Sensitivity genes in wheat and corresponding effector genes in necrotrophs exhibiting inverse gene-for-gene relationship

Pushpendra Kumar Gupta (pkgupta36@gmail.com)
CCS University https://orcid.org/0000-0001-7638-6171
Neeraj Kumar Vasistha
Eternal University Akal College of Agriculture
Pawan Kumar Singh
CIMMYT: Centro Internacional de Mejoramiento de Maiz y Trigo

Research Article

Keywords: Wheat, pathogens, sensitivity genes, resistance genes, necrotrophic effectors, PR proteins

Posted Date: March 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-223024/v1

Abstract

In wheat, genes for resistance (R) as well as susceptibility (S) are now known for several diseases. The S genes also include sensitivity genes like *Tsn1* in wheat. R genes follow a gene-for-gene (GFG) relationship and generally involve biotrophs and S genes particularly sensitivity genes, follow an inverse gene-for-gene relationship (IGFG), generally involving necrotroph or hemi-biotroph pathogens. The toxin (virulence factor) genes of the pathogen and the corresponding sensitivity genes have been described in some detail for the following three pathogens: (i) *Paratagonospora nodorum* (causing Septoria nodorum blotch or SNB); (ii) *Pyrenophora tritici-repentis* (tan spot) and (iii) *Bipolaris sorokiniana* (spot blotch). These and some other pathogens produce several necrotrophic effectors (NEs), which interact directly or indirectly with the products of S genes in the host and produce disease symptoms like necrosis and/or chlorosis. In this article we present a critical review of all the relevant information about the interactions between NEs of the above three pathogens and the corresponding S genes in wheat. The gaps in knowledge and possibilities for future research are also discussed.

Introduction

Wheat (*Triticum aestivum* L.) is the third most important staple food crop worldwide (first two being maize and rice), sometimes also consumed as animal feed (Mauseth 2014). Among cereals, wheat has been estimated to occupy maximum cultivated land area, which was 215.2 million hectares in 2019, giving 22% of the total cereal grain production (FAO 2020). The total global production of wheat grain was 732 million tonnes during 2018-19 (FAO 2019) and ~763 million tonnes in 2019-20 (FAO Release May 7, 2020); in terms of global cereal production, this production level is next to only maize (FAO 2019).

Wheat production is significantly reduced by various biotic and abiotic stresses. The biotic stresses mainly include pathogens like fungi, viruses, bacteria, nematodes, etc., which cause a variety of diseases Among these pathogens, fungal pathogens are alone responsible for 15-20% losses in yield (Figueroa et al. 2018). The fungal diseases include rusts, mildew, blast, bunts, blights, etc. Among these diseases, the diseases caused by necrotrophs and hemi-biotrophs include Septoria nodorum blotch or SNB (*Parastagonospora nodorum*), tan spot (*Pyrenophora tritici-repentis*) and spot blotch (*Bipolaris sorokiniana*) (Fig. 1). A summary of necrotrophs and hemi-biotrophs causing different diseases in wheat is presented in Table 1.

The genetics of disease resistance has been worked out in some detail, not only for diseases caused by biotophs, but also for those caused by necrotrophs and hemi-biotrophs. In case of biotrophs, mainly R genes/QTLs in the host provide resistance, but in case of some necrotrophs, the disease is facilitated by the presence of one or more sensitivity (S) genes in the host, and corresponding virulence genes in the pathogen. The necrotrophic effectors (NEs) encoded by the virulence genes of the poathogen interact directly or indirectly with the product of the dominant sensitivity genes of the host leading to necrosis and/or chlorosis (Tan et al. 2010; Oliver et al. 2012). The biotrophs cause cell death leading to hypersensitive reaction (HR) that is responsible for resistance, due to non-availability of living tissue as food and thereby restricting the pathogen multiplication and growth in the plant (Faris et al. 2010; Liu et al. 2012). The necrotrophs, on the other hand, feed on the dead cells leading to the so-called NE-triggered susceptibility, so that resistance is generally (but not always) achieved through elimination of these dominant sensitivity genes or using their recessive resistant alleles. The differences between biotrophs and necrotrophs are listed in Table 2.

It has been shown that a gene-for-gene (GFG) relationship proposed by Flor (1942) holds good between a R gene of the host and a matching Avr gene in the pathogen, because in the absence of a matching Avr gene in the prevalent race of the pathogen, R gene can not function and provide resistance (Fig. 2a). In contrast, an inverse gene-for-gene (IGFG) relationship holds good for sensitivity genes in case of necrotrophs, because a virulence gene does not provide a

compatible interaction in the absence of a corresponding sensitive gene in the host (Fig. 2b; McDonald et al. 2018; Navathe et al. 2020).

In addition to R genes in case of biotrophs and S genes in case of necrotrophs, quantitative trait loci (QTLs) have also been identified for disease resistance against all pathogens including biotrophs, necrotrophs and hemi-biotrophs. These QTLs have been identified using interval mapping involving different types of mapping populations. Association panels for genome-wide association studies have also been used for identification of marker-trait associations (MTAs; Ruud et al. 2019; Francki et al. 2020). In some cases, a QTL identified through interval mapping may also overlap a resistance R gene as shown in case of *Sb1-4* for resistance against *B. sorokinina* (Gupta et al. 2018). The relative roles of QTLs/R genes and the sensitivity genes has also been assessed and it was shown that QTLs/R genes are the major source of resistance against both biotrophs and necrotrophs, while individual sensitivity genes do not play a major role, particularly for the disease SNB (Cowger et al. 2020), although all sensitivity genes together might play a significant role.

The present review is intended to provide an overview of the dual system of resistance against necrotrophs in wheat, involving GFG for R genes and IGFG involving sensitivity genes, with major emphasis on IGFG. While doing so, we recognize that the work involving GFG is widely known and regularly reviewed. Therefore, in this review, we include a relatively detailed but only a brief account of available information on three pathosystems involving necrotrophs and hemi-biotrophs, where the disease is caused by an interaction between NEs encoded by virulence genes of the pathogens and the proteins encoded by the corresponding sensitivity genes in the host. A relatively detailed account is presented for two diseases, namely SNB and tan spot, where extensive work has been undertaken and a brief account of spot blotch, where only limited literature is available. The review may prove useful for both pathologists and geneticists/plant breeders.

Sensitivity/susceptibility genes in wheat (e.g., *ToxA*-*Tsn1* system)

The identification of sensitivity genes in wheat (including *Tsn1*) as above, and the susceptibility (S) SWEET genes in rice and several other crops created a new area of plant immunity research, which is attracting increased attention of both breeders and pathologists world-over. SWEET genes are not covered in this review, but a summary on SWEET genes and disease resistance is available in a brief article recently published (Gupta 2020). Sensitivity genes, which are independent of dominant R genes, have been identified in wheat for several diseases. These genes are generally dominant in nature and are utilized by the pathogens for a compatible interaction. Recessive alleles or 'loss of function' alleles of these sensitivity genes impart resistance to the host. In the literature, the words sensitivity and susceptibility have sometimes been used interchangeably. For instance, the sensitivity gene *Tsn1* located on wheat chromosome arm 5BL has sometimes been described as susceptibility gene (Friesen et al. 2008). Sensitivity, however, should not be confused with susceptibility, since sensitivity refers to response of the host against a specific NE, while susceptibility means compatible interaction between the host and the pathogen.

The major sensitivity genes in wheat include *Tsn1*, *Tsc1*, *Tsc2* and seven Snn genes (*Snn1* to *Snn7*), which render the host susceptible to a few diseases including SNB, tan spot and spot blotch (Effertz 2002; Friesen and Faris 2004; Faris et al. 2013; Francki 2013; Gao et al. 2015; Navathe et al. 2020). Therefore, resistance against diseases caused by sensitivity genes can be achieved either through elimination of the dominant sensitivity genes or replacing them by alternative recessive alleles. This situation provides for yet another system of disease resistance in addition to the two other systems of disease resistance available for diseases as above. Among these two other systems, one involves dominant R genes and the other involves quantitative resistance loci (QRLs) These two additional classes of genes may not be exclusive, as demonstrated through Mendelization of some QTLs (Kumar et al. 2015). The genes from the above three systems can be pyramided for developing durable and broad-spectrum resistance against diseases (Engler et al. 2005; Navathe et al. 2020).

As many as ~60 genes encoding NEs have been identified for different pathosystems involving necrotrophs (Sperschneider et al. 2018). At least 13 of these NEs in three different pathosystems (8 for SNB, 4 for tan spot and 1 for spot blotch) involving wheat as the host have already been identified and subjected to detailed studies (Friesen et al. 2006, 2008, 2009, 2012; Chu et al. 2010; Faris et al. 2011; Waters et al. 2011; Abeysekara et al. 2012; Crook et al. 2012; Liu et al. 2012; Oliver et al. 2012; Shi et al. 2015; McDonald and Solomon 2018). Horizontal transfer of genes (HGT) encoding NEs from *P. nodorum* to other pathogens has also been demonstrated (Friesen et al. 2006; McDonald et al. 2019).

For wheat, NEs and sensitivity genes involved in the three different pathosystems have been studied in some detail (Fig. 3). The chemical nature of several NEs has also been worked out showing that all NEs are proteinaceous in nature, except ToxC associated with tan spot (*P. tritici-*repentis), which is a polar non-ionic metabolite with low molecular weight, although not fully characterized so far (Effertz et al. 2002; Wegulo 2011). Details of major host-pathogen interactions involving the three pathogens included in this review are summarized in Table 3.

The basic outline of the mechanism involved in compatible/incompatible interactions involving IGFG is now known. Details for individual pathosystems have also been worked out in some cases. The degree of correlation between the level of NE proteins and expression of related sensitivity genes has also been worked out using a number of wheat cultivars; these correlations were also related with field resistance (Tan et al. 2014). In case of tan spot and spot blotch, it has been shown that a clear dominance of interaction between individual NE with corresponding sensitivity gene can cause a disease (e.g., ToxA/ *Tsn1*; Moffat et al. 2014). It has also been reported that all current cultivars grown in Western Australia are sensitive to at least one of the following three SNB NEs: SnToxA, SnTox1 and SnTox3 (Tan et al. 2015). IGFG relationship between sensitivity gene *Tsn1* of the host and *ToxA* gene in *B. sorokiniana* has also been demonstrated recently in several countries including Southern USA, Australia, India, and Mexico (Friesen et al. 2018; McDonald et al. 2018; Navathe et al. 2020; Wu et al. 2020).

Pathosystems involving sensitivity genes in wheat

The available literature on plant immunity largely deals with resistance R genes, such that thousands of R genes are now known for resistance against many diseases in plants. For instance, ~80 Lr genes are now known in wheat for resistance against leaf rust alone. With the availability of whole genome sequences for majority of crop plants (including wheat), we now also know that the number of R genes in a crop like wheat can be as large as >1300 (GrainGenes; https://wheat.pw.usda.gov/GG3/).

A number of sensitivity genes have been identified for several diseases caused by necrotrophs or hemi-biotrophs. Sometimes, the same sensitivity gene may function not only for different isolates of the same pathogen, but also for more than one disease. For instance, *Tsn1* functions as a sensitivity gene for at least three diseases, namely SNB, tan spot and spot blotch (Faris et al. 2010; McDonald et al. 2018; Navathe et al. 2020). A summary of interactions involving the above three necrotrophs/hemi-biotrophs causing diseases in wheat is provided in Table 3. However, sensitivity genes in wheat have been identified only for three of the ten necrotrophs/hemibotrophs listed in Table 1. In future, sensitivity genes may also be discovered for other diseases caused by necrotrophs/hemibiotrophs, including Fusarium head blight (FHB), which is one of the most important diseases of wheat causing major losses in yield in wheat (Hales et al. 2020). For necrotrophs, where wheat sensitivity genes are already known, additional sensitivity genes may also be discovered in future.

In this section of the review, we first describe genes encoding different NEs and the corresponding sensitivity genes for each of the three pathosystems. The recessive alleles of these sensitivity genes provide resistance, but there are also R genes and QTLs which function independently of the sensitivity genes, so that the recessive alleles of sensitivity genes can be deployed along with R genes and QTLs in order to achieve improved resistance against diseases like SNB, tan spot, and spot blotch.

Effector-assisted breeding is also being recommended for disease resistance. This has become possible due to the availability of genome-wide catalogue of effectors (effectoromics) for various pathogens, which can be utilized either through MAS-assisted classical resistance breeding or through transgenic approach. The available literature on effector-assisted breeding has been reviewed by Vleeshouwers and Oliver (2014). The details of sensitivity genes, which can be utilized for future wheat breeding, along with R genes and QTLs for resistance against different diseases are listed in Table 4.

Parastagonophora nodorum-wheat pathosystem

SNB occurs in warm and humid areas of the world causing yield losses of up to 30% (Bhathal et al. 2003); the disease includes both leaf blotch and glume blotch (Fig. 1a). Currently, no cultivar is available with complete resistance/immune reaction to SNB. Therefore, tillage, crop rotation and chemical control are still utilised as disease management practices for control of this disease. *P. nodorum*-wheat pathosystem is also the most extensively studied pathosystem involving necrotrophs, such that *P. nodorum* is also used as a model necrotroph for the study of host-pathogen interactions involving sensitivity genes.

P. nodorum genome is 37 Mb in size with 23 chromosomes. Whole genome sequencing of pathogen has been undertaken for a number of isolates of this pathogen, which include the following: (i) one isolate (SN15) (Hane et al. 2007); (ii) three other isolates, (SN4, SN2000, SN79-1087) (Richards et al. 2018) and (iii) 197 isolates collected from spring, durum, and winter wheat producing regions of USA. The number of genes in this pathogen was initially reported to be 10,762 (Hane et al. 2007), but later revised in two different studies to be 13,569 (Syme et al. 2013, 2016) and 13,379 (Richards et al. 2018). A pan-genome for *Parastagonospora spp* was also developed using genome sequences of 33 different isolates (including 21 isolates of *P. nodorum*), showing wide range of structural variations (SVs), thus providing a resource for the prediction of novel NEs (Syme et al. 2018). It was also shown that different isolates carry genes encoding different NEs. Isolates like SN79-1087 with no known gene encoding NE have also been reported (Richards et al. 2018).

In a more extensive recent study, Richards et al. (2019) conducted whole genome sequencing for 119 isolates to examine effector diversity and to identify genomic regions that are subject to selection pressure specific to populations defined by geographical regions.

NE genes, sensitivity genes and interactions: Following nine interactions involving nine wheat sensitivity genes and eight *P. nodorum* NEs are known (Haugrud et al. 2019). (i) *Tsn1*- SnToxA (Friesen et al. 2006, 2009; Liu et al. 2006; Faris and Friesen 2009; Zhang et al. 2009; Faris et al. 2010, 2011), (ii) *Snn1*-SnTox1 (Liu et al. 2004a, b, Liu et al. 2012; Reddy et al. 2008; Shi et al. 2016b), (iii) *Snn2*-SnTox2 (Friesen et al. 2007, 2009; Zhang et al. 2009), (iv) *Snn3-B1*-SnTox3 (Friesen et al. 2008; Liu et al. 2009; Shi et al. 2016a), (v) *Snn3-D1*-SnTox3 (Zhang et al. 2011), (vi) *Snn4*-SnTox4 (Abeysekara et al. 2009, 2012), (vii) *Snn5*-SnTox5) (Friesen et al. 2012), (viii) *Snn6*-SnTox6 (Gao et al. 2015) and (ix) *Snn7*-SnTox7 (Shi et al. 2015). Among these nine interactions, the first, second and fourth (*Tsn1*- SnToxA*, Snn1*-SnTox1, *Snn3-B1*-SnTox3) have been subjected to relatively detailed studies, because the sensitivity genes and the NE genes involved in these interactions have all been cloned and characterized. A possibility of another unconfirmed interaction (*Snn8*-SnTox8) has also been suggested (Faris et al. 2008).

The interaction of each NE with the product of a specific sensitivity gene, as above, leads to programmed cell death, which allows the corresponding necrotroph to gain nutrients, sporulate and cause the disease (See et al. 2019). The interactions have also been shown to be additive in nature, sometimes also exhibiting epistatic interactions, particularly in the following three interactions: (i) *Snn2-SnTox2* (Friesen et al. 2007), (ii) *Snn3-SnTox3* (Friesen et al. 2008; Phan et al. 2016) and (iii) *Snn5*-SnTox5 (Friesen et al. 2012). However, the role of epistatic interactions in the expression of these interactions is rather limited (Phan et al. 2016).

It has also been shown that, several QTLs also occur in addition to major sensitivity genes. However, the absence of one or more sensitivity genes or presence of their recessive alleles provide disease resistance. The importance of the absence of sensitivity gene in providing resistance relative to that due presence of R genes and QTLs has been shown to be rather limited (see review by Cowger et al. 2020; also see later in this review).

Distribution of NE genes in the pathogen. The distribution of each of the eight NE genes and nine sensitivity genes differs in different wheat growing regions of the world, although data is available mainly from USA, Europe (including UK and Norway) and Australia. Distribution of three NE genes, namely *SnToxA*, *SnTox1* and *SnTox3* has been examined in several studies. Some details of the distribution reported in these studies are summarized in Table 5, which suggest that the gene *SnTox1* is the predominant gene, which is reported to occur in 95.4% of natural populations in USA (as above) and 84% isolates worldwide; these frequencies are not very different from the frequencies of the occurrence of the corresponding sensitivity gene *Snn1* gene in wheat, which has also been reported to be 85% (McDonald et al. 2013).

The predominance of *SnTox1* as above, was not universal, as apparent from the following two reports on SnToxA, where isolates were screened for NE genes. (i) Among Australian isolates, 71 (97%) of 73 isolates (collected from only one field) carried *SnToxA* (Stukenbrock and McDonald 2007; McDonald et al. 2013). This was attributed to the biased sample from a single field and may not represent the situation in whole of Australia (Oliver et al. 2009). (ii) In a diverse sample of 165 *P. nodorum* isolates, from Norway and 9 isolates from other countries, *SnToxA* was found to occur with high frequency in Norwegian *P. nodorum* isolates relative to other parts of Europe, suggesting that *SnToxA* gene is the major virulence factor in Norway (Lin et al. 2020). The disease reaction in interaction *Snn1*-SnTox1 has been observed to range from 0 to 58% and seems to depend on both, the genetic background of the host and that of the pathogen (Liu et al. 2004a; Chu et al. 2010; Phan et al. 2016).

