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Review

Breeding for Tomato Brown Rugose Fruit Virus Resistance

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Abstract

Tomato brown rugose fruit virus (ToBRFV) has had major impacts on tomato production worldwide since its emergence in ~2014. The most critical factor behind the global pandemic of ToBRFV is the escape of the long-standing tomato tobamovirus resistance gene, *Tm-2*^{2}. ToBRFV has spurred research and brought renewed interest to genetic mechanisms of resistance against tobamoviruses for use in commercial tomato breeding. Many new potential sources of resistance to ToBRFV have been reported in peer-reviewed publications and commercial patents. However, the identity of genes responsible for resistance traits remains mostly elusive, and breeding these traits from wild relatives into commercial elite tomato varieties has negatively impacted tomato production by affecting fruit quality and development. *Tm-1* has been the focus of multiple publications investigating the molecular basis in preventing ToBRFV replication, often linked to unknown resistance genes on other chromosomes. The role of *Tm-1* includes complex genetic interactions, expression and gene dosage effects, gene duplications, orthologous variants, and particularly resistance escape mechanisms which can all affect the strength of *Tm-1*-mediated resistance. Other novel resistance traits are also increasingly vulnerable to resistance-breaking isolates. Here, we review recent major developments relating to ToBRFV resistance and breeding of commercial varieties.

Keywords: genetic resistance; rugose; breeding; tomato; tobamovirus; fruit development

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1. Introduction

Tomato brown rugose fruit virus (ToBRFV; *Tobamovirus fructirugosum*) is a major ongoing threat to greenhouse tomato production which can cause significant disease-associated losses and has resulted in drastic changes to production practices worldwide. The rapid global spread of ToBRFV is due to the breakdown and escape of the longstanding resistance mediated by the *Tm-2*^{2} resistance gene, which was then further exacerbated by the efficient mechanical transmission of ToBRFV, globalization of the seed trade, and limitations in preventing the movement of contaminated materials [1–8]. The lack of effective control measures has spurred research aiming to identify new sources of resistance [9]. Traits related to ToBRFV resistance and tolerance have been widely reported from undomesticated related species like *S. ochrantum*, *S. habrochaites*, *S. peruvianum*, *S. pimpinellifolium*, *S. pennelli*, and *S. chilense* [10–14]. While the identification of novel resistance traits is promising, emerging strains of ToBRFV capable of escaping some of these new sources of resistance have already

been reported [12,15–18]. Furthermore, the identity, function, and mechanisms of action of these putative resistance genes are largely unknown [14,19,20]. Breeding these novel traits into commercial elite cultivars has affected fruit development traits, negatively impacting fruit production, quality, flavour, and yield [21,22]. Many resistance screens of wild tomato relatives identified the tobamovirus resistance gene *Tm-1*, necessitating the understanding of both older and novel resistance sources, and how these genes might interact to improve resistance to ToBRFV [23].

1.1. Tobamoviruses and Greenhouse Production

Greenhouse fruit and vegetable production is an intensive system designed to maximize fruit yields through controlled environment agriculture and plant varieties best adapted to these conditions. Many growth factors can be controlled in modern greenhouses, including temperature, irrigation, nutrients, lighting, humidity, carbon dioxide levels, and plant density (Figure 1A) [24,25]. For example, tomato planting density can range from 2.3 plants/m for large varieties (beefsteak and tomato-on-the-vine) to 4.6 plants/m for smaller fruited varieties (grape, cherry, and cocktail), or approximately 10,000–20,000 plants per acre [24,26]. High-density environments can maximize yields, but combined with shared irrigation and intensive plant handling, create optimal conditions for pathogen spread especially for viruses in the *Tobamovirus* genus [23,27–29].



Figure 1. Commercial tomato production and ToBRFV. (**A**) High-density greenhouse tomato production environment. (**B**) Symptoms of ToBRFV on commercially available tomatoes. (**C**) Fruit variation in commercially available tomato fruits from different varieties. From left to right, Beefsteak, Tomato-on-Vine, cocktail, cherry, grape, plum, and roma. Scale bar = 5 cm.

