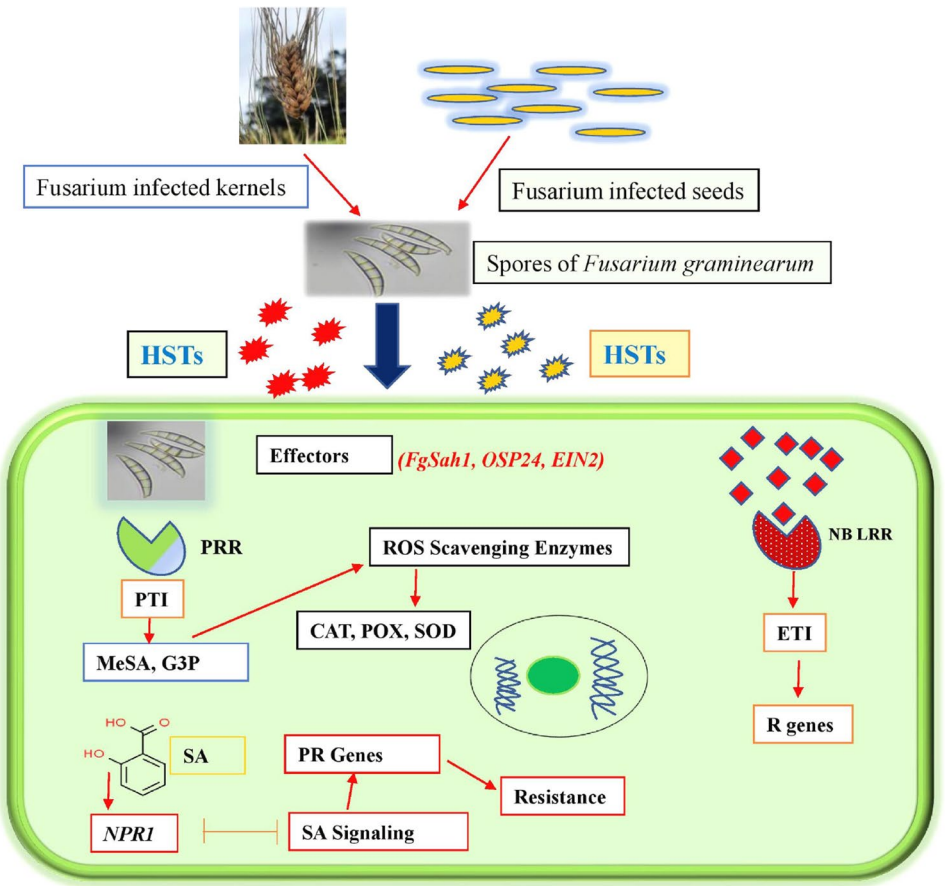

Fig. 1 An overview of pathogen–host interaction and its outcome. Activation of pathogen triggered immunity (PTI) and effector triggered immunity (ETI). F. graminearum spores fall on the kernels of mature wheat plants and exude HSTs, effector proteins necessary for infection establishment, which in turn activate a series of genes involved in the plant's defensive response (R genes, PRs & Transcription factors)

Advanced genetic approaches to identify QTLs, SNPs and resistance genes for FHB

Association mapping to understand *Fusarium graminearum*

The high-resolution method of association mapping, which is based on the theory of linkage disequilibrium, holds great promise for the analysis of complex genetic traits [22]. It is a powerful tool to identify agronomic traits' QTLs and allelic information for trait enhancement. The comparison is based on the correlation between genotype and phenotype and the data collected from the population grown in diverse climatic conditions. When compared to close systems, the data from open system design experiments offer higher mapping resolutions, but it is difficult to foresee where recombination has taken place. The nature of *Fusarium* resistance is still unclear despite thorough information about the annotated genomes. High-throughput genotyping and advances in genome sequencing technology have made association studies in complex genomes simple and comprehensive. *Fhb1* have minor additive effects on phenotypic variation by executing GWA studies for Fusarium resistance in winter wheat breeding lines. In addition, a sizable panel containing a winter elite inbred population contained nonsignificant discern loci with significant effects, in addition to sizable genetic variation [23]. Together, the two studies lend credence to the hypothesis that many genes exert additive effects and contribute to well-recognized QTLs in Fusarium resistance.

Genome-wide association studies (GWAS)

Fusarium head blight (FHB), one of the most destructive fungal disease affecting crop production significantly, spreads considerably due to poor cultural farming practices and climate influences [24]. GWAS is the most promising approach to identify novel QTLs and potential candidate genes governing specific traits in different plant systems. The use of chemical fungicides has deteriorated the soil texture and affected normal microbial flora; hence, it is important to use modern breeding techniques to identify resistant germplasm from the available

