

Rationalization of genes for resistance to *Bremia lactucae* in lettuce

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Abstract Lettuce downy mildew caused by *Bremia lactucae* is the most important disease of lettuce worldwide. Breeding for resistance to this disease is a major priority for most lettuce breeding programs. Many genes and factors for resistance to *B. lactucae* have been reported by multiple researchers over the past ~50 years. Their nomenclature has not been coordinated, resulting in duplications and gaps in nominations. We have reviewed the available information and rationalized it into 51 resistance genes and factors and 15 quantitative trait loci along with supporting documentation as well as genetic and

molecular information. This involved multiple rounds of consultation with many of the original authors. This paper provides the foundation for naming additional genes for resistance to *B. lactucae* in the future as well as for deploying genes to provide more durable resistance.

Keywords *Lactuca* spp. · Resistance genes · Lettuce downy mildew · *Dm* gene · Quantitative trait locus · Plant breeding

Abbreviations

DM Downy mildew
NLR Nucleotide binding-leucine rich repeat-receptor like protein

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MRC	Major resistance cluster
QTL	Quantitative trait locus
TNL	NLR proteins with a Toll/interleukin receptor (TIR) domain at their N-terminus
CNL	NLR proteins lacking a TIR domain often with a coiled-coil (CC) N-terminal domain
IBEB	International Bremia Evaluation Board
USDA	United States Department of Agriculture
DMR6	Downy mildew resistance 6
EMS	Ethyl methanesulfonate

Introduction

Lettuce (*Lactuca sativa*) is one of the most widely consumed vegetable crops worldwide. It has an annual production of more than 3.6 billion tonnes with a value of more than \$2.4 billion in the U.S. (USDA-NASS 2014). Downy mildew (DM) caused by the oomycete pathogen *Bremia lactucae* is the most important disease of lettuce that decreases quality of the marketable portion of the crop. The impact of this disease is often accentuated by postharvest losses that occur during transit and storage. DM can also increase the consequences of microbial contamination by human enteric pathogens (Simko et al. 2015a).

Strategies for control of DM include the combined use of resistant cultivars and fungicides as well as agronomic practices that reduce foliar humidity. The use of fungicides is constrained by high costs and the development of fungicide-resistant strains (Crute 1987; Schettini et al. 1991). Moreover, increasing restrictive regulations aimed at reducing pesticide applications are coming into force; in Europe several chemicals that are effective against *B. lactucae* will be redrawn from the market. The deployment of cultivars carrying dominant resistance genes (*Dm* genes) is the most effective method for controlling DM; however, pathogen variability has led to the rapid defeat of individual *Dm* genes (e.g. Illott et al. 1987). Consequently, the search for new sources resistance to *B. lactucae* has been a continuous, long-term priority of lettuce breeding programs (Crute 1992; Lebeda et al. 2002, 2014). Over 50 genes for resistance have been reported so far and genetically characterized to varying extents (see below for references). In addition, many other sources of resistance have been identified in germplasm screens but have yet to be characterized

genetically (e.g. Farrara and Michelmore 1987; Bonnier et al. 1994; Lebeda and Zinkernagel 2003; Beharav et al. 2006). As more resistance genes are characterized from these and other sources, it is likely that several hundred genes with efficacy against *B. lactucae* will be identified that will require a coordinated, rational nomination process.

This review compiles the knowledge of genetic resistance against *B. lactucae*, summarizing what is known of genes for resistance to *B. lactucae* that has been generated over more than 50 years of lettuce genetics and breeding (Supplemental Fig. 1). Resistance has been reported by multiple researchers leading to duplications in nominations as well as gaps in sequence. The extent of genetic characterization has varied. Genes characterized as single Mendelian loci were designated *Dm* genes, while those that were less well characterized genetically were often but not always termed R-factors. For this review we have rationalized the nomenclature of all of the *Dm* genes and R-factors reported so far and provide the foundation for future designation and use of *Dm* genes.

Historical overview of breeding for resistance to *B. lactucae*

Breeding for resistance to *B. lactucae* in cultivated lettuce has been carried out since the beginning of the last century. Initial breeding efforts utilized resistance identified in old lettuce cultivars (*L. sativa*). French traditional cultivars Gotte à Graine Blanche de Loos and Rosée Printanière were the first sources of resistance (referenced in Crute 1992). Subsequently, resistance was identified in several other cultivars such as Meikoningen, May Queen, Gotte à Forcer à Graine Noire, Bourguignonne Grosse Blonde d'Hiver and Blonde Lente à Monter (Jagger and Chandler 1933; Schultz and Röder 1938; Jagger and Whitaker 1940; Ogilvie 1944; Rodenburg et al. 1960). Later breeding efforts accessed resistance from wild *Lactuca* species. One of the first inter-specific crosses for this purpose was between *L. sativa* cv. Imperial D and DM-resistant *L. serriola* PI104854 (Whitaker et al. 1958). This resistance was used in breeding programs in California during the 50's, that led to the crisphead cv. Calmar (cv. Great Lakes × USDA 45325; Welch et al. 1965) and subsequently cv. Salinas (cv. Calmar × Vanguard 75; Ryder 1979a, b) that is in the pedigree of

many current crisphead cultivars (Mikel 2007, 2013). Contemporary breeding efforts are focused on introgression of new genes from wild species. *L. serriola*, the likely progenitor of cultivated lettuce, and, to a lesser extent, *L. saligna* have been used as donors of resistance genes (Jagger and Whitaker 1940; Crute and Johnson 1976a, b; Lebeda et al. 1980; Bonnier et al. 1994; Witsenboer et al. 1995; Maisonneuve et al. 1999; Jeuken and Lindhout 2002, Michelmore and Ochoa 2006, 2008; Mc Hale et al. 2009, Zhang et al. 2009). *L. virosa* also possesses race-specific resistance to *B. lactucae* (Lebeda and Boukema 1991; Lebeda et al. 2002, Maisonneuve et al. 1999), but its use in breeding programs has been restricted by infertility barriers between *L. virosa* and *L. sativa* (Maisonneuve 2003). Transfer of resistance from *L. virosa* to *L. sativa* has occasionally been enabled by embryo rescue (Maisonneuve 1987; Maisonneuve et al. 1995). Other wild species such as *L. aculeata* are potential sources of resistance that have yet to be used as donors in breeding programs (Jemelková et al. 2015). Currently, introgression of recently identified resistance from *L. serriola*, *L. saligna* and *L. virosa* through repeated backcrosses to *L. sativa* is being carried out by multiple public and commercial breeding programs resulting in a large increase in the number of resistance genes being deployed (e.g. Michelmore and Ochoa 2008; Michelmore et al. 2013a).