Distrubution of sensitivity genes in the host Surveys were also conducted for distribution of different sensitivity genes in wheat cultivars. Some of the available data for distribution of three major sensitivity genes is summarized in Table 6. These results suggest that *Snn1* is not an important sensitivity gene for US wheat programs; instead, *Tsn1* is important for hard winter wheats only, while *Snn3* is important for both soft and hard wheats.

Sensitivity of individual resistant and susceptible cultivars against specific NEs was also examined. For this purpose, NEs were obtained from transgenic *E. coli* and *Pichia pastoris*. (i) In a study conducted in USA, 25 susceptible wheat cultivars (many from SE USA) and a resistant cultivar (NC-Neuse) were tested against different NEs isolated from 37 isolates from different regions of SE USA. It was found that all susceptible cultivars were sensitive to at least one NE, and that the resistant cultivar (NC-Neue) was sensitive to none. Among susceptible cultivars, 32% contained sensitivity gene *Tsn1* and 64% contained sensitivity gene *Snn3*. None was sensitive to *SnTox1*. (ii) In a panel of 480 northwest European varieties (~330 were from the U.K.), sensitivity to SnTox3 (presence of *Snn3*) was higher than that to SnTox1, while sensitivity to SnToxA (presence of *Tsn1*) was rare (Downie et al. 2018). (iii) In 157 Scandinavian spring wheats (including Norwegian, Swedish and CIMMYT lines), sensitivity to SnToxA (presence of *Snn1*) was present in 45% wheats (Ruud et al. 2018).

Use of multiple sensitivity genes. Wheat genotypes with multiple sensitivity genes were also identified. These genotypes produce significantly higher disease reactions relative to those harbouring only a single sensitivity gene (Friesen et al. 2007). Such studies with multiple sensitivity genes need to be conducted for characterization of wheat cultivars in different parts of the world, so that we know the identity of sensitivity genes present in wheat cultivars. Results of these studies can be used to discard out parents harbouring sensitivity genes when breeding for resistance to SNB.

Use of multiple isolates. In a recent study, multiple isolates of the pathogen were used to evaluate the effects of the following three host gene-NE interactions individually and in various combinations: (i) *Tsn1-SnToxA*, (ii) *Snn1-SnTox1*, and (iii) *Snn3-B1-SnTox3*. These results suggested that the IGFG interactions leading to 'NE-triggered susceptibility' in wheat-*P.*

nodorum pathosystem vary in their effects depending on the genetic backgrounds of the pathogen and the host, and that the interplay among the interactions is complex and intricately regulated (Mebrate and Cooke 2001).

Some information is also available regarding distribution of sensitivity genes in wheat genotypes used for cultivation in UK and Europe. It was shown that the host may carry one or more sensitivity genes along with R genes, the latter with a major effect. In wheat, one or more sensitivity genes (present along with R genes and QTLs) produce disease phenotype ranging in severity from 22 to 95% (Sharma 2016). *SnToxA* gene seems to resemble *PtrToxA* gene in its interaction with the sensitivity gene *Tsn1*, which is involved in all the three diseases including tan spot, SNB and spot blotch (Faris et al. 1996; Haen et al. 2004; Liu et al. 2006).

Transcription factors regulating sensitivity gene-NE interactions. Three interactions mentioned above, namely *Tsn1*-SnToxA, *Snn1*-SnTox1 and *Snn3-B1*-SnTox3 have also been shown, each to be positively regulated by the transcription factor Zn2Cys6 of PnPf2 zinc finger family (Tan et al. 2019). Another transcription factor is SnStudA that regulates the central carbon metabolism, mycotoxin production and effector gene expression in *Snn3-B1*-SnTox3 interaction (Ipcho et al. 2010). The target of this transcription factor is WMGGVCCGAA motif and the associated genes were shown to be involved in downregulation for plant cell wall degradation and proteolysis; the genes associated with redox control, nutrient and ion transport were also up-regulated. TFs of the PnPf2 zn finger family were also shown to regulate positively as many as 12 genes that encode effector-like proteins (Jones et al. 2019).

High resolution mapping and cloning of sensitivity genes. Following are some details about these three sensitivity genes, where the description for *Tsn1* will apply for all the three pathogens:

(i) Sensitivity gene *Tsn1*. The *Tsn1* gene is located on chromosome 5BL and is 10,581 bp in length with 4,473 bp covering eight exons, a 161 bp long 5' UTR and a 391 bp long 3' UTR (Fig. 4). The predicted protein is 1,490 amino acids long consisting of of N-terminal serine/threonine protein kinase (S/TPK) domain with ATP binding site, substrate binding site and an activation site and a C-terminal NB-LRR domain, which indicates similarity to the common product of R genes (Friesen et al. 2006; Faris et al. 2010). All domains of *Tsn1* are required for ToxA sensitivity (Manning and Ciuffetti 2005).

Tsn1-ToxA interaction is common among all the three pathosystems involving wheat with SNB, tan spot and spot blotch (Liu et al. 2006). It has been shown that at the transcription level, ToxA can activate wall associated kinases (WAKs) as a defense response (He et al. 1998). It is also possible that ToxA may utilise WAKs for recognition of the product of *Tsn1* (Pandelova et al. 2009). The potential targets of ToxA is the binding protein, ToxABP1 with vitronectin-like sequence (Manning et al. 2007).

(ii) Sensitivity gene *Snn1*. This gene is located on chromosome arm 1BS and was earlier fine-mapped using F_2 population derived from a cross between Chinese Spring (CS) and its disomic substitution line carrying 1B chromosome from either *T. dicocooides* (Reddy et al. 2008) or from wheat cultivar Hope, leading to cloning (Shi et al. 2016b). Later, it was also fine mapped as a QTL through QTL interval mapping using a Multi-parent Advanced Generation InterCross (MAGIC) population involving eight or 1(Cockram et al. 2019). The gene *Snn1* was shown to encod e a member of the wall-associated kinase (WAK) class of plant receptor kinases and was therefore referred to as *TaWAK*. The gene is 3,045 base pairs (bp) long with three exons and a coding sequence of 2,145 bp with 5'and 3'untranslated regions (UTRs) of 164 and 102 bp, respectively. The deduced amino acid sequence indicated that the protein contains conserved wall-associated receptor kinase galac-turonan binding (GUB_WAK), epidermal growth factor–calciumbinding (EGF_CA), transmembrane, and serine/threonine protein ki-nase (S/TPK) domains, with the S/TPK domain predicted to be intracellular and the GUB_WAK and EGF_CA binding domains predicted to be extracellular.

Snn1 gene encodes a protein with a structure like that of PRRs (pattern recognition receptors), which recognize pathogen-associated molecular patterns (PAMPs). The PRR like protein encoded by *Snn1* often resembles a wall-associated kinase

(WAK) protein with domains like PK transmembrane, galacturonan binding and calcium binding domains; this allows early recognition of SnTox1 effector protein and upregulate the PTI pathway (Haugrud et al. 2019; Faris et al. 2019).

(iii) Sensitivity genes *Snn3-B1* and *Snn3-D1*. *Snn1-B1* gene was fine-mapped on the chromosome arm 5BS initially using two F_2 populations derived from crosses involving *SnTox3* sensitive line Sumai3 and two different insensitive lines (Shi et al. 2015) and later using GWAS and composite interval mapping involving a MAGIC population derived from 8 founder parents (Downie et al. 2018). The cloning of *Snn3-D1* (located on 5DS) was reported by Faris et al. (2019) at the 1st International Wheat Congress, held at Saskatoon in July 2019. The gene *Snn3-D1* differed from the two other cloned sensitivity genes (*Tsn1* and *Snn1*). Like the other two cloned sensitivity genes (*Tsn1* and *Snn1*), *Snn3-D1* also carries a S/TPK domain, but it also have some other domains related to the receptor-like kinase and MAP kinase (Winterberg et al. 2014). *Snn3-D1* also differed from *Tsn1* and *Snn1* in its light regulated and circadian expression patterns. This and other characteristics of *Snn3-D1* and how it compares to *Tsn1* and *Snn1* will be known when results of cloning *Snn3-D1* are published. However, one common feature of the above three cloned sensitivity genes is the presence of a PK domain, which indicates that signaling is necessary from the pathogen to exploit programmed cell death in the host.

Cloned NE genes for SNB. Three of the eight NE genes (*SnToxA*, *SnTox1* and *SnTox3*) have also been cloned and characterized (Friesen et al. 2006; Liu et al. 2009, 2012). Following are some details:

(*i*) *SnToxA* gene has two introns, which included a 55 bp intron located in the leader sequence and the other 50 bp intron located at the C-terminal coding region. The gene encodes a 13.2 kDa mature protein, which targets the protein PR-1-5 causing necrosis in the presence of *Tsn1* gene during ToxA-*Tsn1* interaction. The target protein PR-1-5 is present in both ToxA-sensitive and ToxA-insensitive wheat lines; it is only the level of expression that differs (Lu et al. 2009, 2011, 2014).

(*ii*) *SnTox1* gene lies in a 7.6 kb genomic region and has three exons (180 bp, 162 bp and 12 bp) associated with 58 bp long 5'UTR and 164 bp long 3' UTR (Fig 5a). The gene is associated with one downstream gene (SNOG_07153) and three upstream genes (SNOG_07154, SNOG_07155, SNOG_7156; SNOG stands for S nodorum gene) (Fig. 5b; Liu et al. 2012). The gene encodes a cysteine-rich protein carrying a conserved and functional chitin-binding (CB) motif at its C-terminal (Liu et al. 2012; Liu et al. 2016). This CB motif occurs in all necrotrophs and plays a role in the protection of fungus at the time of its initial penetration in the plant tissues (Liu et al. 2016). Some other domains such as two myristoylation sites, N-terminal pyroglutamate, six phosphorylation sites, an RGD cell attachment motif and C domain also occur in mature ToxA proteins (Manning et al. 2004).

(iii) *SnTox3* gene is 693 bp long and carries no introns. It encodes a 25.8 kD protein with 20 amino acid signal sequence and a possible pro-sequence (Liu et al. 2009). Six cysteine residues were also predicted to form disulfide bonds, which were shown to be important for SnTox3 activity. This gene also encodes a 230 aa long pre-pro protein. SnTox3 protein also contains a 20 aa signal peptide along with disulfide bonds formed by the six cysteine residues, which help in stabilisation of mature protein and its protein activity (Liu et al. 2009). The genomic location and structure of the gene *SnTox3* is shown in Fig. 6. An experiment was also conducted for the identification of the interaction between the *P. nodorum* NE protein SnTox3 and PR-1-1 in wheat using yeast-two-hybrid library approach, which indicated that the interaction was associated with the necrosis on the leaves of wheat (Breen et al. 2016).

Mechanism of action of NEs. The mechanism of action for different NEs may also differ and is known for at least two NEs. For instance, SnTox1 functions in the apoplast and directly recognizes Snn1 protein, thus facilitating infection by overcoming the barrier due to wheat chitinases (Liu et al. 2016). SnToxA, on the other hand, is internalized into the cytoplasm and interacts directly or indirectly with the product of gene *Tsn1*. In both cases the NE-Sn interactions activate MAPK signalling, which upregulates defense pathways and leads to release of reactive oxygen species (ROS), which results in cell death (Shi et al. 2016b; Fig. 7).

QTLs for SNB resistance (leaf blotch and glume blotch). *P. nodorum* pathogen is responsible for the development of two SNB diseases in wheat i.e., leaf blotch and glume blotch (including flag leaf and spike blotch). The pattern of inheritance for resistance against the two diseases differ (Shankar et al. 2008; Chu et al. 2010; Wicki et al. 1999; Xu et al. 2004). However, in a number of genetic studies, no distinction was made between leaf blotch and glume blotch. QTLs for resistance against SNB have been identified following both linkage based interval mapping and LD-based GWAS. The QTL analysis for the resistance to this disease was undertaken at two different stages [seedling (leaf blotch) and adult plant stages (flag leaf and spike)], but most of the association mapping studies were conducted at the seedling stage (Supplementary Tables 1 and 2). QTLs for seedling resistance (leaf blotch) have been identified on chromosomes 1A, 1B, 2B, 2D, 3A, 4A, 4B, 4D, 5A, 5B, 5D, 6A, 6D, 7A, 7B and 7D. Similarly, QTLs for adult plant resistance (glume blotch) have been identified on chromosomes 1A, 1B, 2A, 2D, 3A, 3B, 4B, 5A, 5B, 7A and 7B.

As many as ~90 QTLs for SNB have so far been identified through several studies using linkage-based interval mapping involving both bi-parental and multi-parental MAGIC mapping populations (Friesen et al. 2007; Ruud et al. 2017; Lin et al. 2020). Of the 90 QTLs, as many as 24 QTLs had major effects, each explaining >20 percent phenotypic variation (Supplementary Table 1). Similarly, GWAS resulted in identification of 46 MTAs (Gupta et al. 2014; Korte and Farlow 2013; Pascual et al. 2016; Ruud et al. 2019; Halder et al. 2019; Supplementary Table 2). After due validation, the markers associated with QTLs and MTAs can be utilized for MAS for resistance breeding.

In a recent major detailed study conducted by Lin et al. (2020), QTLs were also identified using a MAGIC population (643 RILs). Sixteen QTLs were detected using IM/CIM, being located on chromosomes 2A, 2D, 5B, 6A and 7D. A QTL (*QSnb.niab-5B.2*) overlapping *Tsn1* was also identified on the long arm of chromosome 5B.

High resolution fine mapping has also been undertaken for sensitivity genes for SNB. A high-density genetic linkage map was developed for the region of chromosome 2D, which narrowed down the *Snn2* gene to a 4-cM region, thus facilitating the discovery of closely linked molecular markers for breeding and positional cloning of *Snn2* gene (Zhang et al. 2009). Phenotypic variation (PV) for disease was 47% for the interaction *Snn2*-SnTox2, 20% for the interaction *Tsn1*-SnToxA, and 66% for both interactions taken together, suggesting the utility of these interactions in breeding (Friesen et al. 2007). Saturated gnetic map was also prepared for the region carrying the gene *Snn3* using two crosses between sensitive line Sumai3 and the corresponmding insensitive genotypes (Downie et al. 2918).

Pyrenophora tritici-repentis-wheat pathosystem

Tan spot caused by *P. tritici-repentis* (Ptr) causes a mean yield loss of 5-10% in different parts of the world, which may approach 50% under conditions favorable for the pathogen (DeWolf et al. 1998; Faris et al. 2013). The disease has been reported from different parts of the world including Australia, Canada, the USA, Mexico, South America (Argentina and Brazil), Europe, Africa, and Central Asia (Kazakhstan and Tajikistan). The wide adoption of minimum tillage practices and unconscious widespread cultivation of *Tsn1*-carrying wheats perhaps caused a rise in the incidence of tan spot and its severity throughout the world (Lamari et al. 2005). Tan spot is characterized by two distinct and independent symptoms in the form of necrosis and chlorosis (Fig. 1, b1, b2). It has also been shown that resistance against necrosis and chlorosis are controlled by two independent recessive factors.

Necrotrophic effectors (**NEs**). Three different NEs secreted by Ptr include ToxA, ToxB and ToxC. The presence of a fourth NE (Ptr ToxD) has also been suggested, but no corresponding sensitivity gene for this NE is known (Meinhardt et al. 2003; Ciuffetti et al. 2003). The genes encoding these three NEs were also identified in different isolates of the pathogen and are involved in the following three interactions: *Tsn1-ToxA*, *Tsc1-ToxC* and *Tsc2-ToxB* (Table 3; Faris et al. 2013). Among these three interactions, *Tsn1-ToxA* interaction is common with wheat-*P. nodorum* and wheat-*B. sorokiniana* pathosystem.

Among the three NEs, PtrToxA and PtrToxB are characterized as small effector proteins; ToxA produces necrosis, while ToxB produces chlorosis. ToxC, which also causes chlorosis, has not been characterized and may be the product of a

secondary metabolite gene cluster. There is strong evidence that *P. tritici-repentis* acquired the gene *ToxA* from *P. nodorum* through horizontal gene transfer (Friesen et al. 2006).

In addition to the above three toxins, as many as 38 novel toxins called triticones have been identified (Rawlinson et al. 2019), although only triticone A and triticone B have been purified from *Ptr* and shown to cause necrosis/chlorosis. A biosynthesis gene cluster *TtcA* has also been identified. A deletion of *TtcA* abolished the production of all triticones, but the pathogenicity of mutant *ttcA* was not visibly affected. Triticone A/B gave visisble necrotic symptoms but inhibited the growth of some bacteria like *Bacillus subtilis* and *Rhodococcus erythropolis*, when tested using disk diffusion method, suggesting their antimicrobial activity. No inhibition was observed for gram negative bacteria, like *P. pastoris* (Rawlinson et al. 2019).

A detailed study of the Ptr genome has also been undertaken by R.P. Oliver and his group from Western Australia (Moolhuijzen et al. 2018a, b). The genome is 40.9 Mb in size and has already been fully sequenced, using eight new Ptr isolates representing races 1, 2 and 5, and a new race (for races 1-8, see later). As much as 98% of the genome has been mapped on 10 or more chromosomes, which carry 13,797 annotated genes. Comparative analysis of the whole genome also revealed major chromosomal segmental rearrangements and fusions, highlighting intraspecific genome plasticity (Moolhuijzen et al. 2018a).

PtrToxA is a single copy gene and is characterized by 900 nucleotides long cDNA (PtrNEC) producing a 19.7 kD protein precursor. *Ptr ToxB*, on the other hand, is a multi-copy gene (1-3 Kb in length) producing a protein with a mass of 6.6 kD (Martinez et al. 2001, 2004). The number of copies of *ToxB* in a race has a correlation with the level of virulence. A total of ten identical *ToxB* gene copies were identified, with nine loci associated with chromosome 10 and a single copy with chromosome 5. Multiple *ToxB* gene loci on chromosome 10 were separated by large segments of 31-66 kb long, and exhibit an alternating pattern involving forward and reverse DNA strands, and flanked by transposable elements (Moolhuijzen et al. 2020; Fig. 8). The sequence variability of *PtrToxB* gene among Ptr races of the pathogen has also been reported. Homologues of *PtrToxB* have also been reported from several other pathogens including *Pyrenophora bromi*, suggesting its common origin in early ancestors of the Ascomycota (Andrie et al. 2008).

