Septoria nodorum blotch of wheat: disease management and resistance breeding in the face of shifting disease dynamics and a changing environment

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Abstract

The fungus *Parastagonospora nodorum* is a narrow host range necrotrophic fungal pathogen that causes Septoria nodorum blotch (SNB) of cereals, most notably wheat (*Triticum aestivum* L.). Although commonly observed on wheat seedlings, *P. nodorum* infection has the greatest effect on the adult crop. It results in leaf blotch, which limits photosynthesis and thus crop growth and yield. It can also affect the wheat ear, resulting in glume blotch which directly affects grain quality. Reports of *P. nodorum* fungicide resistance, the increasing use of reduced tillage agronomic practices and high evolutionary potential of the pathogen, combined with changes in climate and agricultural environments, mean that genetic resistance to SNB remains a high priority in many regions of wheat cultivation. In this review, we summarise current information on *P. nodorum* population structure and its implication for improved SNB management. We then review recent advances in the genetics of host resistance to *P. nodorum* and the necrotrophic effectors it secretes during infection, integrating the genomic positions of these genetic loci using the recently released wheat reference genome assembly. Finally, we discuss the genetic and genomic tools now available for SNB resistance breeding and consider future opportunities and challenges in crop health management using the wheat-*P. nodorum* interaction as a model.

Septoria nodorum blotch of wheat: a disease of shifting global importance

Septoria nodorum blotch (SNB) is a fungal disease of wheat (*Triticum aestivum*), a key crop underpinning global food security. SNB is caused by the necrotrophic fungal pathogen *Parastagonospora nodorum* (syn. *Phaeosphaeria nodorum* (E. Müll.), syn. *Leptosphaeria nodorum* (E. Müll.), syn. *Stagonospora nodorum* (Berk.), syn. *Septoria nodorum* (Berk.)) and is prevalent in wheat growing environments with relatively high, or periodically high, rainfall such as regions within Australia, Canada, Scandinavia, central and eastern Europe, eastern USA, and South America. Compared to biotrophic pathogens which require living host tissue, necrotrophs actively kill host tissue during colonisation, subsequently living on the contents of the dead or dying host cells (Laluk & Mengiste, 2010). The visual symptoms of SNB are chlorosis and necrosis of wheat leaf tissue (often in the form of necrotic lesions surrounded by chlorosis, later developing into irregular dark brown lesions), as well as discoloration and necrosis of the glumes, referred to as leaf blotch and glume blotch, respectively (Figure 1) (Solomon et al. 2006). Leaf blotch reduces the plant surface area capable of photosynthesis, therefore limiting overall crop growth and yield, while glume blotch directly affects grain quality. Due to such damage, SNB is known to cause yield losses of up to ~30 % (Bhathal et al. 2003). In practice, SNB disease often occurs in combination with other necrotrophic fungal diseases such as septoria tritici blotch (STB, caused by *Zymoseptoria tritici*) and tan spot (TS, caused by *Pyrenophora tritici-repentis*). When such disease complexes occur, it can often be difficult to visually determine which necrotrophic diseases are present. However, quantitative polymerase chain reaction (qPCR) molecular assays for *P. nodorum* (Oliver et al. 2008), *Z. tritici* (Bearchell et al. 2005) and *P. tritici-repentis* (Antoni et al. 2010) are now available, helping to distinguish the contributors to co-infections of wheat. Additionally, an ITS-RFLP test has been developed that distinguishes between necrotrophic pathogens including *P. nodorum* and *P. tritici-repentis* (Hafez et al. 2020). Before the 1980s, *P. nodorum* was the

dominant pathogen of the leaf blotch complex in Europe (Bearchell et al. 2005). However, SNB has undergone changes in its regional prevalence in recent decades. For example, over the last thirty years there has been a focal shift in much of North Western European countries from *P. nodorum* to *Z. tritici* (Bearchell et al. 2005; Shaw et al. 2008). The underlying reasons for this change are not fully understood and have been attributed to increased levels of *Z. tritici* host susceptibility, changes in climate, higher use of fertilisers use and increased SO_2 emissions (West et al. 2012; Shaw et al. 2008). It is notable that in Norway, *P. nodorum* is still the major necrotrophic fungal pathogen of wheat and that sulphur pollution has not been reported to be higher in Norway than in any other European countries in which *Z. tritici* dominates the wheat leaf blotch complex (Lin et al. 2020a). One possibility is that the overall SNB to STB shift is due to *Z. tritici* being better at adapting to fungicides, although this hypothesis would need further investigation. Nevertheless, *P. nodorum* remains an important pathogen of wheat worldwide, and appears to be moving into new niches. For example, in 2017 it was observed for the first time on emmer wheat (*T. dicoccoides*) in Turkey, and due to changing climatic conditions, SNB has now become a major problem in Himachal Pradesh, India (Cat et al. 2018; Katoch et al. 2019).

Parastagonospora nodorum **lifecycle, infection process and epidemics**

P. nodorum is a fungal pathogen belonging to the Ascomycota as a member of the class Dothideomycetes. As the first of the Dothiodeomycete class of fungal pathogens to have its genome sequenced (37 Mbp; Hane et al. 2007), *P. nodorum* became established as a model for the narrow host range necrotrophic pathogen lifecycle. It is known mostly as a wheat pathogen, but has also been reported to occasionally infect the related cereal crop barley (*Hordeum vulgare*) but with less damage (reviewed by Cunfer 2000), as well as wild grasses (Zhang & Nan, 2018). *P. nodorum* is a necrotrophic fungal pathogen that assimilates nutrients released

after host cell death (De Wit et al. 2009). A recent reclassification of fungal and oomycete pathogens (Hane et al. 2020) differentiated a new grouping described as narrow host range polymertrophs to which *P. nodorum* belongs. This group has a narrow host range (unlike *Botrytis cinera*) and induces immediate cell death so that polymeric plant substances become available for assimilation. This group typically produces proteinaceous effectors to fuel disease progression and triggering the plant's receptors to promote sensitivity and tissue death (De Wit et al. 2009). *P. nodorum* has both asexual and sexual cycles (Figure 2). As part of the asexual cycle, fruiting bodies, called pycnidia, form in lesions on the leaf to promote spore development for local dispersal. In contrast, the sexual life cycle produces ascospores, derived from pseudothecia, that allow long distance aerial dispersion. The presence of both sexual and asexual reproduction mechanisms is hypothesised to provide *P. nodorum* with a high evolutionary potential, resulting in increased diversity and fast clonal reproduction of favourable genotypes (Ruud & Lillemo, 2018). The primary inoculum of SNB is mostly forcibly discharged ascospores originating from wheat debris, although it is also seed-transmitted. Reduced tillage (the practice of minimising disturbance of the soil by allowing crop stubble to remain on the ground rather than being incorporated into the soil or discarded) is advocated to reduce soil erosion and limit water evaporation. However, this practice leads to higher amounts of infected wheat straw on the soil surface, which can serve as primary inoculum (Ficke et al. 2018). Once the pathogen has established the initial infection on a plant, large amounts of pycnidiospores can be produced and subsequently spread by rain-splash. Indeed, the high density of wheat fields makes it easier for pycnidiospores to spread to neighbouring plants. Semi-dwarf varieties of wheat may have a higher risk of secondary *P. nodorum* infection due to the close vertical spacing of the leaves, as conidia, produced by pycnidia, are sent on an upward trajectory by water droplets (Bahat et al. 1980). This is

particularly relevant as the majority of modern wheat varieties have a short 'semi-dwarf' stature.

Genetic structure of the *P. nodorum* pathogen population

As *P. nodorum* undergoes frequent sexual reproduction, the resulting genetic recombination results in high genetic diversity in the pathogen population (McDonald & Linde, 2002). Isolates from the Middle East have been found to possess the highest genetic diversity globally. Indicating it is highly probable that the Fertile Crescent serves as the *P. nodorum* centre of origin (Ghaderi et al. 2020). Over the years, studies of *P. nodorum* population structure have been undertaken using a variety of different molecular marker types. Of the various populations investigated to date, sourced from a wide range of geographic locations, studies have typically found little population substructure and high genetic diversity (Blixt et al. 2008; Keller et al. 1997; Lin et al. 2000a; McDonald et al. 2012; Murphy et al. 2000; Stukenbrock et al. 2006). For example, genetic studies carried out on *P. nodorum* populations collected from Europe and the USA found evidence of high gene flow but little evidence of genetic differentiation between populations (Keller et al. 1997), with similar results observed for populations from Australia (Murphy et al. 2000) and Norway (Lin et al. 2020a). Indeed, high levels of genetic diversity have even been found among isolates collected from the same lesion (McDonald et al. 1994). The most notable investigation to go against this general trend was an analysis of an international *P. nodorum* population sourced from five continents, where moderate differentiation was observed between geographically divided populations (Stukenbrock et al. 2006). More recently, Richards et al. (2019) carried out a comprehensive analysis of the population structure and genome evolution of 197 *P. nodorum* isolates collected across the United States from durum, spring and winter wheat varieties, finding evidence of two *P. nodorum* populations that corresponded to the Upper Midwest and South-Eastern US.

Interestingly, most isolates in the South-Eastern US population lacked the effector *SnToxA*. This correlated with the lack of the ToxA effector sensitivity gene *Tsn1* in winter wheat varieties that were widely planted in the region thus suggesting that host genotype is a strong driver on the maintenance of effector genes.

Notably, most regional *P. nodorum* population genetic studies have been carried out using isolates sampled across a narrow timeframe, and thus offer limited insight into potential changes in the population structure over time. However, recently Phan et al. (2020) have examined the population structure of 155 *P. nodorum* isolates collected over a 44 year period across the South-Western Australian wheat growing region. Analysis of genetic polymorphisms using 28 simple sequence repeat (SSR) markers revealed that the population consisted of genetically distinct groups. Most isolates sampled were attributed to 'core groups' that possessed the highest level of genetic diversity in the Australian population, and these groups were found throughout locations and times. Isolates belonging to 'non-core groups' possessed a much lower level of genetic diversity, with limited distribution across locations and time. It was also observed that changes in group genotypes occurred during periods that coincided with major changes in the mass adoption of popular wheat cultivars across large areas of the Australian wheat cultivation zone. It was hypothesised that core groups maintain genetic variability whilst non-core groups emerge in response to large-scale changes in cultivar near-monocultures. Finally, work investigating the genetic diversity of *P. nodorum* and the closely related pathogen species *P. avenaria* f. sp. *tritici* 1 (*Pat*1) shows evidence of hybridisation at a frequency of ~4%, indicating that such gene transfer could be an additional source of genetic diversity in those regions in which the range of the two species overlap (McDonald et al. 2012).

