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J. D. Faris · W. L. Li · D. J. Liu
P. D. Chen · B. S. Gill

Candidate gene analysis of quantitative disease resistance in wheat

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Abstract Knowledge of the biological significance underlying quantitative trait loci (QTLs) for disease resistance is generally limited. In recent years, advances in plant-microbe interactions and genome mapping have lead to an increased understanding of the genes involved in plant defense and quantitative disease resistance. Here, we report on the application of the candidate-gene approach to the mapping of QTLs for disease resistance in a population of wheat recombinant inbreds. Over 50 loci, representing several classes of defense response (DR) genes, were placed on an existing linkage map and the genome was surveyed for QTLs associated with resistance to several diseases including tan spot, leaf rust, Karnal bunt, and stem rust. Analysis revealed QTLs with large effects in regions of putative resistance (R) genes, as previously reported. Several candidate genes, including oxalate oxidase, peroxidase, superoxide dismutase, chitinase and thaumatin, mapped within previously identified resistance QTLs and explained a greater amount of the phenotypic variation. A cluster of closely linked DR genes on the long arm of chromosome 7B, which included genes for catalase, chitinase, thaumatins and an ion channel regulator, had major effects for resistance to leaf rust of adult plants under conditions of natural infestation. The results of this study indicate that many minor resistance QTLs may be from the action of DR genes, and that the candidate-gene approach can be an efficient method of QTL identification.

Key words Wheat · Quantitative trait loci · Candidate gene · Disease resistance · Molecular mapping

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J. D. Faris · B. S. Gill (✉)
The Wheat Genetics Resource Center and Department of Plant Pathology, Kansas State University, Manhattan, KS 66506, USA
Fax: + 1-785-532-5692
E-mail: bsg@ksu.edu

W. L. Li · D. J. Liu · P. D. Chen
Department of Agronomy, Nanjing Agricultural University, Nanjing, 210095, People's Republic of China

Introduction

The use of molecular markers for the construction of genetic linkage maps in segregating populations permits the estimation of the number, positions, and degrees of effects of polygenes affecting quantitative trait loci (QTLs). QTL studies allow the dissection of the continuous phenotypic variation into contributions from discrete genetic factors. It is possible to determine whether QTLs are specific to certain plant tissues, developmental stages, phenotypic scoring methods, or pathogenic races. However, knowledge of the biological mechanisms underlying individual QTLs is not well understood.

The candidate-gene approach has emerged as a promising method of merging QTL analysis with the extensive data available on the cloning and characterization of genes involved in plant defense. Here, genes potentially involved in the biochemical pathways leading to trait expression are employed as molecular markers for QTL analysis. This approach has been applied successfully in several experiments (Goldman et al. 1993; Causse et al. 1995). However, Byrne et al. (1996) presented the most compelling case for linking candidate genes involved in the flavone synthesis pathway of maize with the host defense response phenotype associated with QTL resistance to corn earworm. In this case, the *p1* locus, coding for a transcriptional activator, together with three other candidate genes, accounted for 75.9% of the phenotypic variation for resistance.

The candidate-gene approach is ripe for the analysis of resistance QTLs. First, large numbers of complex and polygenic forms of disease resistance have been described (Yu et al. 1991; Heun 1992; Bubeck et al. 1993; Kreike et al. 1993; Nordari et al. 1993; Young et al. 1993; Dirlewanger et al. 1994; Leonards-Schippers et al. 1994; Wang et al. 1994; Byrne et al. 1996; Pecchioni et al. 1996; Steffenson et al. 1996; Young 1996; Faris et al. 1997). Secondly, the study of molecular plant-microbe interactions has led to the cloning and characterization of many genes involved in plant defense (for reviews see Bowles 1990; Yun et al. 1997).

Two broad classes of genes concerned with plant defense are those involved in the recognition process (resistance or R genes), and those involved in the defense-response process (DR genes). A number of R genes have been cloned (for a review see Bent 1996) and have been shown to share common sequence motifs, reflecting related functions in signal-transduction pathways (Martin et al. 1993; Jones et al. 1994; Whitham et al. 1994; Lawrence et al. 1995; Song et al. 1995; Staskawicz et al. 1995; Cai et al. 1997). These recognition-type resistance genes are best characterized as genes controlling high levels of resistance. DR genes produce products that are directly implicated in plant defense or can be involved in the biosynthesis of defense compounds such as phytoalexins. Many DR genes have been cloned and characterized, but their chromosomal locations and their contributions to phenotypic expression are not well known. Some DR genes are thought to act downstream from R genes and are probably regulated by one or more signal-transduction pathways, while others are constitutively expressed or pathogen-inducible. It is therefore possible that DR genes may be responsible for the effects of some resistance QTLs.