Genetics of sensitivity. A genetic analysis of Tox B sensitivity was conducted using an association mapping panel (*n* = 480) and a MAGIC population (*n* founders = 8, *n* progeny = 643) that were genotyped with a 90K SNP array. *ToxB* sensitivity was found to be highly heritable ($h2 \geq 0.9$) and was controlled predominantly by *Tsc2* locus on chromosome 2B in a 1921 kb long interval that contains 104 genes in the reference genome of ToxB-insensitive variety 'Chinese Spring' (Corsi et al. 2020). A minor *ToxB* sensitivity QTL was also identified on chromosome 2A. These resources can be used for deployment of recessive allele of *Tsc2* using MAS.

As a result of extensive studies on tan spot during the last 40 years, we now have the following resources for conducting research on this disease: (i) a wheat differential set for tan spot, which included Salamouni (universal resistant), Glenlea (sensitive to Ptr ToxA), 6B365 (sensitive to Ptr ToxC), and 6B662 (sensitive to Ptr ToxB). The hard spring wheat line ND495 was included in the differentials set as a susceptible control; (ii) a rating scale for lesion type disease; (iii) basic race classification system involving eight races (Table 7); the four differential genotypes can differentiate between the known eight races of the pathogen. Details about three NEs-sensitivity combinations are summarized in Table 3 (Faris et al. 1997, 1999; Effertz et al. 2001, 2002).

Distribution of Ptr NE genes. The pathogen Ptr is known to have 8 races (race 1-8), representing all possible combinations of *ToxA*, *ToxB* and *ToxC* (Table 7). Isolates belonging to each race were collected both from bread wheat and durum wheat, although race 1 in hexaploid wheat is believed to have originated from durum wheat. Three isolates, namely Asc1 (race 1), D308 (race 3) and Alg3–24 (race 5) were found to carry genes *Ptr ToxA, Ptr ToxC*, and *Ptr ToxB* respectively. The distribution of the genes encoding three different NEs differs widely not only in different parts of the world, but also in the

area occupied by the same set of wheat genotypes. Of these, ToxA is the most widely distributed, being present in ~80% of the world's isolates (Friesen et al. 2006); this is a small protein that induces a strong necrotic response in wheat lines carrying the gene *Tsn1* (Faris et al. 2010) on chromosome 5BL.

Distribution of races 1-8 among isolates. The distribution of eight Ptr races in different isolates from a particular geographical region or from different geographical regions have also been examined. Following are some examples: (i) In Tunisia, using four wheat differential genotypes (mentioned above), virulence was examined for 73 single-spore isolates, and the results indicated that 68 isolates belonged to race 7; 3 belonged to race 5 and one each to race 2 and 4, suggesting that race 7 is the predominant race in Tunisia. PCR was also performed to examine the frequencies of each of the three genes (*ToxA*, *ToxB* and *toxB*), but not for ToxC, which has not been cloned and sequenced, so that primers could not be designed for this gene. *ToxA* was present in 37 (51%) isolates, *ToxB* was present in 71 (97%) isolates with its homolog *toxB* present in 68 (93%) isolates (Kamel et al. 2019). A subset of 22 isolates was also subjected to sequencing resolving sequence polymorphism in *ToxA* and *ToxB/toxB* (Kamel et al. 2019). (ii) In Australia, races 1 and 2 are the most predominant races, although races 5-8 are also common, which were rarely found in the Americas. (iii) In Algeria, among 55 isolates, races 1, 4, 5, 6, 7 and 8 were found and a new virulence pattern was identified. Isolates with this pattern induced necrosis in durum wheat but not in the common wheat genotypes. A majority of the isolates represented races 1 (41%) and 7 (40%), while races 4, 5, 6, and 8 were rare; race 1 occurred in all regions (Benslimane et al. 2011). (iv) In Morocco, majority of isolates were classified as races 5 and 6, both carrying *Ptr ToxB* (Gamba et al. 2017). (v) In the centre of origin of wheat (Middle East, North Africa, and the Caucasus regions), the situation was rather complex, with the occurrence of all the eight races and all the three effectors. (vi) In Western Canada, race composition varied, when distribution of 144 Ptr isolates was examined in durum wheat, bread wheat and grasses; R1 and R2 were common in wheat and occurred in equal frequencies in durum wheat; R1 was twice as frequent as R2 on winter bread wheat; R3 was recovered only from durum wheat and R4 was the only race recovered from grasses (Wet et al. 2021) (for a Review and References, see Kamel et al. 2019).

Assessment of sensitivity. In a recent study, 40 Australian spring wheat varieties were examined for sensitivity to ToxA and disease response to a race 1 specific wild-type Ptr isolate carrying *ToxA* and *ToxC* (See et al. 2018). *ToxA* sensitivity was generally associated with disease susceptibility (compatible interaction) but did not always give the expected symptoms. When wild type and *toxA* mutant isolates were used for infection, majority of *Tsn1* varieties exhibited lower disease scores with *toxA* mutants (as expected), but several varieties exhibited no distinct differences between wild-type and *toxA* mutant. This pattern suggested that ToxA is not the sole major cause of tan spot disease, and that the appearance of the disease partly also depends on the background of the host. It is thus suggested that ToxA may need aditional factors to cause infection (See et al. 2018).

Cloned sensitivity genes for tan spot. Among the sensitivity genes, *Tsn1* (common among three necrotrophs) has already been cloned and characterized (Fig. 4). The details of this genes were already described earlier, while describing cloned sensitivity gene for *P. nodorum*. The other two sensitivity genes *Tsc1* and *Tsc2* are yet to be cloned and characterized, but markers have been developed for these two other sensitivity genes. A variety 'Maris Dove' was also identified to be the historic source of *Tsc2* alleles in the wheat germplasm. A minor sensitivity QTL was also identified on chromosome 2A. The marker developed in this study can be used for MAS aimed at selection of insensitive genotypes exhibiting disease resistance (Corsi et al. 2020)

Cloned NE genes for tan spot. Among products of cloned NE genes, PtrToxB (6.6 kD) is a polar and low-molecular-mass molecule (Effertz et al. 2002) encoded by the multiple-copies of the gene, which carries a 261-bp open reading frame (ORF) within its sequence (Strelkov et al. 2002). The protein PtrToxB is recognised by the sensitivity gene *Tsc2* (located on chromosome arm 2BL) and produces chlorosis on the leaf surface of wheat (Orolaza et al. 1995; Friesen and Faris 2004). Ptr ToxC has not been fully characterized and purified; mode of action of this NE is also not known. However, its partial characterization and purification has been reported (Lamari and Bernier 1991; Gamba et al. 1998; Effertz et al. 2002).

Interactions between sensitivity genes and NEs. Among the three interactions, namely *Tsn1-ToxA*, *Tsc1-ToxC* and *Tsc2-ToxB*, the interaction between *Tsn1* and ToxA has been shown to be negatively affected when mutation occurs at different motifs of the Tsn protein (Manning et al. 2004). The interaction *Tsc2-ToxB* is unique to tan spot and leads to upregulation of several wheat genes encoding proteins like RLKs, pathogenicity related proteins, components of jasmonic acid, and phenyl propanoid pathways and WRKY transcription factors (Pandelova et al. 2012). Some physiological changes have also been observed, which decrease chlorophyll a and b and overlap with the symptom development and ROS accumulation (Pandelova et al. 2012; Ciuffetti et al. 2010). Other details of this interaction are given in Table 3.

An additive interaction of sensitivity gene *Tsn1* with *Tsc1* and *Tsc2* has also been reported for tan spot in bread wheat (Liu et al. 2017) but not in durum wheat (Virdi et al. 2016). It is therefore apparent that elimination of one or more sensitivity genes along with introgression of R genes/QTLs should be a good strategy for developing resistant cultivars.

NEs regulating transcription factors and other proteins. ToxA and ToxB both induce upregulation of WRKY transcription factors, PR proteins and receptor-like kinases (RLKs) (Adhikari et al. 2009; Pandelova et al. 2009, 2012). The responses also include activation of phenylpropanoid and JA pathways and accumulation of ROS and disruption of photosystem (Adhikari et al. 2009; Pandelova et al. 2009, 2012). However, the response of the host to ToxB differs in host genotypes with a single dominant R gene (Singh et al. 2008a, b) and those with a single recessive gene (Singh et al. 2010).

Insertion element PtrHp1 in *ToxA* gene. A novel 166 bp insertion element (PtrHp1) was also detected in *ToxA* gene from isolates from many regions of the world (Australia, Europe, North and South America and the Middle East, Denmark, Germany, and New Zealand). PtrHp1 perfectly matched 59 bp inverted repeat hairpin structure located downstream of the *ToxA* coding sequence in the 3' UTR exon. Further examination revealed that PtrHp1 elements were distributed throughout the genome. Analysis of genomes of isolates from Australia and North America had 50–112 perfect copies of PtrHp1 that often overlap other genes. The hairpin element appears to be unique to Ptr and the lack of ancient origins in other species suggests that PtrHp1 emerged after speciation of Ptr (Moolhuijzen et al. 2018b).

R genes and QTLs for tan spot resistance. Resistance genes (R genes or major QTLs) providing resistance against tan spot have also been identified. Among these R genes, *Tsr7* locus was also identified in tetraploid wheat using a set of Langdon durum-wild emmer (*Triticum turgidum* ssp. *dicoccoides*) disomic chromosome substitution lines. Durum cultivar Langdon, which is susceptible to tan spot became resistant with the substitution of chromosome 3B from the wild emmer accession IsraelA (Faris et al. 2020). *Tsr7* locus in tetraploid wheat was later found to be the same as the race-nonspecific QTL previously identified in the hexaploid wheat cultivars BR34 and Penawawa. Four user-friendly SNP-based semi-thermal asymmetric reverse PCR (STARP) markers co-segregated with *Tsr7* and should be useful for MAS (Faris et al. 2020).

More than 20 QTL studies were also conducted in hexaploid and tetraploid wheats for identification of QTLs for resistance against tan spot in wheat. These QTL studies resulted in identification of as many as >160 QTLs, a number of these QTLs explained >20% phenotypic variation (Supplementary Table 1). Utilizing the results of QTL studies, a meta-QTL analysis was also conducted leading to identification of 19 meta-QTLs that were derived from 104 QTLs (Liu et al. 2020a, b for details of all QTL studies and for meta-QTL analysis). Three race nonspecific meta-QTLs were also identified, one each on chromosomes 2A, 3B and 5A. These three meta-QTLs had large phenotypic effects, each responsible for resistance to multiple races in both bread and durum wheats.

GWA studies were also conducted leading to identification of 242 significant MTAs (Supplementary Table 2), although a large number of these could be false positives. Most QTLs and MTAs were associated with seedling resistance and very few studies have been conducted for the identification of QTLs associated with adult plant resistance (Supplementary Table 1 and 2). The markers associated with the above meta-QTLs and those involved in MTAs can be utilized for MAS in wheat breeding programmes after due validation.

Candidate genes were also identified for 16 of the above 19 meta-QTL; the number of candidate genes for individual meta-QTL ranged from 2 to 85, many of these located on chromosome 2B. A number of these candidate genes encoded NBS- and/or LRR-like proteins and co-localised with sensitivity gene *Tsc2*. However, none of these candidate genes could be *Tsc2*, because genome sequence utilized for identification of candidate genes belonged to CS, which is insensitive to Ptr ToxB.

PR genes. The level of the expression of most PR genes has also been shown to be up-regulated due to effector protein ToxA during infection and increases over time (Pandelova et al. 2009). Glucanases (PR-2) and chitinases (PR-4) represent the largest group of PR genes displaying differential expression in which majority of glucanases belong to the family of β-1,3-glucanases (glucan endo-1,3-β-glucosidases). A downregulation of the expression of some genes of glucanases such as (1–3,1–4)-β-glucanases has also been reported (Pandelova et al. 2009).

Bioplaris sorokiniana-wheat pathosystem: *BsToxA*-*Tsn1*system

B. sorokiniana is a hemi-biotroph and is the causal organism for wheat diseases including spot blotch (Fig. 1a) and common root rot (CRR), which are responsible for major yield losses in several parts of the world (Gupta et al. 2018a, b). The gene *ToxA*, initially reported to be present in *P. nodorum* and *P. tritici repentis* (Friesen et al. 2018) has also been identified in some *B. sorokiniana* isolates from USA (South Central Texas), Australia, India and Mexico. It was also shown that a *B. sorokiniana* isolate harbouring *ToxA* (dominant alleles of sensitivity gene) is more virulent on wheat lines carrying the sensitivity gene *Tsn1* (McDonald et al. 2018; Navathe et al. 2020).

The gene *ToxA* is embedded in 12-kb AT-rich genomic region of each of the three pathogens. Near the edges of the gene, a decay has been reported, which has been attributed to repeat-induced polymorphism (RIP) (Fig. 9). Small indels, which differ in size in the three pathogens have also been reported in the promoter region of the gene; this indel is 148-bp in *BsToxA*, 238-bp in *PtrToxA* and 43 bp in *SnToxA* (McDonald et al. 2012, 2018; also see Fig. 9). The haplotype organization of three *ToxA* genes (*BsToxA*, *PtrToxA* and *SnToxA*) also differed.

The frequencies of pathogen isolates carrying *BsToxA* and the wheat genotypes carrying *Tsn1* also differ in different parts of the world. In Australia, 12 (34%) of the 35 isolates of *B. sorokiniana* isolates carried *ToxA*, while in India 77 (70%) of the 110 *B. sorokiniana* isolates carried *ToxA*. In a solitary report of the frequency of *Tsn1* gene from India, the sensitivity gene was present in 81 (36.8%) of 220 Indian wheat cultivars screened (Navathe et al. 2020). However, presence of *Tsn1* gene does not always guarantee susceptibility to the pathogen carrying *ToxA* gene, as shown in the material surveyed in Australia and India. In Australia and India, it was reported that sometimes an isolate lacking *ToxA* is still highly virulent on non-*Tsn1* cultivars, while a cultivar containing *Tsn1* can still be resistant to isolates carrying ToxA gene. These results suggest that there are additional factors in the wheat genome, which control resistance; these additional factors may include R genes and QTLs controlling resistance to spot blotch (Navathe et al. 2020; see later).

Sensitivity-related QTLs against *B. sorokiniana* have also been identified in barley, where recessive alleles of *Rcs5* and *Rcs6/Scs2* provided resistance to spot blotch (Leng et al. 2018; Gupta et al. 2018a). Two additional QTLs (*QSbs-1H-P1* and *QSbs-7H-P1h*) for susceptibility to spot blotch were also identified in barley (Leng et al. 2020); of these two QTLs, *QSbs-7H-P1* mapped to the same region as *Rcs5* gene, but *QSbs-1H-P1* was a new QTL.

QTLs for spot blotch resistance. Resistance to spot blotch is mainly associated with the major R genes (*Sb1-Sb4*) as well as QTLs, which may or may not overlap the known major genes (Lillemo et al. 2013, Kumar et al. 2015; Lu et al. 2016; Zhang et al. 2020). The genetics of resistance to spot blotch has also been studied taking the disease as a quantitative trait (Gupta et al. 2018). It has been shown that some major QTL identified through QTL mapping found to be inherited in a Mendelian manner, so that these later designated as *Sb1* (flanking markers *Xgwm1220–Xgwm295* on chromosome arm 7DS) and *Sb2* (*QSb.bhu-5BL*) in two independent studies (Lillemo et al. 2013; Kumar et al. 2015). *Sb1* gene is also associated with *Lr34*, which is an important gene for leaf rust resistance (Lillemo et al. 2013).

Using bulked segregant analysis (BSA), *Sb3* gene was also fine-mapped on chromosome arm 3BS near two other QTLs (*QSb.bhu-3B* and *QSb.cim-3B*; Lu et al. 2016). The fourth resistance gene *Sb4* was recently identified and mapped on chromosome arm 4BL using segregant RNA-Seq (BSR-Seq) analysis and SNP mapping (Zhang et al. 2020). The locus with *Sb4* carried 21 genes.

In addition to the four major genes as above, 38 QTLs (including 12 QTLs with >20% PVE) using QTL interval mapping (Supplementary Table 1) and 79 MTAs using GWAS were also identified (Supplementary Table 2). These QTL analysis and association studies were conducted at seedling as well as at adult plant stages (Supplementary Table 1 and 2).

Conclusions And Future Perspectives

Disease resistance in plants including wheat can be race-specific or race non-specific, the latter sometimes also described as adult plant resistance (APR). Both these types of disease resistance are generally controlled by R genes, which have been subjects of detailed studies. The plant immunity involving these R genes has also been subjected to detailed studies at the molecular level, leading to the development of zig-zag model involving PTI, ETS and ETI (Jones and Dangl 2006). During the last > 25 years, > 300 R genes and a number of Avr genes have also been cloned, thus providing an opportunity to study the interaction between the products of R genes of the host and the corresponding Avr genes in the pathogen at the molecular level (for a review, see Kourelis and van der Hoorn 2018). In majority of examples of R genes, gene-for-gene (GFG) relationship proposed by Flor (1942, 1956) holds good. However, disease resistance controlled by susceptibility genes like SWEET genes for bacterial blight (BB) in rice (Gupta 2020) and sensitivity genes like *Tsn1* in wheat follow an inverse gene-for-gene (IGFG) relationship with corresponding Avr genes in the pathogen (Navathe et al. 2020). This is an area of research on disease resistance, which has witnessed immense activity in recent years. As a result, a number of sensiticvity genes in wheat for three important diseases (SNB, Tan Spot and Spot Blotch) and the corresponding Avr (NE) genes in the form of toxin producing genes (Tox genes) in the pathogens (*P. nodorum*, *P. tritici-repentis* and *B. sorokiniana*) have been identified. Some of these genes (both sensitivity genes in the host and NE genes in the pathogen) have also been cloned and characterized generating information about the molecular mechanism involved in plant immunity involving these pathosystem. In this review, a comparison has first been made between the general molecular mechanisms involved in resistance against biotrophs and necrotrophs. This was followed by a brief review of information on the above three pathosystems. In summary, perhaps only about a dozen NE genes and an equal number of corresponding sensitivity genes are now known, which have been described in this review. In future more sensitivity genes in wheat and other corps and the corresponding Tox genes in the pathogens exhibiting IGFG may be discovered.