166 **SNB disease management**

167 Disease management of SNB includes cultivar resistance (considered in more detail in the next
168 section), fungicide treatment, seed cleaning and stubble management. Despite decades of
169 breeding effort, all current wheat cultivars retain a significant level of susceptibility (Aguilar
170 et al. 2005). Reduced tillage practices are becoming increasingly common all around the world,
171 and significant correlations have been observed between the amount of residue and SNB
172 disease severity in the field (Mehra et al. 2015). Residue management can effectively decrease
173 the amount of primary inoculum and reduce disease severity (Solomon et al. 2006). SNB
174 transmission via seed is regularly reported in some parts of the world such as the eastern USA
175 but rarely elsewhere (Bennett et al. 2007). Seed fungicide treatment, directed primarily to
176 control bunts and smuts, seems to be an efficient way to eradicate SNB from seed stocks.
177 However, fungicidal control of foliar and glume SNB is more problematic. SNB typically
178 occurs in combination with other diseases (tan spot, STB, yellow rust and powdery mildew),
179 and is not normally the most predominant disease. The conditions where SNB is dominant are
180 currently limited to particular geographic locations where yield is typically under 3-4 tonnes
181 per hectare, as well as on lower value feed cereals such as triticale where fungicidal applications
182 are limited in number and dose.
183
184 Before its relative decline in much of north-western Europe at or around the year 2000, *P.*
185 *nodorum* was considered a model pathogen for fungicide discovery (Dancer et al. 1999). All
186 the current major fungicide classes are efficient at controlling SNB: sterol demethylation
187 inhibitors (DMIs), Qo inhibitors (QoIs) and Succinate Dehydrogenase Inhibitors (SDHIs).
188 Reports of fungicide resistance in SNB are relatively rare. Resistance to QoI fungicides in
189 Sweden was reported in isolates collected between 2003 and 2005 (Blixt et al. 2009) and
190 resistance to DMI fungicides has been reported in isolates collected before 2000 in Denmark,

Sweden and Switzerland (Pereira et al. 2017, see also https://www.biorxiv.org/content/10.1101/2020.03.26.010199v1.full). To our knowledge, no reports of resistance to SDHI fungicides have been made.

Fungicide resistance management focusses on reducing the selection pressure for resistance, by minimising dose and number of applications and using mixtures and alternations (Jørgensen et al. 2017). The primary foci of foliar fungicide application in wheat are normally yellow rust, STB and powdery mildew. The latter two diseases are particularly adept at evolving resistance (Oliver & Hewitt, 2014). QoI resistance was detected in both pathogens within two years of QoI application in 2001 (Bartlett et al. 2002). Control of STB by DMIs was substantially compromised by about the year 2010 (Cools et al. 2013). In the last decade, SDHIs became the main weapon against STB but resistance was well developed by 2016 in the UK and Ireland (Dooley et al. 2016). As SNB is not typically the only, or most dominant, pathogen amongst the disease complexes present in most geographic regions, it is possible that SNB has been inadvertently protected against resistance evolution by the development of resistance in the more damaging pathogen forcing a change in fungicide regime. New fungicides were introduced, lower doses applied and either mixtures or rotations carried out. As a result, SNB is not commonly subject to sustained pressure from a single mode of action class and has therefore likely only relatively rarely developed resistance.

Genetics of wheat sensitivity to *P. nodorum*: necrotrophic effectors and host response

While chemical control represents an important part of SNB disease management, the use of cultivars with increased genetic resistance helps to underpin more economically and environmentally sustainable wheat production. Resistance to both SNB leaf blotch and glume blotch are quantitatively inherited, but are reported to be controlled by different genetic

mechanisms (Chu et al. 2010; Wicki et al. 1999). Increased disease severity is also associated with shorter plant height and later plant maturation. However, residual resistance that is not associated with these traits is identifiable. It is this residual genetic resistance, along with the identification of host-specific gene-for-gene interactions determining the *P. nodorum*-wheat pathosystem (Liu et al. 2004), that provide immediate opportunities to further explore host genetic resistance in wheat breeding (Ruud & Lillemo, 2018).

Necrotrophic fungal pathogens are known to secrete effectors (typically proteins, but also low-molecular weight phytotoxic metabolites) during host infection which act as virulence factors facilitating disease development. The presence of effectors, also known as 'host selective toxins', was first described in 1933 through the study of the host-pathogen interaction between *Alternaria alternata* and Japanese pear, *Pirus serotine* (Tanaka, 1933). Since then, effectors and their corresponding host sensitivity loci have been identified in numerous necrotrophic fungal and bacterial plant pathogens (reviewed by Laluk & Mengiste, 2010). The necrotic response in a sensitive host plant is hypothesised to help pathogen colonisation, promoting infection and ultimately providing a rich nutrient source (Oliver & Solomon, 2010). This is known as effector-triggered susceptibility (ETS) and is genetically induced via an `inverse gene for gene system' (Friesen et al. 2007). Understanding the genetics of host sensitivity to such effectors provides the opportunity to break down at least some components of the genetics of field resistance into their constitutive parts. *P. nodorum* is thought to derive nutrients from dying plant tissue, utilizing secreted effectors. These effectors induce a hypersensitive response in the host, which takes the form of programmed cell death (Friesen et al. 2007; Liu et al. 2009; Oliver et al. 2012). Evidence of eight *P. nodorum* effectors have been described to date, and designated SnToxA, SnTox1, SnTox2, SnTox3, SnTox4, SnTox5, SnTox6 and SnTox7, along with nine corresponding major wheat sensitivity loci *Tsn1* (Faris et al. 2010), *Snn1* (Shi et al.

2016), *Snn2* (Friesen et al. 2007), *Snn3-B1*/*Snn3-D1* (Friesen et al. 2008; Zhang et al. 2011), *Snn4* (Abeysekara et al. 2012), *Snn5* (Friesen et al. 2012), *Snn6* (Gao et al. 2015) and *Snn7* (Shi et al. 2015), respectively. Of these, only three effectors (SnToxA, SnTox1, SnTox3) and two host sensitivity loci (*Tsn1* and *Snn1*) have been identified at the gene level, discussed in more detail below. In addition to these major host loci, several minor effector sensitivity QTLs have been identified in wheat (Supplementary Table 1) (Cockram et al. 2015; Downie et al. 2018; Lin et al. 2020b; Phan et al. 2016).

ToxA-Tsn1 interaction: ToxA was first discovered to be secreted *by P. nodorum* in 2006 (Friesen et al. 2006) and found to have 99.7 % DNA sequence similarity to the previously identified ToxA gene from *P. tritici-repentis* (subsequently termed here, PtrToxA). Due to the monomorphism of *PtrToxA* compared to the high levels of *ToxA* diversity, it is thought *ToxA* was introduced into the *P. tritici-repentis* genome through interspecific gene transfer from *P. nodorum* (Friesen et al. 2006). The corresponding host sensitivity locus, *Tsn1*, was first discovered in 1996 as conferring sensitivity to PtrToxA (Faris et al. 1996), and later confirmed as the corresponding host sensitivity locus for *P. nodorum* ToxA (Liu et al. 2006). This interaction was found to significantly contribute to disease incidence, accounting for up to 62% of disease severity at the seedling stage (Liu et al. 2006) and up to 20% at adult plant stage (Friesen et al. 2009). *Tsn1* is typically present at relatively high frequencies in wheat germplasm, e.g. 59% of Canadian varieties representing wheat development over that last century (Hafez et al. 2020). *Tsn1* encodes a predicted protein containing three predicted domains: a serine/threonine protein kinase (S/TPK) (with ATP binding, substrate binding site and activation loop), a nucleotide binding site (NBS) and 24 leucine-rich repeats (LRRs) (Faris et al. 2010). NBS-LRRs form the largest class of plant resistance (*R*) genes, and are well documented as controlling race-specific resistance to biotrophic fungal pathogens (Dubey &

Singh, 2018). Tsn1 is localised to the chloroplast and does not directly interact with ToxA (Faris et al. 2010). However, ToxA has been shown to interact with the dimeric PR-1-type pathogenesis-related protein, TaPR-1-5, to activate Tsn1-controlled cell death pathways (Breen et al. 2016). *Tsn1* expression is subjected to regulation by light and the circadian clock, providing a possible explanation for the light dependent nature of the ToxA-*Tsn1* interaction (Faris et al. 2010; Manning & Ciuffetti, 2005). Recently, it was shown that another wheat and barley pathogen *Bipolaris sorokiniana*, the cause of spot blotch, also possesses a *ToxA* gene that likely originated from *P. nodorum*, pointing to a selective advantage of carrying the virulence factor ToxA (Friesen et al. 2018).

Tox1-*Snn1 interaction*: Tox1 was first characterized as a host selective effector produced in *P. nodorum* culture filtrates interacting with the wheat sensitivity locus *Snn1* on chromosome 1B (Liu et al. 2004). *Tox1* encodes a cysteine rich protein with 117 amino acids which is light dependent and critical for fungal penetration (Liu et al. 2012) and serves a dual function: binding host chitinases to protect fungal infection and causing host tissue death to promote infection (Liu et al. 2016). The Tox1-*Snn1* interaction was found to contribute up to 58 % and 19 % of SNB at juvenile and mature plant stages, respectively (Liu et al. 2004; Phan et al. 2016). The recent map-based cloning of *Snn1* found it to encode a galacturonic acid binding (GUB) wall associated kinase (WAK), and to possess calcium binding epidermal growth factor (EGF CA) and serine/threonine kinase (S/TPK) domains (Shi et al. 2016). WAK proteins are known to be members of pattern recognition receptors (PRRs) which directly interact with pathogen-associated molecular patterns (PAMPs), such as oligogalacturonides (OGs), which trigger programmed cell death and are involved in plant defence mechanisms against biotrophic pathogens (Brutus et al. 2010).