In this paper, we describe the use of candidate genes involved in defense response for the QTL analysis of resistance to several diseases in a segregating population of wheat (*Triticum aestivum* L. emend. Thell. $2n = 6x = 42$, AABBDD genomes) recombinant inbreds. This population segregates for resistance to various fungal diseases including tan spot [*Pyrenophora tritici-repentis* (Died) Drechs], stem rust (*Puccinia graminis* Pers. f. sp *tritici* Eriks. & E. Henn.), Karnal bunt (*Tilletia indica* Mitra), and several pathotypes of leaf rust (*Puccinia recondita* Roberge ex Desmaz. f. sp. *tritici* Eriks. & E. Henn.) We show that DR genes may be responsible for several previously identified resistance QTLs.

Materials and methods

Plant material

The mapping population consists of 114 recombinant inbred (RI) lines developed from a cross between the hard red spring wheat cultivar 'Opata 85' and a synthetic hexaploid wheat, W-7984, as described by Nelson et al. (1995c). The synthetic was produced from the cross between the durum wheat (*Triticum turgidum* L. $2n = 4x = 28$, AABB genomes) cultivar 'Altar 84' and *Aegilops tauschii* Coss. [syn. *Aegilops squarrosa* L., syn. *T. tauschii* (Coss.) Schmal. $2n = 2x = 14$, DD genome].

Disease screening

Disease ratings for resistance to leaf rust were described in Nelson et al. (1997). Briefly, for seedling resistance, young seedlings were inoculated with the Mexican *P. recondita* pathotypes TBD/TM and BBB/BN which are avirulent on resistance genes *Lr23* and *Lr27* + *Lr31*, respectively. Infection types were recorded 10 days after inoculation using a scale similar to that of Stakman et al. (1962). For adult plant resistance, plants artificially inoculated with pathotype BBB/BN and NCJ/BN were scored for reaction to disease based on the modified Cobb scale (Peterson et al. 1948), and under natural infestation were scored using a 0 to 9 scale based on the proportion of leaf area covered by uredia.

Disease inoculations and ratings for reaction to tan spot were described in Faris et al. (1997). Descriptions of methods and results for reactions to stem rust and Karnal bunt were presented in Nelson et al. (1995b) and (1998), respectively. All disease ratings can be found in the Graingenes database (http://wheat.pw.usda.gov/graingenes.html).

Map construction

The genetic linkage map constructed in the ITMI population now consists of more than 1000 genetic markers, and maps have been published for chromosomes of group 1 (Van Deynze et al. 1995), group 2 (Nelson et al. 1995b), group 3 (Nelson et al. 1995c), group 6 (Marino et al. 1996), and groups 4, 5, and 7 (Nelson et al. 1995a). As with the disease ratings, all maps and mapping data can be obtained from the Graingenes database. For this study, 36 clones representing seven classes of defense-response proteins were probed and produced 58 polymorphic loci. All DR gene probes detecting disease-QTL associations were mapped on the entire population. All clones are included in the Kansas State University Plant Biotechnology Center defense-response gene collection (J. Chittoor and J. Leach, personal communication). The sources of clones and the relevant mapping details are described in Li et al. (1998).

Candidate-gene analysis

The map used in this study employed 508 genetic markers including the candidate genes. Simple linear regression analysis was used to identify candidate genes associated with resistance at the 0.01 level of probability. Interval-regression mapping (Haley and Knott 1992) was then performed on chromosome linkage groups possessing markers with significant single-factor effects. A LOD threshold of about 3.0 in this RI population yields an experiment-wise significance level of 0.05 (Lander and Botstein 1989). However, because we are surveying the effects of candidate genes as opposed to anonymous DNA markers, this threshold was not applied and more emphasis was placed on the significance of the single-factor regression analysis. For this study, a higher probability of committing a Type-I error is tolerated to reduce the chances of committing a Type-II error (declaring non-significance of a significant candidate gene). Therefore, interval regression maps of chromosomes with candidate genes that have a single-factor significance of $P < 0.01$ are presented, as well as chromosomes harboring QTLs with major

effects. All candidate genes significant at $P < 0.01$ were tested for interactions with all other markers. QTLs not involving candidate genes or known resistance genes are not presented. All calculations were performed using the computer program QGene v.2.27 (Nelson 1997).