We also believe that in the area dealing with sensitivity genes following IGFG model there are gaps, which need to be filled through future research. For instance, although much is known about the pathosystems dealing with SNB and Tan spot, the information dealing with spot blotch (caused by *Bipolaris sorokiniana*) has just started being generated and hardly any work is available on pathosystems involving necrotrophs causing the following diseases: (i) fusariun head blight (FHB) caused by *F. graminearum*; (ii) eye spot caused by *Tapesia yallundae* (syn *Pseudocercosporella herpotrichoides*, W-type anamorph); (iii) septoria tritici blotch (STB) caused by *Zymoseptoria tritici*. We also believe that for diseases like spot blotch caused by necrotrophs, both GFG and IGFG may operate in parallel. Further studies involving scoring of allelic states of genes involved in GFG and IGFG models need to be undertaken to resolve this issue. In a recent study on spot blotch involving analysis of *Tsn1-ToxA* system following IGFG, we ourselves discovered that the wheat genotypes carrying recessive allele of sensitivity gene (*tsn1*) can also be susceptible and vice versa; variation in the level of disease caused by ToxA positive isolates was also noticed (Navathe et al. 2020). This suggests that the relationship between a sensitivity gene in the host and the corresponding virulence gene in the pathogen is not so simple, suggesting further detailed investigations.

Declarations

Acknowledgements

N.K.V. acknowledges the support of a National Postdoctoral Fellowship (PDF/2016/000012) granted by SERB-DST, New Delhi, India.

Author contribution statement PKG conceived the idea for writing this review. All authors contributed to writing of the manuscript. The manuscript was read and revised by all authors and fnalized by PKG.

Data availability statement Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare no conficts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Abeysekara NS, Friesen TL, Keller B, Faris JD (2009) Identification and characterization of a novel host-toxin interaction in the wheat-*Stagonospora nodorum* pathosystem. Theor Appl Genet 120:117–126
2. Abeysekara NS, Friesen TL, Liu ZH, McClean PE, Faris JD (2010) Marker development and saturation mapping of the tan spot Ptr ToxB sensitivity locus *Tsc2* in hexaploid wheat. Plant Genome 3:179–189
3. Abeysekara NS, Faris JD, Chao S, McClean PE, Friesen TL (2012) Whole-genome analysis of Stagonospora nodorum blotch resistance and validation of the SnTox4-*Snn4* interaction in hexaploid wheat. Phytopathology 102:94–104
4. Adhikari TB, Bai J, Meinhardt SW, Gurung S, Myrfield M, Patel J (2009) *Tsn1*-mediated host responses to ToxA from *Pyrenophora tritici-repentis*. Mol Plant–Microbe Interact 22:1056–1068
5. Aguilar V, Stamp P, Winzeler M, Winzeler H, Schachermayr G, Keller B et al (2005) Inheritance of weld resistance to stagonospora nodorum leaf and glume blotch and correlations with other morphological traits in hexaploid wheat (*Triticum aestivum* L.). Theor Appl Genet 111:325–336
6. Andrie RM, Schoch CL, Hedges R, Spatafora JW, Ciuffetti LM (2008) Homologs of ToxB, a host-selective toxin gene from *Pyrenophora tritici*-repentis, are present in the genome of the sister species *Pyrenophora bromi* and other members of the Ascomycota. Fungal Genet Biol 45:363–377
7. Aoki T, O'Donnell K (1999b) Morphological characterization of *Gibberella coronicola* sp. nov., obtained through mating experiments of *Fusarium pseudograminearum*. Mycoscience 40:443–453
8. Arseniuk E, Czembor PC, Czaplicki A, Song QJ, Cregan PB, Hoffman DL et al (2004) QTL controlling partial resistance to Stagonospora nodorum leaf blotch in winter wheat cultivar Alba. Euphytica 137:225–231
9. Barr ME (1977) *Magnaporthe, Telimenella*, and *Hyponectria* (*Physosporellaceae*). Mycologia 69:952–966
10. Benslimane H, Lamari L, Benbelkacem A, Sayoud R, Bouznad Z (2011) Distribution of races of *Pyrenophora tritici-repentis* in Algeria and identification of a new virulence type. Phytopathol Mediterr 50:203–211
11. Bertucci M, Brown-Guedira G, Murphy JP, Cowger C (2014) Genes conferring sensitivity to *Stagonospora nodorum* necrotrophic effectors in Stagonospora nodorum blotch-susceptible U.S. wheat cultivars. Plant Dis 98:746–753
12. Breen S, Williams SJ, Winterberg B, Kobe B, Solomon PS (2016) Wheat PR-1 proteins are targeted by necrotrophic pathogen effector proteins. Plant J 88:13–25
13. Chu CG, Friesen TL, Xu SS, Faris JD (2008) Identification of novel tan spot resistance loci beyond the known host-selective toxin insensitivity genes in wheat. Theor Appl Genet 117:873–881

14. Chu CG, Chao S, Friesen TL, Faris JD, Zhong S, Xu SS (2010) Identification of novel tan spot resistance QTLs using an SSR-based linkage map of tetraploid wheat. Mol Breed 25:327–338
15. Ciuffetti LM, Manning VA, Martinez JP, Pandelova I, Andrie RM (2003) Proteinaceous toxins of *Pyrenophora tritici-repentis* and investigation of the site-of-action of Ptr ToxA. In: Rasmussen JB, Friesen TL, Ali S (eds) Fourth international wheat tan spot and spot blotch workshop, North Dakota Agric Exp Station, Fargo, July 21–24, 2002. Proceedings. North Dakota, pp 96–102
16. Ciuffetti LM, Manning VA, Pandelova I, Betts MF, Martinez JP (2010) Host-selective toxins, Ptr ToxA and Ptr ToxB, as necrotrophic effectors in the *Pyrenophora tritici-repentis*–wheat interaction. New Phytol 187:911–919
17. Cockram J, Scuderi A, Barber T, Furuki E, Gardner KA, Gosman N et al (2015) Fine-mapping the wheat *Snn1* locus conferring sensitivity to the *Parastagonospora nodorum* necrotrophic effector SnTox1 using an eight founder multiparent advanced generation inter-cross population. G3 (Bethesda) 5:2257–2266
18. Corsi B, Percival-Alwyn L, Downie RC, Venturini L, Iagallo EM, Mantello CC et al (2020) Genetic analysis of wheat sensitivity to the ToxB fungal effector from *Pyrenophora tritici-repentis*, the causal agent of tan spot. Theor Appl Genet 133:935–950
19. Cowger C, Ward B, Brown-Guedira G, Brown J (2020) Role of effector-sensitivity gene interactions and durability of quantitative resistance to Septoria nodorum blotch in eastern U.S. wheat. Front Plant Sci 11:155
20. Crook AD, Friesen TL, Liu ZH, Ojiambo PS, Cowger C (2012) Novel necrotrophic effectors from *Stagonospora nodorum* and corresponding host sensitivities in winter wheat germplasm in the southeastern United States. Phytopathology 102:498–505
21. Dastur JF (1942) Notes on some fungi isolated from 'black point' affected kernels in the central provinces. Ind J Agri Sci 12:731–742
22. De Wolf ED, Effertz RJ, Ali S, Francl LJ (1998) Vistas of tan spot research. Can J Plant Pathol 20:349–370
23. Downie RC, Bouvet L, Furuki E, Gosman N, Gardner KA, Mackay IJ et al (2018) Assessing European wheat sensitivities to *Parastagonospora nodorum* necrotrophic effectors and fine-mapping the *Snn3-B1* locus conferring sensitivity to the effector SnTox3. Front Plant Sci 9:881
24. Drechsler C (1923) Some graminicoulous species of *Helminthosporium*. Int J Agric Res 24:614–670
25. Effertz RJ, Anderson JA, Francl LJ (2001) Restriction fragment length polymorphism mapping of resistance to two races of *Pyrenophora tritici*-repentis in adult and seedling wheat. Phytopathology 91:572–578
26. Effertz RJ, Meinhardt SW, Anderson JA, Jordahl JG, Francl LJ (2002) Identification of a chlorosis-inducing toxin from *Pyrenophora tritici-repentis* and the chromosomal location of an insensitivity locus in wheat. Phytopathology 92:527–533
27. Engler JA, Favery B, Engler G, Abad P (2005) Loss of susceptibility as an alternative for nematode resistance. Curr Opin Biotech 16:112–117
28. Faris JD, Anderson JA, Francl LJ, Jordahl JG (1996) Chromosomal location of a gene conditioning insensitivity in wheat to a necrosis-inducing culture filtrate from *Pyrenophora tritici-repentis*. Phytopathology 86:459–463
29. Faris JD, Anderson JA, Francl LJ, Jordahl JG (1997) RFLP mapping of resistance to chlorosis induction by *Pyrenophora tritici-repentis* in wheat. Theor Appl Genet 94:98–103
30. Faris JD, Li WL, Liu DJ, Chen PD, Gill BS (1999) Candidate gene analysis of quantitative disease resistance in wheat. Theor Appl Genet 98:219–225
31. Faris JD, Friesen T (2005) Identification of quantitative trait loci for race-nonspecific resistance to tan spot in wheat. Theor Appl Genet 111:386–392
32. Faris JD, Friesen TL, Lu H, Reddy L, Zhang Z, Liu Z et al (2008) Genetic analysis of host-toxin interactions in the wheat–*Stagonospora nodorum* pathosystem. In: Raupp WJ (ed) The Annual Wheat Newsletter: Wheat genetic and

genomic resources center, Manhattan, Kansas State University, pp 13

33. Faris JD, Friesen TL (2009) Reevaluation of a tetraploid wheat population indicates that the *Tsn1*-ToxA interaction is the only factor governing susceptibility to Stagonospora nodorum blotch. Phytopathology 99:906–912
34. Faris JD, Zhang Z, Lu HJ, Lu SW, Reddy L, Cloutier S et al (2010) A unique wheat disease resistance-like gene governs effector-triggered susceptibility to necrotrophic pathogens. Proc Natl Acad Sci USA 107:13544–13549
35. Faris JD, Zhang Z, Rasmussen JB, Friesen TL (2011) Variable expression of the *Stagonospora nodorum* effector SnToxA among isolates is correlated with levels of disease in wheat. Mol Plant–Microbe Interact 24:1419–1426
36. Faris JD, Liu Z, Xu SS (2013) Genetics of tan spot resistance in wheat. Theor Appl Genet 126:2197–2217
37. Faris JD, Zhang Z, Friesen TL (2019) A tale of three wheat genes reveals the ability of a necrotrophic pathogen to bamboozle diverse host targets. In: 1st International Wheat Congress, Saskatoon, Saskatchewan, Canada, July 21–26, 2019. Abstract No. 019196
38. Faris JD, Overlander ME, Kariyawasam GK, Carter A, Xu SS, Liu Z (2020) Identification of a major dominant gene for race-nonspecific tan spot resistance in wild emmer wheat. Theor Appl Genet 133:829–841
39. Figueroa M, Hammond-Kosack KE, Solomon PS (2018) A review of wheat diseases: a field perspective. Mol Plant Pathol 19:1523–1536
40. Flor HH (1942) Inheritance of pathogenicity in *Melampsora lini*. Phytopathology 32:653–669
41. Flor HH (1956) The complementary genie systems in flax and flax rust. Adv Genet 8:29–54
42. Food and Agriculture Organization of the United Nations (2019) FAOSTAT statistical database. Rome
43. Food and Agriculture Organization of the United Nations (2020) FAOSTAT statistical database. Rome
44. Francki MG (2013) Improving *Stagonospora nodorum* resistance in wheat: a review. Crop Sci 53:355–365
45. Francki MG, Walker E, McMullan CJ, Morris WG (2020) Multi-location evaluation of global wheat lines reveal multiple QTL for adult plant resistance to Septoria nodorum blotch (SNB) detected in specific environments and in response to different isolates. Front Plant Sci 11:771
46. Friesen TL, Faris JD (2004) Molecular mapping of resistance to *Pyrenophora tritici-repentis* race 5 and sensitivity to Ptr ToxB in wheat. Theor Appl Genet 109:464–471
47. Friesen TL, Stukenbrock EH, Liu Z, Meinhardt S, Ling H, Faris JD et al (2006) Emergence of a new disease as a result of interspecific virulence gene transfer. Nat Genet 38:953–956
48. Friesen TL, Meinhardt SW, Faris JD (2007) The *Stagonospora nodorum*-wheat pathosystem involves multiple proteinaceous host-selective toxins and corresponding host sensitivity genes that interact in an inverse gene-for-gene manner. Plant J 51:681–692
49. Friesen TL, Zhang Z, Solomon PS, Oliver RD, Faris JD (2008) Characterization of the interaction of a novel *Stagonospora nodorum* host-selective toxin with a wheat susceptibility gene. Plant Physiol 146:682–693
50. Friesen TL, Chu CG, Liu ZH, Xu SS, Halley S, Faris JD (2009) Host-selective toxins produced by *Stagonospora nodorum* confer disease susceptibility in adult wheat plants under field conditions. Theor Appl Genet 118:1489–1497
51. Friesen TL, Faris JD (2012) Characterization of plant–fungal interactions involving necrotrophic effector-producing plant pathogens. In: Bolton MD, Bart PHJT (eds) Plant fungal pathogens: Methods and Protocols. Methods Mol Biol 835:191–207
52. Friesen TL, Chu C, Xu SS, Faris JD (2012) SnTox5-*Snn5*: a novel *Stagonospora nodorum* effector-wheat gene interaction and its relationship with the SnToxA-*Tsn1* and SnTox3-*Snn3-B1* interactions. Mol Plant Pathol 13:1101–1109
53. Friesen TL, Holmes DJ, Bowden RL, Faris JD (2018) ToxA is present in the U.S. *Bipolaris sorokiniana* population and is a significant virulence factor on wheat harboring *Tsn1*. Plant Dis 102:2446–2452

54. Gamba FM, Lamari L, Brûlé-Babel AL (1998) Inheritance of race-specific necrotic and chlorotic reactions induced by *Pyrenophora tritici-repentis* in hexaploid wheats. Can J Plant Pathol 20:401–407
55. Gamba FM, Filippo M, Bassi FM, Finckh MR (2017) Race structure of *Pyrenophora tritici-repentis* in Morocco. Phytopathol Mediterr 56:119–126
56. Gao Y, Faris JD, Liu Z, Kim YM, Syme RA, Oliver RP et al (2015) Identification and characterization of the SnTox6-*Snn6* interaction in the *Parastagonospora nodorum*-wheat pathosystem. Mol Plant – Microbe Interac 28:615–625
57. Ghaderi F, Sharifnabi B, Javan-Nikkhah M, Brunner PC, McDonald BA (2020) SnToxA, SnTox1, and SnTox3 originated in *Parastagonospora nodorum* in the Fertile Crescent. Plant Pathol 69:1482–1491
58. Gonzalez-Hernandez JL, Singh PK, Mergoum M, Adhikari TB, Kianian SF, Simsek S et al (2009) A quantitative trait locus on chromosome 5B controls resistance of *Triticum turgidum* (L.) var. diccocoides to Stagonospora nodorum blotch. Euphytica 166:199
59. Gupta PK, Kulwal PL, Jaiswal V (2014) Association mapping in crop plants: opportunities and challenges. Adv Genet 85:109–147
60. Gupta PK, Chand R, Vasistha NK, Pandey SP, Kumar U, Mishra VK et al (2018a) Spot blotch disease of wheat: the current status of research on genetics and breeding. Plant Pathol 67:508–531
61. Gupta PK, Vasistha NK, Aggarwal R, Joshi AK (2018b) Biology of *Bipolaris sorokiniana* (syn. *Cochliobolus sativus*) in genomics era. J. Plant Biochem Biotech 27:123–138
62. Gupta PK (2020) SWEET genes for disease resistance in plants. Trends Genet S0168-9525:30207–30209
63. Haen KM, Lu HJ, Friesen TL, Faris JD (2004) Genomic targeting and high-resolution mapping of the *Tsn1* gene in wheat. Crop Sci 44:951–962
64. Hafez M, Gourlie R, Despins T, Turkington TK, Friesen TL, Aboukhaddour R (2020) *Parastagonospora nodorum* and related species in western Canada: genetic variability and effector genes. Phytopathology 110:1946–1958
65. Halder J, Zhang J, Ali S, Sidhu JS, Gill HS, Shyamal K et al (2019) Mining and genomic characterization of resistance to tan spot, Stagonospora nodorum blotch (SNB), and Fusarium head blight in Watkins core collection of wheat landraces. BMC Plant Biol 19:480
66. Hales B, Steed A, Giovannelli V, Burt C, Lemmens M, Molnár-Láng M, Nicholson P (2020) Type II Fusarium head blight susceptibility conferred by a region on wheat chromosome 4D. J Exp Bot 16:4703–4714
67. Hane JK, Lowe RG, Solomon PS, Tan KC, Schoch CL, Spatafora JW et al (2007) Dothideomycete plant interactions illuminated by genome sequencing and EST analysis of the wheat pathogen *Stagonospora nodorum*. Plant Cell 19:3347–3368
68. Haugrud ARP, Zhang Z, Richards JK, Friesen TL, Faris JD (2019) Genetics of variable disease expression conferred by inverse gene-for-gene interactions in the wheat-*Parastagonospora nodorum* pathosystem. Plant Physiol 180:420–434
69. He ZH, He D, Kohorn BD (1998) Requirement for the induced expression of a cell wall associated receptor kinase for survival during the pathogen response. Plant J 14:55–63
70. lpCho SVS, Tan K-C, Koh G, Gummer J, Oliver RP, Trengove RD et al (2010) The transcription factor StuA regulates central carbon metabolism, mycotoxin production, and effector gene expression in the wheat pathogen *Stagonospora nodorum*. Eukaryot Cell 9:1100–1108
71. Johnson T (1947) A form of *Leptosphaeria avenariaon* wheat in Canada. Can J Res Sect C 25:259–270
72. Johnson T (1952) Cultural variability in *Septoria avenae* Frank. Can J Bot 30:318–330
73. Jones J, Dangl J (2006) The plant immune system. Nature 444:323–329
74. Jones DAB, John E, Rybak K, Phan HTT, Singh KB, Lin SY et al (2019) A specific fungal transcription factor controls effector gene expression and orchestrates the establishment of the necrotrophic pathogen lifestyle on wheat. Sci Rep 49:15884