Tobamoviruses have been a persistent issue in greenhouse production [27–29]. Currently, there are 37 recognized species of tobamoviruses that can infect plant species across at least 30 different plant families including *Solanaceae*, *Brassicaceae*, *Cucurbitaceae* and *Mal-*

vaceae as the primary and most economically affected families. Major tobamoviruses that have impacted greenhouse production include tobacco mosaic virus (TMV; *Tobamovirus tabaci*), tomato mosaic virus (ToMV; *Tobamovirus tomatotessellati*), tomato mottle mosaic virus (ToMMV; *Tobamovirus maculatesselati*), pepper mild mottle virus (PMMoV; *Tobamovirus capsici*), cucumber green mottle mosaic virus (CGMMV; *Tobamovirus viridimaculae*), and the recently emerged ToBRFV [6,8,29,30]. TMV, ToMV, and ToMMV have previously been issues in greenhouse tomato production but were largely controlled by the *Tm-2*^{2} resistance gene [31]. PMMoV and CGMMV are ongoing issues in pepper and cucumber greenhouse production, respectively, but their impact has been mitigated through genetic resistance and vaccination [32–34]. Tobamoviruses are easily transmitted through mechanical contact from tools, workers, insects, and seeds [6,23,27,35–37]. Efficient mechanical transmission when combined with high-density plantings, large production greenhouses, and intensive plant management can rapidly devastate production (Figure 1A) [38]. As cultural controls are laborious and have limited ability to reduce the spread of tobamoviruses, genetic resistance is generally preferred in all types of production systems [30,39].

The tobamovirus genome consists of a 6.4-kb, single-stranded, positive-sense RNA molecule that encodes four protein-coding open reading frames (ORFs) Cgy [40]. The genomic RNA also contains a 5′-m(7) Guanosine cap and a tRNA-like 3′ structure with a terminal cytosine-cytosine-adenine trinucleotide [41]. A small 124–132 kDa replication protein (p126) is encoded by ORF1, while ORF2 encodes a second replication protein of 181–189 kDa (p183) that partially overlaps with p126 and is translated through a stop codon readthrough mechanism [24,42,43]. The p126 protein also plays a role in RNA silencing suppression [44]. ORF3 encodes a 28–31 kDa movement protein (MP or 30K) that facilitates cell–cell movement, and ORF4 codes for a 17–18 kDa coat protein (CP), which polymerizes to form a viral particle around the RNA genome, facilitating systemic movement and plant–plant transmission [24]. Viral proteins can often be multifunctional and can have diverse roles in promoting viral replication and suppressing host defenses [44,45].

Viral proteins can also function as avirulence factors, recognized by host immunity proteins to initiate defense responses [46]. For example, the Tm-1 protein recognizes the tobamovirus p126 and p183 replication proteins and specifically binds to their RNA helicase domain to prevent viral replication [47,48]. Some resistance gene products recognize and interact with specific tobamovirus proteins to initiate a hypersensitive response (HR) to prevent viral infection, such as that of the Tm-2 protein, which recognizes the MP [49], and the tobacco N protein which recognizes the p126 protein [50–53]. Finally, the proteins encoded by the pepper *L* gene recognize the tobamovirus CP [32]. Almost all known tobamoviral proteins can be recognized by the host immune system, highlighting the diversity of resistance mechanisms available to combat tobamovirus infection [23]. The mutation of host factors required for viral replication, such as the *TOBAMOVIRUS MULTIPLICATION* (*TOM*) genes [54,55], can also result in resistance by preventing the formation of a functional viral replication complex [40,54]. Together, a wide variety of resistance genes can suppress tobamovirus infections in commercial production systems, but which ones could be involved in the control of ToBRFV remains largely unclear [28,30].

1.2. ToBRFV Emergence and Worldwide Spread

Prior to the emergence of ToBRFV, *Tm-2* was the most widely used resistance gene in tomato production systems, providing stable and durable resistance to tobamoviruses [1,31,56]. The ability of ToBRFV to evade *Tm-2*^{2} mediated extreme resistance makes it a very successful pathogen [4,5,7]. However, Tm-2^2 can still recognize the ToBRFV MP and trigger an attenuated HR, and thus plants harbouring the *Tm-2*^{2} allele may retain partial, dose-dependent resistance to ToBRFV [57]. *Tm-2* and *Tm-2*^{2} encode Nucleotide-

Binding Leucine-Rich Repeat (NB-LRR) domains, which recognize the tobamovirus MP to initiate a hypersensitive response (HR) resulting in the death of infected cells [58,59]. While certain isolates of ToMV can escape *Tm-2*^{2} mediated resistance, they did not cause widespread issues to the industry [31,49,60]. Since *Tm-2*^{2} targets the tobamovirus MP, some studies have suggested that escaping *Tm-2*^{2} mediated resistance could result in impaired viral movement, inhibition of viral spread, and reduced competition with other tobamoviral MPs in the absence of *Tm-2*^{2} [7] These possible effects could explain the dominance and durability of *Tm-2*^{2} in commercial tomato varieties.