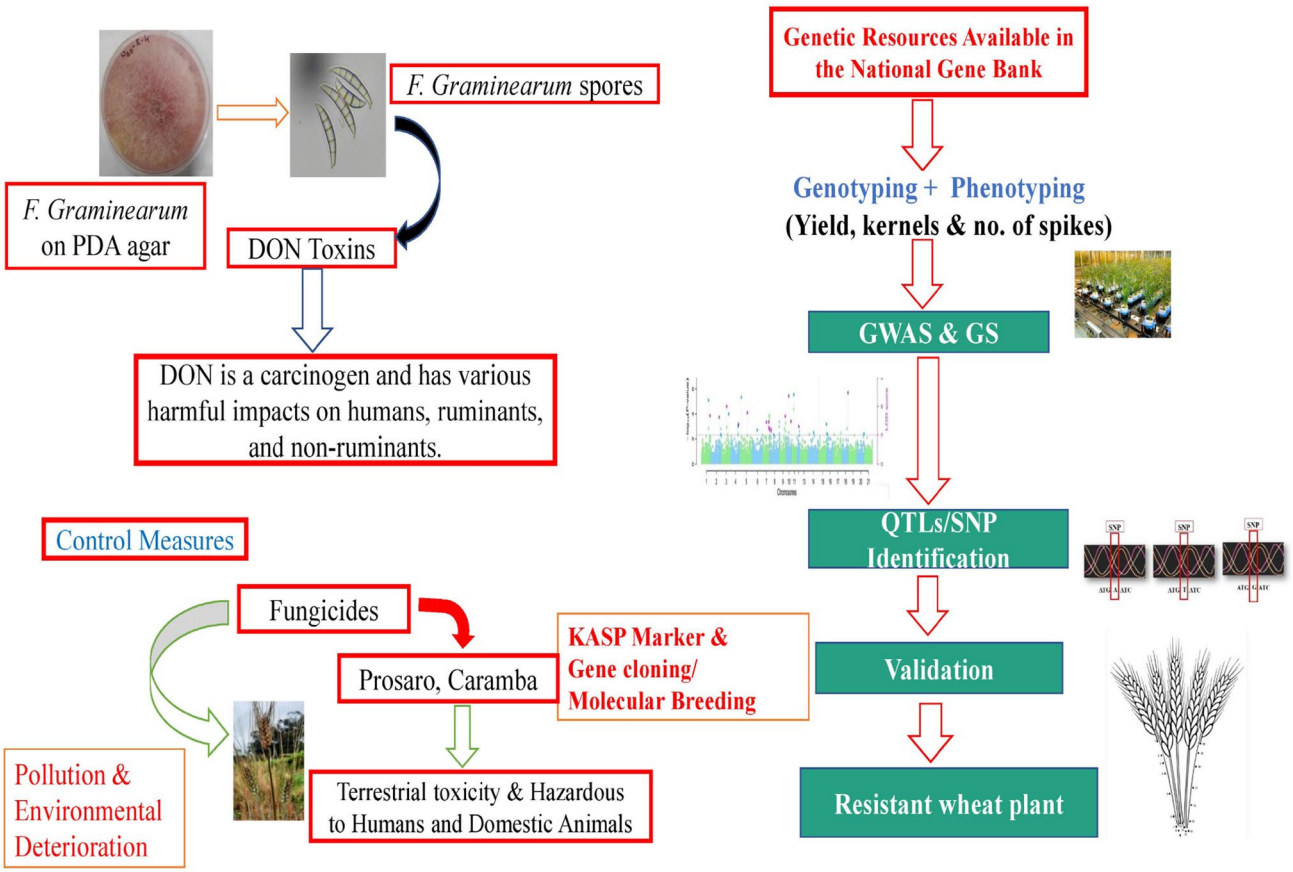

Fig. 2 Fusarium graminearum grown on PDA media and spores were visualized under 40× compound microscope, production of Deoxynivalenol (DON) toxin and its harmful effects on human beings. Similarly, Fusarium Head Blight control measures by using chemical fungicides (Prosaro and Caramba) and utilization of available germplasm in the national gene banks for GWAS and GS studies to identify resistant lines and to further evaluate by developing KASP markers

core sets (Fig. 2). In Wheat, GWAS have been used for various useful agronomic traits, including yield [25, 26, 27], seed quality, milling, baking properties [162829] flag leaves, head emergence [30], pre- and postharvest yields (CHECK) [31] and pathogen resistance [32, 33, 34, 35]. Among the various array of pathosystems, one of the highly emerging and devastating pathosystems is FHB caused by *F. graminearum*. It was studied using association genetics approach in wheat [36] as well as in barley, rye, triticale, and oat [34]. An experimental delineation was used to ascertain associations between genetic variants and corresponding traits in defined samples from the population [37, 38]. The predominant objective of such studies is to understand the biology of plant disease under the presumption that a superior interpretation will lead to prevention of the disease cycle and pathogenesis [39, 40]. It has also been flourishingly accomplished for more finely delineating the relative role of regulatory genes under the environmental influence for assisting risk prediction. However, the connection of GWAS to biology is not direct because an association with a genomic locus or genetic variant is not directly explanatory with respect to the functional target gene or the regulatory mechanism through which the concerned variant is associated with corresponding phenotypic differences [41, 42, 43]. However, as reviewed herein, new types of data generated from analytical methods integrated with advanced molecular technologies have provided opportunities to bridge the knowledge gap from sequence to consequence.

Resistance toward Fusarium in Durum wheat is a quantitative trait and is governed by different QTLs identified in and mapped to 21 chromosomes (Table 2). QTLS identified through GWAS studies are distributed evenly among different chromosomes (Fig. 3). With the shift in the era of genomics, advancement from conventional linkage mapping to genome-wide association studies has enlightened the molecular aspect of host pathosystems with greater capability and high determination for identifying and classifying favorable genetic loci culpable for the desired traits in an economic and evanescent way [44]. To overcome the bottlenecks of conventional breeding, next-generation sequencing (NGS) supportive genomic tools were used for enhanced breeding efficiency for disease resistance against rapidly evolving pathogens. The main advantage of NGS techniques employed for pathosystem studies is that they utilize target-enrichment sequencing (TES), whole-exome sequencing, genotyping-by-sequencing (GBS) and diversity array technology (DArT) to generate a tremendous number of single nucleotide polymorphisms (SNPs) in inexpensive ways.