Genetics of resistance and nomenclature of resistance genes

Extensive classical genetic studies have been carried out for the resistance of lettuce to *B. lactucae*. The gene-for-gene interaction between *L. sativa* and *B. lactucae* was first elaborated by Crute and Johnson (1976a, b). This interaction is now one of the best characterized gene-for-gene plant-pathogen relationships (Farrara et al. 1987; Hulbert and Michelmore 1985; Ilott et al. 1987, 1989). At least 28 *Dm* genes are currently known that provide high levels of resistance against specific isolates of *B. lactucae* (Table 1). Although most *Dm* genes confer complete resistance, some *Dm* genes show incomplete resistance that varies depending on the environmental conditions and the isolate of *B. lactucae*. Low temperature decreases the effectiveness of several *Dm* genes (Judelson and

Michelmore 1992). Cultivars carrying *Dm6* and *Dm7* may exhibit partial resistance associated with macroscopically visible hypersensitive necrosis (Crute and Norwood 1978). Additionally, gene dosage affects the resistance phenotype of some *Dm* genes, for example *Dm17* under high pathogen pressure (Maisonneuve et al. 1994). Some lettuce cultivars such as Iceberg and Grand Rapids exhibit resistance at the adult plant stage in the field that cannot be attributed to *Dm* genes (Milbrath 1923; Verhoeff 1960; Crute and Norwood 1981). This quantitative resistance phenotype (Norwood and Crute 1985; Grube and Ochoa 2005) has so far been shown to be inherited polygenically (Simko et al. 2013); transgressive segregation resulting in elevated resistance has been observed in progeny from cvs. Grand Rapids × Iceberg (Grube and Ochoa 2005; Simko et al. 2013). Some cultivars such as Green towers and Cobham Green have no known *Dm* genes and are used as susceptible lines to grow *B. lactucae* isolates; however, the European isolate Serr84/99 is avirulent on Cobham Green and there is some evidence suggesting polygenic resistance in this cultivar (Maisonneuve 2011b). Most accessions of *L. saligna* are completely resistant to isolates of *B. lactucae* derived from *L. sativa*; therefore, this species has been proposed to be a non-host for downy mildew (Bonnier et al. 1992; Petrželová et al. 2011; van Treuren et al. 2013); this complete resistance is in part determined by several quantitative trait loci (QTLs) operating at different developmental stages (Jeuken and Lindhout 2002; Jeuken et al. 2008, Zhang et al. 2009; Den Boer et al. 2013). However, the mechanism of resistance in *L. saligna* is still unresolved. Stacking of these QTLs in 10 pairwise combinations hardly showed an increase in the level of resistance suggesting that epistatic interactions play a role (De Boer et al. 2014; Den Boer 2014).

The genetic studies have resulted in the identification of numerous *Dm* genes and R-factors. In order to remove duplications in nomenclature and evaluate the genetic evidence for *Dm* genes and R-factors, we reviewed all the primary literature reporting resistance to *B. lactucae* in lettuce. When possible, this involved multiple rounds of consultation with the authors and with the lettuce genetics and breeding community at large. This resulted in the classification of 28 *Dm* genes and 23 R-factors that provide resistance to specific isolates of *B. lactucae* (Table 1). Resistance was assigned a *Dm* designation when supported by

Table 1 Compilation of information available for genes and genetic factors for resistance to *Bremia lactucae* in lettuce