As infection rates can rapidly reach 100% in a greenhouse causing severe economic losses [38], ToBRFV has resulted in significant changes to production practices including changes to infrastructure (increased use of LED lights), improved biosecurity, shortened production cycles, increased seed and plant testing, and increased regulation of seed trade [61]. More recently, the identification of resistance traits from wild tomato relatives and their introgression into commercial varieties has altered fruit development traits, resulting in reduced fruit quality, harvesting and production efficiencies, and increased labour (Figure 1B). These changes have disturbed optimum tomato production conditions, reducing marketable fruit yields and increasing costs for producers.

Major symptoms on the fruit can include brown rugose spots, incomplete ripening, or even open fruit in severe cases (Figure 1B) [6]. Recognizable signs of infection on young plants include stunting, bleaching or chlorosis of young growing leaves, shoestring-like leaves and other deformations, mosaic and bubbling, and more. Plant health can continue to deteriorate as the disease progresses, resulting in aborted fruit and necrotic flowers, further reducing yields. The virus can also spread asymptomatically, infecting plants before growers are aware. Resistance genes can break down over time through viral mutagenesis, which can also be exacerbated during heat waves, causing a sudden appearance of symptoms in many plants [15,17,62,63]. Finally, Tobamoviruses are difficult to eradicate, and can persist in greenhouses and on clothing for up to six months [64–67]. Without prompt eradication of ToBRFV, infection frequencies can rise, resulting in increased virus titers in the environment and facilitating re-infection of subsequent crops [38]. Given the significant losses caused by ToBRFV, identification of durable and robust resistance against this virus is paramount in the sector.

1.3. Tomato Domestication and Breeding for Resistance

Many different varieties of tomatoes are commercially available, arising from a broad reservoir of genetic diversity derived from a complex history of domestication (Figure 1C) [68,69]. Tomato domestication likely first occurred approximately 7000 years ago and became a complex process even before its introduction to Europe during the Columbian exchange in the 16th century [70,71]. Early reports of tomatoes cultivated by the Aztecs described a wide variety of fruit sizes, shapes, and colours dating back to 1577 [71]. Domestication of tomatoes has continued to the present day, including adaptations for greenhouse production systems [72]. Tomato breeding has become increasingly complex and international, with common global movement of seeds and bulking for large-scale commercial production systems [61]. The increased globalization of the tomato seed industry has facilitated the rapid worldwide spread of ToBRFV.

Wild tomato species are native to western South America from Ecuador to Chile. They can grow in a wide variety of habitats from sea level to high in the Andean mountains, in both arid and rainy climates [73]. At least 11 distinct species are recognized, including the domesticated tomato (*S. lycopersicum*) and wild relatives including *S. pimpinellifolium*, *S. cheesmaniae*, *S. galapagense*, *S. chilense*, *S. chmielewskii*, *S. habrochaites*, *S. pennellii*, *S. neorickii*, *S. peruvianum* north, and *S. peruvianum* south [73]. These diverse species represent valuable

genetic resources for the identification of new disease resistance traits for commercial varieties, although they exhibit substantial variation in fruit morphology and developmental characteristics [74–76]. *S. pimpinellifolium* has smaller currant-type fruits and has likely had many contributions to modern tomatoes [77,78]. *S. pimpinellifolium* has been used extensively to study fruit development characteristics and has already had large impacts on the domesticated tomato [77,79]. *S. habrochaites* is more distantly related to domesticated tomatoes, and produces fruit that are much smaller, green, and have increased trichomes [80,81].

Fruit maturation is a complex process, and commercial production values many different qualities, including fruit weight, size, shape, homogenous ripening times, taste, aroma, and more [82,83]. Many genes are involved in fruit developmental processes, and at least 28 different quantitative trait loci (QTL) are associated with fruit weight in tomatoes (Table 1) [79,82]. The gene *FRUIT WEIGHT 2.2* (FW2.2) can affect up to 30% of fruit weight and is a regulator of cell division [84]. *FASCIATED* (*FAS*), *SUN*, *OVATE*, and *LOCULE NUMBER* (*LC*) are major determinants of fruit shape in *S. lycopersicum* [75,85]. Introgression of genes from wild relatives can often lead to undesirable traits when interbred with commercial tomato varieties, such as small fruit size, low yield, poor flavor, or delayed maturity [22,86,87].