Genome-wide association analysis (GWAS) was performed to identify genomic variants that were statistically associated with markers or traits of interest. Diverse population collections were genotyped and phenotype followed by associating them using various statistical models. (Fig. 4). By eliminating the false discovery rate (FDR), the frequency usage of economical, abundant and authentic genotyping markers, viz., SNPs, is extensively employed in crop genetic studies [70, 71]. It comprehends in-depth analysis of genetic variants present all through the genomes of diverse ultimately individuals for decoding of individual genotype–phenotype relations. It also provides an exhaustive perception of numerous constraining associations for perplexing traits aligned with disease resistance in various crop plants, including wheat, rye and barley [72]. Another advantage of GWAS is the exploration of recombination/linkage events that occur erstwhile in unrelated individuals to identify alleles in linkage disequilibrium [73, 74]. Notably, it basically provides candidate gene trait discovery and cross transcriptional expression studies.

Statistical models for GWAS

Genome-wide association studies (GWAS) attempt to predict the association of specific traits (phenotypes) with genetic variants (genotypes) by using suitable statistical models at the population level. Phenotypic information can be obtained by systematically measuring the phenotype (that may be any physical and physiological traits) that can be influenced by various genetic and environmental factors. Individual genotyping is usually performed using microarrays for common variations and next-generation sequencing technologies such as whole exome sequencing (WES) or whole genome sequencing (WGS) for rare variants. Due to the current trend of reducing the expense of next-generation sequencing, it is possible to conduct genotyping studies on such a large scale. Resequencing the entire genome could uncover almost all genetic variations. Genotypic information along with phenotypic data can be analyzed to identify genetic markers (SNPs, SSRs, etc.), QTLs or candidate genes associated with a particular trait.

The input files for GWAS usually include the genotype file, i.e., marker information, and the phenotype file, i.e., trait information of different individuals. Following the data input, producing reliable GWAS results requires meticulous quality control in the beginning itself and the use of other auxiliary information in GWAS models, e.g., population structure and kinship information.

Testing for associations

Depending on whether the phenotype is continuous (such as plant height, grain yield, etc.) or binary (such as the presence or absence of disease), linear, mixed effect or logistic

Table 2 Summary of genes/QTLs found in Wheat germplasm for FHB resistance using GWAS approach.

Source of resistance allele	Chromosome	% Variation explained	Markers	FHB trait	Association with	Plant material	Phenotyping	References
Sumai 3	3BS	15.4	Xcdo981	FHB spread		Sumai 3 × Stoa, 112 RIL	Fusarium graminearum, SFI: 2 greenhouse exp.	[45]
Stoa	4B	7.2	Xwg909	FHB spread		Sumai 3 × Stoa, 112 RIL	Fusarium graminearum, SFI: 2 greenhouse exp.	[45]
ND2603	3AL	9.1	Xbcd941	FHB spread		ND2603 × Butte86, 139 RIL	Fusarium graminearum, SFI: 2 greenhouse exp.	[46]
Ning 7840	3BS	60	AFLP markers	FHB spread		Ning 7840 × Clark, 133 RIL	Fusarium graminearum, SFI: 3 greenhouse exp.	[47]
Fukuhokomugi	n.d.	–	Xopz10.680–Xopaf06.345	FHB spread		Fukuhokomugi × Oligo Culm, 110 DH	Fusarium graminearum, sprinkler inoculation, field exp.	[48]
CM-82,036	3BS	92.6	Xgwm533–Xgwm493	DON resistance		CM-82,036 × Remus, 94 DH	DON infiltration, SFI: 2 greenhouse exp.	[49]
Ning 894,037	3BS	42.5	Xbarc133–Xgwm493	FHB spread		Ning 894,037 × Alondra, 218 RIL	Fusarium graminearum, SFI: 3 greenhouse & 1 field exp.	[50]
Alondra	2DS	12.1	Xgwm296–Xgwm261	FHB spread		Ning 894,037 × Alondra, 218 RIL	Fusarium graminearum, SFI: 3 greenhouse & 1 field exp.	[50]
Ning 894,037	6BS	4.4	Xgwm88–Xgwm644	FHB spread		Ning 894,037 × Alondra, 218 RIL	Fusarium graminearum, SFI: 3 greenhouse & 1 field exp.	[50]
Huapei 57 – 2	3AS	8.1	Xgwm5	FHB spread		Huapei 57 – 2 × Patterson, 163 RIL	Fusarium graminearum, SFI: 1 field & 2 greenhouse exp.	[51]
Patterson	5BL	7.1	Xbarc59	FHB spread		Huapei 57 – 2 × Patterson, 163 RIL	Fusarium graminearum, SFI: 1 field & 2 greenhouse exp.	[51]
Wuhan 1	2DL	9	Xgwm539	FHB spread		Wuhan 1 × Nyu Bai, 110 DH2	Fusarium graminearum, SFI: 2 greenhouse exp., SPRAY: 2 field exp.	[52]
Nyu Bai2	3BSc	4	Xgwm566	FHB severity		Wuhan 1 × Nyu Bai, 110 DH2	Fusarium graminearum, SFI: 2 greenhouse exp., SPRAY: 2 field exp.	[52]
DH181	2DS	11.1–12.8	Xwmc144–Xgwm539	FHB incidence, FHB spread, kernel infection		DH181 × AC Foremost, 174 DH	Fusarium graminearum, SFI: 3 greenhouse exp.; SPRAY: 2 field exp.	[53]
AC Foremost	3 A	11.8	Xwmc264–Xwmc428	FHB incidence		DH181 × AC Foremost, 174 DH	Fusarium graminearum, SFI: 3 greenhouse exp.; SPRAY: 2 field exp.	[53]