Results and discussion

Tan spot

Faris et al. (1997) screened the RI population for reaction to tan spot and scored the reactions based on infection type and the percent of leaf area diseased. They identified a QTL with major effects on chromosome 1A (*QTsc.ndsu*), two QTLs with lesser effects on chromosome 4A, two minor QTLs on chromosomes 1B and 3B, and an epistatic interaction between the marker detecting the major QTL on chromosome 1A and a marker on chromosome 2D. The best multiple-regression model consisted of a QTL each on 1A and 4A, and the epistatic interaction, and explained 49.0% of the phenotypic variation.

Faris et al. (1997) identified the marker *Xfba211* on 4AL as having the greatest association with tan spot resistance in that region ($R^2 = 0.107$). Subsequent analysis of the tan spot-resistance QTL after mapping the defense-response genes in this population revealed that *Oxo2-4A* (oxalate oxidase) and *1433a-4A* (ion channel regulator) are more significantly associated with disease resistance and explain more of the phenotypic variation than *Xfba211* (Fig. 1a, Table 1).

One of the limitations of QTL mapping is that adequate genome coverage is essential. Here, the mapping of *1433-4A* and *Oxo2-4A* increased the resolution around the QTL previously identified by *Xfba211*. The significance of *Oxo2-4A* (Table 1) suggests that it may detect the gene responsible for the resistance governed by this QTL.

A new multiple-regression model was constructed using the marker *Oxo2-4A* (data not shown). The best multiple-regression model included the marker for the major QTL on chromosome 1A, the epistatic interaction and *Oxo2-4A*, and explained 58.0% of the phenotypic variation.

Oxalate oxidase has been shown to be induced in barley seedlings in response to attack by the powdery mildew fungus (Dumas et al. 1995; Zhang et al. 1995). It is possible that oxalate oxidase is either regulated by a putative R gene, or is pathogen induced and regulated by an independent pathway. The major QTL identified on chromosome 1AS (*QTsc.ndsu*) may be an R gene involved in recognition of the pathogen. Resistance at both the 1A and the 4A loci was contributed by the synthetic parent, but no statistical interaction between the 1AS and the 4AL loci was detected.

Leaf rust

The leaf-rust phenotypic scoring data collected after inoculation with a pathotype avirulent to the seedling leaf-rust resistance gene *Lr23* (Nelson et al. 1997) was analyzed with the candidate genes included in the marker data set. Regression analysis revealed that the *Per2-2B* (peroxidase) locus, which maps near the known location of *Lr23* on chromosome 2BS, is associated with resistance to the pathotype used in inoculation and explains 31.3% of the phenotypic variation (Fig. 1b, Table 1). *Xtam72* was previously identified as the marker most closely associated with *Lr23* (Nelson et al. 1997) and explained 14.2% of the variation. *Per2-2B* maps approximately 10 cM distal to *Xtam72* and is separated by two markers [*Sod-2B* (superoxide dismutase) and *Xmwg950*] with less significant effects than either *Xtam72* or *Per2-2B*. High-resolution mapping of this region will be needed to determine if the significance of *Per2-2B* is due to the presence of the peroxidase itself, or if the effects are due to the linkage with *Lr23*.

An interaction between the *Lr23* region on chromosome 2B and a region on chromosome 2D known to possess the suppressor *SuLr23* was described (Nelson et al. 1997). Here, analysis of *Per2-2B* indicated the same interaction in addition to an interaction with the marker *XksuH7* on chromosome 3B (data not shown). A multiple-regression model consisting of *Per2-2B* and the two interactions explains 61.5% of the phenotypic variation for this trait. The region represented by *1433a-4A* and *Oxo2-4A* was also significantly associated with resistance and explained 10% of the variation, but did not retain significance in the multiple-regression model.

Nelson et al. (1997) showed that the seedling resistance genes *Lr27* and *Lr31*, which map on chromosomes 3BS and 4BL, respectively, are complementary. *Pal-3B* (phenylalanine ammonium lyase) is closely linked to *Lr27* and it is unclear whether it is actually contributing to resistance. In addition to these chromosomal regions, the *Tha1-7D* (thaumatin) marker on the distal tip of chromosome 7DL was significantly associated with resistance to the corresponding pathotype (Fig. 1c, Table 1). The thaumatin detected by *Tha1-7D* may itself be partially responsible for contributing to resistance, or an additional gene(s) that maps closer to the telomere of 7DL that has(ve) not yet been detected may be involved.