Similar to traits controlling fruit development, wild tomato species can express unique and novel resistance traits which are not present in domesticated tomatoes. The resistance gene *Tm-1*, which confers tolerance to ToMV, was first reported from *S. habrochaites* in 1939 [88,89]. The *Tm-2* gene and the *Tm-2*^{2} allele, which provided resistance to ToMV, were both identified in *S. peruvianum* and used in over 90% of commercial tomato varieties, providing durable resistance to tobamoviruses for over 60 years [2,72]. While these genes have had substantial impacts on the greenhouse tomato industry, integrating sources of resistance from wild tomato relatives into commercial varieties is complex and can present significant challenges [69,90]. Some species have genetic barriers that make crossing with cultivated tomatoes difficult [91,92]. Genes associated with resistance can be linked to loci involved in vegetative growth or fruit development, which can cause linkage drag and reduced production in elite varieties [93–96].

Self-incompatibility prevents self-fertilization and helps maintain genetic diversity in species by promoting outcrossing but can lead to sterility in hybrids or failure to express resistance genes in the offspring [92,97]. Hybrids resulting from cross pollination between tomatoes and their closest relative, *S. pimpinellifolium*, can behave like intraspecific tomato hybrids, suggesting few chromosomal differences between these species [91]. Both species can self-pollinate and are compatible, making hybridization between them easier than with other species within the *Solanum* genus. By contrast, hybridization between *S. lycopersicum*, *S. peruvianum*, and *S. habrochaites* can display sterility, segregation distortion, and reduced recombination, suggesting structural differences in their chromosomes [91]. *Tm-2*^{2} is associated with a region of reduced recombination, which can affect fruit development and quality [72,87,96]. However, studies of the introgression of *Tm-2* only reported minor or variable effects on commercial fruit yields, while introgression of the *Ty-1* gene, which confers resistance to tomato yellow leaf curl virus (*Begomovirus coheni*), could reduce yields by up to 50% [98].

While many new putative resistance genes have been identified, most QTLs associated with resistance appear on chromosomes also associated with genes regulating fruit development (Figure 2). Many genes controlling fruit weight and shape in tomato have been identified on the same chromosomes as genomic regions associated with ToBRFV resistance, especially chromosomes 2 and 11 (Table 2) [99]. This correlation has resulted in issues with uniform fruit ripening, changes in cluster sizes, and other changes to yield

and fruit maturation. Furthermore, there are over 10,000 varieties of tomatoes available commercially, and breeding resistance traits into multiple varieties is a lengthy process.

In commercial varieties of tomatoes, levels of resistance are defined by the International Seed Federation (ISF), which updated its definitions of resistance in 2022 (ISF, 2022). They describe three levels of pathogen–plant interactions: susceptibility; intermediate resistance, where pathogen symptoms are restricted to a moderate degree; and high resistance, which can still present minor symptoms. These definitions are more broadly consistent with tolerance traits that confer repression of viral replication and symptoms, while still allowing for infection and potential spread of the virus, which can lead to resistance escape [100]. Communications from seed companies regarding ToBRFV have changed substantially since the release of cultivars advertised as highly resistant, only for resistance to break down in infected greenhouses. More recently, many seed companies have provided disclaimers stating that immunity to ToBRFV does not exist. A recent genome-wide association study of ToBRFV resistance traits using 161 tomato accessions reported that the virus could be detected even in highly resistant plants, which is consistent with tolerance traits as opposed to immunity [20,100].