Table 2 (continued)

Source of resistance allele	Chromosome	% Variation explained	Markers	FHB trait	Association with	Plant material	Phenotyping	References
W14	5 A	24	Xbarc117–Xbarc186	FHB incidence		W14 × Pion2684, 96 DH lines	Fusarium graminearum, SFI: 2 greenhouse exp., SPRAY: 1 field exp.	[54]
CS-SM3-7ADS	4D	10.8	Xcfd84–Xwmc331	FHB spread		CS-SM3- 7ADS × Annong8455, 92 RIL	Fusarium graminearum, SFI: 1 greenhouse exp., 1 field exp.	[55]
CJ 9306	5AS	5.2	Xgwm425–Xbarc186	DON content		Veery × CJ 9306, 152 RIL	Fusarium graminearum, SFI: 3 greenhouse exp.	[56]
Sumai 3	3BS	–	Xsts3B.189–Xsts3B.206	FHB spread		F7 heterozygous plant, 382 recombinants	Fusarium graminearum, SFI: 2 greenhouse exp.	[57]
Nyu Bai	3BS	–	Xsts3B.80–Xsts3B.66	FHB spread		HC374 × 3*98B69-L47, 66 BC2F3 (from 420)	Fusarium graminearum, SFI: one greenhouse exp.	[58]
Wangshuibai	3BS	13.7–23.8	Xbarc147–Xgwm493	FHB spread		Wangshuibai × Alondra, 104 RILS	Fusarium graminearum, SFI: 3 field exp. & 2 greenhouse exp.	[59]
Alondra	1B	15.6	XeTCGmAGC.7–XeACCG-mCTC.7	FHB spread		Wangshuibai × Alondra, 104 RILS	Fusarium graminearum, SFI: 3 field exp. & 2 greenhouse exp.	[60]
Frontana	6B	6.7	Xs23m14.4	FHB severity, FHB incidence		Remus × Frontana, 180 DH	Fusarium graminearum, Fusarium culmorum, SPRAY: 3 field exp.	[61]
Remus	2 A	7.9	Xs13m26.4	FHB severity		Remus × Frontana, 180 DH	Fusarium graminearum, Fusarium culmorum, SPRAY: 3 field exp.	[62]
Seri82	1BL	7.9	Xe38m50.10–Xe32m65.10	FHB severity		Seri82 × Frontana; 171 F3 plants, 120 RIL	Fusarium graminearum, SPRAY: 2 field exp.	[61]
Chokwang	3BS	6	Xgwm533	FHB spread		Chokwang × Clark, 79 RIL (mapping), 240 RIL (validation)	Fusarium graminearum, SFI: 4 + 1 greenhouse exp.	[53]
Sincron	1BL1RS	–	Gli-R1	FHB spread		Sincron × F1054 W, 108 RIL	Fusarium gaminearum; SFI: 3 field exp.	[62]
F201R	1B	12.4	Xbarc8	FHB spread		Patterson × F201R, 318 (118) RIL	Fusarium graminearum, SFI: 3 greenhouse exp.	[50]
Patterson	3D	3.8	Xgwm341	FHB spread		Patterson × F201R, 318 (118) RIL	Fusarium graminearum, SFI: 3 greenhouse exp.	[50]
Goldfield	2B	12	Xwmc149	FHB incidence	Narrow flower opening	Patterson × Goldfield, 100 RIL	Fusarium graminearum, grain spawn: 5 field exp.	[63]
Arina	6DL	22.1	Xcfd19a–Xcfd47	FHB severity	Plant height, heading date	Arina × Forno, 240 RIL	Fusarium culmorum, SPRAY: 6 field exp.	[64]

Table 2 (continued)

Source of resistance allele	Chromosome	% Variation explained	Markers	FHB trait	Association with	Plant material	Phenotyping	References
Forno	3AL	10	Xwmc264–Xgwm155	FHB severity		Arina × Forno, 240 RIL	Fusarium culmorum, SPRAY: 6 field exp.	[64]
Cansas	1BS	16.5	Xe38m52.378–Xgwm131	FHB severity		Cansas × Ritmo, 94 RIL	Fusarium culmorum, SPRAY: 4 field exp.	[65]
Ritmo	1DS	8.2	Xs16m22.162–Xwhs2001-1D	FHB severity		Cansas × Ritmo, 94 RIL	Fusarium culmorum, SPRAY: 4 field exp.	[65]
Cansas	7BS	11	Xgwm46–Xe42m58.394	FHB severity		Cansas × Ritmo, 94 RIL	Fusarium culmorum, SPRAY: 4 field exp.	[65]
Hussar	1 A	9.7	Xs26m12.188	FHB severity	plant height	G16-92 × Hussar, 136 RIL	Fusarium culmorum, SPRAY: 4 field exp.	[66]
G16-92	2BL	14.1	Xgwm501–Xgwm47	FHB severity		G16-92 × Hussar, 136 RIL	Fusarium culmorum, SPRAY: 4 field exp.	[66]
Triticum durum cv. 'Strongfield'	2BS	26	Xwmc474–Xwmc175	FHB spread		Blackbird × Strongfield, 85 DH	Fusarium graminearum, SFI: 1 greenhouse exp.	[67]
Triticum carthlicum cv. 'Blackbird'	6BS	23	Xgwm518–Xbarc125	FHB spread		Blackbird × Strongfield, 85 DH	Fusarium graminearum, SFI: 1 greenhouse exp.	[67]
AQ24788-83	1AS	6.5	IWB63682	FHB severity	plant height and fowering date	Luke×AQ24788-83, 154 RILs	Fusarium graminearum, Spray: Field	[68]
Luke	5AS	9.8	IWA7777	FHB severity	plant height and fowering date	Luke×AQ24788-83, 154 RILs	Fusarium graminearum, Spray: Field	[68]
Ji5265	2DL	29.8	GBS12056–GBS19302	FHB spread		Ji5265 × Wheaton,179 RILs	Fusarium graminearum,SFI,greenhouse experiments	[69]
Ji5267	6BL	5.8	GBS27681–GBS25473	FHB spread		Ji5265 × Wheaton,179 RILs	Fusarium graminearum,SFI,greenhouse experiments	[69]
Ji5270	2AS	4.7	GBS8222–GBS22105	FHB spread		Ji5265 × Wheaton,179 RILs	Fusarium graminearum,SFI,greenhouse experiments	[69]