The population segregates for *Lr34* which confers adult-plant horizontal-type resistance to leaf rust. Adult plants were scored for reaction to leaf rust after artificial inoculation and under natural infestation (Nelson et al. 1997). In each case, the chromosomal region harboring *Lr34* on 7DS, which is flanked by markers *Xwg834* and *Xbcd1438*, was highly associated with resistance. Under artificial inoculation conditions using two different pathotypes, the *Oxo2-4A*/*1433a-4A* region contributed to resistance (Fig. 1d, Table 1).

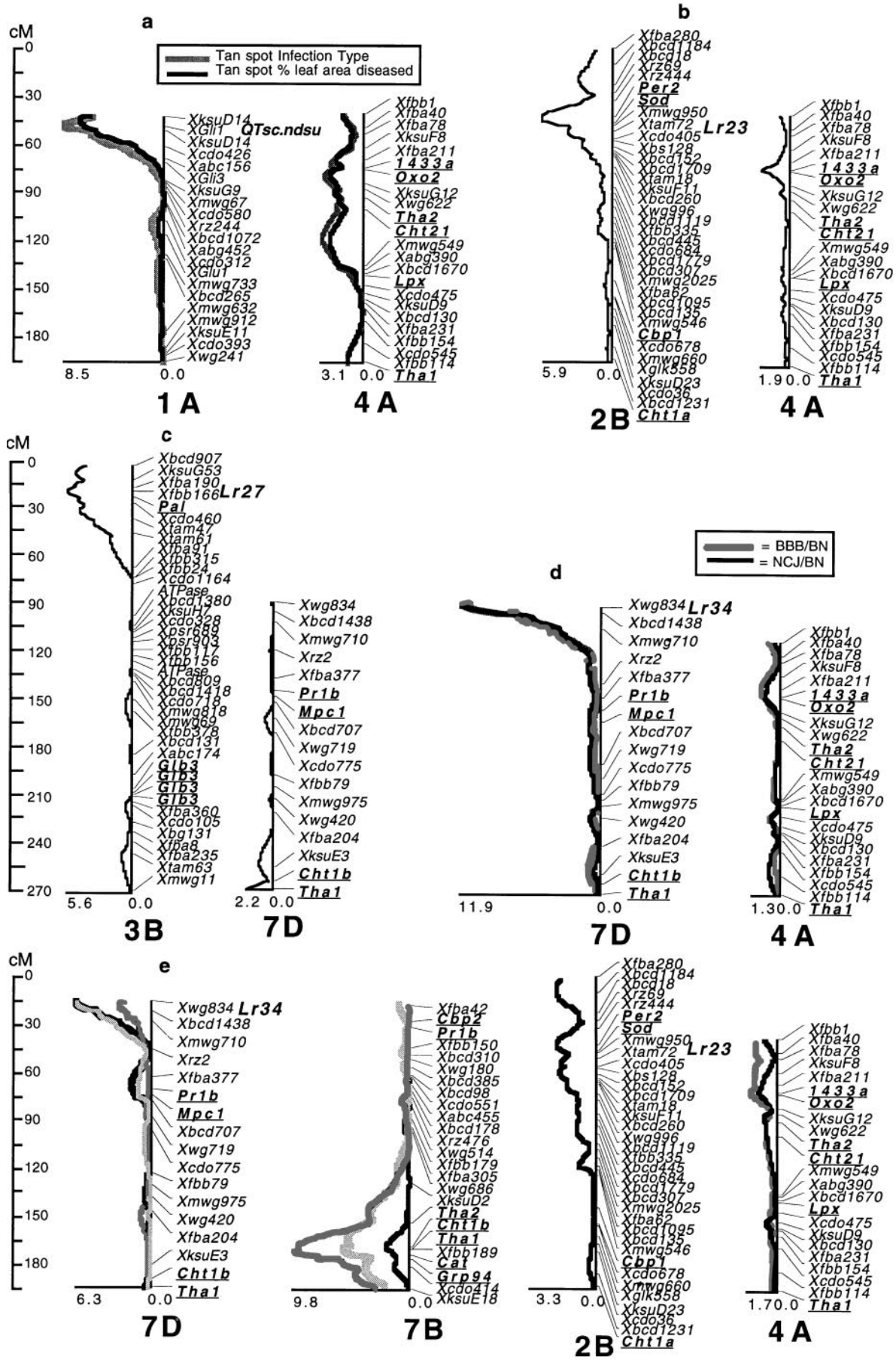
a
cM
Tan spot Infection Type
Tan spot % leaf area diseased
QTsc.ndsu
1 A
4 A
b
Lr23
2B
4 A
c
Lr27
3B
7D
d
= BBB/BN
= NCJ/BN
Lr34
7D
4 A
e
Lr34
7D
7B
Lr23
2B
4 A