75. Kamel S, Cherif M, Hafez M, Despins T, Aboukhaddour R (2019) *Pyrenophora tritici-repentis* in Tunisia: race structure and effector genes. Front Plant Sci 10:1562
76. Korte A, Farlow A (2013) The advantages and limitations of trait analysis with GWAS: a review. Plant Methods 9:29
77. Kourelis J, van der Hoorn RAL (2018) Defended to the nines: 25 years of resistance gene cloning identifies nine mechanisms for R protein function. The Plant Cell tpc.00579.2017: doi.10.1105/tpc.17.00579
78. Kumar S, Röder MS, Tripathi SB, Kumar S, Chand R, Joshi AK et al (2015) Mendelization and fine mapping of a bread wheat spot blotch disease resistance QTL. Mol Breed 35:218
79. Kumar U, Joshi AK, Kumar S, Chand R, Röder MS (2010) Quantitative trait loci for resistance to spot blotch caused by *B. sorokiniana* in wheat (*T. aestivum* L.) lines 'Ning 8201' and 'Chirya 3'. Mol Breed 26:477–491
80. Lamari L, Bernier CC (1991) Genetics of tan necrosis and extensive chlorosis in tan spot of wheat caused by *Pyrenophora tritici-repentis*. Phytopathology 81:1092–1095
81. Lamari L, Strelkov SE, Yahyaoui A, Orabi J, Smith RB (2003) The identification of two new races of *Pyrenophora tritici-repentis* from the host center of diversity confirms a one-to-one relationship in tan spot of wheat. Phytopathology 93:391–396
82. Lamari L, McCallum BD, Depauw RM (2005) Forensic pathology of Canadian bread wheat: the case of tan spot. Phytopathology 95:144–152
83. Leng Y, Zhao M, Wang R, Steffenson BJ, Brueggeman RS, Zhong S (2018) The gene conferring susceptibility to spot blotch caused by *Cochliobolus sativus* is located at the Mla locus in barley cultivar Bowman. Theor Appl Genet 131:1531–1539
84. Leng Y, Zhao M, Fiedler J, Dreiseitl A, Chao S, Li X, Zhong S (2020) Molecular mapping of loci conferring susceptibility to spot blotch and resistance to powdery mildew in barley using the sequencing-based genotyping approach. Phytopathology 110:440–446
85. Léveillé JH (1841) Description de quelques espèces nouvelles de Champignons. Ann des Sci Nat 16:235–242
86. Lillemo M, Joshi AK, Prasad R, Chand R, Singh RP (2013) QTL for spot blotch resistance in bread wheat line Saar co-locate to the biotrophic disease resistance loci *Lr34* and *Lr46*. Theor Appl Genet 126:711–719
87. Lin M, Ficke A, Cockram J, Lillemo M (2020) Genetic structure of the Norwegian *Parastagonospora nodorum* population. Front Microbiol 11:1280
88. Liu ZH, Friesen TL, Rasmussen JB, Ali S, Meinhardt SW, Faris JD (2004a) Quantitative trait loci analysis and mapping of seedling resistance to Stagonospora nodorum leaf blotch in wheat. Phytopathology 94:1061–1067
89. Liu ZH, Faris JD, Meinhardt SW, Ali S, Rasmussen JB, Friesen TL (2004b) Genetic and physical mapping of a gene conditioning sensitivity in wheat to a partially purified host selective toxin produced by *Stagonospora nodorum*. Phytopathology 94:1056–1060
90. Liu Z, Friesen TL, Ling H, Meinhardt SW, Oliver RP, Rasmussen JB, Faris JD (2006) The *Tsn1*-ToxA interaction in the wheat-*Stagonospora nodorum* pathosystem parallels that of the wheat-tan spot system. Genome 49:1265–1273
91. Liu Z, Faris JD, Oliver RP, Tan KC, Solomon PS, McDonald MC, McDonald BA, Nunez A, Lu S, Rasmussen JB, Friesen TL (2009) SnTox3 acts in effector triggered susceptibility to induce disease on wheat carrying the *Snn3* gene. PLoS Pathog 5:e1000581
92. Liu Z, Zhang Z, Faris JD, Oliver RP, Syme R, McDonald MC, McDonald BA, Solomon PS, Lu S, Shelver WL, Xu S (2012) The cysteine rich necrotrophic effector SnTox1 produced by *Stagonospora nodorum* triggers susceptibility of wheat lines harboring *Snn1*. PLoS Pathog 8:e1002467
93. Liu ZH, Galagedara NN, Li X, Chao S, Xu S, Faris JD et al (2017) Genome wide association mapping of resistance to tan spot in durum wheat. In: Plant Health, Aug 8, 2017. The American Phytopathological Society (APS) 3340 Pilot Knob Road St. Paul, MN 55121, USA

94. Liu Y, Zhang Q, Salsman E, Fiedler JD, Hegstad JB, Liu Z, Faris JD, Xu SS, Li X (2020a) QTL mapping of resistance to tan spot induced by race 2 of *Pyrenophora tritici*-repentis in tetraploid wheat. Theor Appl Genet 133:433–442
95. Liu Y, Salsman E, Wang R et al (2020b) Meta-QTL analysis of tan spot resistance in wheat. Theor Appl Genet 133:2363–2375
96. Richards JK, Stukenbrock EH, Carpenter J, Liu Z, Cowger C, Faris JD, Friesen TL (2019) Local adaptation drives the diversification of effectors in the fungal wheat pathogen *Parastagonospora nodorum* in the United States. PLoS Genet 15:e1008223
97. Lu HJ, Fellers JP, Friesen TL, Meinhardt SW, Faris JD (2006) Genomic analysis and marker development for the *Tsn1* locus using bin-mapped ESTs and flanking BAC contigs. Theor Appl Genet 112:1132–1142
98. Lu S, Friesen TL, Faris JD (2009) Identification of ToxA-interacting proteins suggests a possible role for pathogenesis-related protein 1 (PR-1) in mediating *Stagonospora nodorum*–wheat interactions. In: 14th International Congress on Molecular Plant–Microbe Interactions (MPMI), Quebec City, Canada
99. Lu S, Friesen TL, Faris JD (2011) Molecular characterization and genomic mapping of the pathogenesis-related protein 1 (PR-1) gene family in hexaploidy wheat (*Triticum aestivum* L.). Mol Genet Genom 285:485–503
100. Lu S, Faris JD, Sherwood R, Friesen TL, Edwards MC (2014) A dimeric PR-1-type pathogenesis-related protein interacts with ToxA and potentially mediates ToxA-induced necrosis in sensitive wheat. Mol Plant Pathol 15:650–663
101. Lu P, Liang Y, Li D, Wang Z, Li W, Wang G, Wang Y, Zhou S, Wu Q, Xie J, Zhang D (2016) Fine genetic mapping of spot blotch resistance gene *Sb3* in wheat (*Triticum aestivum*). Theor Appl Genet 129:577–589
102. Manning VA, Andrie RM, Trippe AF, Ciuffetti LM (2004) Ptr ToxA requires multiple motifs for complete activity. Mol Plant–Microbe Interact 17:491–501
103. Manning VA, Ciuffetti LM (2005) Localization of Ptr ToxA produced by *Pyrenophora tritici-repentis* reveals protein import into wheat mesophyll cells. Plant Cell 17:3203–3212
104. Manning VA, Hardison LK, Ciuffetti LM (2007) PtrToxA interacts with a chloroplast-localized protein. Mol Plant–Microbe Interact 20:168–177
105. Martinez JP, Ottum SA, Ali S, Francl LJ, Ciuffetti LM (2001) Characterization of the *ToxB* gene from *Pyrenophora tritici-repentis*. Mol Plant–Microbe Interact 14:675–677
106. Mauseth JD (2014) Botany. Jones and Bartlett Publishers, Burlington
107. McDonald MC, Razavi M, Friesen TL, Brunner PC, McDonald BA (2012) Phylogenetic and population genetic analyses of *Phaeosphaeria nodorum* and its close relatives indicate cryptic species and an origin in the Fertile Crescent. Fungal Genet Biol 49:882–895
108. McDonald MC, Oliver RP, Friesen TL, Brunner PC, McDonald BA (2013) Global diversity and distribution of three necrotrophic effectors in *Phaeosphaeria nodorum* and related species. New Phytol 199:241–251
109. McDonald MC, Solomon PS (2018) Just the surface: advances in the discovery and characterization of necrotrophic wheat effectors. Curr Opin Microbiol 46:14–18
110. McDonald MC, Ahren D, Simpfendorfer S, Milgate A, Solomon PS (2018) The discovery of the virulence gene ToxA in the wheat and barley pathogen *Bipolaris sorokiniana*. Mol Plant Pathol 19:432–439
111. Mebrate SA, Cooke BM (2001) Response of wheat cultivars to infection by *Stagonospora nodorum* isolates mixture on detached and intact seedling leaves. Euphytica 122:263–268
112. Meinhardt SW, Ali S, Ling H, Francl L (2003) A new race of *Pyrenophora tritici*-repentis that produces a putative host-selective toxin. In: Rasmussen JB, Friesen TL, Ali S (eds) International Wheat Tan Spot and Spot Blotch workshop, North Dakota Agricultural Experimental Station, Fargo, July 21–24, 2002, Proceedings. North Dakota State University, North Dakota, pp 117–119

113. Mihuta-Grimm L, Foster RL (1989) Scab on wheat and barley in southern Idaho and evaluation of seed treatment for eradication of *Fusarium spp*. Plant Dis 73:769–771
114. Moffat CS, See PT, Oliver RP (2014) Generation of a ToxA knockout strain of the wheat tan spot pathogen *Pyrenophora tritici-repentis*. Mol Plant Pathol 15:918–926
115. Moolhuijzen P, See PT, Hane JK, Shi G, Liu Z, Oliver RP, Moffat CS (2018a) Comparative genomics of the wheat fungal pathogen *Pyrenophora tritici-repentis* reveals chromosomal variations and genome plasticity. BMC Genom 19:279
116. Moolhuijzen PM, See PT, Oliver RP, Moffat CS (2018b) Genomic distribution of a novel *Pyrenophora tritici-repentis* ToxA insertion element. PLoS One 13:e0206586
117. Moolhuijzen P, See PT, Moffat CS (2020) PacBio genome sequencing reveals new insights into the genomic organisation of the multi-copy *ToxB* gene of the wheat fungal pathogen *Pyrenophora tritici-repentis*. BMC Genom 21:645
118. Navathe S, Yadav PS, Chand R, Mishra VK, Vasistha NK, Mehar PK, Joshi AK, Gupta PK (2020) A study of ToxA-*Tsn1* patho-system for spot blotch susceptibility in Indian wheats: An example of inverse gene-for-gene relationship. Plant Dis 104:71–81
119. Oliver RP, Rybak K, Solomon PS, Ferguson-Hunt M (2009) Prevalence of ToxA-sensitive alleles of the wheat gene *Tsn1* in Australian and Chinese wheat cultivars. Crop Pasture Sci 60:348–352
120. Oliver RP, Friesen TL, Faris JD, Solomon PS (2012) *Stagonospora nodorum*: from pathology to genomics and host resistance. Ann Rev Phytopathol 50:23–43
121. Orolaza NP, Lamari L, Ballance GM (1995) Evidence of a host specific chlorosis toxin from *Pyrenophora tritici-repentis*, the causal agent of tan spot of wheat. Phytopathology 85:1282–1287
122. Pandelova I, Betts MF, Manning VA, Wilhelm LJ, Mockler TC, Ciuffetti LM (2009) Analysis of transcriptome changes induced by Ptr ToxA in wheat provides insights into the mechanisms of plant susceptibility. Mol Plant 2:1067–1083
123. Pandelova I, Figueroa M, Wilhelm LJ, Manning VA, Mankaney AN, Mockler TC, Ciuffetti LM (2012) Host-selective toxins of *Pyrenophora tritici-repentis* induce common responses associated with host susceptibility. PLoS One 7:e40240
124. Pascual L, Albert E, Sauvage C, Duangjit J, Bouchet JP, Bitton F, Desplat N, Brunel D, Le Paslier MC, Ranc N, Bruguier L (2016) Dissecting quantitative trait variation in the resequencing era: complementarity of bi-parental, multi-parental and association panels. Plant Sci 242:120–130
125. Phan HT, Rybak K, Furuki E, Breen S, Solomon PS, Oliver RP, Tan KC (2016) Differential effector gene expression underpins epistasis in a plant fungal disease. Plant J 87:343–354
126. Phan HT, Rybak K, Bertazzoni S, Furuki E, Dinglasan E, Hickey LT, Oliver RP, Tan KC (2018) Novel sources of resistance to Septoria nodorum blotch in the Vavilov wheat collection identified by genome-wide association studies. Theor Appl Genet 13:1223–1238
127. Quaedvlieg W, Kema GHJ, Groenewald JZ, Verkley GJM, Seifbarghi S, Razavi M, Mirzadi Gohari A, Mehrabi R, Crous PW (2011) *Zymoseptoria gen*. nov.: a new genus to accommodate Septoria-like species occurring on *graminicolous* hosts. Persoonia 26:57–69
128. Rawlinson C, See PT, Moolhuijzen P, Li H, Moffat CS, Chooi YH, Oliver RP (2019) The identification and deletion of the polyketide synthase-nonribosomal peptide synthase gene responsible for the production of the phytotoxic triticone A/B in the wheat fungal pathogen *Pyrenophora tritici-*repentis. Environ Microbiol 21:4875–4886
129. Reddy L, Friesen TL, Meinhardt SW, Chao S, Faris JD (2008) Genomic analysis of the *Snn1* locus on wheat chromosome arm 1BS and the identification of candidate genes. Plant Genome 1:55–66
130. Reis EM (1985) Doencas do trigo III. Fusariose. Brasil, Merck Sharp Dohme

131. Richards JK, Wyatt NA, Liu Z, Faris JD, Friesen TL (2018) Reference quality genome assemblies of three *Parastagonospora nodorum* isolates differing in virulence on wheat. G3 (Bethesda) 8:393–399
132. Ruud AK, Windju S, Belova T, Friesen TL, Lillemo M (2017) Mapping of SnTox3–*Snn3* as a major determinant of field susceptibility to Septoria nodorum leaf blotch in the SHA3/CBRD × Naxos population. Theor Appl Genet 130:1361–1374
133. Ruud AK, Dieseth JA, Lillemo M (2018) Effects of three *Parastagonospora nodorum* necrotrophic effectors on spring wheat under Norwegian field conditions. Crop Sci 58:159–168
134. Ruud AK, Dieseth JA, Ficke A, Furuki E, Phan HTT, Oliver RP, Tan KC, Lillemo M (2019) Genome-wide association mapping of resistance to Septoria nodorum leaf blotch in a nordic spring wheat collection. Plant Genome 12:1–15
135. Scharen AL, Eyal Z, Huffman MD, Prescott JM (1985) The distribution and frequency of virulence genes in geographically separated populations of Leptosphaeria nodorum. Phytopathology 75:1463–1468
136. Schnurbusch T, Paillard S, Fossati D, Messmer M, Schachermayr G, Winzeler M (2003) Detection of QTLs for Stagonospora glume blotch resistance in Swiss winter wheat. Theor Appl Genet 107:1226–1234
137. See PT, Marathamuthu KA, Iagallo EM, Oliver RP, Moffat CS (2018) Evaluating the importance of the tan spot ToxA–*Tsn1* interaction in Australian wheat varieties. Plant Pathol 67:1066–1075
138. See PT, Iagallo EM, Oliver RP, Moffat CS (2019) Heterologous expression of the *Pyrenophora tritici*-repentis effector proteins ToxA and ToxB, and the prevalence of effector sensitivity in Australian cereal crops. Front Microbiol 10:182
139. Sharma S (2019) Genetics of wheat domestication and Septoria nodorum blotch susceptibility in wheat. Dissertation, North Dakota State University
140. Shi G, Friesen TL, Saini J, Xu SS, Rasmussen JB, Faris JD (2015) The wheat *Snn7* gene confers susceptibility on recognition of the *Parastagonospora nodorum* necrotrophic effector SnTox7. Plant Genome 8:1–10
141. Shi G, Zhang Z, Friesen TL, Bansal U, Cloutier S, Wicker T, Rasmussen JB, Faris JD (2016a) Marker development, saturation mapping, and high-resolution mapping of the Septoria nodorum blotch susceptibility gene *Snn3-B1* in wheat. Mol Genet Genom 291:107–119
142. Shi G, Zhang Z, Friesen TL, Raats D, Fahima T, Brueggeman RS, Lu S, Trick HN, Liu Z, Chao W, Frenkel Z (2016b) The hijacking of a receptor kinase-driven pathway by a wheat fungal pathogen leads to disease. Sci Adv 2:e1600822
143. Shoemaker RA (1959) Nomenclature of *Drechslera* and *Bipolaris*, grass parasites segregated from '*Helminthosporium*'. Can J Bot 37:879–887
144. Shoemaker RA (1962) Drechslera Ito. Can J Bot 40:809–836
145. Shoemaker RA, Babcock CE (1989) Diadema. Can J Bot 67:1349–1355
146. Singh PK, Gonzalez-Hernandez JL, Mergoum M, Ali S, Adhikari TB, Kianian SF, Elias EM, Hughes GR (2006) Identification and molecular mapping of a gene in tetraploid wheat conferring resistance to *Pyrenophora tritici-repentis* race 3. Phytopathology 96:885–889
147. Singh PK, Mergoum M, Ali S, Adhikari TB, Hughes GR (2008a) Genetic analysis of resistance to *Pyrenophora tritici-repentis* races 1 and 5 in tetraploid and hexaploid wheat. Phytopathology 98:702–708
148. Singh PK, Mergoum M, Gonzalez-Hernandez JL, Ali S, Adhikari TB, Kianian SF, Elias EM, Hughes GR (2008b) Genetics and molecular mapping of resistance to necrosis-inducing race 5 of *Pyrenophora tritici-repentis* in tetraploid wheat. Mol Breed 21:293–304
149. Singh PK, Mergoum M, Adhikari TB, Shah T, Ghavami F, Kianian SF (2010) Genetic and molecular analysis of wheat tan spot resistance effective against *Pyrenophora tritici-repentis* races 2 and 5. Mol Breed 25:369–379
150. Singh PK, Singh S, Deng Z, He X, Kehel Z, Singh RP (2019) Characterization of QTLs for seedling resistance to tan spot and Septoria Nodorum Blotch in the PBW343/Kenya Nyangumi wheat recombinant inbred lines population. Int J Mol Sci 20:5432