SnTox3-*Snn3-B1 interaction*: The *P. nodorum* effector SnTox3 was first identified by Friesen et al. (2008), and the protein sequence later characterised as a 25.8 kDa immature protein, with the first 20 residues of the 230 aa chain forming a signal peptide for secretion (Liu et al. 2009). Tox3 has six cysteine residues that form disulphide bonds, at least one of these bonds is essential for biological function. Recent work has shown that an avirulent *P. nodorum* strain could become virulent with just the addition of the 693 bp intron-free *Tox3* (Liu et al. 2009; Waters et al. 2011). Discovery of SnTox3 led to the identification of the corresponding wheat sensitivity locus, *Snn3* (more recently termed *Snn3-B1*), on the short arm of chromosome 5B. This interaction has been shown to explain 24 % of the phenotypic variation in field SNB resistance/susceptibility, and more than 51 % of the variation in seedling inoculation (Ruud et al. 2017). Culture filtrate containing SnTox3 was first produced using a wild-type *P. nodorum* isolate, SN15, and host sensitivity was genetically mapped using the BR34 x Grandin wheat population (Friesen et al. 2008) and later confirmed in subsequent studies (e.g. Downie et al. 2018; Phan et al. 2016; Shi et al. 2016; Lin et al. 2020b). While a *Snn3-B1* homoeologue was found on chromosome 5D in the diploid wild wheat relative *Aegilops tauschii* (*Snn3-D1*) (Zhang et al. 2011), a corresponding locus on the D sub-genome of hexaploid wheat has not been reported. As was the case for ToxA, yeast-two-hybrid studies have shown that the Tox3 protein interacts with PR-1 proteins (Breen et al. 2016)

P. nodorum effectors hijack pathways involved in biotrophic pathogen host defence signalling

Given *Tsn1* and *Snn1* both encode classes of proteins that are well known to control disease resistance in biotrophic pathogens, it is hypothesised that *P. nodorum* has evolved to hijack existing pathways in order to become a susceptibility pathway for necrotrophs (Faris et al. 2010; Shi et al. 2016; Faris & Friesen, 2020). Specifically, it is thought that host recognition

316 of SnTox1 activates pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI)
317 and that ToxA/PtrToxA recognition activates effector-triggered immunity (ETI). The finding
318 that Tox1 does not enter the plant cell (Liu et al. 2016) indicates that its recognition is mediated
319 via host membrane-bound proteins. This fits both with the prediction that Snn1 spans the host
320 cell membrane and contains extracellular binding domains (Liu et al. 2016; Shi et al. 2016),
321 and with the interaction of Snn1 with Tox1 *in vitro* (Shi et al. 2016). As noted by Shi et al.
322 (2016), while the expression patterns of PTI and ETI pathways overlap, the expression patterns
323 of certain classes of genes commonly differ. Activation of mitogen-activated protein kinase
324 (*MAPK*) genes have been shown to be transient in PTI responses, whilst their expression is
325 more prolonged during ETI (Tsuda & Katagiri, 2010). Notably, the rapid and transient
326 upregulation of *TaMAPK3* in a compatible *Snn1*-Tox1 interaction within 15 minutes of Tox1
327 infiltration further implicates the PTI pathway (Shi et al. 2016). Finally, it has been noted that
328 wheat varieties carrying both *Tsn1* and *Snn1* have higher levels of necrosis than varieties
329 carrying either *Tsn1* or *Snn1* alone, indicating that simultaneous hijacking of both the PTI and
330 ETI pathways for necrotrophic effector (NE) triggered susceptibility enhances pathogen
331 survival and reproduction (Chu et al. 2010; Shi et al. 2016).
332
333 ***Epistatic interactions between P. nodorum effectors and between host sensitivity loci***
334 The NE–*Snn* model supports additive contributions to disease from each compatible interaction
335 (Friesen et al. 2007; Tan et al. 2012). However, epistatic interactions are also evident. For
336 example, SnTox5-*Snn5* and SnTox6-*Snn6* are epistatic to *Snn3-B1* (et al Friesen. 2012; Gao et
337 al. 2015). Similarly, Friesen et al. (2008) showed that the SnToxA-*Tsn1* interaction is epistatic
338 to SnTox3-*Snn3-B1*, and that the SnTox3-*Snn3-B1* interaction is only evident in the absence
339 of a compatible SnTox2-*Snn2* interaction (Friesen et al. 2008). The epistatic effects on SnTox3-
340 *Snn3-B1* were further explored in subsequent work using a series of effector gene deletion

mutants generated in the *P. nodorum* strain SN15. While the SnTox1-*Snn1* interaction dominated seedling sensitivity using the wild-type SN15 strain, deletion of the *SnTox1* gene in SN15 led to an increase in *SnTox3* expression in the pathogen and the identification of *Snn3-B1* as contributing to host sensitivity at the seedling stage (Phan et al. 2016). Furthermore, a modified strain of SN15 in which *SnToxA, SnTox1* and *SnTox3* were deleted unmasked a sensitivity QTL in the region of the *Snn2* locus which was not identified using the wild-type or *SnTox1* mutant strain, indicating that *SnToxA* and/or *SnTox3* could be epistatic to *Snn2* (Phan et al. 2016). Unlike ToxA, it was found that Tox3 interacts with a broad range of PR-1 proteins and it has been hypothesised that interactions with TaPR-1 proteins facilitate host infection (Breen et al. 2016). As more effectors and host sensitivity loci are cloned and their allelic diversity characterised, it is likely that the identification of new alleles at these loci will further increase the complexity of the NE-*Snn* network. Thus, the epistatic and allelic interactions occurring between effectors in the pathogen, and between sensitivity loci in the host, take what are largely relatively simple gene-for-gene interactions to create a more complex set of possible interactions. As the effect of a NE–host receptor interaction can vary depending on the presence or absence of other effectors and receptors present at the time of infection makes this disease typically quantitative and difficult to predict.

Genetics of wheat sensitivity to *P. nodorum* at the juvenile and adult plant stages

In order to characterise the *P. nodorum*-wheat pathosystem and use this information to improve SNB resistance, knowledge of host resistance to target pathogens at the juvenile and adult stages are commonly investigated. Resistance to SNB at both of these plant stages is polygenic and large genotype-by-environment interactions are observed (Fried & Meister, 1987; Wicki et al. 1999). Correlation between seedling and adult plant resistance is generally reported to be low (e.g. Francki 2013; Fried & Meister, 1987; Rosielle & Brown, 1980; Ruud & Lillemo

366 2018; Shankar et al. 2008; Tommasini et al. 2007). This has been suggested to be due to the
367 use of different isolates in greenhouse seedling testing compared to those used in adult plant
368 field trials (Ruud & Lillemo 2018; Ruud et al. 2017). Additionally, as the natural *P. nodorum*
369 population is usually genetically diverse, it is difficult to identify representative isolates for
370 greenhouse assays, and field testing can be affected by cross-infection with the natural *P.*
371 *nodorum* population. Such complications mean that even where the same isolate mixtures are
372 used for greenhouse and field trials, correlation between seedling and flag leaf disease scores
373 can be low (0.31) or even not significant between seedling and glume blotch severity (Shankar
374 et al. 2008). Despite this, there are examples of relatively high correlations when the same
375 isolate is used for both seedling and field testing (Jönsson, 1985). Genetic mapping of seedling
376 SNB resistance has identified genetic loci on all 21 wheat chromosomes except for
377 chromosomes 1D and 3D (Abeysekara et al. 2009; Adhikari et al. 2011; Arseniuk et al. 2004;
378 Czembor et al. 2003; Friesen et al. 2006, 2007, 2012; Gao et al. 2015; Gonzalez-Hernandez et
379 al. 2009; Gurung et al. 2014; Hu et al. 2019; Jighly et al. 2016; Lin et al. 2020b; Liu et al. 2004,
380 2015; Phan et al. 2016; Ruud et al. 2017, 2019; Rybak et al. 2017). Similarly, numerous adult
381 plant QTLs have been identified: across 16 chromosomes for leaf blotch (1A, 1B, 2A, 2B, 2D,
382 3A, 3B, 4A, 4B, 5A, 5B, 6A, 6B, 7A, 7B and 7D (Aguilar et al., 2005; Czembor et al. 2019;
383 Francki et al. 2011, 2018, 2020; Friesen et al. 2009; Lin et al. 2020b, 2020c; Lu & Lillemo,
384 2014; Phan et al. 2016; Ruud et al. 2017, 2019; Shankar et al. 2008), and 12 chromosomes for
385 glume blotch (2A, 2B, 2D, 3A, 3B, 4A, 4B, 5A, 5D, 6A, 6B and 7D (Aguilar et al. 2005;
386 Czembor et al. 2019; Francki et al. 2018; Jighly et al. 2016; Lin et al. 2020b; Schnurbusch et
387 al. 2003, Shankar et al. 2008; Shatalina et al. 2014; Tommasini et al. 2007; Uphaus et al. 2007).
388 All QTLs are listed in Supplementary Table 1.
389

While it has been clear from the outset that NE-*Snn* interactions are relevant to seedling resistance, discussion of their importance on SNB resistance in the field is ongoing (Francki, 2013). However, there is now mounting evidence that at least some NE-*Snn* interactions also contribute to susceptibility to SNB in the field. Friesen et al. (2009) used an isolate producing both ToxA and Tox2 for spray inoculation in the field on a mapping population segregating for *Tsn1*, *Snn2* and *Snn3-B1*, finding *Tsn1* and *Snn2* to explain 18 % and 15 % of the phenotypic variation for SNB resistance, respectively. Significant correlation between ToxA sensitivity and SNB disease severity have been observed in an association mapping panel under Norwegian field conditions (Ruud et al. 2019). Another study applied artificial inoculation of an isolate producing all three known NEs, showing *Snn1* explained 19 % of the phenotypic variation for adult plant disease severity (Phan et al. 2016). Similarly, studies in Norway have found *Snn3-B1* to affect field SNB disease susceptibility using a bi-parental population (Ruud et al. 2017).