R gene	Chr. position (MRC) Christophoulou et al. (2015a, b)	RGC family Christophoulou et al. (2015a, b)	Gene type	Source species- source cultivar/ID*	Country of origin	Differential cultivar/line for detection
<i>Dm1</i>	MRC2			<i>L. sativa</i> , Blondine (CGN04529*)	The Netherlands	Lednický (CGN14317*)
<i>Dm2</i>	MRC2			<i>L. sativa</i> , Meikoningen, May Queen	Germany	UCDM2 (CGN11338*)
<i>Dm3</i>	MRC2	<i>RGC2</i>	CNL	<i>L. sativa</i> , Gotte à Forcer à Graine Noire, Passion Blanche à Graine Noire (CGN04716*)	France	Dandie (CGN05813*)
<i>Dm4</i>	MRC4	<i>RGC12</i>	TNL	<i>L. sativa</i> , German type		R4T57D (CGN11403*)
<i>Dm5</i>	MRC1	<i>RGC1</i>	CNL	<i>L. serriola</i> , PI 167150*	Turkey	Valmaine (CGN05249*)
<i>Dm6</i>	MRC2	<i>RGC2</i>	CNL	<i>L. serriola</i> , PI 91532*	Russia	Sabine (CGN09380*)
<i>Dm7</i>	MRC4	<i>RGC12</i>	TNL	<i>L. sativa</i> , Romaine Blonde Lente à Monter	France	LSE 57/15 (CGN24779*)
<i>Dm8</i>	MRC1	<i>RGC1</i>	CNL	<i>L. serriola</i> , PI 104584*	Russia	Same as for <i>Dm5</i>
<i>R9</i>				<i>L. sativa</i> , Bourguignonne Grosse Blonde d'Hiver (CGN04605*)	France	
<i>Dm10</i>	MRC1			<i>L. sativa</i> , Sucrine (CGN04858*) or Little Gem	France	UCDM10 (CGN11339*)
<i>Dm11</i>	MRC4	<i>RGC12</i>	TNL	<i>L. serriola</i> , PI 273596*	Germany	Capitan (CGN05140*)
<i>R12</i>				<i>L. sativa</i> , British Hilde (CGN04623*)	The Netherlands	Hilde II (CGN04623*)
<i>Dm13</i>	MRC3	<i>RGC21</i>	CNL	<i>L. sativa</i> , Pennlake (CGN11440*)	USA	Pennlake (CGN11440*)
<i>Dm14</i>	MRC2	<i>RGC2</i>	CNL	<i>L. sativa</i> , Gelber Winterkönig	The Netherlands	UCDM14 (CGN11340*)
<i>Dm15</i>	MRC2			<i>L. serriola</i> , PIVT1309 (CGN05099*)	Israel	PIVT 1309, NumDM15
<i>Dm16</i>	MRC2	<i>RGC2</i>	CNL	<i>L. serriola</i> , LSE/18 (CGN11402*)	Czechoslovakia	LSE/18, CGDm16
<i>Dm17</i>	MRC1			<i>L. serriola</i> , LS102 (CGN24780*)	France	LS102, NumDm17
<i>Dm18</i>	MRC2	<i>RGC2</i>	CNL	<i>L. serriola</i> , LS17	France	Colorado (CGN24778*)
<i>R19</i>				<i>L. serriola</i> × <i>L. sativa</i> hybrid line CS-RL	Sweden	
<i>R20</i>				<i>L. virosa</i> , LS241	France	
<i>R21</i>				<i>L. virosa</i> , LS238	France	
<i>R22</i>				<i>L. serriola</i> , PI 491229*	Greece	
<i>R23</i>				<i>L. serriola</i> , CGN05153*	Russia	

Table 1 continued

R gene	Chr. position (MRC) Christopoulou et al. (2015a, b)	RGC family Christopoulou et al. (2015a, b)	Gene type	Source species- source cultivar/ID*	Country of origin	Differential cultivar/line for detection
Dm24	MRC4			<i>L. serriola</i> , CGN14255*	Hungary	
Dm25	MRC1			<i>L. serriola</i> , CGN14255*	Hungary	RYZ2164
R26				<i>L. serriola</i> , CGN14256*	Hungary	
R27				<i>L. serriola</i> , CGN14270*	Hungary	
R28				<i>L. serriola</i> , CGN14280*	Hungary	
R29				<i>L. serriola</i> , PI 491178*	Turkey	
R30				<i>L. serriola</i> , W66336A*	Russia	
R31				<i>L. serriola</i> , W66331A*	Russia	
R32				<i>L. saligna</i> LJ81632*		R32 (UC9602)
R33				<i>L. saligna</i> LJ85314*		
R34				<i>L. serriola</i> , LJ85292*		
R35				<i>L. virosa</i> , LJ85289*		
Dm36	MRC1			<i>L. saligna</i>	Israel	Ninja (CGN20716*)
Dm37	MRC1			<i>L. saligna</i> PIVT 1306 (CGN05315*)	Israel	Discovery (CGN24530*)
Dm38	MRC4			<i>L. serriola</i> , PIVT1168 (CGN10886*)		Argelès (CGN24676*)
Dm39	MRC8C			<i>L. sativa</i> cv. Olof		
R40				<i>L. sativa</i> , Amplus		Amplus
R41				<i>L. sativa</i> , PI 491226*	Greece	
R42				<i>L. serriola</i> , PI 491108*	Turkey	
Dm43	MRC1			<i>L. serriola</i> , CGN14263*	Hungary	
Dm44	MRC4	RGC12	TNL	<i>L. serriola</i> , CGN14263*	Hungary	
Dm45	MRC1	RGC1	CNL	<i>L. saligna</i> , UC04US2509		
R46				<i>L. saligna</i> , PI 491206*	Greece	
R47				<i>L. saligna</i> , PI 491208*	Greece	
Dm48	MRC4			<i>L. serriola</i> , Accession 309/99	France	
R49				<i>L. serriola</i> , Accession 218/00	Sweden	
Dm50	MRC2			<i>L. sativa</i> , La Brillante (CGN05170*)	France	
Dm51	MRC9C			<i>L. saligna</i> , CGN15705*	Georgia	
I				<i>L. serriola</i> , LJ88356*	Sweden	