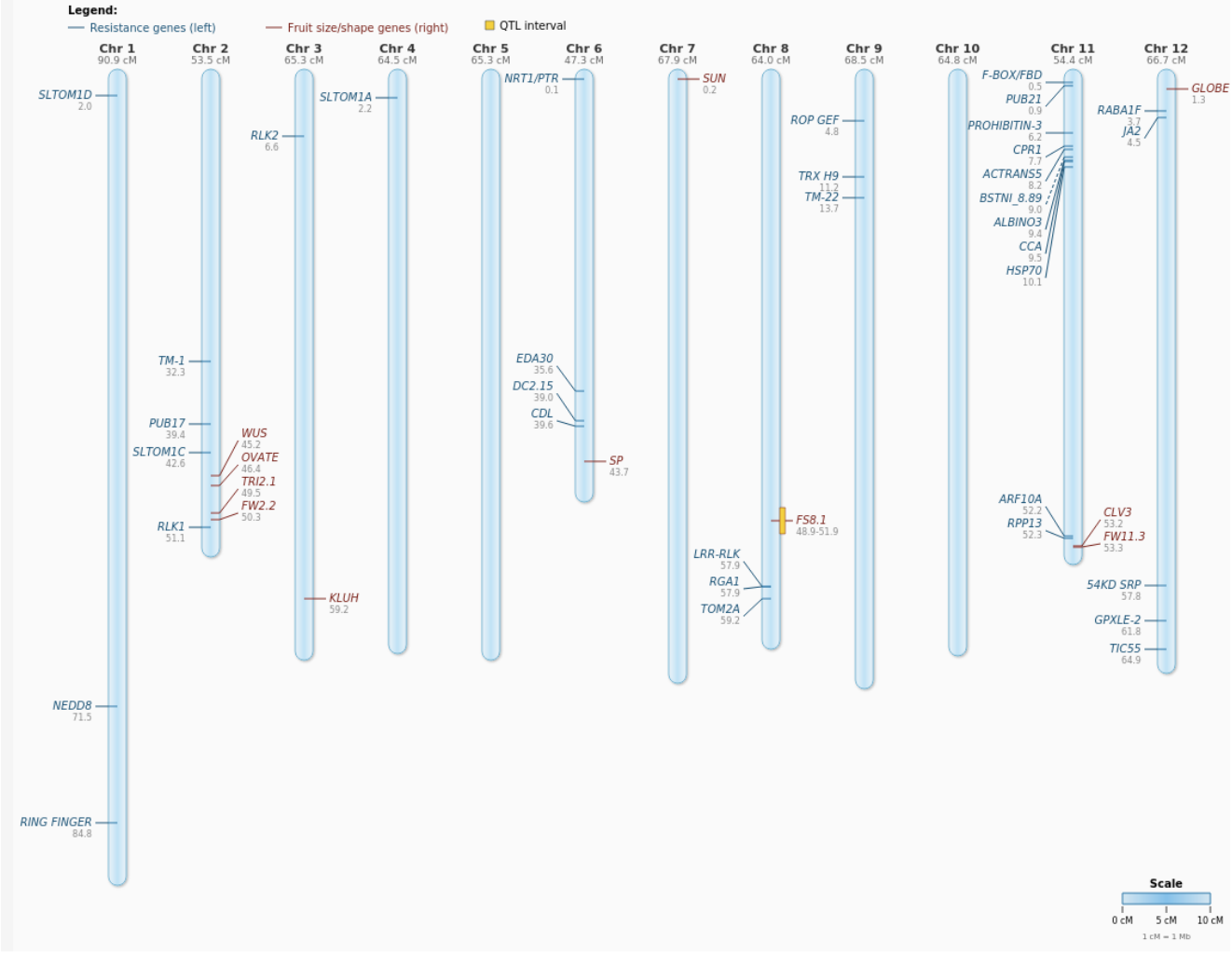


Figure 2. Linkage map of genes involved in fruit development and putative ToBRFV resistance traits. Putative and known resistance genes are labelled on the left-hand side of each chromosome, while genes involved in fruit development are listed on the right. Regions corresponding to QTL intervals are shown in yellow. Genetic locations in cM are listed under each gene.

Table 1. Chromosomal location of major fruit development-associated genes.

Gene or QTL Name	Chromosome	Trait(s) Affected	Candidate Gene(s)	Citation
fw2.2	2	Fruit weight	FW2.2	[84]
LC	2	Locule number, fruit shape	*WUS*	[75,85]
OVATE	2	Fruit shape (pear-shaped)	*OVATE*	[75,85,101]
tri2.1	2	Fruit shape (triangular)	-	
fw3.2	3	Fruit weight	*KLUH*	[102]
fw6.3	6	Fruit weight	*SELF-PRUNING (SP)*	
SUN	7	Fruit shape (elongation)	*SUN*	[75,85,103]
fs8.1	8	Fruit shape (elongation)	-	
fw11.3	11	Fruit weight	-	
FAS	11	Locule number, fruit shape	*CLV3*	[75,85]
GLOBE	12	Fruit shape (length)	-	[75,85]

Table 2. ToBRFV resistance genes identified in patents.

Patent #	Assignee(s)	Chr.	Gene	Gene ID
WO2021161615A1	Takii and Co., Ltd., National Agriculture and Food Research Organization	1	*SlTOM1d*	101252618
WO2023156569A1	Syngenta Crop Protection AG Switzerland	1	Ring Finger Protein	101249497
WO2023156569A1	Syngenta Crop Protection AG Switzerland	1	*NEDD8*	101257615
WO2021161615A1	Takii and Co., Ltd., National Agriculture and Food Research Organization	2	*SlTOM1c*	778361
WO2021213892A1	Nunhems BV	2	*Rug-1*	
WO2022018734A1	Philoseed Ltd.	2	Uncharacterized ncRNA	112940897
WO2023194291A1	Syngenta Crop Protection AG Switzerland, Takii and Co., Ltd., Rijk Zwaan Zaadteelt en Zaadhandel BV, Nunhems Netherlands BV	2	*Pub17*	101245319
WO2025005231A1	Kikkoman Corp, Tokyo University of Agriculture and Technology NUC	3	*RLK2*	101264597
CN118374510A	Shandong Agricultural University	4	*EXA1*	
WO2021161615A1	Takii and Co., Ltd., National Agriculture and Food Research Organization	4	*SlTOM1a*	778313
WO2023242393A1	Syngenta Crop Protection AG Switzerland, Takii and Co., Ltd., Rijk Zwaan Zaadteelt en Zaadhandel BV, Nunhems Netherlands BV	4	*Pub21*	101265502
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	6	*NRT1/PTR*	101245952
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	6	*ESDA30*	101267715
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	6	*DC2.15*	101263716
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	6	*CDl*	101245769
RU2817119C2	Enza Zaden Beheer BV	8	*RGA1*	101248228
WO2020147921A1	Enza Zaden Beheer BV	8	LRR receptor-like serine/threonine-protein kinase	104648980
WO2022013452A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	8	*TOM2A*	101262238
WO2024223901A1	Vilmorin SA	8	*RGA1*	101248228