Further cross-comparison of juvenile plant and adult plant sensitivity with major and minor effector and culture filtrate sensitivity loci have historically been problematic due to factors such as the relatively large genetic intervals identified and the use of different genetic mapping populations and genetic marker systems. Genetic mapping of response to *P. nodorum* infection has mainly relied on different bi-parental wheat populations. However, more recently association mapping (Cockram et al. 2015; Downie et al. 2018; Ruud et al. 2019; Tommasini et al. 2007) and multi-founder (e.g. Lin et al. 2020b, 2020c) populations have also been used. While each type of population comes with its own advantages and disadvantages (reviewed by Cockram & Mackay, 2018), one benefit of association mapping and multi-founder populations is that allelic variation at the genomic locations controlling the target traits are more likely to be sampled than might be the case in bi-parental populations, and the effects of these alleles

415 are assessed in a wider range of genetic backgrounds. This allows straightforward cross-
416 comparison of QTLs for numerous related traits within a single genetic mapping population.
417 Furthermore, the availability of high-density genotyping platforms and a wheat reference
418 genome assembly (IWGSC, 2018) means that cross-comparison of previously published SNB
419 QTLs identified using different genetic mapping populations is much more straightforward to
420 do. Here, we have used these resources to anchor previously published QTLs controlling host
421 response to *P. nodorum* infection, as well as infiltration using culture filtrates and necrotrophic
422 effectors, to the wheat physical map (Figure 3; Supplementary Table 1). The results help
423 highlight several interesting observations. For example, recent studies using multiparent
424 advanced generation inter-cross (MAGIC) populations constructed using wheat varieties
425 grown in UK (Mackay et al. 2014) and German (Stadlmeier et al. 2018) agronomic
426 environments have allowed genetic control of resistance to *P.* nodorum, as well as sensitivity
427 to known effectors, to be assessed in experimental populations that capture relatively high
428 amounts of genetic variation (Lin et al. 2020b, 2020c). Field testing of SNB resistance
429 identified robust co-localising QTLs on the long arm of chromosome 2A controlling leaf blotch
430 in the UK MAGIC (*QSnb.niab-2A.3*; Lin et al. 2020b) and German MAGIC (*QSnb.nmbu-2A.1*;
431 Lin et al. 2020c) populations, as well as culture filtrate sensitivity QTL that co-locate to the
432 same locus in the UK MAGIC population (Lin et al. 2020b). This chromosome 2A QTL is
433 located within the confidence interval for the seedling resistance QTL *QSnb.fcu-2A*
434 (Abeysekara et al. 2009) and the SNB resistance QTL *Qsnb.cur-2AS.1* (Phan et al. 2016).
435 However, whether these QTL represent the same underlying locus is not currently known, and
436 the *Qsnb.cur-2AS.1* physical interval is notably large. Nevertheless, collectively these results
437 suggest that an as-yet uncharacterised necrotrophic effector present in *P. nodorum* culture
438 filtrate used by Lin et al. (2020b) interacts with the *QSnb.niab-2A.3* locus and is implicated in
439 the control of SNB resistance in adult plants. While Lin et al. (2020b) also found a QTL

controlling glume blotch to colocalise to the same genetic locus on chromosome 2A, the allelic effects at the QTL were predicted to be opposite to those for glume blotch, suggesting that a different mechanism may be involved. This supports previous reports that resistance to leaf blotch and glume blotch are thought to predominantly be controlled by different genetic mechanisms (Aguilar et al. 2005; Chu et al. 2010; Francki et al. 2018; Schnurbusch et al. 2003; Shankar et al. 2008).

Analysis of additional culture filtrate sensitivity QTL and minor-effect effector sensitivity QTL finds several to co-locate with genetic loci controlling adult plant SNB resistance (Figure 3, Supplementary Table 1), further supporting the presence of additional effector sensitivity loci relevant to field resistance. For example, *QTox3.niab-2A.1* controlling Tox3 sensitivity (Downie et al. 2018) co-locates with a QTL for adult plant leaf blotch (*QSnb.niab-2A.4*, also controlling seeding resistance, Lin et al. 2020b), all in the same eight-founder MAGIC population. Additionally, SNB resistance QTL *QSnb.niab-3A* and *QSnb.niab-6A.2* identified in the MAGIC population collocated with a culture filtrate sensitivity QTL (Lin et al. 2020b) and the previously reported effector sensitivity locus *Snn6* (Gao et al. 2015; Arseniuk et al. 2004), respectively. The co-location of culture filtrate/effector sensitivity loci with SNB QTL indicates that natural variation at genetic loci controlling additional components of effector sensitivity pathways may play a role in modulating adult plant resistance phenotype. Whether there are additional NE-*Snn* interactions playing roles in adult plant susceptibilities is still yet to be determined.

Common QTL between SNB and tan spot diseases of wheat

Increasing numbers of publications on QTL mapping of both SNB and tan spot has revealed a number of common QTL between the two diseases. That *Tsn1* confers sensitivity to both ToxA

and PtrToxA is a well-known example (Friesen et al. 2006), although investigation of resistance to *P. tritici-repentis* and *P. nodorum* using a bi-parental tetraploid wheat (*T. durum*) population indicated while the *Tsn1*-ToxA interaction was important for *P. nodorum* infection, it did not play a significant role in *P. tritici-repentis* interaction in the tetraploid wheat *T. durum* system, and that this was likely due to low *PtrToxA* expression in *P. tritici-repentis* (Virdi et al. 2016).

P. nodorum resistance/sensitivity QTL *Qsnb.cur-2AS.1* (Phan et al. 2016) which was detected at the seedling and adult plant stage has also been found to be a major contributor to tan spot resistance in seedlings and mature plants (Manisha et al. 2017; Phan et al. 2016). A QTL identified on the long arm of chromosome 5A is another instance of shared common genomic regions significantly associated with both diseases (Hu et al. 2019). This phenomenon may indicate that the two diseases possibly share common susceptibility/resistance mechanisms. It would be interesting to find out if they have more effectors in common. The mutual interactions could be promising targets for wheat breeders, as they could introduce resistance to both diseases - especially for those QTL with relatively large effect and at both the seedling and adult plant stages.

Roles of new technology-based and breeding approaches in delivering genetic gains in SNB resistance

Advances in the understanding of SNB resistance have been applied in breeding programmes since 2005. For example, sequencing the *P. nodorum* genome revealed the presence of *ToxA* and that it was the source of the related gene previously identified in *P. tritici-repentis*. It was a simple matter to express the gene in microbial hosts, infiltrate the protein into wheat seedling leaves and determine whether plants were sensitive or not. An important factor was that these

assays could be carried out with equipment as simple as a refrigerator and a needleless syringe; even a greenhouse was not essential. As such, crop breeders found this assay practical and accurate. Armed with expressed ToxA since 2005, Tox3 since 2011 and Tox1 since 2012, researchers and breeders could determine the relationship between effector sensitivity and cultivar susceptibility. For *P. tritici-repentis* in Australia, a very simple picture emerged; all isolates of the pathogen carried *PtrToxA*, and sensitivity to this effector in wheat was strongly correlated with tan spot disease susceptibility. Large numbers of ToxA doses were distributed to breeders over the next few years and the use of ToxA sensitive wheat grown was reduced by half in three years. Considering these changes in more detail in more recent periods, the total area sown to *tsn1* wheat varieties in Western Australia increased from 69.9% in 2009–2010 to well over 85% in 2018 (Oliver et al. 2014; Western Australia Crop Growing Guide 2020; https://www.cbh.com.au/en/customers) and no detectable yield penalty is associated with insensitivity to ToxA (Oliver et al. 2014; Vleeshouwers & Oliver, 2014). The application of "effector-assisted breeding" to SNB was more complicated. In Australia, effectively all *P. nodorum* isolates carried all three effectors, but the relationship between effector insensitivity and cultivar resistance was not as clear cut. As noted above, epistasis between NE genes was apparent. Nonetheless the elimination of effector sensitivity genes has never been shown to decrease SNB resistance or to have any other deleterious effect. It either has no effect or a positive effect on resistance. Analysis of the *ToxA* sequence in a diverse *P. nodorum* isolate collection indicates that the gene is positively selected (Stuckenbrock & McDonald, 2007). It is likely that *ToxA* will continually evolve into forms that are more potent in host cell death induction unless *Tsn1* is bred out from widely planted wheat germplasms (Tan et al. 2012). In the case of Tox1 sensitivity, while the gene underlying the sensitivity locus *Snn1* has been cloned, the natural genetic variants determining insensitivity have not been formally identified. For Tox3 sensitivity, while highly significant markers closely linked to *Snn3-B1* have been

identified in experimental mapping populations, the observation that these markers provide surprisingly low prediction of Tox3 sensitivity in screens of wider germplasm collections (eg Downie et al. 2018) indicates that multiple sensitivity alleles may be present. Similarly, while the *WAK* gene underlying the Tox1 sensitivity locus *Tsn1* has been cloned using a bi-parental population, the natural variant(s) controlling insensitivity have not yet been determined, and so screening with the Tox1 protein remains likely the most pragmatic approach for robustly determining sensitivity, at least until the causative variant(s) controlling insensitivity are identified.

In the coming years, the use of other emerging technologies will help speed up the identification and functional characterisation of SNB/effector resistance genes and provide efficient routes to use these in breeding programmes. Here we briefly summarise a subset of these resources and approaches, ending with an example of how a combination of these could be applied to future SNB resistance research and breeding.