Table 1 continued

R gene	Chr. position (MRC) Christopoulou et al. (2015a, b)	RGC family et al. (2015a, b)	Christopoulou et al. (2015a, b)	Gene type	Source species- source cultivar/ID*	Country of origin	Differential cultivar/line for detection
2					??		RYZ910457
3					??		Bedford
4					??		Balesta
5					??		Bellisimo
6					??		Femke
7					<i>L. saligna</i> , CGN9311*	Israel	
8					<i>L. saligna</i> , CGN5318*	Israel	
9					<i>L. saligna</i> , CGN5282*		
10					<i>L. saligna</i> , CGN5147*	Italy	
R gene	Example isolates with <i>avr</i> gene	<i>Bremia</i> isolate for detection (IBEB) ^a	Notes	References	Gene	Chr. position	
<i>Dm1</i>	CS1, C82P24	BI:3,17	Present in Cristallo, Spartan Lakes and Mildura	Tjallingii and Rodenburg (1967), Moravec et al. (1999)	Crute and Johnson (1976a)	Hulbert and Michelmore (1985), Farrara et al. (1987), Paran et al. (1991), Mc Hale et al. (2009)	
<i>Dm2</i>	CS2, C83M40	BI:3,5,11–13	Present in Cristallo	Schultz and Röder (1938)	Crute and Johnson (1976a)	Hulbert and Michelmore (1985), Farrara et al. (1987), Mc Hale et al. (2009)	
<i>Dm3</i>	SF5, C1101327	BI:1,3,4,6,11,12,18, 22,24,25,28-30	Present in Mildura	Ogilvie (1944), Rodenburg et al. (1960)	Crute and Johnson (1976a)	Hulbert and Michelmore (1985), Farrara et al. (1987), Paran et al. (1991), Mc Hale et al. (2009)	
<i>Dm4</i>	SF3, C82P24	BI:5,13,17	R4T57D derived from Amplus	Ogilvie (1944)	Crute and Johnson (1976a)	Hulbert and Michelmore (1985), Farrara et al. (1987), Mc Hale et al. (2009)	
<i>Dm5</i>	CS5, CS12	BI:1,5,7	Introgressed from 2 sources. Same specificity as <i>Dm8</i> (Witsenboer et al. 1995)	Leeper et al. (1963), Lebeda et al. (1980), Witsenboer et al. (1995)	Crute and Johnson (1976a)	Hulbert and Michelmore (1985), Farrara et al. (1987), Mc Hale et al. (2009)	
<i>Dm6</i>	SF3, SF5	BI:1,4–6,13,15,17	Present in Avoncrisp, Avonfiance and Ardenite (Johnson et al. 1977)	Lebeda et al. (1980), Lebeda (1984), Norwood et al. (1983)	Crute and Johnson (1976a), Lebeda (1984)	Hulbert and Michelmore (1985), Farrara et al. (1987), Mc Hale et al. (2009)	
<i>Dm7</i>	SF5, C14C1485	BI:1,2,6,14,19	Present in Mesa 659	Jagger and Chandler (1933)	Crute and Johnson (1976a)	Hulbert and Michelmore (1985), Farrara et al. (1987), Mc Hale et al. (2009)	
<i>Dm8</i>	CS1, C82P24	BI:1,5,7	Present in Avoncrisp, Calmar, Salinas. Same specificity as <i>Dm5</i>	Jagger and Whitaker (1940), Witsenboer et al. (1995)	Crute and Johnson (1976a), Johnson et al. (1977)	Hulbert and Michelmore (1985), Farrara et al. (1987), Mc Hale et al. (2009)	

Table 1 continued

R gene	Example isolates with <i>avr</i> gene	<i>Bremia</i> isolate for detection (IBEB) ^a	Notes	References	Gene	Chr. position
				Source/cultivar		
<i>R9</i>	C82P24, NL6		Multiple genes, 9A & 9B?. BGBH also has <i>Dm4</i> + 5/8 + 10 + 13 + 14.	Jagger and Whitaker (1940), Rodenburg et al. (1960)	Crute and Johnson (1976a)	
<i>Dm10</i>	CS45, C83M47		UCDM10 derived from Sucrine	Reported in Channon and Smith (1970)	Crute and Johnson (1976a)	Hulbert and Michelmore (1985), Farrara et al. (1987), Mc Hale et al. (2009)
<i>Dm11</i>	CS1, R19, Tv	Bl:1-5,7,10,11,17	Maybe multiple genes	Crute and Johnson (1976b), Lebeda et al. (1980)	Johnson et al. (1978)	Hulbert and Michelmore (1985), Farrara et al. (1987), Mc Hale et al. (2009)
<i>R12</i>	CS6**			Crute and Lebeda (1981)	Crute and Lebeda (1981), Lebeda (1984)	
<i>Dm13</i>	CS1, CS7, CS12		Present in Empire, Vanguard 75, Blondine and Kinemontepas	Ryder (1979), Crute and Lebeda (1983), Rodenburg et al. (1960)	Crute and Lebeda (1981), Yuen and Lorbeer (1983), Lebeda (1984), Hulbert and Michelmore (1985)	Farrara et al. (1987), Mc Hale et al. (2009)
<i>Dm14</i>	CG1, NL6248	Bl:5,15,16,18,20,21, 23-26,28	UCDM14 derived from Gelber Winterkönig	Farrara et al. (1987)	Farrara et al. (1987)	Farrara et al. (1987), Mc Hale et al. (2009)
<i>Dm15</i>	C83M47, CS12	Bl:1,2,4,6,7,10,13-16, 18-20,23-26,28,31	NunDm15 derived from P1VT 1309. May have polygenic Reg resistance from Cobham Green (Maisonneuve 2011a, b)	Reported in Farrara et al. (1987)	Farrara et al. (1987)	Farrara et al. (1987), Paran et al. (1991), Mc Hale et al. (2009)
<i>Dm16</i>	C82P24, CS9**	Bl:1-7,10,13-15, 17,19,22,27,30,31	CGDm16 derived from LSE/18. May have the polygenic Reg resistance from Cobham Green (Maisonneuve 2011a, b). May have same gene as Kinemontepas	Rodenburg et al. (1960), Norwood et al. (1981), Lebeda (1984)	Farrara et al. (1987)	Farrara et al. (1987), Paran et al. (1991), Mc Hale et al. (2009)
<i>Dm17</i>	SF5, C82P24	Bl:1-7,10-26,28	NunDm17 derived from LS102. May have polygenic Reg resistance from CobhamGreen (Maisonneuve 2011a, b)	Maisonneuve et al. (1994)	Maisonneuve et al. (1994)	Maisonneuve et al. (1994), Mc Hale et al. (2009)