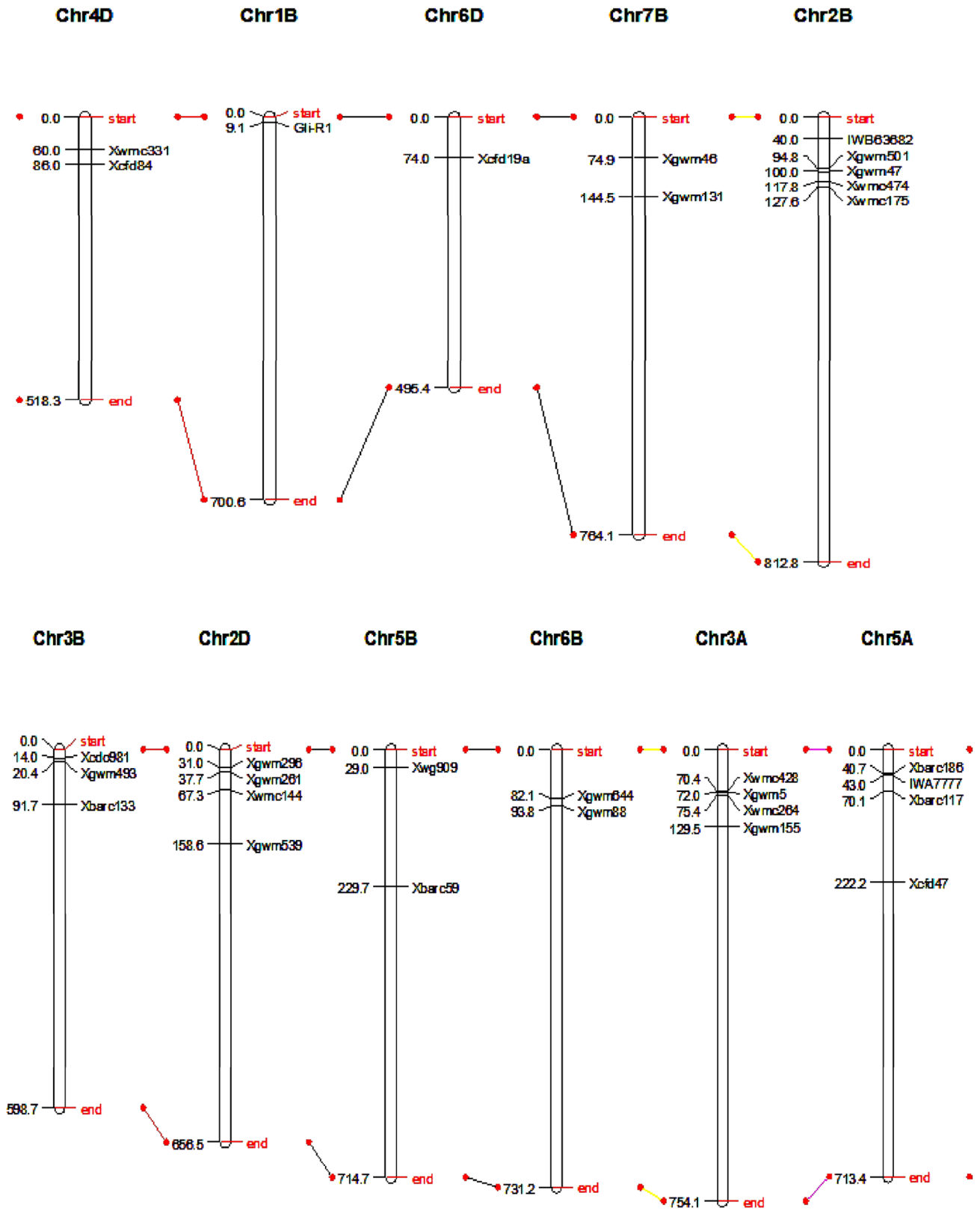

Fig. 3 A physical map of the quantitative trait loci (QTLs) identified for FHB resistance in Wheat germplasm by GWAS technique, as well as their distribution across the various chromosomes