Table 2. *Cont.*

Patent #	Assignee(s)	Chr.	Gene	Gene ID
WO2020249996A1	Vilmorin SA	9	Rop guanine nucleotide exchange factor	101268788
WO2021245282A1	Vilmorin SA	9	*Thioredoxin H9*	101259660
WO2022091104A1	Israel Ministry of Agriculture and Rural Development	9	*Tm-2²*	101255420
CN118307651A	Shandong Agricultural University	9	*Tm-2²*	101255420
CN118772252A	Shandong Agricultural University	9	*Tm-2²*	101255420
CN118772251A	Shandong Agricultural University	9	*Tm-2²*	101255420
CN118725060A	Tsinghua University	9	*Tm-2²*	101255420
WO2022117884A1	Vilmorin SA	9	*Tm-2²*	101255420
CN116847729A	Vilmorin SA	9	*Tm-2²*	101255420
CN116732220A	Beijing Bona Oriental Agricultural Technology Development Co., Ltd., Henan Qidu Agricultural Technology Co., Ltd., Henan Agricultural University	11	*TBR11*	
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	11	F-box/FBD/LRR-repeat protein	101262770
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	11	*RPP13-like protein 1*	101252658
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	11	*ARF10A*	100529137
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	11	*Prohibitin-3*	101253149
WO2020018783A1	Seminis Vegetable Seeds Inc	11	Uncharacterized	101245908
WO2020249996A1	Vilmorin SA	11	Acetyltransferase component 5	101264480
WO2021110855A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	11	*CCA*	101243854
WO2021170868A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	11	Albino 3 like	101246494
WO2021245282A1	Vilmorin SA	11	Unknown QTL	
WO2022018734A1	Philoseed Ltd.	11	*F-box protein CPR1*	101260686
WO2023095144A1	Israel Ministry of Agriculture and Rural Development	11	*CCA*	101243854
WO2024223901A1	Vilmorin SA	11	*DDRAC5PDH*	101264480
WO2024223901A1	Vilmorin SA	11	*HSP70*	100134914
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	12	*RABA1f*	101256357
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	12	*JA2*	543526
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	12	*54kD SRP*	544156
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	12	*GPXle-2*	101267098
WO2019110130A1	Rijk Zwaan Zaadteelt en Zaadhandel BV	12	*TIC55*	101252762
WO2020249996A1	Vilmorin SA	6 or 9	Unknown protein	101244776

1.4. Identification of New Sources of Resistance

Since the emergence of ToBRFV in 2014, promising sources of intermediate and high resistance to ToBRFV have been identified in the wild species *S. habrochaites* [12,13,104],

S. peruvianum [12], *S. chilense*, *S. ochrantum* [13], and *S. pimpinellifolium* [10,14]. While these results are promising, further characterization of these traits is required. It is unclear whether some of the resistance identified is due to the same gene(s) or if multiple different resistance mechanisms are present [14]. Additionally, no peer-reviewed report has conclusively demonstrated that one gene is responsible for a resistance trait, nor is the identity of any of these putative resistance genes clearly established. Resistance can also vary substantially within species, and multiple alleles with different efficiencies could exist in these populations, similar to how *Tm-2* was initially discovered and used for resistance to Tobamoviruses before the *Tm-2*^{2} allele was identified [105]. Understanding the molecular mechanisms underlying these putative resistance genes and their interactions could allow for the development of more robust tomatoes. Finally, understanding how fruit development-related genes could be linked to putative resistance genes is crucial to facilitating introgression of resistance traits while minimizing effects on fruit development (Figure 2).