Table 1 continued

R gene	Example isolates with <i>avr</i> gene	<i>Bremia</i> isolate for detection (IBEB) ^a	Notes	References		
				Source/cultivar	Gene	Chr. position
<i>Dm18</i>	CS9, NL6, S1	BI:1-7,10-16,19,21,23	Present in El Dorado and Mariska. <i>Dm18</i> in Mariska from LS17 (pers. comm. to B. Maisonneuve). <i>Dm18</i> in El Dorado from Mariska. Different cultivars may have different complements of genes at this locus	Crute et al. (1986)	Lebeda and Blok (1991), Maisonneuve et al. (1994)	Bonnier et al. (1994), Maisonneuve et al. (1994), Mc Hale et al. (2009)
<i>R19</i>	NL1 to NL16		Present in Libusa. Seems to have <i>Dm18</i> + <i>Dm1</i> specificity (J. Schut pers. comm.)	Lebeda and Blok (1991), Lebeda et al. (2002), Lebeda and Zinkemagel (2003)	Lebeda et al. (2002), Lebeda and Zinkemagel (2003)	
<i>R20</i>	NL16, CS49/83	BI:20,21	Renamed R20. Previously designated R41/42. Present in INRA line ViAE. Two genes	Maisonneuve et al. (1999)	Maisonneuve et al. (1999), Maisonneuve (2003)	
<i>R21</i>	NL16, CS49/83	BI:20,21	Renamed R21. Previously designated R39/40. Present in INRA line ViCQ. Possibly two genes	Maisonneuve et al. (1999)	Maisonneuve et al. (1999), Maisonneuve (2003)	
<i>R22</i>	NL7, NL16		Renamed R22. Previously designated R30	Bonnier et al. (1994)	Bonnier et al. (1994)	
<i>R23</i>	NL1, NL2		CGN05153 = PIVT1544 also has <i>Dm7</i> .	Bonnier et al. (1994)	Bonnier et al. (1994)	
<i>Dm24</i>	NL1 to NL16		Present in Versai (<i>Dm18</i> + <i>Dm24</i>) that was derived from <i>L. serriola</i> CGN14255 (Rijk Zwaan Breeding B.V.)	Bonnier et al. (1994)	Bonnier et al. (1994)	J. Schut, pers. comm.
<i>Dm25</i>	NL1 to NL16	BI:1-7,10-26,28	Present in Salvisius that was derived from <i>L. serriola</i> CGN14255 (Rijk Zwaan Breeding B.V.)	Bonnier et al. (1994) ^a	Bonnier et al. (1994)	J. Schut, pers. comm.
<i>R26</i>	NL3 to NL16		CGN14256 also has R24	Bonnier et al. (1994)	Bonnier et al. (1994)	
<i>R27</i>	NL1 to NL16		CGN14270 also has R24	Bonnier et al. (1994)	Bonnier et al. (1994)	
<i>R28</i>	NL3 to NL7		CGN14280 also has R24	Bonnier et al. (1994)	Bonnier et al. (1994)	
<i>R29</i>	NL3 to NL16		PI491178 also has R24	Bonnier et al. (1994)	Bonnier et al. (1994)	

Table 1 continued

R gene	Example isolates with <i>avr</i> gene	<i>Bremia</i> isolate for detection (IBEB) ^a	Notes	References	Gene	Chr. position
				Source/cultivar		
R30		C01O879,C93D14	Previously designated R28. Present in UC2205 that also has <i>Dm8</i> + <i>Dm13</i>	Michelmore and Ochoa (2006), Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
R31		C01O879,C93D14	Previously designated R29. Present in UC2206 that also has <i>Dm8</i> + <i>Dm13</i>	Michelmore and Ochoa (2006), Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
R32		C01O622,C96O504	Same specificity as <i>Dm18</i> . Present in UC02201 that also has <i>Dm4</i> + <i>Dm8</i> + <i>Dm13</i> .	Michelmore and Ochoa (2002)	Michelmore and Ochoa (2002)	
R33		C01O879,C93D14	Present in UC2202 that also has <i>Dm8</i> + <i>Dm13</i>	Michelmore and Ochoa (2006), Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
R34		C01O879,C93D14	Present in UC2203 that also has <i>Dm8</i> + <i>Dm13</i>	Michelmore and Ochoa (2006), Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
R35		C01O879,C93D14	Present in UC2204 that also has <i>Dm8</i> + <i>Dm13</i> .	Michelmore and Ochoa (2006), Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
<i>Dm36</i>	NL16, SR2	BI:1-7,10-20,22-25, 27-31	Ninja has additional R-genes. Maybe present in Titan.	Van Ettekovén and Van der Arend (1999), Maisonneuve et al. (1999), Lebeda and Zinkemägel (2003)	Lebeda and Zinkemägel (2003), Maisonneuve et al. (1999), Maisonneuve (2007, 2011a, b)	Michelmore (2010)
<i>Dm37</i>	SAR2, E705	BI:1,2,4-7,10-16,18-20, 22-24,27,28,30,31	Present in FrR _{sal-1} (Maisonneuve 2003). Discovery also has <i>Dm7</i>	Van Ettekovén and Van der Arend (1999), Guenard et al. (1999)	Maisonneuve (2007, 2011a, b)	J. Schut, pers. comm.
<i>Dm38</i>	SAR3, E705	BI:1,3-7,10-18,20-22,25,31		Van Ettekovén and Van der Arend (1999), Guenard et al. (1999), Maisonneuve et al. (1999)	Maisonneuve et al. (1999)	J. Schut, pers. comm.