Table 1 Major markers and candidate genes, their chromosomal locations, significance values, and the parental allele contributing to the resistance of tan spot and leaf rust in the population of wheat recombinant inbreds derived from the cross of W-7984 with Opata 85

Disease	Marker (Gene)[a]	Chromosome	Source of resistance	R^2	*P*
Tan spot IT[b]	*XGli1* (*QTsc.ndsu*)	1AS	W-7984	0.350	< 0.00001
	Oxo2/1433a	4AL	W-7984	0.175	0.0001
Tan spot %LAD[c]	*XGli1* (*QTsc.ndsu*)	1AS	W-7984	0.285	< 0.00001
	Oxo2/1433a	4AL	W-7984	0.134	0.0001
Leaf rust[d]	*Per2* (*Lr23?*)	2BS	W-7984	0.331	< 0.00001
	Oxo2/1433a	4AL	Opata 85	0.100	0.0011
Leaf rust[e]	*XksuG53* (*Lr27*)	3BS	Opata 85	0.162	< 0.00001
	Pal	3BS	Opata 85	0.135	0.0050
	Tha1	7DL	Opata 85	0.168	0.0018
Leaf rust[f]	*Xwg834* (*Lr34*)	7DS	Opata 85	0.415	< 0.00001
	Oxo2/1433a	4AL	Opata 85	0.080	0.0067
Leaf rust[g]	*Xwg834* (*Lr34*)	7DS	Opata 85	0.428	< 0.00001
	Oxo2/1433a	4AL	Opata 85	0.068	0.0140
Leaf rust[h]	*Xwg834* (*Lr34*)	7DS	Opata 85	0.080	0.0034
	Cht1b/Tha1/Cat	7BL	Opata 85	0.400	< 0.00001
	Oxo2/1433a	4AL	Opata 85	0.062	0.0089
Leaf rust[i]	*Xwg834* (*Lr34*)	7DS	Opata 85	0.224	< 0.00001
	Cht1b/Tha1/Cat	7BL	Opata 85	0.110	0.0024
	Per2 (*Lr23?*)	2BS	W-7984	0.157	< 0.00001
	Oxo2/1433a	4AL	Opata 85	0.112	0.0091
	Pr1b/Mpc1	7DS	Opata 85	0.081	0.0053
Leaf rust[j]	*Xwg834* (*Lr34*)	7DS	Opata 85	0.241	< 0.00001
	Cht1b/Tha1/Cat	7BL	Opata 85	0.422	< 0.00001

[a] Descriptions of marker symbols are presented in Li et al. (1998)
[b] IT = tan spot infection-type lesions were rated as described (Faris et al. 1997)
[c] % LAD = percent leaf area diseased by tan spot
[d] Seedlings were artificially inoculated with pathotype TBD/TM (Nelson et al. 1997)
[e] Seedlings were artificially inoculated with pathotype BBB/BN (Nelson et al. 1997)
[f,g] Adult plants were artificially inoculated with pathotypes BBB/BN and NCJ/BN, respectively (Nelson et al. 1997)
[h,i,j] Adult plant were scored for 3 different years under conditions of natural infestation (Nelson et al. 1997)

Under conditions of natural infestation, in addition to the *Lr34* region, a region on the long arm of 7B, which consists of a cluster of DR genes, was strongly associated with resistance in each case (Fig. 1e, Table 1). William et al. (1997) analyzed the quantitative resistance in a different population of RI lines and suggested that there were two closely linked QTLs on chromosome 7BL that were at least as effective at contributing to resistance as *Lr34*. The mapping in our study revealed that at least five DR genes are clustered in this region. The catalase (*Cat-7B*), thaumatin (*Tha1-7B*), and chitinase (*Cht1b-7B*) genes appear to be the most responsible for contributing to resistance, but from this study we are not able to depict if all are contributing equally or if only one is the primary contributor to resistance.