While there is little published research regarding the identity and function of these genes, there are several patents filed related to ToBRFV resistance traits available online. The number of patents related to ToBRFV resistance genes or varieties was first reported in 2018. By 2023, Sánchez-Sánchez et al. reported a total of 28 patents related to ToBRFV resistance, and that number has increased dramatically since then before reaching a peak in 2024 before declining rapidly in 2025, suggesting that most easily identifiable genetic resources for ToBRFV resistance have been mined (Figure 3) [106]. As of August 2026, there were a total of 79 ToBRFV resistance-related patents available on google patent (https://patents.google.com/) (Table 2). Most patents were filed by major tomato breeding companies including Rijk Zwaan, Enza Zaden, BASF, Syngenta, and more. Academic institutions and governments have also filed patents related to ToBRFV resistance (Table 2). We examined all available patents for named genes or sequence data associated with resistance or tolerance claims, and these sequences were mapped to the tomato genome to better understand which chromosomal regions are linked to ToBRFV resistance (Table 2).

Most sequences available in patents mapped to chromosomes 2, 8, 9, and 11 (Figure 2, Table 2). The *Tm-1* gene and two *TOM* homologues, *TOM1c* and *TOM1d*, map to chromosome 2. *Tm-1* clearly plays a role in tobamovirus resistance, but there is evidence that *Tm-1* mediated resistance is not durable, and multiple reports of resistance escape have been published [16,17,107–110]. *Tm-1* is a semi-dominant gene originally introgressed from *S. habrochaites* and encodes a 754-amino-acid protein. This protein is composed of an uncharacterized N-terminal domain and a C-terminal TIM barrel-like domain, of which only the N-terminal domain is required for inhibition of tobamovirus replication [107,111,112]. Certain polymorphisms in the p126 ORF of ToBRFV have been reported to reduce the effectiveness of *Tm-1*, causing it to fail to prevent viral replication and symptom development [16,17]. One study examined the interactions between *Tm-1* and ToBRFV over an extended period of time and showed that while systemic infection was prevented up to 50 days post infection, symptoms were evident by 100 days post infection [16]. Studies of longer duration are therefore required to fully examine *Tm-1* mediated resistance. Other studies describe breakdown of *Tm-1* mediated resistance under elevated temperatures [62,113]. *Tm-1* expression levels can also have major impacts on the effectiveness of resistance, with overexpression lines significantly reducing viral accumulation [108].

Further complicating matters, *Tm-1* orthologues from *S. habrochaites* and *S. pennellii* have shown more promise in reducing viral replication [108–110,114]. Amino acid alignments of *Tm-1* allelic variants from these species show divergence between resistant and susceptible alleles, particularly in the region responsible for interacting with the viral replicase [109,110]. Allelic variations of *Tm-1* do display differential resistance re-

sponses to tobamoviruses, which can also be affected by homozygosity or gene expression levels [47,107,108,110]. *Tm-1* overexpression lines can significantly reduce viral accumulation [108]. Two independent *S. habrochaites* genome assemblies (accessions LA1353 and ZY59) contain a segmental duplication of the *Tm-1* genomic region, creating a gene duplication of *Tm-1*, with the two orthologues being 96% identical to each other [108]. Another recent study demonstrated that using *Tm-1* in grafted rootstock can reduce ToBRFV soil transmission rates, but not prevent infection, providing further evidence of the usefulness of *Tm-1* in the future of ToBRFV resistance [110]. Optimizing sequence variants and other interacting factors could help enhance *Tm-1* mediated resistance and reduce resistance escape.