Table 1 continued

R gene	Example isolates with <i>avr</i> gene	<i>Bremia</i> isolate for detection (IBEB) ^a	Notes	References		
				Source/cultivar	Gene	Chr. position
<i>Dm39</i>	NL14, NL16	BI:15–18,22,24–28	<i>Dm39</i> interacts with <i>Rim4</i> from <i>L. saligna</i> CGN05271 in Chr9 (Jeuken and Lindhout 2002)	Jeuken and Lindhout (2002)	Jeuken et al. (2009)	Jeuken et al. (2009)
<i>R40</i>	C99O706, C96O504**		Amplus also has <i>Dm2</i> + <i>Dm4</i> .	Michelmore and Ochoa (1999)	Michelmore and Ochoa (2002)	
<i>R41</i>	C01O879, C83M47		Present in UC7105	Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
<i>R42</i>	C01O879, C83M47		Present in UC7106	Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
<i>Dm43</i>	C01O879, C82P24			Mc Hale et al. (2009)	Mc Hale et al. (2009)	Mc Hale et al. (2009)
<i>Dm44</i>	C01O879, C93D14			Mc Hale et al. (2009)	Mc Hale et al. (2009)	Mc Hale et al. (2009)
<i>Dm45</i>	C01O879, C93D14		Present in UC12104	Michelmore and Ochoa (2008), Michelmore et al. (2013a)	Michelmore (2008), Michelmore et al. (2013a)	Michelmore (2008)
<i>R46</i>	C01O879, C82P24		Present in UC7107	Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
<i>R47</i>	C01O879, C82P24		Present in UC7108	Michelmore and Ochoa (2008)	Michelmore and Ochoa (2008)	
<i>Dm48</i>	C01O879, C07O1133		Present in UC07CS100	Michelmore et al. (2011)	Michelmore et al. (2011)	Michelmore (2010)
<i>R49</i>	C01O879, C07O1133		Present in UC07CS101	Michelmore et al. (2011)	Michelmore et al. (2011)	
<i>Dm50</i>	C01O879, C11O1352	BI:10–26,28–30	Present in La Brillante	Rodenburg et al. (1960), Simko et al. (2015b)	Simko et al. (2015b)	Simko et al. (2015b)
<i>Dm51</i>		BI:21,24		Den Boer (2014)	Den Boer (2014)	Den Boer (2014)
1			Present in Mildura	Lebeda et al. (2002)	Lebeda et al. (2002)	
2	C89D36, C01O879	BI:1–7,10–27,29,30	New source of resistance in differential set ^b			
3	SF5, C14C1485	BI:1–7,10–16,18–31	New source of resistance in differential set ^a			

Table 1 continued

R	Example isolates with <i>avr</i> gene	<i>Bremia</i> isolate for detection (IBEB) ^a	Notes	References	Gene Chr. position
				Source/cultivar	
4	C82P24, C83M47	BI:1,3-7,10-21,23-26, 28-31	New source of resistance in differential set ^d		
5	C82P24, C83M47	BI:4-7,10-31	New source of resistance in differential set ^d		
6	C01O879, C82P24		Femke also has <i>Dm1.1</i> . Same specificity as Design		
7	C01O879, C82P24		Present in UC12100	Michelmore and Ochoa (2008), Michelmore et al. (2013a)	
8	C82P24, C15C1622		Present in UC12101	Michelmore and Ochoa (2008), Michelmore et al. (2013a)	
9	C01O879, C82P24		Present in UC12102	Michelmore and Ochoa (2008), Michelmore et al. (2013a)	
10	SF5, C15C1622		Present in UC12103	Michelmore and Ochoa (2008), Michelmore et al. (2013a)	

MRC major resistance cluster, *RGC* resistance gene candidate, *IBEB* International Bremia Evaluation Board

* PI: ID in the Germplasm Resources Information Network (GRIN, United States). CGN: ID in the Centre for Genetic Resources (CGN, The Netherlands)

** First isolate used to report resistance

^a International Bremia Evaluation Board (IBEB) from the International Seed Federation (ISF). <http://www.worldseed.org/isf/ibeb.html>

genetic evidence and mapped to a single locus in the lettuce genome. Resistances were designated as R-factors, when the resistance specificity as determined by reactions to isolates of *B. lactucae* indicated presence of new resistance genes; however, such resistances had not (yet) been shown to be monogenic or mapped. Over eighty percent of the *Dm* genes and R-factors were identified in wild *Lactuca* species collected in Europe (Table 1). Most of these resistances have been introgressed into cultivars of *L. sativa* as part of breeding programs in Europe and the USA. Parallel research and breeding efforts resulted in several duplicate designations for resistance from different sources. Seven resistances were therefore renamed to remove duplications and to fill in gaps in the sequence of designations; resistances identified in the same study were kept adjacent to the extent possible (Table 1). Fifteen major QTLs for resistance to *B. lactucae* have so far been identified (Table 2). The QTLs were renamed to be consistent with the convention for describing QTLs in lettuce, in which a QTL is prefixed with 'q' followed by capital letters indicating resistance to the disease (DMR in this case) and two numbers indicating the chromosomal linkage group followed by the number of the QTL on that linkage group.

Some lettuce cultivars possess the same resistance specificity, despite the fact that their resistances were introgressed from different sources, sometimes even from different *Lactuca* species. Linkage analysis of *Dm5* and *Dm8* and parallel genetics of virulence in *B. lactucae* demonstrated that both resistances are controlled by the same gene (Norwood and Crute 1984; Hulbert and Michelmore 1985). These resistances were identified from different accessions of *L. serriola* collected from Turkey and Russia (Jagger and Whitaker 1940; Leeper et al. 1963; Lebeda et al. 1980) and have different molecular haplotypes (Witsenboer et al. 1995). Similarly, *Dm38* and *R24* cosegregate and share specificities (J. Schut, unpublished). *Dm38* and *R24* were introgressed from *L. serriola* sources from Czechoslovakia and Hungary, respectively (Bonnier et al. 1994; Maisonneuve et al. 1999). Similarly, *Dm18* and *R32* cosegregate and have the same specificity; both resistances were rendered ineffective simultaneously by a change in virulence in *B. lactucae* (Petrželová et al. 2013). *Dm18* originated from *L. serriola* LS17, while *R32* originated from *L. saligna* LJ81632, suggesting either conservation since the

diversification of these *Lactuca* species or independent convergent evolution of these genes. *Dm36* in cv. Ninja has been reported to be identical to *Dm37* in cv. Discovery based on reactions to European isolates and had been named *Rsal-1* (Maisonneuve 2007, 2011a); however, this conclusion is not supported by the reactions of Ninja and Discovery to Californian isolates (C. Tsuchida and L. Parra, unpublished). Both *Dm36* and *Dm37* were introgressed from accessions of *L. saligna* from Israel (B. Moreau, pers. comm.), but the identity of the donor for *Dm36* is uncertain and both resistances may have originated from the same source. Resolution of the relationship of *Dm36* to *Dm37* awaits analysis at the sequence level.