151. Sperschneider J, Dodds PN, Singh KB, Taylor JM (2018) ApoplastP: prediction of effectors and plant proteins in the apoplast using machine learning. New Phytol 217:1764–1778
152. Sprague R (1950) Diseases of cereals and grasses in North America. Ronald Press, New York
153. Strelkov SE, Lamari L, Balance GM (1998) Induced chlorophyll degradation by a chlorosis toxin from *Pyrenophora tritici-repentis*. Can J Plant Pathol 20:428–435
154. Strelkov SE, Lamari L, Sayoud R, Smith R (2002) Comparative virulence of chlorosis-inducing races of *Pyrenophora tritici-repentis*. J Plant Pathol 24:29–35
155. Strelkov SE, Lamari L (2003) Host-parasite interactions in tan spot [*Pyrenophora tritici-repentis*] of wheat. Can J Plant Pathol 25:339–349
156. Stukenbrock EH, McDonald BA (2007) Geographical variation and positive diversifying selection in the host-specific toxin *SnToxA*. Mol Plant Pathol 8:321–332
157. Sutton BC (1976) Angiopoma Lev, 1841, an earlier name for *Drechslera* Ito, 1930. Mycotaxon 3:377–380
158. Syme RA, Hane JK, Friesen TL, Oliver RP (2013) Resequencing and comparative genomics of *Stagonospora nodorum*: sectional gene absence and effector discovery. G3 (Bethesda) 3:959–969
159. Syme RA, Tan KC, Hane JK, Dodhia K, Stoll T, Hastie M, Furuki E, Ellwood SR, Williams AH, Tan YF, Testa AC (2016) Comprehensive annotation of the *Parastagonospora nodorum* reference genome using next-generation genomics, transcriptomics, and proteogenomics. PLoS One 11:e0147221
160. Syme RA, Tan KC, Rybak K, Friesen TL, McDonald BA, Oliver RP, Hane JK (2018) Pan-*Parastagonospora* comparative genome analysis–effector prediction and genome evolution. Gen Biol Evol 10:2443–2457
161. Tadesse W, Hsam SL, Zeller (2006a) Evaluation of common wheat varieties for tan spot resistance and chromosomal location of resistance gene in the cultivar “Salamouni”. Plant Breed 125:318–322
162. Tadesse W, Hsam SL, Zeller FJ (2006b) Identification and monosomic analysis of tan spot resistance genes in synthetic wheat lines (*Triticum turgidum* L × *Aegilops tauschii* Coss.). Crop Sci 46:1212–1217
163. Tadesse W, Schmolke M, Hsam SL, Mohler V, Wenzel G, Zeller FJ (2007) Molecular mapping of resistance genes to tan spot [*Pyrenophora tritici-repentis* race 1] in synthetic wheat lines. Theor Appl Genet 114:855–862
164. Tadesse W, Schmolke M, Hsam SL, Mohler V, Wenzel G, Zeller FJ (2010) Chromosomal location and molecular mapping of a tan spot resistance gene in the winter wheat cultivar Red Chief. J Appl Genet 51:235–242
165. Tan KC, Oliver RP, Solomon PS, Moffat CS (2010) Proteinaceous necrotrophic effectors in fungal virulence. Funct Plant Biol 37:907–912
166. Tan KC, Waters OD, Rybak K, Antoni E, Furuki E, Oliver RP (2014) Sensitivity to three *Parastagonospora nodorum* necrotrophic effectors in current Australian wheat cultivars and the presence of further fungal effectors. Crop Pasture Sci 65:150–158
167. Tan KC, Phan HT, Rybak K, John E, Chooi YH, Solomon PS, Oliver RP (2015) Functional redundancy of necrotrophic effectors-consequences for exploitation for breeding. Front Plant Sci 6:501
168. Tan KC, Jones D, Rybak K, Phan H, John E, Singh KB, Oliver RP (2019) Identification and functional characterisation of genes regulated by the PnPf2 Zn2Cys6 transcription factor in *Parastagonospora nodorum*. In: IS-MPMI XVIII Congress, July 14–18, 2019, Glasgow, Scotland, pp 778
169. Tuori RP, Wolpert TJ, Ciuffetti LM (1995) Purification and immunological characterization of toxic components from cultures of *Pyrenophora tritici-repentis*. Mol Plant–Microbe Interact 8:41–48
170. Uphaus J, Walker E, Shankar M, Golzar H, Loughman R, Francki M, Ohm H (2007) QTL identified for resistance to Stagonospora glume blotch in wheat in the USA and Australia. Crop Sci 47:1813–1822
171. Virdi SK, Liu Z, Overlander ME, Zhang Z, Xu SS, Friesen TL, Faris JD (1916) New insights into the roles of host gene-necrotrophic effector interactions in governing susceptibility of durum wheat to tan spot and Septoria nodorum

blotch. G3 (Bethesda) 6:4139–4150

172. Wallwork H, Lichon A, Sivanesan A (1992) *Drechslera wirreganensis* - a new hyphomycete affecting barley in Australia. Mycol Res 96:886–888
173. Waters OD, Lichtenzveig J, Rybak K, Friesen TL, Oliver RP (2011) Prevalence and importance of sensitivity to the *Stagonospora nodorum* necrotrophic effector SnTox3 in current Western Australian wheat cultivars. Crop Pasture Sci 62:556–562
174. Weber GF (1922) II. Septoria diseases of wheat. Phytopathology 12:537–585
175. Wegulo SN (2011) Tan spot of cereals. The plant health instructor. doi:10.1094/PHI-I-2011-0426-01
176. Wicki W, Winzeler M, Schmid JE, Stamp P, Messmer M (1999) Inheritance of resistance to leaf and glume blotch caused by *Septoria nodorum* Berk. in winter wheat. Theor Appl Genet 99:1265–1272
177. Winterberg B, Du Fall LA, Song X et al (2014) The necrotrophic effector protein SnTox3 re-programs metabolism and elicits a strong defence response in susceptible wheat leaves. BMC Plant Biol 14:215
178. Wu L, He X, Lozano N, Zhang X, Singh PK (2020) ToxA, a significant virulence factor involved in wheat spot blotch disease, exists in the Mexican population of *Bipolaris sorokiniana*. Trop Plant Pathol. doi.org/10.1007/s40858-020-00391-4
179. Xu SS, Friesen TL, Mujeeb-Kazi A (2004) Seedling resistance to tan spot and Stagnospora nodorum blotch in synthetic hexaploid wheats. Crop Sci 44:2238–2245
180. Yaegashi H, Udagawa S (1978) The taxonomical identity of the perfect state of *Pyricularia grisea* and its allies. Can J Bot 56:180–183
181. Zhang Z, Friesen TL, Simons KJ, Xu SS, Faris JD (2009) Development, identification, and validation of markers for marker-assisted selection against the *Stagonospora nodorum* toxin sensitivity genes *Tsn1* and *Snn2* in wheat. Mol Breed 23:35–49
182. Zhang Z, Friesen TL, Xu SS, Shi G, Liu Z, Rasmussen JB, Faris JD (2011) Two putatively homoeologous wheat genes mediate the recognition of SnTox3 to confer effector-triggered susceptibility to *Stagonospora nodorum*. Plant J 65:27–38
183. Zhang P, Guo G, Wu Q, Chen Y, Xie J, Lu P, Li B, Dong L, Li M, Wang R, Yuan C (2020) Identification and fine mapping of spot blotch (*Bipolaris sorokiniana*) resistance gene *Sb4* in wheat. Theor Appl Genet 133:2451–2459

Tables

Table 1 Necrotrophs and hemibiotrophs causing diseases in wheat

Pathogen (teleomorph)	Anamorph	Disease caused	Reference
Parastagonospora nodorum (Berk.)	*Stagonospora nodorum* [Berk.] Castellani & E.G. Germano)	Septoria Nodorum Blotch (SNB)	Weber 1922; Sprague 1950; King et al. 1983; Scharen et al. 1985
Pyrenophora tritici-repentis (Died)	*Drechslera tritici*-repentis (Died)	Tan spot	Drechsler 1923; Shoemaker 1959, 1962
Cochliobolus sativus (S. Ito & Kurib.) Drechsler ex Dastur	*Bipolaris sorokiniana*	Spot Blotch (SB)	Dastur 1942; Shoemaker 1959
Phaeosphaeria avenaria f. sp. Tritici 1 (Pat 1)	*Stagonospora avenae* f. sp. triticea	Septoria avenae blotch	Johnson 1947, 1952; Shoemaker and Babc 1989
Pyrenophora wirreganensis	*Drechslera wirreganensis*	Wirrega blotch	Wallwork et al. 1992
Pyrenophora semeniperda	*Drechslera campanulata*	Ring spot	Léveillé 1841; Sutton 1976
Zymoseptoria tritici (Desm.) Quaedvlieg and Crous	*Mycosphaerella graminicola* (Fuckel) J. Schrot. in Cohn); *Septoria tritici* (Rob in Desm.)	Leaf Blotch (LB); *Septoria tritici* blotch (STB)	Quaedvlieg et al. 2011
Gibberella zeae	*F. graminearum*	Fusarium head blight or scab	Mihuta-Grimm and Foster 1989; Reis 1985
Gibberella coronicola	*F. culmorum*	Crown rot	Aoki and O'Donnell 1999
Magnaporthe grisea (Hebert) Barr	*Pyricularia grisea* (Saccardo), syn. *P. oryzae* (Cavara)	Wheat blast	Barr 1977; Yaegashi and Udagawa 1978

Table 2 A comparison of characteristics of biotrophs and necrotrophs (http://www.davidmoore.org.uk/21st_Century_Guidebook_to_Fungi_PLATINUM/Ch14_10.htm).

Biotrophs pathogen	Necrotrophs pathogen
Appressoria or haustoria produced	Appressoria/haustoria normally not produced
Resistance is controlled by SA-dependent host-defense pathways	Resistance controlled by JA and Et-dependent host-defence pathways
Gene-for-gene (GFG) relationship holds good	Generally quantitative resistance and/or Inverse gene-for-gene (IGFG) relationship
Difficult to culture	Easy to culture
Direct entry or through natural openings	Entry via wounds or natural openings
Survive on host or as dormant propagules	Survive as competitive saprotrophs
Survive on living tissues	Survive on living/dead tissues
Cells not killed rapidly; hypersensitive reaction (HR) in resistant genotype	Host cells killed rapidly
Few lytic enzymes/toxins are produced	Cell-wall-degrading (lytic) enzymestoxins
Often systemic	Seldom systemic
Attack vigorous; any stage	Attack weak, young/damaged plants
Narrow host range	Wide host range
Intercellular growth of pathogen	Intercellular/intracellular growth
Effectors: Avr proteins recognized by matching resistance (R) proteins.	Effectors: host-specific or host-selective toxins (HST).
Disease caused by suppressing PTI/ETI,	Disease due to interaction of HSTs (NEs) with products of sensitivity genes

Table 3 A summary of interactions between NEs and sensitivity genes and some related details

HST sensitivity gene interaction	Pathotypes	Differential lines	Mass of HSTs	Experimental populations/	Markers	Symptoms	Ref#
I. Wheat-*P. nodorum* interactions							
Tsn1-SnToxA	Sn2000, Sn6, Sn15, Sn1501	BG261	13.2 kDa	RILs: BR34 × Grandin,	$5BL^{M1*}$	Necrosis chlorosis	1
Snn1-SnTox1	Sn4, Sn5, Sn6, Sn2000	W-7984	10.3 kDa	RILs: W-7984 × Opata 85	$1BS^{M2*}$	Necrosis	2
Snn2-SnTox2	Sn4, Sn5 Sn1501, Sn6	BG223	7-10 kDa	RILs: BR34 × Grandin	$2DSM^{3*}$	Extensive necrosis	3
Snn3B1-SnTox3	Sn4, Sn79+SnToxA, Sn1501, SN15KO18, Sn79+SnTox3A, Sn79+SnTox3B	BG220	25.8 kDa	F_2: TA2377 × BG220	$5BS^{M4*}$		4
Snn3D1-SnTox3	Sn4, Sn79+SnToxA, Sn1501, SN15KO18, Sn79+SnTox3A, Sn79+SnTox3B	BG220	25.8 kDa	F_2: TA2377 × AL8/78	$5DS^{M5*}$	Necrosis chlorosis	5
Snn4-SnTox4	Sn99CH 1A7a	AF89, ITMI44	10.3 kDa	RILs: Arina × Forno	$1AS^{M6*}$	Mottled necrosis	6
Snn5-SnTox5	Sn2000 Sn2000KO6-1, Sn1501	LP29, ITMI44	10-30 kDa	RILs: Durum Lebsock × T. turgidum, Lebsock × PI 94749	4BLM7*	Necrosis chlorosis	7
Snn6-SnTox6	Sn6	ITMI37	12 kDa	RILs: Opata 85 × W-7984	$6AL^{M8*}$	Necrosis chlorosis	8
Snn7-SnTox7	Sn6	CTm208	< 30 kDa	RILs: CS-Tm2D × CS	$2D^{M9*}$	Necrosis chlorosis	9
II. Wheat-*P. tritici* repentis interaction							
Tsn1-ToxA	Ptr Race 1, 2	Glenlea	13.2kDa (protein)	RILs: CS × CS-DIC 5B F_2: LDN × LDN-DIC 5B	$5BL^{M1*}$	Necrosis chlorosis	10
Tsc1-ToxC	Ptr Races 1, 3	Glenlea, 6B365	Not a protein	RILs: Opata 85 × W-7984	$1AS^{M10*}$	Chlorosis	11
Tsc2-ToxB	Ptr Race 5, 6, 7, 8	6B662, Coulter	6.5 kDa (protein)	NIAB and BMW MAGIC population	$2BS^{M11*}$	Chlorosis	12
III. Wheat-*B. sorokiniana* interaction							
Tsn1-BsToxA	TexD16Bs1; other Aus/Ind pathotypes	BG261	13.2kDa	RILs: Arina × Forno	$5BL^{M1*}$	Necrosis	13

***= Associated molecular markers; M1* =** *Xfcg17, Xfcg9, XBF483506, XBM138151.1, Xgwm260-Xbarc73 Xgwm1043, glk165, Xfcp623, Xfcp620, Xfcp394;* **M2* =** *XksuD14; Xmwg546, Xmwg546, Xcdo1312, XksuG12, Xksu912, Xcdo1508, Xbcd361, Xbcd758, and Xksu927, Xfcp618 and Xpsp3000, Xbcd183, Xbcd1030 (Tetraploid wheat), Xgwm33.1, Xfcp1, Xfcp394, Xfcp620, XBF293222, XBE422980, XBE637568, XBE605202, Xpsp3000;* **M3*=** *Xgwm614, Xbarc95, Xcfd56, Xcfd51, XTC253803, XTC240114, XBE489611;* **M4* =** *Xgwm234, Xcfd20, Xcfb306, XBE606637, XBF200555, Xcfd20, XBF293016, Xcfb306, Xmag705; Xfcp654, Snn3-B1, Xmag705, XTC266536, Xfcp654, Xfcp665, Xfcp652*

Xmag705, XTC266536; **M5*** = *XBE606637, Xbarc130, Xcfd18, Xhbg337, XBF200555, Xgwm190, Xbarc130, XBE585732, Xcfd18, Xhbg337, Xgwm190;* **M6***=*XBE9590632, XBG262267, XBG262975, Xcfd58.1, XBG262267, XBG262975, Xcfd58.1, Xksum104, Xksum182.1;* **M7*** = *Xbarc163, Xcfd22, Xwmc349;* **M8***= *XBE424987, XBE403326;* **M9***= *Xcfd44, Xcfd50;* **M10*** = *XGli1, Xhbd152, XksuM182, XksuM104, Xgwm136, XksuD14;* **M11***= *Kukri_c63748_1453, RAC875_c38018_278, TC339813, BE444541, BS00072620_51*

#= References; 1# = (Tuori et al. 1995; Liu et al. 2006; Chu et al. 2010) **2# =** (Liu et al. 2004a,b; Reddy et al. 2008; Friesen et al. 2007; Faris and Friesen 2009; Liu et al. 2009; Zhang et al. 2009; Shi et al. 2015; Liu et al. 2016); **3# =** (Friesen et al. 2007; Friesen et al. 2008; Zhang et al. 2009); **4# =** (Friesen et al. 2008, 2012; Liu et al. 2009; Zhang et al. 2011); **5# =** (Zhang et al. 2011); **6# =** (Abeysekara et al. 2009); **7# =** (Friesen et al. 2012); **8# =** (Gao et al. 2015); **9#=** (Shi et al. 2015); **10# =** (Tuori et al. 1995; Strelkov and Lamari 2003; Haen et al. 2004; Lu et al. 2006; Faris et al. 2010; 2013; See et al. 2019); **11#=** (Faris et al. 1997; Effertz et al. 2002; Lamari et al. 2003; Wegulo 2011); **12#=** (Strelkov et al. 1998; Lamari et al. 2003; Abeysekara et al. 2010; Corsi et al. 2020); **13#=** (Tuori et al. 1995; Friesen et al. 2018; McDonald et al. 2018; Navathe et al. 2020)

Table 4 Sensitivity genes, QTLs and R genes for three wheat diseases

I. Septoria Nodorum Blotch (SNB) caused by *Parastagonospora nodorum*
Sensitivity genes/QTLs: Tsn1, Snn1 (Qsnb.fcu-1BS, Qsnn.niab-5A), Snn2, Snn3 (Qsnb.fcu-5BS), Snn4 (*QSnb.fcu-1A*)*, Snn5, Snn6, Snn7, Qsng.pur-2DL.1, Qsn.ndsu.1BL, Qsng.pur-2DL.2, Qsnb.fcu-5BL.1, Qsnb.cur-4BL Qsnb.cur-2AS1, Qsnb.cur-3AL, Qsnb.cur-6BS, Qsnb.cur-2DS, Qsnb.cur-2AS2* and *Qsnb.cur2BS* (1*) *R genes: SnbTM, and SnbAes1, snn1, Snb1, Snb2* and *Snb3* (1#)
II. Tan Spot (TS) caused by *Pyrenophora tritici-repentis*
Sensitivity gene/QTLs: Tsn1, Tsc1, Tsc2, QTsc.niab-2A and *QTsc.ndsu-1AS* (2*) *R genes: Tsr1, Tsr2, Tsr3, Tsr4, Tsr5, Tsr6, Tsr7, TsrHar, TsrAri* and *TsrAes1* (2#)
III. Spot Blotch (SB) caused by *Bipolaris sorokiniana*
Sensitivity gene/QTLs: Tsn1 (3*) *R genes: Sb1, Sb2, Sb3* and *Sb4* (3#)

, #=** References: **1 (Faris et al. 2010; Cockram et al. 2015; Friesen et al. 2008, 2009, 2012; Abeysekara et al. 2012; Shi et al. 2015); **1#** (Uphaus et al. 2007; Abeysekara et al. 2012; Schnurbusch et al. 2003; Arseniuk et al. 2004; Gonzalez-Hernandez et al. 2009; Aguilar et al. 2005; Lin et al. 2020); **2*** (Faris et al. 1997, 1999, 2010, Effertz et al. 2001, 2002; Liu et al. 2017), **2#** (Faris et al. 1996, 2013, 2020; Singh et al. 2006, 2008a,b, 2019; Tadesse et al. 2006a,b, 2007, 2010, Meinhardt et al. 2003; Touri et al. 1995; Friesen and Faris 2004; Faris and Friesen 2005; Zhang et al. 2019; Chu et al. 2008), **3#** (Kumar et al. 2010; Lillemo et al. 2013; Kumar et al. 2015; Lu et al. 2016; Zhang et al. 2020); **4*** (Hales et al. 2020).