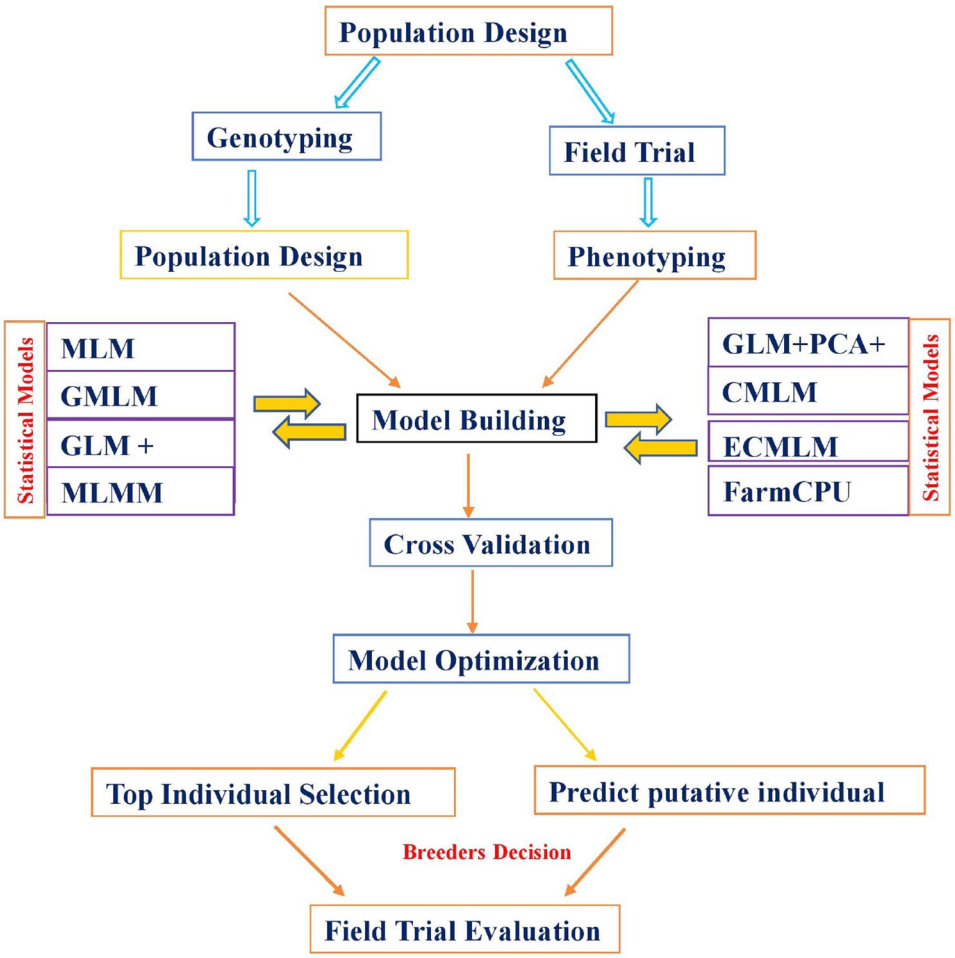

Fig. 4 A diagrammatic representation of genome-wide association studies (GWAS) and genomic selection (GS), as well as the selection of germplasm lines and the use of statistical models for predicting GEBVs values, field-based analysis, and genotyping

regression models are typically employed in GWAS to test for associations. To account for stratification and eliminate confounding effects from demographic characteristics, covariates such as age, sex, and ancestry are added, with the caveat that this may impair statistical power for binary traits in ascertained samples. However, adding an additional individual-specific random effect linear or logistic mixed model to account for genetic relatedness among individuals might improve statistical power for discovery of variants that might be associated with a particular trait or disease. Furthermore, it is important to remember that genotypes of genetic variants that are physically close together are not independent because they are in linkage disequilibrium; this test dependency should be considered as well while performing GWAS.

The following equation depicts the linear regression model for testing the association between a marker and the studied trait:

$$Y \sim X\alpha + Z_s\beta_s + e$$

$$e \sim N\left(0, \sigma_e^2 I\right)$$

where Y is a vector of phenotype values, X is a matrix assigning records to phenotypes fixed effect, α is a corresponding vector of fixed effects sizes (e.g., the mean, population structure effects, and age), Z_s is a vector of genotype values for all individuals at genetic variations, σ_e^2 is the corresponding fixed effect size of genetic variants, β_s measures residual variance and I is an identity matrix.

There are numerous statistical models to find associations between marker loci and a variety of traits, ranging from simple to highly complex. Accurate decoding of complex traits in diverse populations requires more comprehensive statistical models that address false positives using the background information of genotypes. At the same time, the number of false negatives due to overcorrection is checked. Confounding effects due to population structure and kinship, i.e., relationship among individuals is considered by further using these covariates in the statistical model. STRUCTURE [75], PCA [76], and a discriminant analysis of principal components (DAPC) [77] are methods for determining population organization by using the information of genetic

markers. Furthermore, false positives aroused due to common ancestry and family relatedness can be efficiently addressed by incorporating a kinship matrix into the statistical model. One of the most often used such methods for estimating family relatedness among individuals in a diverse population is IBS, i.e., identity-by-state [78].

A typical method for reducing false positives is to use population structure (Q) and a kinship matrix (K) as variables in mixed linear models (LMMs). Since [79] published the first MLM of association mapping, several MLM-based techniques have been introduced [80]. However, MLM-based models may result in an increased number of false negatives, which may lead to the omission of certain potentially valuable associations [81]. False negative associations may arise during multiple comparison adjustments for evaluating statistical significance. Multiple comparison approaches are available in relation to association mapping for determining the significance threshold in the literature, of which the false discovery rate (FDR) [82] and Bonferroni correction [83] are most commonly used for determining the significance threshold. However, a very stringent threshold might result in a high rate of false negatives. As a result, proper care should be taken while selecting statistical models and thresholds, as they are crucial steps in detecting true trait-specific markers that may be located inside or in high LD with genes that govern trait variation while minimizing both false-positive and false-negative associations.

These models are all referred to as single-locus models because they perform a one-dimensional genome scan by examining one marker at a time and then repeating the whole procedure for each marker in the dataset. However, the true genetic model for complex traits that are governed by multiple loci at the same time cannot be completely explained by single locus models. Multilocus association mapping models have been suggested as a solution to this problem since they accept the input from multiple loci simultaneously [84].