The genetic location is known for 28 *Dm* genes. As in other plants, resistance genes are clustered in the lettuce genome. The known *Dm* genes are located in major resistance clusters (MRCs) along with genes determining resistance to other diseases (Table 1; Hulbert and Michelmore 1985; Farrara et al. 1987; Bonnier et al. 1994; Mc Hale et al. 2009; Christopoulou et al. 2015a, b). MRC1 contains *Dm5/8*, *Dm10*, *Dm17*, *Dm25*, *Dm36*, *Dm37*, *Dm43*, *Dm45*, as well as *Tu* and *Mo2* for resistance to Turnip Mosaic Virus (TMV) and Lettuce Mosaic Virus (LMV) respectively, and *qFUS1.1* and *qFUS1.2* for resistance to wilt caused by *Fusarium oxysporum* f.sp. *lactucae*. MRC2 includes *Dm1*, *Dm2*, *Dm3*, *Dm6*, *Dm14*, *Dm15*, *Dm16*, *Dm18*, *Dm50* and *qDMR2.2*, along with *Tvr* for resistance to Tomato Bushy Stunt Virus (TBSV), *Ra* for root aphid resistance, and *qANTI* for resistance to anthracnose. MRC4 contains *Dm4*, *Dm7*, *Dm11*, *Dm24*, *Dm38*, *Dm44* and *Dm48* as well as *qFUS4.1* for resistance to *Fusarium* wilt. MRC9A contains *qDMR9.1*, *qDMR9.2* and *qDMR9.3*, and *qVERT9.1* for resistance to wilt caused by *Verticillium dahliae* (Christopoulou et al. 2015a, b). *Dm39* was initially mapped at a locus similar to MRC9A based on analysis of an interspecific F₂ population derived from *L. saligna* CGN05271 × *L. sativa* cv. Olof (Jeuken and Lindhout 2002); however, this resistance phenotype turned out to be due to an interaction between a *L. saligna*-allele of *Rin4* at MRC9A and the *L. sativa*-allele of *Dm39* at MRC8C (Jeuken et al. 2009). In *Arabidopsis* *Rin4* is a negative regulator of basal defense and known to be the target for three effectors of *Pseudomonas syringae* and guarded by two R-genes (Axtell and Staskawicz 2003; Mackey et al. 2002).

Table 2 Compilation of information available for quantitative trait loci for resistance to *Bremia lactucae* in lettuce identified at the seedling and adult plant levels

QTLs	Chromosomal position/ MRC	Source species & cultivar/ID	Country of origin	Notes	References		
					Source/cultivar	Gene	Chr. position
qDMR2.1	Chr2	<i>L. sativa</i> , Iceberg	USA	Field Resistance. Identified in Grand Rapids × Iceberg	Milbrath (1923), Crute and Norwood (1981), Grube and Ochoa (2005)	Simko et al. (2013)	Simko et al. (2013)
qDMR5.1	Chr5	<i>L. sativa</i> , Iceberg	USA	Field Resistance. Identified in Grand Rapids × Iceberg	Milbrath (1923), Crute and Norwood (1981), Grube and Ochoa (2005)	Simko et al. (2013)	Simko et al. (2013)
qDMR9.1	MRC9A	<i>L. sativa</i> , Grand Rapids	USA	Field Resistance. Identified in Grand Rapids × Iceberg	Verhoeff (1960), Crute and Norwood (1981), Grube and Ochoa (2005)	Simko et al. (2013)	Simko et al. (2013)
qDMR2.2	MRC2	<i>L. sativa</i> , La Brillante	France	Seedling and adult plant resistance. Identified in Salinas 88 × La Brillante	Simko et al. (2012)	Simko et al. (2015b)	Simko et al. (2015b)
qDMR4.1	Chr4	<i>L. sativa</i> , La Brillante	France	Seedling and adult plant resistance. Identified in Salinas 88 × La Brillante	Simko et al. (2012)	Simko et al. (2015b)	Simko et al. (2015b)
qDMR4.2	Chr4	<i>L. sativa</i> , La Brillante	France	Seedling and adult plant resistance. Identified in Salinas 88 × La Brillante	Simko et al. (2012)	Simko et al. (2015b)	Simko et al. (2015b)
qDMR7.1	Chr7	<i>L. sativa</i> , La Brillante	France	Seedling and adult plant resistance. Identified in Salinas 88 × La Brillante	Simko et al. (2012)	Simko et al. (2015b)	Simko et al. (2015b)
qDMR9.2	MRC9A	<i>L. sativa</i> , La Brillante	France	Seedling and adult plant resistance. Identified in Salinas 88 × La Brillante	Simko et al. (2012)	Simko et al. (2015b)	Simko et al. (2015b)
qDMR7.2	Chr7	<i>L. saligna</i> , CGN05271	France	Seedling and adult plant resistance. Identified in CGN5271 × <i>L. sativa</i> cv. Olof. Previously designated Rbq1	Jeuken and Lindhout (2002)	Jeuken and Lindhout (2002), Jeuken et al. (2008)	Jeuken and Lindhout (2002)
qDMR1.1	Chr1	<i>L. saligna</i> , CGN05271	France	Seedling and adult plant resistance. Identified in CGN5271 × <i>L. sativa</i> cv. Olof. Previously designated Rbq2	Jeuken and Lindhout (2002)	Jeuken and Lindhout (2002), Jeuken et al. (2008)	Jeuken and Lindhout (2002)
qDMR9.3	MRC9A	<i>L. saligna</i> , CGN05271	France	Seedling and adult plant resistance. Identified in CGN5271 × <i>L. sativa</i> cv. Olof. Previously designated Rbq3	Jeuken and Lindhout (2002)	Jeuken and Lindhout (2002), Jeuken et al. (2008)	Jeuken and Lindhout (2002)
qDMR3.1	MRC3	<i>L. saligna</i> , CGN05271	France	Seedling and adult plant resistance. Identified in CGN5271 × <i>L. sativa</i> cv. Olof. Previously designated rbq4	Jeuken and Lindhout (2002)	Jeuken et al. (2008), Zhang et al. (2009)	Den Boer et al. (2013)