Table 5 Distribution (%) of three Tox genes among isolates of *P. nodorum*

Region	*SnToxA*	*SnTox1*	*SnTox3*	Reference
Norwegian	69	53	76	Ruud et al. 2018
North Dakota, South Dakota and Minnesota	96	100	62	Richards et al. 2019
Eastern USA	4.0	88	52	Richards et al. 2019
USA	63.4	95.4	58.9	Richards et al. 2019
Fertile Crescent	95	97	72	Ghaderi et al. 2020
Southeastern United States	15	74	39	Crook et al. 2012
World-wide collection	18	26	22	McDonald et al. 2013
Europe	12	89	67	McDonald et al. 2013
Norwegian	67.9	46.1	47.9	Lin et al. 2020
Canada	69.2	80.7	76.9	Hafez et al. 2020

Table 6 Distribution (%) of three major wheat sensitivity genes for SNB in wheat germplasm

Region	*Tsn1*	*Snn1*	*Snn3*	Reference
Australia	63	71.7	91.3	Tan et al. 2014
USA	32	0	64	Bertucci et al. 2014
Canada	59	32.9	56.9	Hafez et al. 2020
Russia	29.3	26.8	51.2	Phan et al. 2018
Kazakhstan	27.7	28.6	63.6	Phan et al. 2018
India	66.7	58.3	77.8	Phan et al. 2018
Pakistan	59.4	71.9	68.8	Phan et al. 2018
British French, German and Dutch	9.1	28	42	Downie et al. 2018

Table 7 Eight races of *P. tritici-repentis* and their NE constitution

Race	NE Constitution
1	Ptr ToxA + Ptr ToxC
2	Ptr ToxA
3	Ptr ToxC
4	No effector (non-pathogenic)
5	Ptr ToxB
6	Ptr ToxB + Ptr ToxC
7	Ptr ToxA + Ptr ToxB
8	Ptr ToxA + Ptr ToxB + Ptr ToxC

Figures

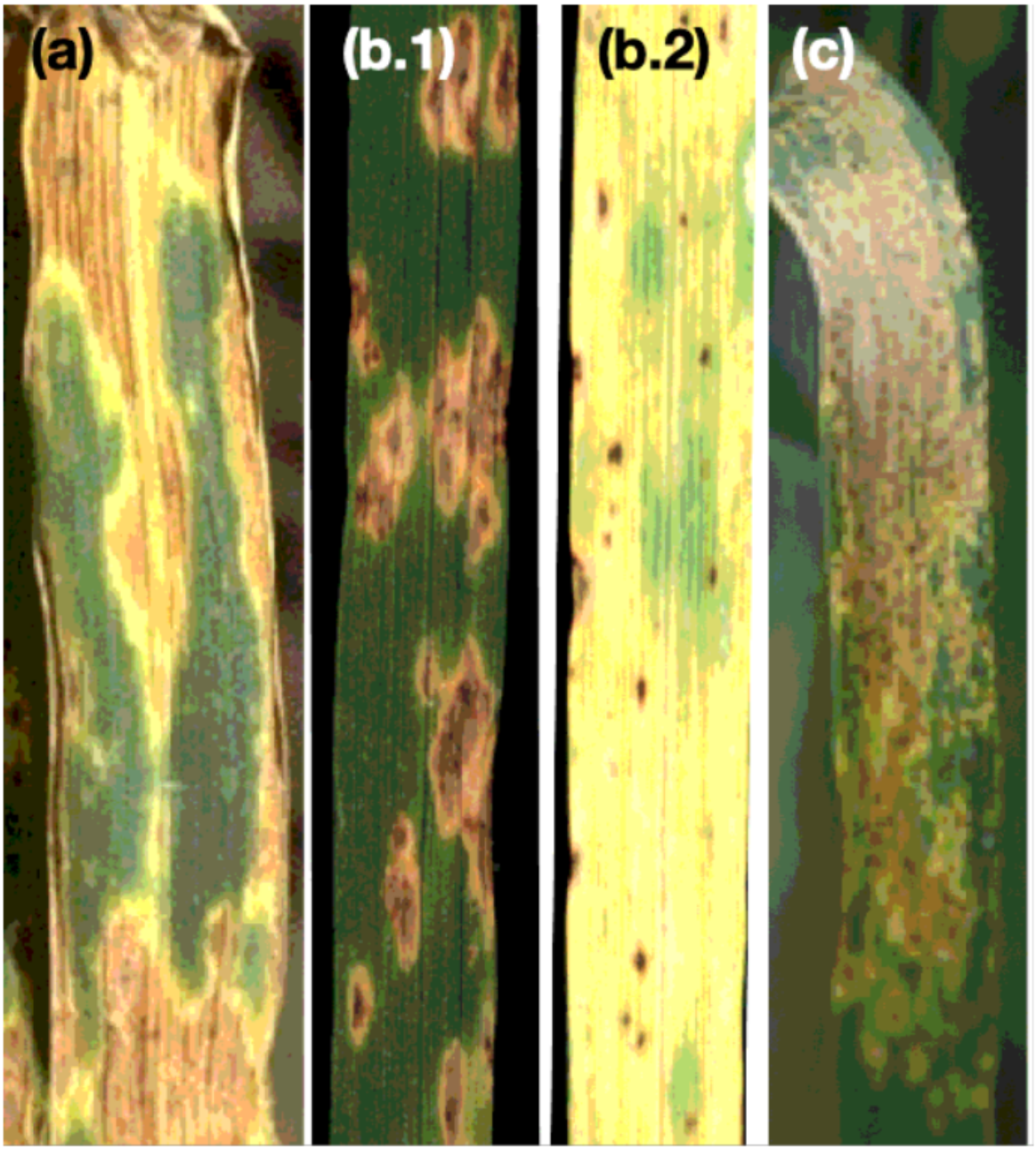

Figure 1

The visual symptoms of three necrotrophic diseases. (a) Septoria nodorum blotch; (b) tan spot (b1 and b2 showing necrosis and chlosis) and (c) spot blotch.

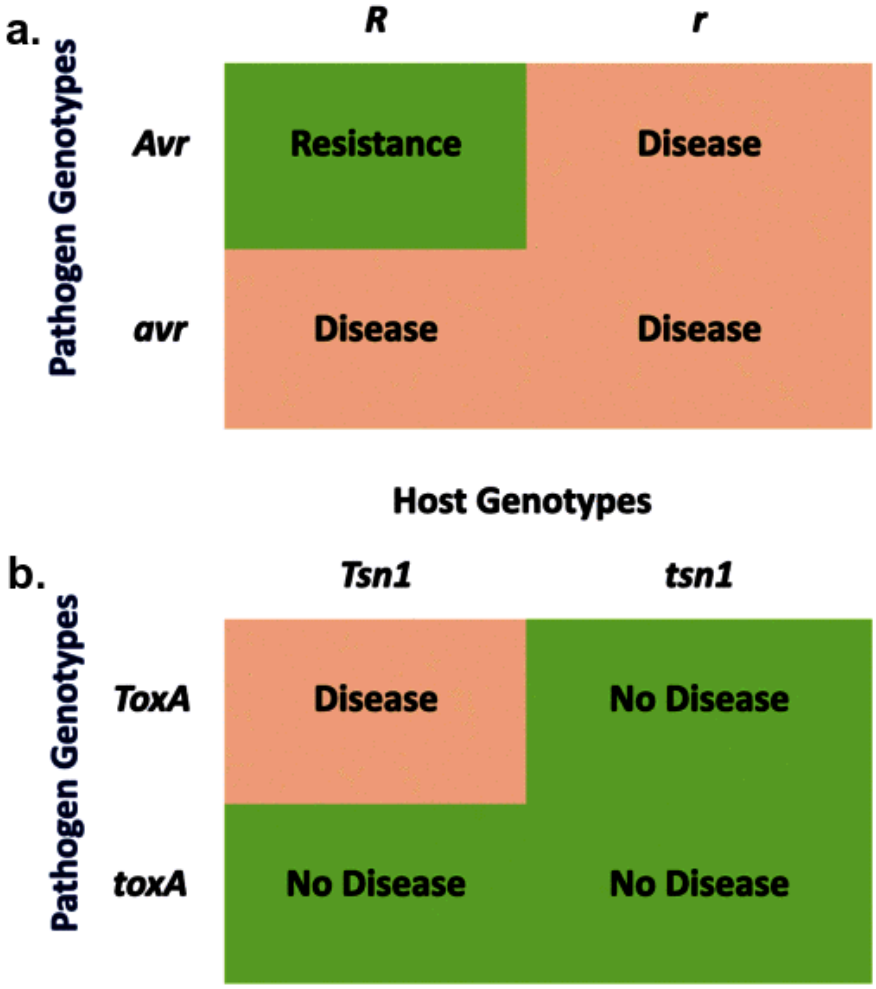

Figure 2

Two different models for host- pathogen interactions in plants: (a) gene-for gene (GFG) model, proposed by Flor (1956) and (b) an inverse gene-for gene (IGFG) model that was discovered recently in a number of necrotrophic diseases in wheat.

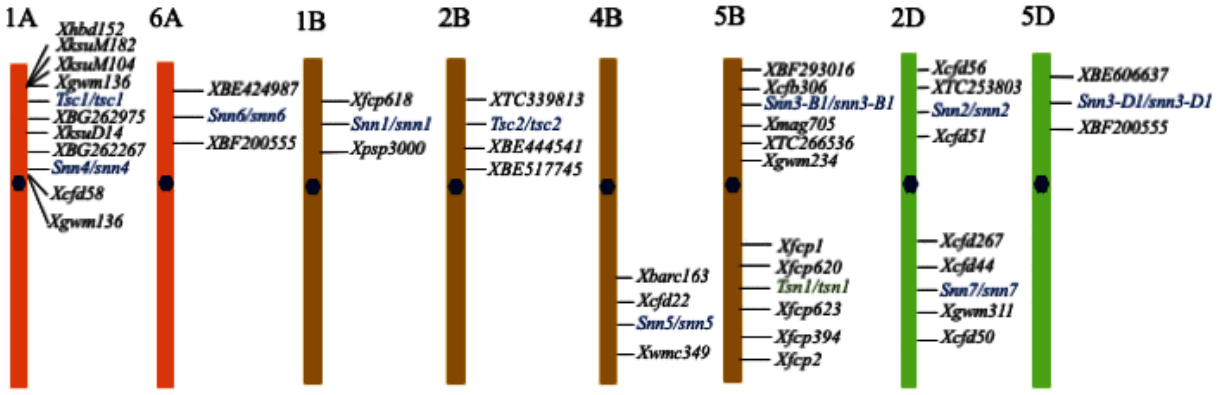

Figure 3

A graphical representation of chromosomal locations of sensitivity/ susceptibility related genes/QTLs of tan spot (green), SNB (blue) and their associated molecular markers.

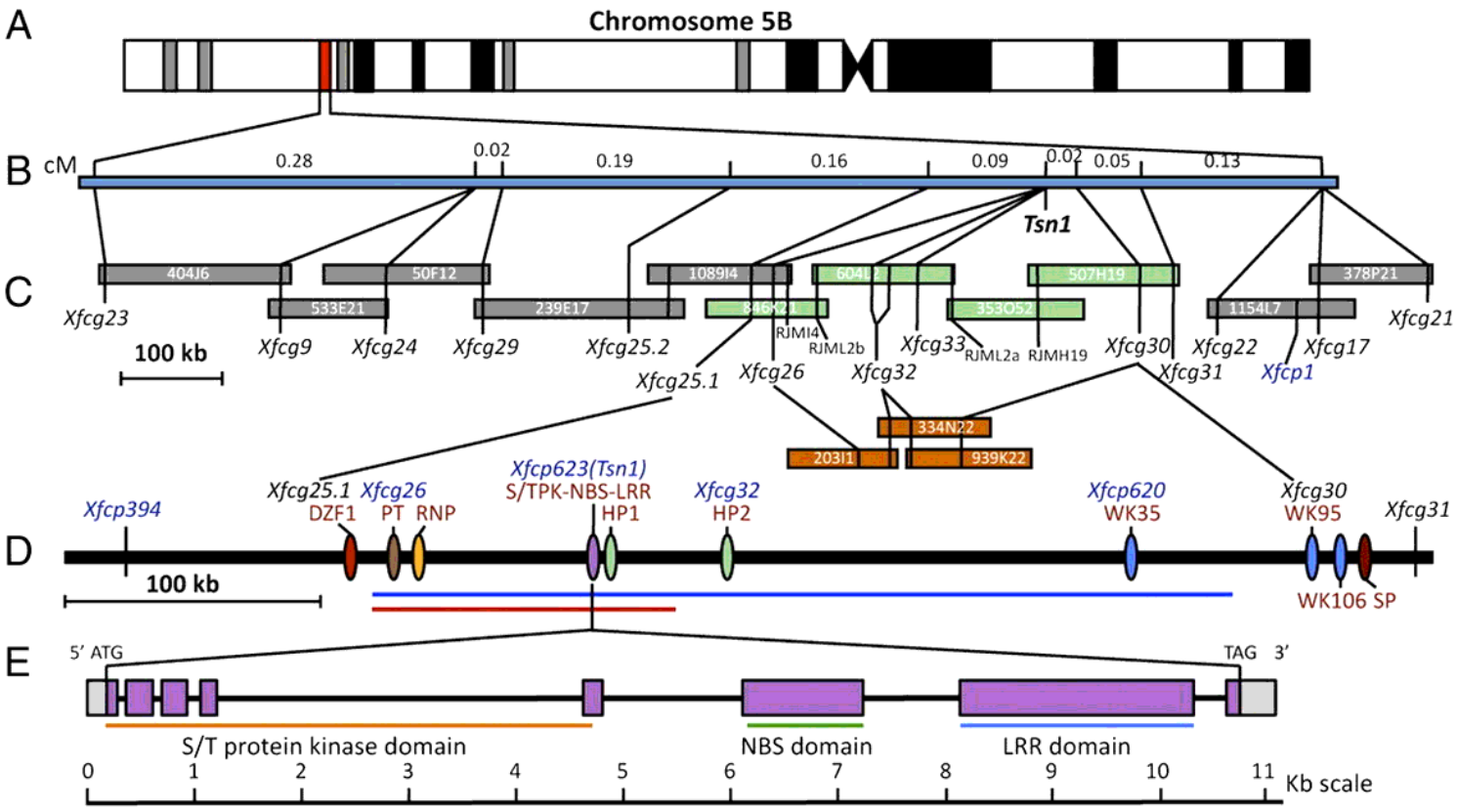

Figure 4

Map-based cloning of the Tsn1 gene. (A) The Tsn1 gene, located on wheat chromosome 5BL in the genome, is shown in red. (B) Genetic linkage map indicate the Tsn1 gene region. (C) A physical map based on the BAC of the Tsn1 region that anchored to the genetic map. Old LDN BACs map described by Lu and Faris (2006) has been shown in gray. The 5B and 5A BACs reported by (Faris et al. 2010) are given in green and orange colour, respectively. (D) Ovals shape structure is showing the predicted genes (ovals with names in dark red) and markers (names beginning with an "X"). Markers given in blue colour were used for association mapping. The candidate genes regions are indicated by blue and red lines defined by recombination in the mapping population and association mapping, respectively. (E) Purple and Gray colour shown the Exons and UTRs of Tsn1 respectively (based on Faris et al. 2010).