Access to the wheat gene space within a target genetic interval is a key resource to help identify causative genes and variants. While a wheat reference genome is now available (IWGSC, 2018), it has been constructed using an Asian landrace called 'Chinese Spring', genetically distant to the wheat grown in most of the world. This may be particularly relevant to effector sensitivity, as of the two cloned effector sensitivity loci in wheat, allelic variation at the *Tsn1* locus conferring ToxA sensitivity is due to the presence or absence of the underlying gene (Faris et al. 2010). As 'Chinese Spring' is insensitive to ToxA, the wheat reference genome assembly lacks the *Tsn1* gene. To help address such issues, the construction of genome assemblies for several additional bread wheat varieties are underway. This includes 14 cultivars via the 10+ Wheat Genomes Project (www.10wheatgenomes.com) and the founders of the UK

MAGIC population (https://gtr.ukri.org/projects?ref=BB%2FP010741%2F1). To help annotate the genes in any new wheat assembly, and to provide information on where and when a gene within your genomic region of interest is expressed, high-throughput RNA sequencing using next-generation sequencing platforms can be undertaken. This can be done using relatively short read technologies (e.g. RNA-seq using Illumina platforms), or long-read technologies to sequence full-length transcripts (e.g. Isoform Sequencing using PacBio platforms or Nanopore technology). By combining genomic and RNA sequence datasets, candidate genes and polymorphisms within a target genomic region can be identified. Candidate genes can then be explored using reverse genetic approaches. Currently, a TILLING (Targeting Local Lesions in Genomes) population with an associated exome capture-based genomic sequence databased is available for the wheat variety 'Cadenza' (Krasileva et al. 2017), allowing lines with putative deleterious mutations to be identified *in silico* and ordered. Alternatively, transgenic approaches such as RNA interference (RNAi), CRISPR/Cas9 gene editing and virus-induced gene silencing (VIGS) are all now used in wheat (e.g. Travella et al. 2006; Shan et al. 2013; Scofield et al. 2005). For further reading on the routes for wheat gene functional annotation, see the recent review by Adamski et al. (2020).

Next, we outline a case study for SNB improvement based on the environmentally stable adult plant resistance QTL *QSnb.niab-2A.3* identified in the UK MAGIC population by Lin et al. (2020b). First, to rapidly generate suitable germplasm to further the investigation of this locus, the residual genetic variation present in MAGIC RILs could be exploited to generate a pair of nearly isogenic lines (NILs) for a given QTL in a single generation (as described in more detail by Scott et al. 2020). This NIL pair could be inter-crossed to generate F_1 seed, and the F_1s selfed to produce large numbers of F_2 seed. As the culture filtrate from *P. nodorum* isolate 203649 was found to identify a QTL at the *QSnb.niab-2A.3* locus, F_2 individuals could be

565 screened for genetic recombination within the target interval, and their F_3 progeny phenotyped
566 at the seedling stage for sensitivity to culture filtrate. This subset of recombinant lines, and
567 their progenies, would be used to further refine the genetic interval. Once sufficient genetic
568 mapping resolution is obtained, the gene content in the interval could be determined by
569 projecting the genomic sequence and gene annotations of the relevant MAGIC founders onto
570 the interval, and RNA-seq and IsoSeq gene expression data from leaf tissues harvested from
571 the NIL germplasm pre- and post- culture filtrate infiltration overlaid. Collectively, these
572 datasets would allow candidate genes within the genetic interval to be identified and accurately
573 annotated via bioinformatic analysis of the DNA variants, gene expression and splice variant
574 data generated. Subsequently, VIGS could be used to transiently silence candidate genes at the
575 seedling stage, and any effect on sensitivity to culture filtrate infiltration determined. Further
576 functional validation of the candidates prioritised/validated by VIGS could then be assessed at
577 the adult plant stage using stable gene silencing methods such as CRISPR/Cas9. Diagnostic
578 markers for the natural causative polymorphisms underlying the functionally validated gene
579 would be developed for marker assisted selection, preferably using genotyping systems
580 commonly used by wheat breeding companies, such as Kompetitive Allele-Specific PCR
581 (KASP) assays (LGC Biosearch Technologies).
582
583 It is important to mention that application of the marker-informed breeding methodology
584 'genomic selection' is now feasible in large genome crop species such as wheat (reviewed by
585 Sun et al. 2019). Rather than relying on explicit identification of the QTL/genes underlying the
586 target trait, genomic selection exploits the ability to cheaply generate high-density genetic
587 marker datasets across the genome, and use this alongside phenotypic data generated in a
588 'training set' lines to use the markers to predict the performance of their progeny across
589 multiple subsequent generations. This allows selection to be applied based on genetic marker

590 data and phenotypic data on the training set alone, without the need for field-based phenotypic
591 selection in multiple subsequent rounds of population advancement. This potentially reduces
592 breeding cycle time, increases selection accuracy and increases selection intensity. Genomic
593 selection is likely to be a major source of improvement in plant breeding practice over the next
594 decades, and the methodologies can also likely be modulated to incorporate additional datasets
595 such as diagnostic markers in order to help improve prediction accuracy (Mackay et al. 2020).
596 Numerous studies have followed on from the first report of genomic selection in wheat (De los
597 Campos et al. 2009) and include studies of diseases such as yellow rust (Ornella et al. 2012),
598 Fusarium head blight (Herter et al. 2019) and STB (Herter et al. 2019). Of these, the study
599 conducted by Herter et al. (2019) using 1120 lines derived from 14 bi-parental families found
600 that while genomic selection provided a selection advantage of ~10 % for fusarium head blight,
601 no significant advantage was observed for STB resistance (Herter et al. 2019). This suggests
602 that for phenotypes with strong genotype × environment interaction, genomic selection appears
603 to be challenging (Herter et al. 2019). Based on the published literature, genomic selection has
604 not been explicitly applied to SNB improvement, indicating a possible as yet untested route for
605 genetic improvement. We also noted that genome editing approaches such as CRISPR/Cas9
606 would be well suited for host-pathogen interactions that follow the inverse gene-for-gene
607 model, whereby host effector sensitivity loci could be edited to make them insensitive. In the
608 future, we might see application of genomic selection methodology that combine targeted
609 selection against NE sensitivity alleles and/or selection for gene edited NE insensitivity alleles
610 along with the use of genome-wide markers to capture all small-effect loci in a cost-effective
611 manner for plant breeding programs.
612

613 **General conclusions**

Ultimately, the most efficient control of SNB will involve a combined approach based on agricultural and agronomic practices, disease monitoring and genetic improvement. The widespread adoption of conservation agriculture including limited tillage methods means that SNB is likely to increase in prevalence in areas where ploughing has previously been the norm. Methods to improve the genetic resistance of cultivars will surely remain the most important method of control. So far, no full genetic resistance to SNB has been identified. It is becoming increasingly apparent that SNB is found not only in the presence of easily distinguished diseases like yellow rust and powdery mildew, but also with the symptomatically similar diseases such as STB, tan spot and possibly spot blotch as well. Selection for resistance to diseases occupies a substantial amount of time and resources available to breeders, particularly as yield and quality will always be prioritised. Furthermore, we know very little about how diseases interact. This is a particular area of fascination given that three of these pathogens share effectors.

Breeding for resistance to SNB has always been challenging because full evaluation of a new cultivar requires the use of adult plants under field conditions. Inoculation with a representative set of isolates adds to the difficulties. One clear recommendation to emerge from recent studies is to make large annual isolate collections especially from the current most resistant cultivar. These new isolates can be assessed phenotypically for new effectors and virulence characteristics as well as genotypically to track for selected chromosomal regions. Any new effectors can be expressed and assessed for their role in virulence. The main value of the isolate collections is that they allow the rational selection of the minimum set that represents the total phenotypic variance of the pathogen to which resistance should be sought. Finally, based on our current understanding of *P. nodorum* epidemiology and host resistance, we provide the following recommendations for SNB management:

1. Establish annual *P. nodorum* isolate collections and disease outbreak monitoring programmes.
2. Use these contemporary *P. nodorum* isolates to test for cultivar resistance and assess for the presence of new effectors.
3. Where genetic structure is observed in a regional pathogen population, undertake rapid genotypic analysis to monitor the population.
4. Grow wheat cultivars with differing genetic background to avoid a build-up of a specialised pathogen population, especially in areas where minimum tillage practices are common.
5. Where local pathogen populations contain known effector genes, grow wheat varieties with insensitive alleles at the corresponding host loci.
6. Continue wheat research and development activities to identify and deploy additional sources of SNB genetic resistance.

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Author contributions

RD, MinL and JC wrote the manuscript. MinL and JC undertook bioinformatic analysis. All other authors edited the manuscript and contributed to scientific supervision and/or discussions.