It is interesting that the cluster of DR genes on 7BL was strongly associated with resistance under natural infestation conditions but not, in any case, of the artificial inoculation of leaf rust on adult plants. It may be that, under artificial inoculation conditions, the plants are rapidly overwhelmed with pathogen and the DR genes have not been given time to respond to the magnitude needed for resistance; whereas, under conditions of natural infestation, the plants are consistently exposed to a "low dose" of pathogen and the DR genes are active. Alternatively, the DR gene(s) on 7BL may have some race specificity and did not respond to the pathotypes employed in the artificial inoculation experiments.

Fig. 1a–e Genome map locations of resistance genes and defense-response genes associated with QTLs for resistance to leaf rust and tan spot in the population of recombinant inbred lines derived from the cross between W-7984 and Opata 85. Short arms of chromosomes are toward the top of the maps and contours to the left of chromosomes show LOD scores for interval mapping based on disease ratings. Maximum LOD scores are shown at the base of maps. Markers representing defense-response genes are *bold and underlined*. **a** Interval analysis for seedling reaction to tan spot under artificial inoculation using *P. tritici-repentis* isolate Pti2. **b** Interval analysis for seedling reaction to a leaf rust pathotype avirulent to *Lr23* (TBD/TM). **c** Interval analysis for seedling reaction to a leaf rust pathotype avirulent to *Lr27* + *Lr31* (BBB/BN). **d** Interval analysis for adult plant reaction to leaf rust under artificial inoculation with two different pathotypes. **e** Interval analysis for adult plant reaction to leaf rust under conditions of natural infestation in 3 different years

In addition to the 7BL DR gene cluster, the region on chromosome 4AL represented by *Oxo2-4A* and *1433a-4A* was significant in two of the three natural infestation experiments. The peroxidase locus (*Per2*) on chromosome 2BS was involved in conditioning resistance in one of the experiments. But, as mentioned above, this may or may not be attributed to close linkage with *Lr23*. A second region on 7DS consisting of *Pr1b* and *Mpc1*, the marker representing the maize flavonoid metabolic pathway gene *c1*, was significant in one experiment.

Other diseases

Several candidate genes were also associated with minor QTLs for powdery mildew, Karnal bunt, and stem rust (data not shown). For powdery mildew, *Oxo2-4A* again was associated with resistance, in addition to a thaumatin (*Tha1-2D*) which mapped to chromosome 2DL. Markers representing flavanol 7-o-methyl transferase (*Fmt-1B*) and chalcone synthase (*Chs-1B*), which co-segregated on chromosome 1BS, and a chitinase (*Cht1B-7B*) within the DR gene cluster on 7BL, were associated with Karnal bunt resistance. *Grp94-7B*, an ion channel regulator which also lies within the cluster of DR genes on 7BL, contributed to stem rust resistance.

Candidate genes identified in multiple experiments

Several DR genes contributed as minor resistance QTLs in multiple experiments suggesting that such genes are race-nonspecific. Furthermore, the region of chromosome 4AL detected by *Oxo2-4A*/*1433a-4A* was involved with resistance to two different diseases; tan spot and leaf rust. Oxalate oxidase, peroxidase, superoxide dismutase, lipoxygenase, and catalase are all involved in the production, or modulation, of active oxygen species or in the oxidative burst which may directly or indirectly reduce pathogen viability and spread. For example, these enzymes may play a central role in triggering the hypersensitive response (HR), in the crosslinking and lignification of the cell wall, and in transducing signals to adjacent non-challenged cells (for reviews see Mehdy 1994; Tenhaken et al. 1995; Lamb and Dixon 1997).

Allelic variation and/or variation in expression are pre-requisites for the detection of the contribution to resistance of individual DR genes. Most probes used in the mapping of these DR genes hybridized to multiple fragments; however, many of these bands were monomorphic and thus uninformative. Also, it is possible that for some DR genes, the alleles from each parent contribute equally to resistance. In such a case, the association would go undetected.

The identification of candidate genes that contribute to quantitative resistance can circumvent the molecular cloning of these QTLs. The genes themselves that are responsible for resistance provide breeders with a very efficient molecular marker to aid in selecting desirable alleles at QTLs and to make the most-desirable allelic combinations. However, these resistance QTLs involving candidate genes will need to be mapped at a much higher genetic resolution to determine if they actually do coincide with the candidate gene of a distinct, but related, function.

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