Table 2 continued

QTLs	Chromosomal position/ MRC	Source species & cultivar/ID	Country of origin	Notes	References		
					Source/cultivar	Gene	Chr. position
qDMR2.3	Chr2	<i>L. saligna</i> , CGN05271	France	Seedling and adult plant resistance. Identified in CGN5271 × <i>L. sativa</i> cv. Olof. Previously designated rbq5	Jeuken and Lindhout (2002)	Jeuken et al. (2008), Zhang et al. (2009)	Den Boer et al. (2013)
qDMR8.1	Chr8	<i>L. saligna</i> , CGN05271	France	Seedling and adult plant resistance. Identified in CGN5271 × <i>L. sativa</i> cv. Olof. Previously designated rbq6	Jeuken and Lindhout (2002)	Jeuken et al. (2008), Zhang et al. (2009)	Den Boer et al. (2014)
qDMR4.3	Chr4	<i>L. saligna</i> , CGN05271	France	Seedling and adult plant resistance. Identified in CGN5271 × <i>L. sativa</i> cv. Olof. Previously designated rbq7	Jeuken and Lindhout (2002)	Jeuken et al. (2008), Zhang et al. (2009)	Den Boer et al. (2013)

QTL Quantitative trait locus, *MRC* Major resistance cluster

There has been only limited characterization of specific *Dm* genes at the molecular level. Each phenotypic MRC spans multiple megabases in the lettuce genome and encompasses complex clusters of genes encoding nucleotide binding-leucine rich repeat, receptor-like proteins (NLRs). Sequence analysis of 385 NLR-encoding genes in the reference lettuce genome identified 25 multigene families and 17 singletons of resistance gene candidates (RGCs) that could be classified as TNL- or CNL-encoding types, depending on the presence or absence of Toll interleukin 1 receptor domain (TIR) at the N-terminus (Christopoulou et al. (2015b)). Functional analysis of NLR-encoding genes that co-segregated with *Dm* phenotypes using RNAi demonstrated four NLR-encoding multigene families that were required for 13 *Dm* phenotypes (Table 1). Only two individual *Dm* genes have been cloned so far. The map-based cloning of *Dm3*, encoding a CNL type of NLR, was confirmed by transgenic complementation (Shen et al. 2002). *Dm7* was identified on the basis of multiple EMS-induced mutations (Christopoulou et al. 2015a).

Implications for control of downy mildew

This review provides the foundation for naming *Dm* genes in future. Genetic dissection of R-factors into their Mendelian components will reveal the number

and genomic position of the underlying *Dm* genes. Genetic dissection of QTLs will also reveal candidate genes, although they may not be of the NLR type. Germplasm screens will continue to identify many new sources of resistance that are likely to be conferred by new *Dm* genes. The International Bremia Evaluation Board (IBEB; <http://www.worldseed.org/isf/ibeb.html>) should be consulted in order to coordinate the naming of such new *Dm* genes. IBEB currently consists of representatives from Europe and the US who are knowledgeable of efforts to control DM in lettuce and genetics of resistance to *B. lactucae*. IBEB should therefore serve in an advisory capacity to avoid duplications and ensure sequential designation.

Genomic analyses show that the MRCs are complex clusters of multiple NLRs. One or more genes could be conferring a resistance phenotype depending on which isolate is used to detect it. Simple segregation analysis of the host alone does not reveal how many genes are effective at a single Mendelian locus. This can be revealed by segregation analysis of the virulence phenotype in *B. lactucae*; however, this is a slow and labor intensive process. The potential presence of multiple effective genes at a single locus has consequences; recombination at a MRC during backcross programs may result in loss of some *Dm* genes and parallel introgressions from the same source of resistance may result in different subsets of *Dm* genes being retained. There is some evidence for this

occurring with *Dm18* (Wroblewski et al. 2007). Detailed genetic analysis of MRCs may result in the identification of multiple *Dm* genes and require revision/splitting of current *Dm* designations.

Genome sequencing and assembly has revealed that all plant genomes contain many, usually hundreds, of NLR-encoding genes. Therefore, all plants have many resistance genes; even if active specificities have yet to be recognized. Consequently, avirulence factors recognized by additional *Dm* genes in the cultivars described in this paper may be identified in the future, particularly in isolates from *L. serriola*. Although these *Dm* genes are effective in limiting migration of isolates from *L. serriola* onto *L. sativa*, they are of marginal relevance to control of DM in cultivated lettuce; however, they will be relevant when introgression of a new resistance specificity from a wild species inadvertently replaces such *Dm* genes, and consequently introduces susceptibility to isolates from the wild species.

Resistance to DM can also be mediated by recessive genes. DMR6 in Arabidopsis is necessary for susceptibility to downy mildew; a recessive *dmr6* allele derived by mutation results in resistance against *Hyaloperonospora arabidopsidis* (Van Damme et al. 2005, 2008). A *DMR6* ortholog has been identified in lettuce, where its over-expression increases host susceptibility to *B. lactucae* (Stassen et al. 2012; Zeilmaker 2012). Natural variation in *DMR6* that confers resistance to *B. lactucae* has yet to be identified.

The plethora of known resistance genes and those now in multiple public and commercial breeding pipelines provides the opportunity for rational deployment of resistance genes (*Dm* and QTLs; Michelmore et al. 2013b). Pyramids of resistance genes based the nomenclature proposed here that are effective against the diversity of *B. lactucae* should be generated so as to maximize the evolutionary hurdle required for *B. lactucae* to become virulent. Pyramids of dissimilar sets of resistance genes should be deployed in the different lettuce types so as to provide heterogeneity in the selection pressure acting on the pathogen population. This should result in more durable resistance to DM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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