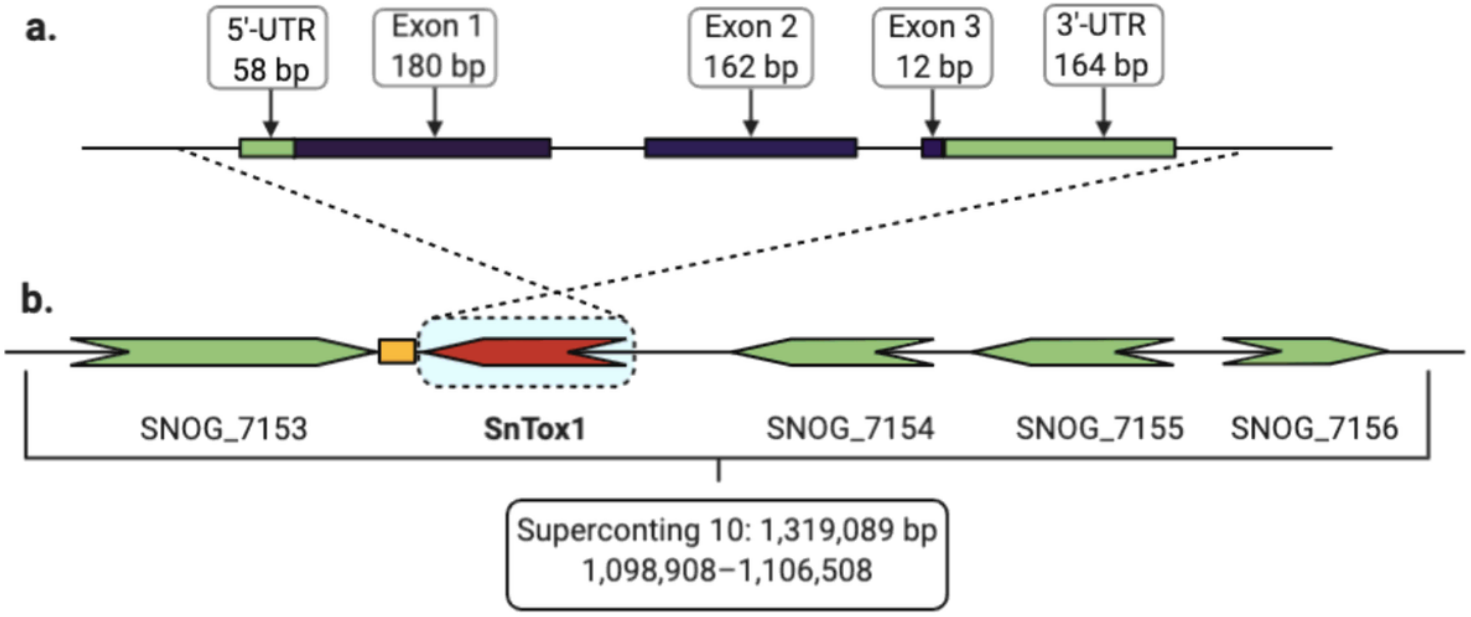

Figure 5

Genomic location and structure of SnTox1. a. The structure of SnTox1 gene containing both 5' and 3' untranslated regions (green bars) and three exons (purple bars) b. A graphical representation of SnTox1 gene and associated genomic region. SnTox1 gene is flanked by four other genes (boxed arrows, SNOG7153 to SNOG7156) and a short, truncated molly-type retrotransposon sequence (yellow rectangle). The sequences are located within the supercontig 10 of the assembled SN15 genome sequence. (Based on Liu et al. 2012)

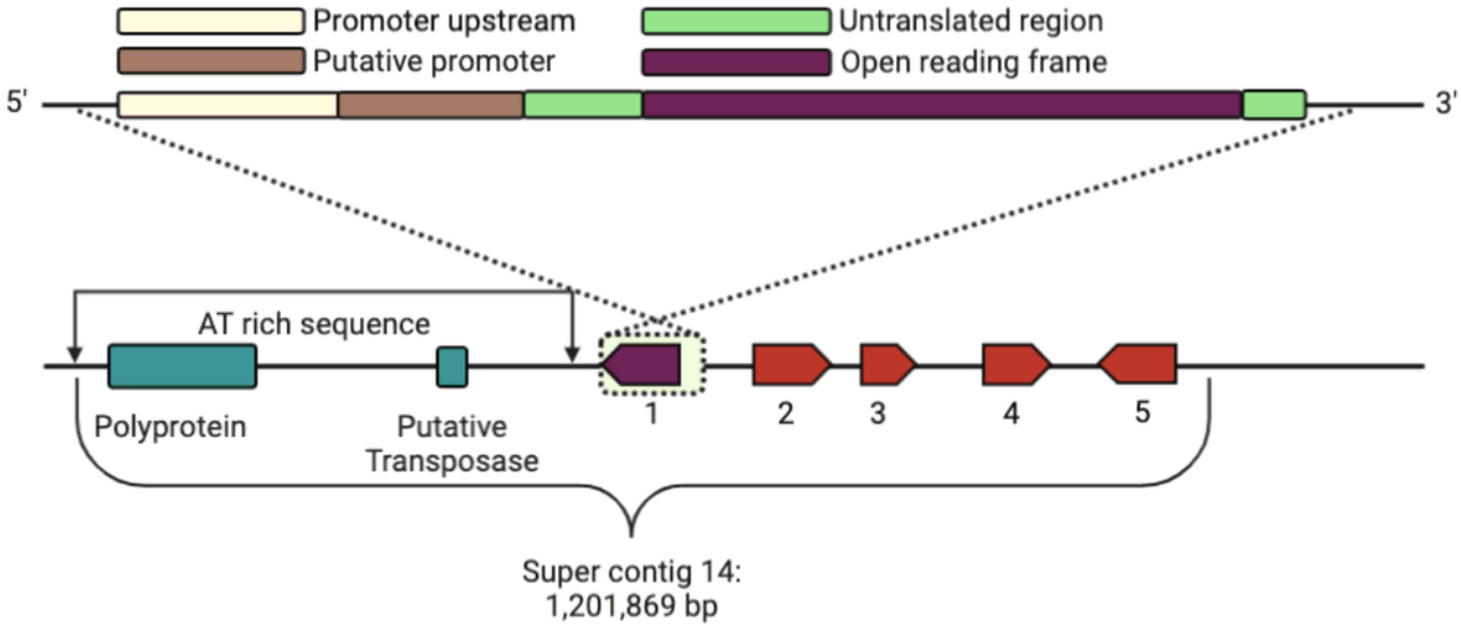

Figure 6

Structure of super-contig 14, conatining gene SnTox3, showing details of the structure of this gene including promoter region, upen reading frame (ORF) and the two untranslated regions. (reproduced from Liu et al. 2009)

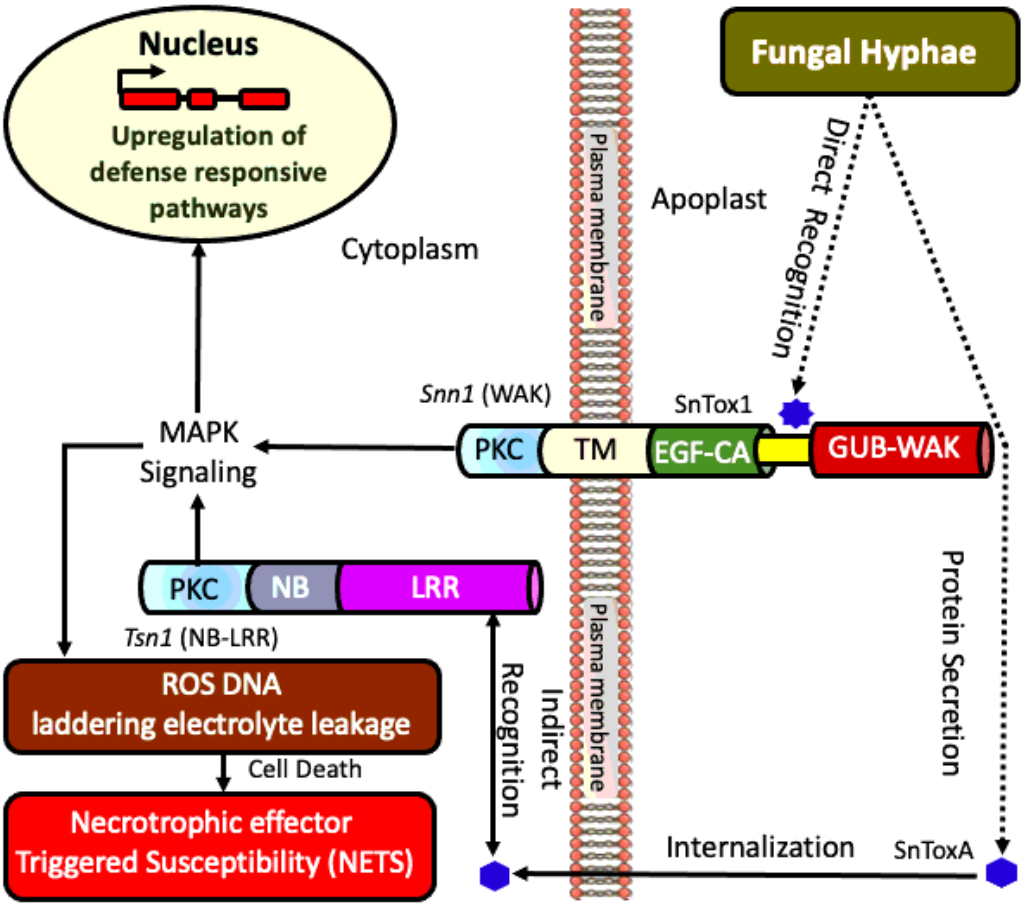

Figure 7

An overview of the Snn1-SnTox1 and Tsn1-SnToxA interactions and known downstream events that result in NETS in the wheat-P. nodorum pathosystem. The proteins SnTox1 (blue star) and SnToxA (blue hexagon) are secreted by the fungus. SnToxA is internalized into cytoplasm of the cell, but SnTox1 is not. Upon recognition of SnTox1 and SnToxA by the Snn1 and Tsn1 proteins, respectively, signaling leads to up-regulation of defense response pathways and events resulting in programmed cell death ultimately providing a means for the pathogen to gain nutrients and reproduce. Plants with either Tsn1 or Snn1 are susceptible, and plants with both genes experience even higher levels of disease. Elimination of both genes makes the plant resistant (from Shi et al. 2016b).

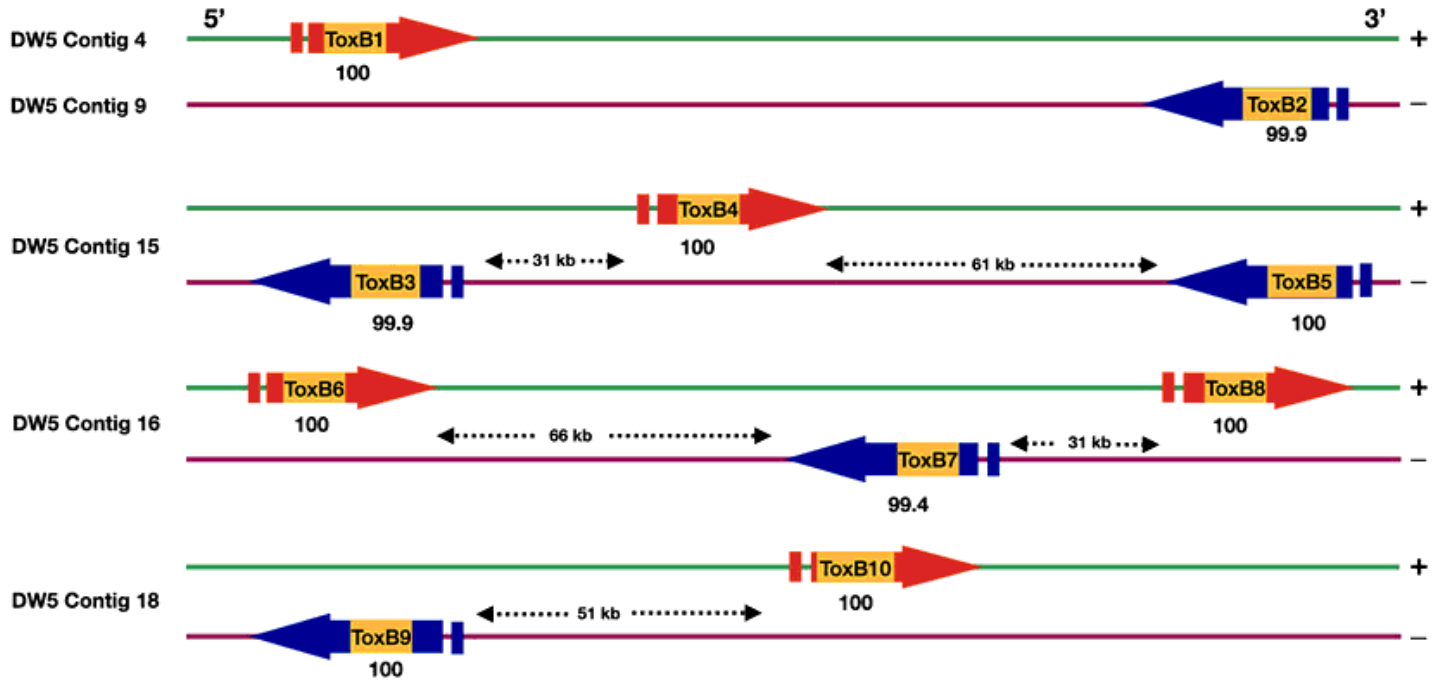

Figure 8

Five different contigs of P tritici-repentis genome showing positions of 10 different ToxB loci on forward and reverse strands. Blue arrows represent Tox B loci in the forward strand and by green arrows show ToxB loci in the reverse strand. In each case, the coding sequence is shown in yellow.

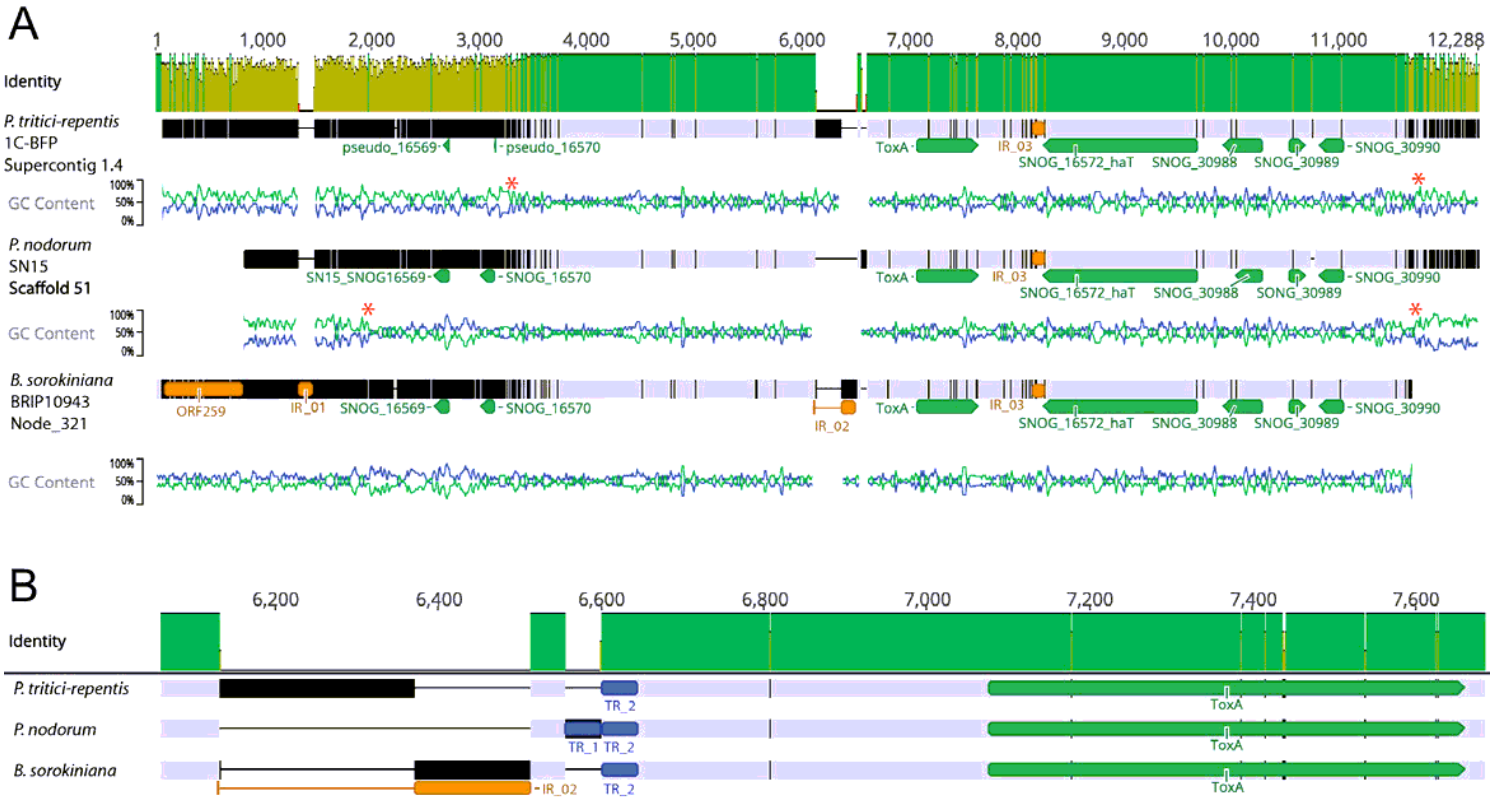

Figure 9

Alignment of the ToxA containing region from P. tritici-repentis, P. nodorum and B. sorokiniana. (A) Total alignment of the 12kb homologous region between the three species. This view shows the differences in ATrichness (green line), large increases are denoted by red asterisks. The decay in identity near the edges of the region can be attributed to RIP. All annotated genes are shown using gene accession number from P. nodorum (green bars). (B) Differences in the promoter of ToxA due to the presence of small indels. In P. tritici-repentis there is a 238bp insertion, which has no homology to any other organism. In P. nodorum, a single 43bp indel is present, which is a simple repeat of the same 43bp preceding the indel (blue bars). In B. sorokiniana there is a 148bp indel, which forms a near-perfect DNA hairpin (from McDonald et al. 2018).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SuppTable1.doc
- SuppTable2.doc