Some popular models for GWAS include the following:

(1) Analysis of variance (ANOVA).

(2) General linear model (GLM).

(3) GLM with principal component analysis (GLM + PCA).

(4) MLM with principal component analysis and Kinship matrix for family relatedness estimates (GLM + PCA + K) [79].

(5) Compressed MLM (CMLM) [80].

(6) Enriched compressed MLM (ECMLM) [85].

(7) Settlement of the MLM under a progressively exclusive relationship (SUPER) [86].

(8) Multiple loci MLM (MLMM) [87].

(9) Fixed and random model circulating probability unification (FarmCPU) [81].

Models listed from (1) to (7) are single locus models, while (8) and (9) are multi locus models. Furthermore, single-locus models, such as the general linear model (GLM) and the mixed linear model (MLM), require multiple tests that undergo an FDR, Bonferroni correction [88] or other matrices for multiple comparison adjustments. The typical FDR or Bonferroni correction is often too conservative, which results in many important loci associated with the target traits being eliminated as they do not satisfy the stringent criterion for significance test. Multilocus models are better alternatives for GWAS, as they do not require such adjustments, and thus more marker−trait associations may be identified. Recently, several new multilocus GWAS models, such as multilocus RMLM (mrMLM, [84], fast multilocus random-SNP-effect EMMA (FASTmrEMMA, [89], and iterative modified-Sure independence screening EM-Bayesian LASSO (ISIS EM-BLASSO, [90], and few more efficient models have been developed.

Genomic selection (GS), a promising tool to recognize Fusarium wheat-pathosystem

Genomic selection (GS), a form of marker-assisted selection that was first presented by complete it. [91], uses genetic markers that span the entire genome to ensure that all loci for quantitative traits are in linkage disequilibrium with at least one marker. In this study, an individual's Genomic Estimated Breeding Values (GEBVs) were calculated using genotypic data from every marker in the genome. A training population must be created for every successful GS programme so that individuals, lines, and varieties may be genotyped for genomic markers dispersed throughout the whole genome and should be representative of the entire population. The training individuals are further put through comprehensive phenotyping for the desired underlying trait. Using phenotype as a response and genotype as an independent variable, the information about genotype and phenotype is utilized to build an appropriate statistical model. Some of the training data may also be used to validate the fitted model. GEBVs of the individuals of the breeding population (where only information of genotyped individuals is available with no phenotypic records) are calculated using their genotyped information, where the marker effect is estimated from the developed model. Ultimately, individuals/line/variety from the breeding population can be selected based on the superiority of their estimated value of GEBVs. The whole process of genomic selection can be better understood through Fig. 4.

Statistical methods for implementing genomic selection

A simple linear model, sometimes also referred to as least squares regression or simple least squares regression (OLS), is the first step in the GS process of selecting the appropriate candidates.

$$Y = 1_n\mu + X\beta + \varepsilon$$

where

Y = $n \times 1$ vector of observations; μ is the mean; $\beta = p \times 1$ vector of marker effects; $\varepsilon = n \times 1$ vector of random residual effects; X =design matrix of order $n \times p$ (where each row represents the genotype/individuals/lines (n) and column corresponds to marker (p),$\varepsilon \sim N\left(0, \sigma_e^2\right)$

One major problem in linear models using several thousand genome-wide markers is that the number of markers (p) exceeds the number of observations (n), i.e., genotype/individuals/lines, which creates the problem of over parameterization (large 'p' and small 'n' problem (p > > n)). To solve the large 'p' and small 'n' problem, one alternative is to use a subset of the significant markers. For this purpose, [91] used a modified version of least squares regression. However, during this process, we may end up losing some crucial marker information. Consequently, utilizing ridge regression (RR), a penalised regression-based method, is an effective way to address the over parameterization issue in linear models [91]. Additionally, it addresses multicollinearity issues (i.e., correlated predictors, e.g., SNPs or markers). Similar to penalised regression, the least absolute shrinkage and selection operator (LASSO) [92, 93] employs the l1 penalised least squares criteria to obtain a sparse solution. Most statistical models assume that each marker contributes equally to variation, even though this is not true for all traits. As a result, it is important to predict the variation in the markers depending on the genetic architecture of the trait. For this purpose, several Bayesian models have been proposed where it is assumed that there is some prior distribution of marker effects, e.g., Bayes A, Bayes B, Bayes Cπ and Bayes Dπ [91, 92, 93, 94]. Apart from this, best linear unbiased prediction (BLUP), which is based on a mixed-model approach, is one of the most commonly used genomic prediction techniques in traditional and advanced animal and plant breeding studies [64 – 60]. However, the performance of the genomic prediction models discussed above performs well for traits with simple genetic architecture, i.e., additive, but their performance becomes very poor in the case of complex genetic architectures, i.e., additive, epistatic, and their interaction. In such cases, a model-free approach, i.e., nonparametric models, is more suitable [95]. A nonparametric statistical model in relation to genomic prediction has been used, e.g., the NW (Nadaraya-Watson) estimator [95], RKHS (Reproductive Kernel Hilbert Space) [96], SVM (support vector machine) [97] ANN (Artificial Neural Network) [95] and RF (Random Forest) [98].