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Supplementary Table legends

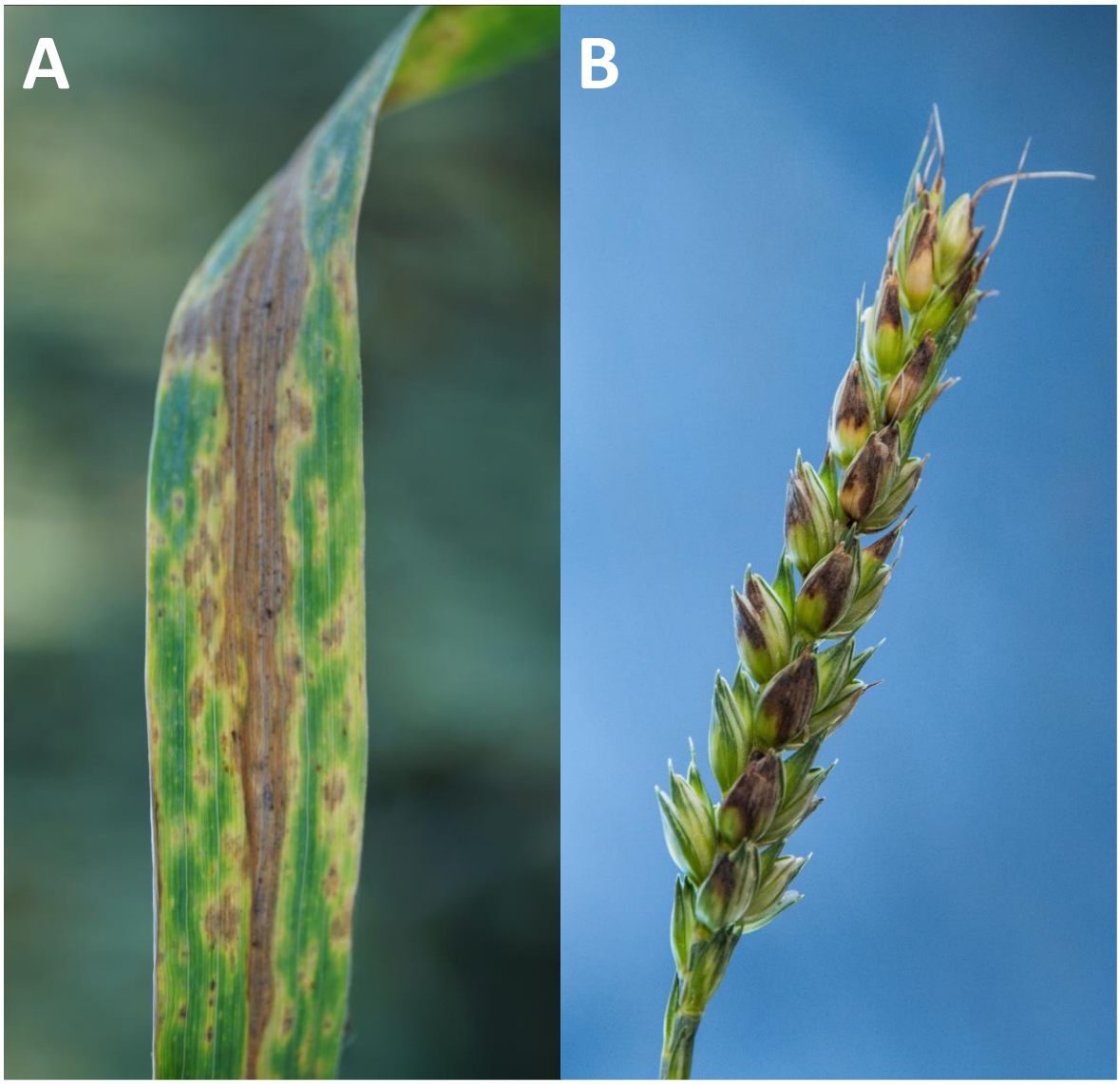
Supplementary Table 1. Summary of QTLs for *P. nodorum* infection, culture filtrate infiltration and effector sensitivity. QTLs, and relevant cloned genes from wheat, are anchored to the reference wheat genome assembly (cultivar Chinese Spring, RefSeq v1.0. IWGSC, 2018). Anchoring was undertaken using marker DNA sequences as queries for BLASTn searches of the wheat reference genome. Where BLASTn hits were identified on a non-target homoeologous location, and the e-values for the homoeologues were comparable, physical location is reported for the homoeologue on the chromosome identified by the relevant genetic map. Genetic markers for which no associated DNA sequences could be found for BLASTn analysis are highlighted in red.

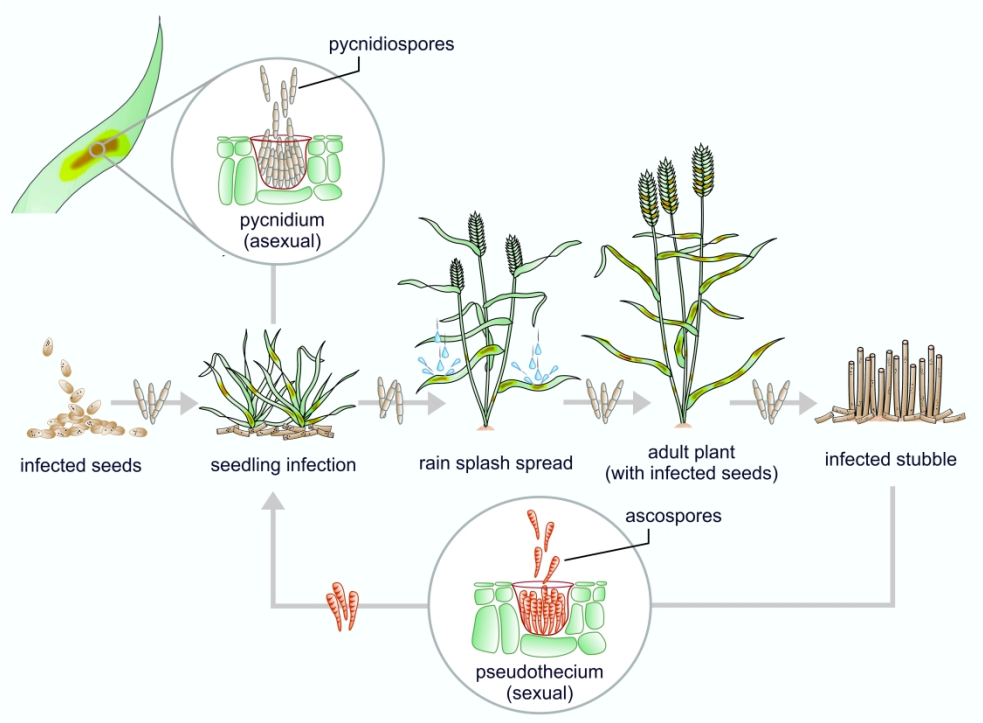
Figure legends

Figure 1. Septoria nodorum botch (SNB) symptoms in bread wheat. (A) On leaves. (B) On the spikelets of a wheat inflorescence (ear).

Figure 2. Illustration of the *Parastagonospora nodorum* infection cycle on wheat. Initial infection of wheat seedlings is via *P. nodorum* ascospores present in infected stubble, or via seeds infected with *P. nodorum* mycelium which produce pycnidiospores under wet or humid conditions. Pycnidiospores produced as a result of this initial infection can then be spread via rain splash or wind, causing secondary infection further up the wheat canopy as the crop matures, and can result in infection of the wheat ears.

Figure 3. Projection of published QTLs for SNB leaf blotch (black), glume blotch (blue), culture filtrate/effector infiltration sensitivity at the seedling stage (brown) and seedling *P. nodorum* resistance (green) onto the wheat reference genome assembly (RefSeq v1.0; IWGSC, 2018). The locations of relevant cloned wheat genes are shown in red. QTL are named according to their publication, and full details for all QTL are listed in Supplementary Table 1.