The methods outlined previously in this section are based on single-trait genomic selection (STGS), i.e., models consider the information of each trait independently. However, in such situations, we may lose some additional information, e.g., high correlation among the traits and pleiotropic effects of genes, if available. In such cases, multi-trait genomic selection (MTGS)-based methods may provide more accurate GEBVs and subsequently higher prediction accuracy [99, 100, 101, 102]. Number of MTGS-based methods have been studied in relation to GS, e.g., MRCE (Multivariate Regression with Covariance Estimation) [103], Multivariate mixed model approach [104105), Bayesian multitrait model [104], and cGGM (conditional Gaussian Graphical Models) [104106]. Recently, multi-trait and multi-environment models have also been implemented in real and empirical studies and have reported higher prediction accuracy [107, 108].

GWAS/GS: implemented to understand Fusarium durum pathosystems

The demand for staple food crops will rise tremendously with the increasing world population by 2050 [109]. Bread wheat (*Triticum aestivum*) is a major staple crop globally, and its ally Durum wheat is the second largest cultivated and consumed crop worldwide for its pasta and macaroni [5]. The enhancement in Fusarium infestation is likely due to the expansion in the conserved tillage practices, use of pathogen-susceptible wheat genotypes, and utmost climate change in small grain cereals [110]; however, various advances in cultural practices have been employed to detect such a devastating pathosystems [111] but still uncover resistant genotypes, which is the most effective and sustainable approach in crop breeding against such deleterious pathogens. Wild germplasm, especially tetraploid wheat, is a rich source of deployable resistance genes; however, the complex host pathogen system makes it utilizable for crop improvement programs [110]; however, selecting robust resistant genotypes from large genetic resources is challenging. The pathogen is largely inherited quantitatively and fluctuates by host genotype and environment; however, in such cases, genomic selection is an advanced tool that provides comprehensive prediction accuracy; however, its accuracy for genomic selection footprints revolves around large factors, such as the genetic architecture of requisitioned traits, the number of questioned traits, and the utmost use of significant statistical models for concerned traits [110]. It also provides genetic breeding value, which acts as a selection marker for preferred genotypes with superior resistance.

Fusarium DON toxin and its management

The genetically complex resistance mechanisms for FHB are alarming and need to be tackled with timely consideration of wheat growth and utility; furthermore, the genotype vs. environment interaction has additive effects on disease severity [112]. Fusarium infestations not only reduce grain quantity but also quality to a large extent through the secretion and accumulation of toxin, specifically deoxynivalenol (DON), zearalenone (ZEN), HT-2, and T-2, which negatively affect seed quality, resulting in a dreadful situation for animal and human health [113, 114]. The resistance mechanism of cereal hosts against Fusarium has been broadly classified into six categories based on pathogenesis and disease cycle. Crop residues may harbour primary inoculum in the form of perithecia and sporodochia (1) initially, type I resistance for initial infection by the pathogen/pathotypes; (2) infection followed by spreading to nearby tissues is considered type II resistance (3) type III resistance for kernel infection (4) type IV resistance exhibited against toxin secretion and its accumulation on kernels, and (5) type V displayed for tolerance [115]. Although numerous quantitative trait loci (QTL) have been explored against multiple pathotypes of Fusarium in wheat and other cereal crops with different enormities of consequences [74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117]. A QTL and its effect across multiple environments are thought to be stable, indicating greater practical breeding efficiency than minor ones. However, in the context of this devastating pathogen, only a few notable and stable QTLs have been identified so far. One preeminent locus identified as Fhb1, from Chinese wheat Wangshuibai and Sumai 3 which was detected on chromosome 3BS, is one of the best characterized locus with a major additive effect and stable resistance. Fhb1 was reported as a pore-forming toxin-like gene (PFT) QTL [117].

Notably, only a few cultivars were found to have moderate resistance to immune, suggesting that resistance genes other than *fhb1* could be present. These were identified in the middle to lower Yangtze River include Yangmai11, 12, 16, 23 and 158. These genotypes have been approved to be released and become main producing cultivars [118]. In majority of cultivars, which belongs to Yangmai series do not carry and transmit the *Fhb1* locus to progeny [10], indicating that alternative resistance providing elements or cascade may be present in these cultivars and could be easily applied to breeding against such noxious diseases. Exploration of more Fusarium-resistant wheat germplasm for disease-resistant breeding programs, as well as their use in generating Fusarium-resistant loci and their association with trait discovery, is therefore critical for breeding wheat varieties with robust Fusarium resistance.

Implications in breeding for FHB

Wheat is one the most important cereal crops in the world. Wheat covers the maximum agricultural land of the world and supplies 20% of nutritional needs to the world population. Research efforts on FHB resistance breeding in durum wheat is comparatively lower than bread wheat (*T. aestivum*) due to less area of cultivation and production quantity. This makes, developing resistant cultivars for FHB is a challenging task in durum wheat. Screening wild germplasm (particularly tetraploid species) and landraces for FHB, identification of novel genomic regions/QTLS using high throughput techniques (GWAS and GS) and introgression in elite backgrounds are the most optimistic approaches in FHB breeding.

Conclusion and future directions

This review provides a thorough overview of the current status and future developments in FHB management strategies, its etiological agent, and its impact on wheat productivity through the integration of advanced genomic tools, including association mapping, GWAS and GS. Using genomic methods, it is possible to identify candidate genes, genomic areas, and marker data for a variety of qualitative and quantitative features. In addition, developing elite disease-resistant cultivars requires a better understanding of host immune defense against pathogens. Therefore, using cutting-edge genomic tools will provide novel information about the function of fungal virulence factors and help us to understand the interactions between Fusarium and its hosts. To meet the future food demands of the expanding global population, we anticipate that these tools will further assist in the development of elite resistant cultivars with high yields. Additionally, FHB DON toxin is a major concern for wheat export and cultivation. Early detection and management will reduce the risk of contamination because DON is a carcinogen and has health-related complications in both humans and animals.

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Declarations

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