A
B



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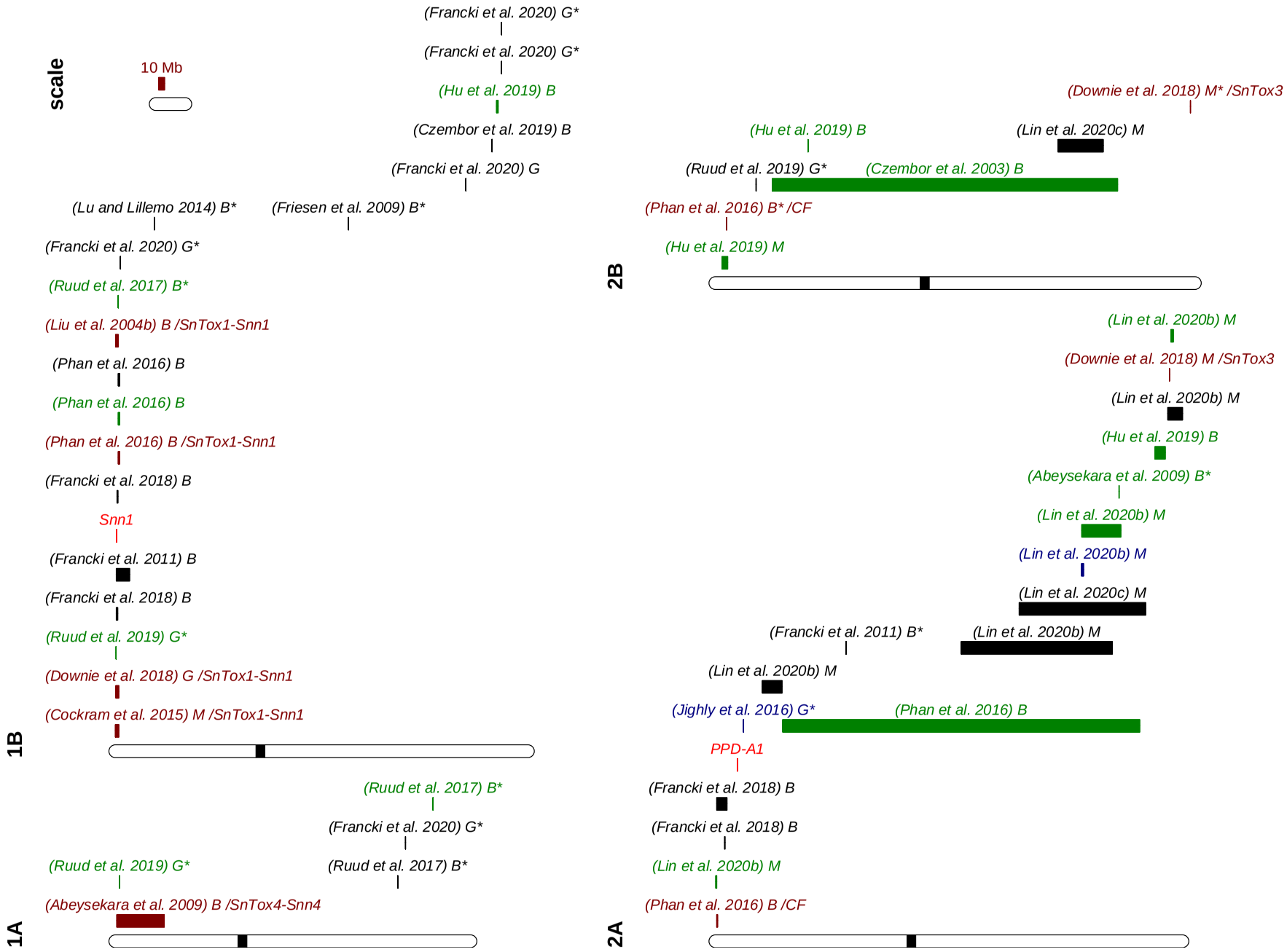
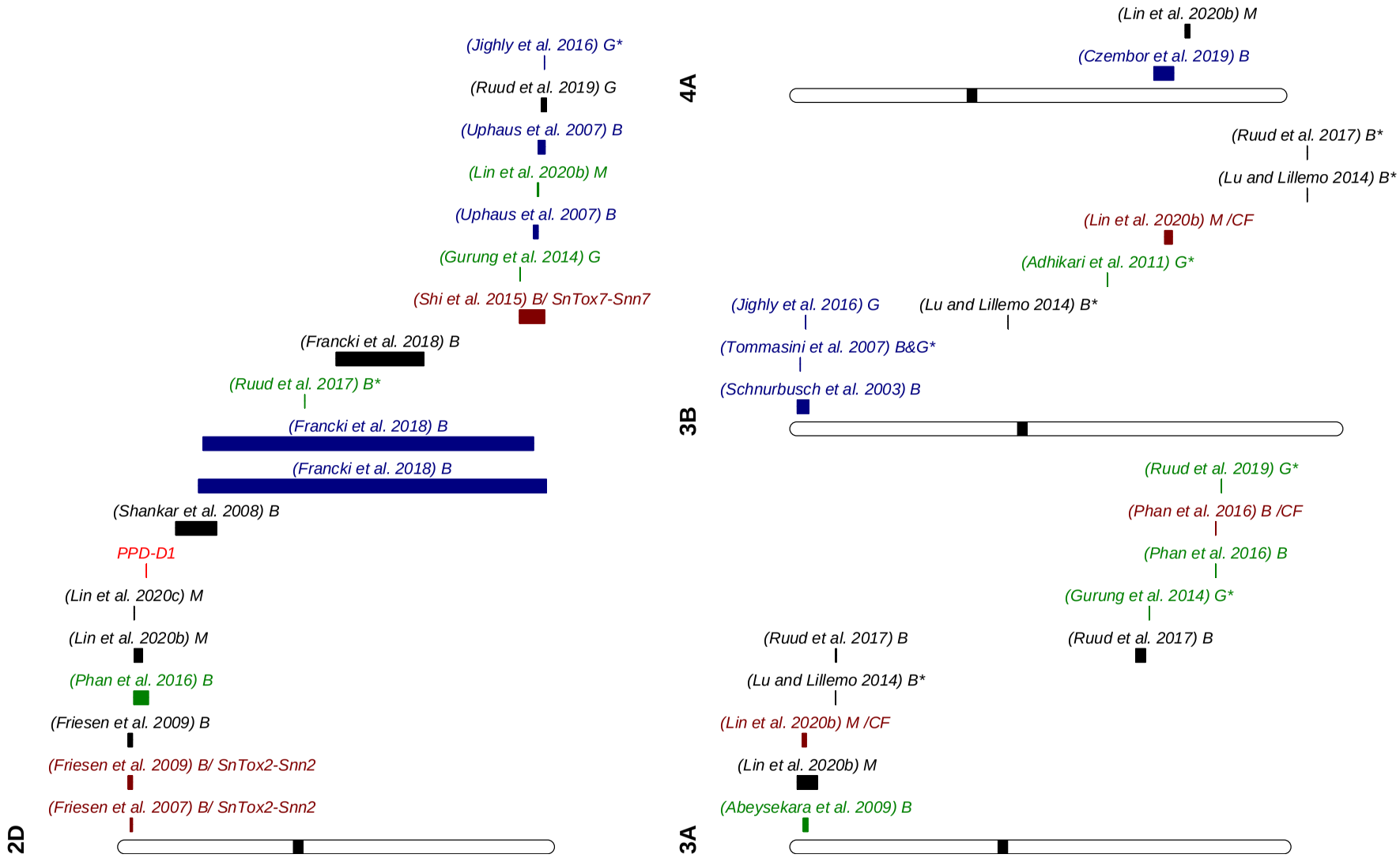
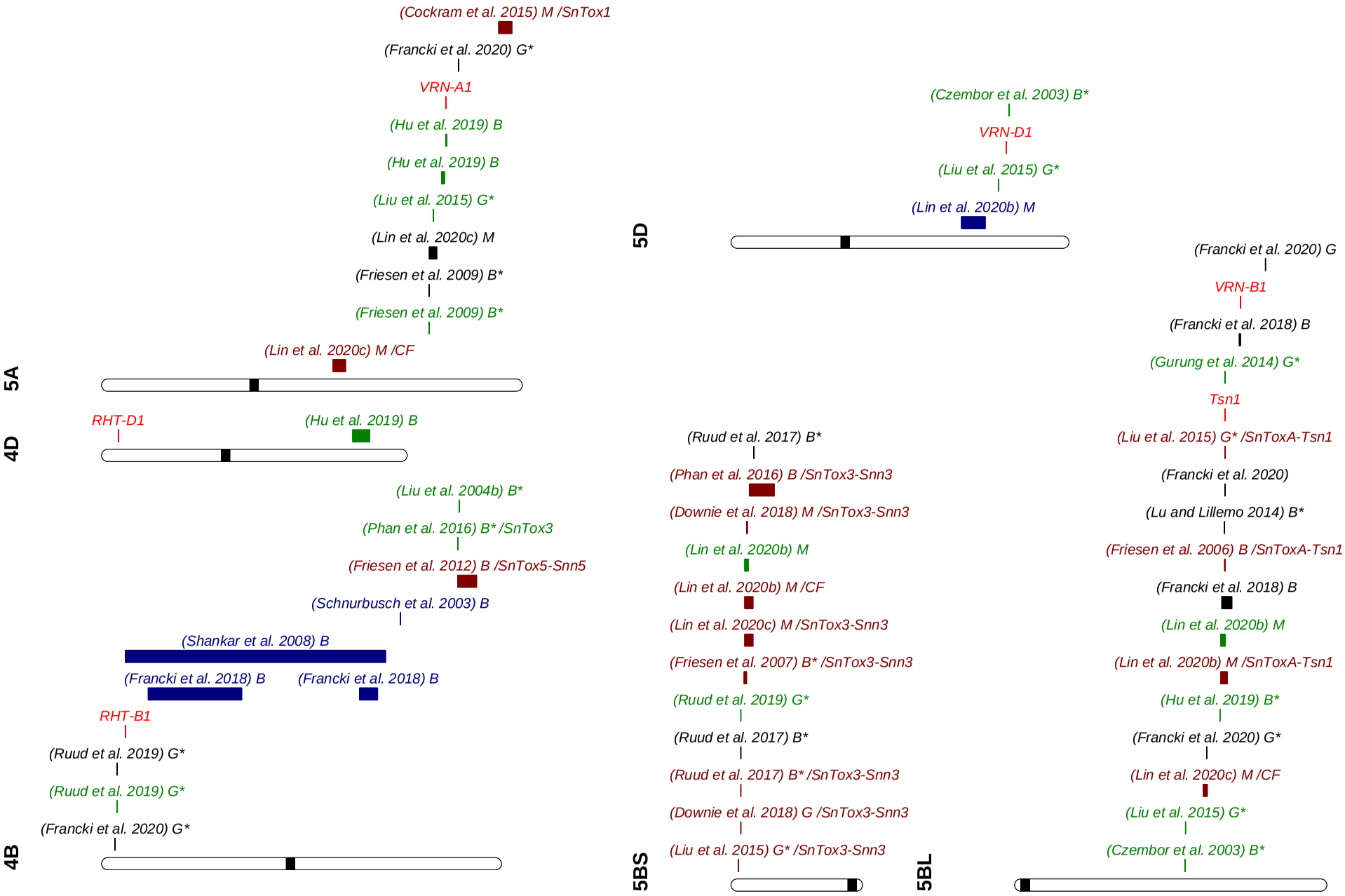
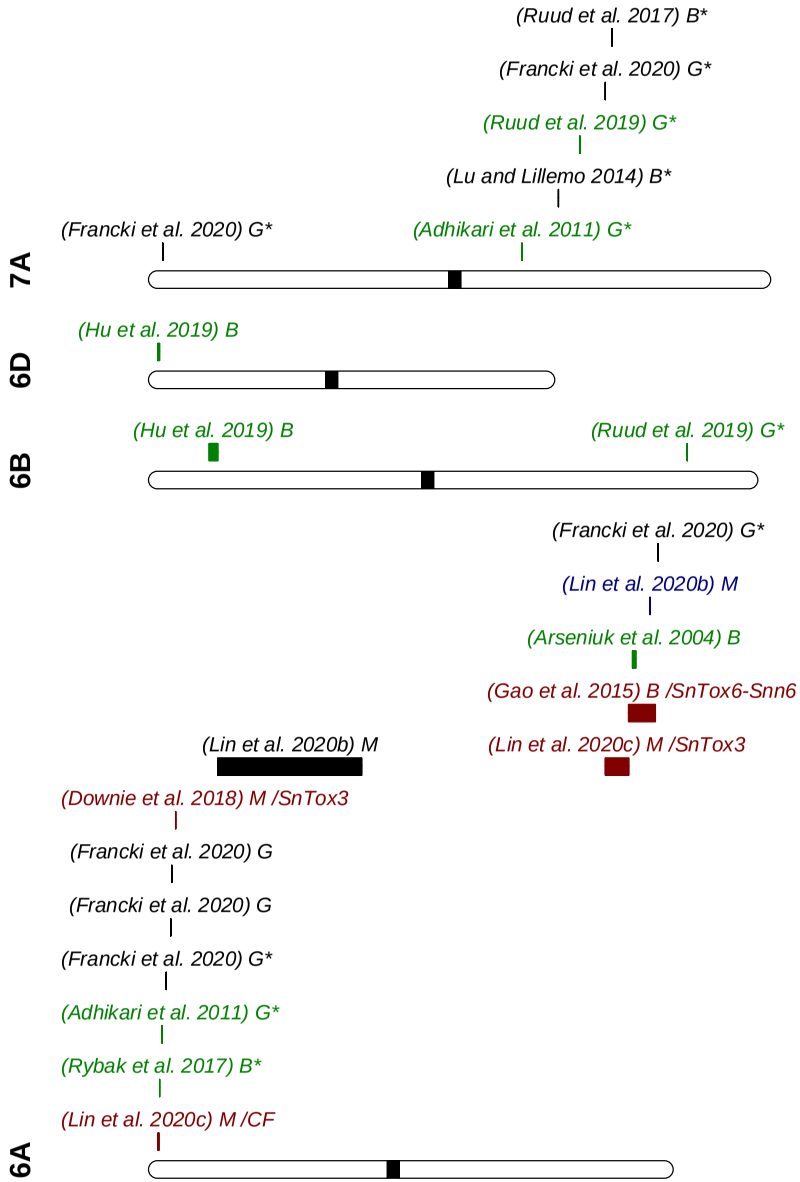
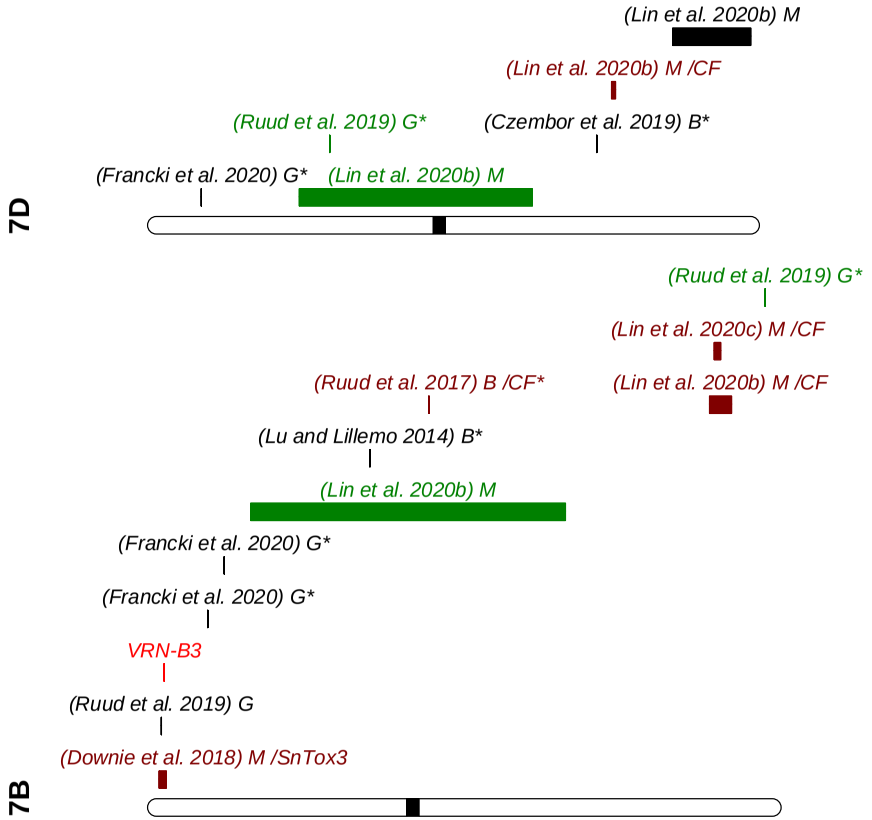
205x153mm (600 x 600 DPI)


scale
10 Mb
1A
(Abeysekara et al. 2009) B /SnTox4-Snn4
(Ruud et al. 2019) G*
(Ruud et al. 2017) B*
(Francki et al. 2020) G*
(Ruud et al. 2017) B*
1B
(Cockram et al. 2015) M /SnTox1-Snn1
(Downie et al. 2018) G /SnTox1-Snn1
(Ruud et al. 2019) G*
(Francki et al. 2018) B
(Francki et al. 2011) B
Snn1
(Francki et al. 2018) B
(Phan et al. 2016) B /SnTox1-Snn1
(Phan et al. 2016) B
(Phan et al. 2016) B
(Liu et al. 2004b) B /SnTox1-Snn1
(Ruud et al. 2017) B*
(Francki et al. 2020) G*
(Lu and Lillemo 2014) B*
(Friesen et al. 2009) B*
(Francki et al. 2020) G
(Czembor et al. 2019) B
(Hu et al. 2019) B
(Francki et al. 2020) G*
(Francki et al. 2020) G*
2A
(Phan et al. 2016) B /CF
(Lin et al. 2020b) M
(Francki et al. 2018) B
(Francki et al. 2018) B
PPD-A1
(Jighly et al. 2016) G*
(Phan et al. 2016) B
(Lin et al. 2020b) M
(Francki et al. 2011) B*
(Lin et al. 2020b) M
(Lin et al. 2020c) M
(Lin et al. 2020b) M
(Lin et al. 2020b) M
(Abeysekara et al. 2009) B*
(Hu et al. 2019) B
(Lin et al. 2020b) M
(Downie et al. 2018) M /SnTox3
(Lin et al. 2020b) M
2B
(Hu et al. 2019) M
(Phan et al. 2016) B* /CF
(Ruud et al. 2019) G*
(Czembor et al. 2003) B
(Hu et al. 2019) B
(Lin et al. 2020c) M
(Downie et al. 2018) M* /SnTox3


(Jighly et al. 2016) G*
(Ruud et al. 2019) G
(Uphaus et al. 2007) B
(Lin et al. 2020b) M
(Uphaus et al. 2007) B
(Gurung et al. 2014) G
(Shi et al. 2015) B/ SnTox7-Snn7
(Francki et al. 2018) B
(Ruud et al. 2017) B*
(Francki et al. 2018) B
(Francki et al. 2018) B
(Shankar et al. 2008) B
PPD-D1
(Lin et al. 2020c) M
(Lin et al. 2020b) M
(Phan et al. 2016) B
(Friesen et al. 2009) B
(Friesen et al. 2009) B/ SnTox2-Snn2
(Friesen et al. 2007) B/ SnTox2-Snn2
2D
(Lin et al. 2020b) M
(Czembor et al. 2019) B
4A
(Ruud et al. 2017) B*
(Lu and Lillemo 2014) B*
(Lin et al. 2020b) M /CF
(Adhikari et al. 2011) G*
(Jighly et al. 2016) G
(Lu and Lillemo 2014) B*
(Tommasini et al. 2007) B&G*
(Schnurbusch et al. 2003) B
3B
(Ruud et al. 2019) G*
(Phan et al. 2016) B /CF
(Phan et al. 2016) B
(Gurung et al. 2014) G*
(Ruud et al. 2017) B
(Ruud et al. 2017) B
(Lu and Lillemo 2014) B*
(Lin et al. 2020b) M /CF
(Lin et al. 2020b) M
(Abeysekara et al. 2009) B
3A


(Cockram et al. 2015) M /SnTox1
(Francki et al. 2020) G*
VRN-A1
(Hu et al. 2019) B
(Hu et al. 2019) B
(Liu et al. 2015) G*
(Lin et al. 2020c) M
(Friesen et al. 2009) B*
(Friesen et al. 2009) B*
(Lin et al. 2020c) M /CF
5A
RHT-D1
(Hu et al. 2019) B
4D
(Liu et al. 2004b) B*
(Phan et al. 2016) B* /SnTox3
(Friesen et al. 2012) B /SnTox5-Snn5
(Schnurbusch et al. 2003) B
(Shankar et al. 2008) B
(Francki et al. 2018) B
(Francki et al. 2018) B
RHT-B1
(Ruud et al. 2019) G*
(Ruud et al. 2019) G*
(Francki et al. 2020) G*
4B
(Czembor et al. 2003) B*
VRN-D1
(Liu et al. 2015) G*
(Lin et al. 2020b) M
5D
(Ruud et al. 2017) B*
(Phan et al. 2016) B /SnTox3-Snn3
(Downie et al. 2018) M /SnTox3-Snn3
(Lin et al. 2020b) M
(Lin et al. 2020b) M /CF
(Lin et al. 2020c) M /SnTox3-Snn3
(Friesen et al. 2007) B* /SnTox3-Snn3
(Ruud et al. 2019) G*
(Ruud et al. 2017) B*
(Ruud et al. 2017) B* /SnTox3-Snn3
(Downie et al. 2018) G /SnTox3-Snn3
(Liu et al. 2015) G* /SnTox3-Snn3
5BS
(Francki et al. 2020) G
VRN-B1
(Francki et al. 2018) B
(Gurung et al. 2014) G*
Tsn1
(Liu et al. 2015) G* /SnToxA-Tsn1
(Francki et al. 2020)
(Lu and Lillemo 2014) B*
(Friesen et al. 2006) B /SnToxA-Tsn1
(Francki et al. 2018) B
(Lin et al. 2020b) M
(Lin et al. 2020b) M /SnToxA-Tsn1
(Hu et al. 2019) B*
(Francki et al. 2020) G*
(Lin et al. 2020c) M /CF
(Liu et al. 2015) G*
(Czembor et al. 2003) B*
5BL


7A
(Francki et al. 2020) G*
(Adhikari et al. 2011) G*
(Lu and Lillemo 2014) B*
(Ruud et al. 2019) G*
(Francki et al. 2020) G*
(Ruud et al. 2017) B*
6D
(Hu et al. 2019) B
6B
(Hu et al. 2019) B
(Ruud et al. 2019) G*
6A
(Lin et al. 2020b) M
(Downie et al. 2018) M /SnTox3
(Francki et al. 2020) G
(Francki et al. 2020) G
(Francki et al. 2020) G*
(Adhikari et al. 2011) G*
(Rybak et al. 2017) B*
(Lin et al. 2020c) M /CF
(Lin et al. 2020c) M /SnTox3
(Gao et al. 2015) B /SnTox6-Snn6
(Arseniuk et al. 2004) B
(Lin et al. 2020b) M
(Francki et al. 2020) G*


7D
(Francki et al. 2020) G*
(Lin et al. 2020b) M
(Ruud et al. 2019) G*
(Czembor et al. 2019) B*
(Lin et al. 2020b) M /CF
(Lin et al. 2020b) M
7B
(Downie et al. 2018) M /SnTox3
(Ruud et al. 2019) G
VRN-B3
(Francki et al. 2020) G*
(Francki et al. 2020) G*
(Lin et al. 2020b) M
(Lu and Lillemo 2014) B*
(Ruud et al. 2017) B /CF*
(Lin et al. 2020b) M /CF
(Lin et al. 2020c) M /CF
(Ruud et al. 2019) G*