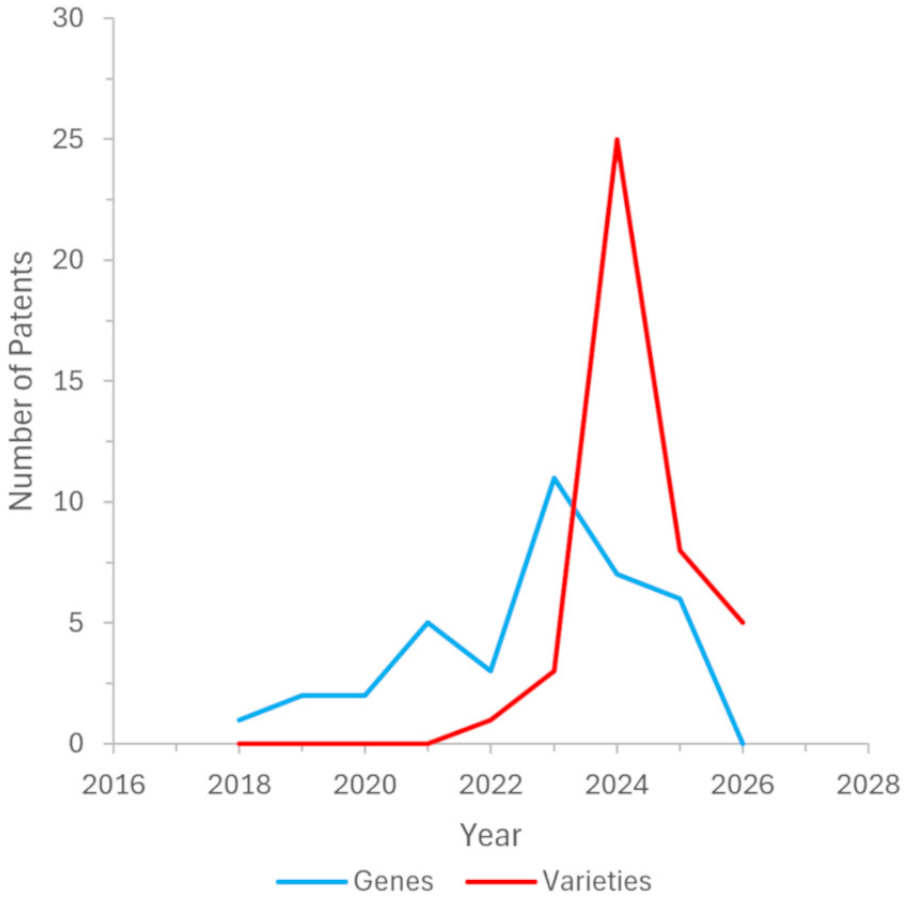


Figure 3. Number of patents published per year related to ToBRFV resistance genes or varieties.

The tobamovirus p126 protein is a multifunctional protein that plays a key role in viral replication complex (VRC) assembly. While *Tm-1* is a resistance gene that recognizes the p126 protein to prevent VRC assembly, other host factors are involved in facilitating VRC assembly, such as the *TOM* genes, which encode transmembrane domain proteins [54,115]. Resistance against ToBRFV and other Tobamoviruses may therefore be achieved through the mutation of such host factors, including multiple *TOM* homologues (*TOM1a*/*TOM3*/*TOM1b*), though these genes have strong patent controls [54,55,116,117]. TOM1 has also been shown to interact with ARL8, an ADP-ribosylation factor (ARF)-like small GTP-binding protein [118]. ARL8 is therefore another putative host factor involved in tobamovirus replication [40]. These genes are all believed to be involved in the production of VRCs and hence required for productive infections [40].

RGA1 and *TOM2a* are located on Chr. 8, along with a LEUCINE RICH REPEAT receptor-like serine/threonine-protein kinase. *RGA1* (Solyc08g075630) was initially identified in a screen of *S. habrochaities* accessions, and one patent reported that silencing

of this one gene could abolish resistance previously identified in this line [15,63,119]. *RGA1* encodes an orthologue of a resistance gene conveying resistance to late blight in potato [119,120]. *RGA1* encodes a NB-LRR containing protein with similar domains to *Tm-2* and is therefore a putative resistance gene that could confer some level of tolerance to ToBRFV [119,120]. However, ToBRFV resistance-breaking isolates linked to this gene have already been reported (Zisi et al., 2024; Fougere et al., 2025) [15,17]. Amino acid polymorphisms have been identified in the viral MP of resistance breaking isolates of ToBRFV, including N82K [15] and T115R [17], suggesting *RGA1* is not a durable resistance gene against ToBRFV. However, sequences of the *RGA1* gene are highly variable from different accessions, suggesting that multiple *RGA1* alleles may be present in natural populations, which could prove useful against ToBRFV [13].

Nine patents contained information on resistance genes located on Chr. 9, which is also the location of the *Tm-2* gene. *Tm-2* is the focus of 7 of these 9 patents, with multiple descriptions of restoring *Tm-2* function against ToBRFV through mutagenesis of 14 amino acids (Figure 4). Two recent peer-reviewed studies examined the possibility of restoring *Tm-2*^{2} function against ToBRFV, but there is little consensus between commercial patents and the scientific literature regarding which amino acid substitutions could facilitate this (Figure 4) [121,122]. A recent study reported two amino acid polymorphisms (S723Y and N744D) that could restore *Tm-2* function against ToBRFV, while also maintaining efficacy against TMV [122]. Other reports have shown that *Tm-2*^{2} retains partial function against ToBRFV, and that *Tm-2*^{2} overexpression lines can enhance resistance [57]. Beyond *Tm-2*, tomatoes contain approximately 267 other NB or NB-LRR genes, including *RGA1*, which could also be useful for adaptation in disease resistance [123].

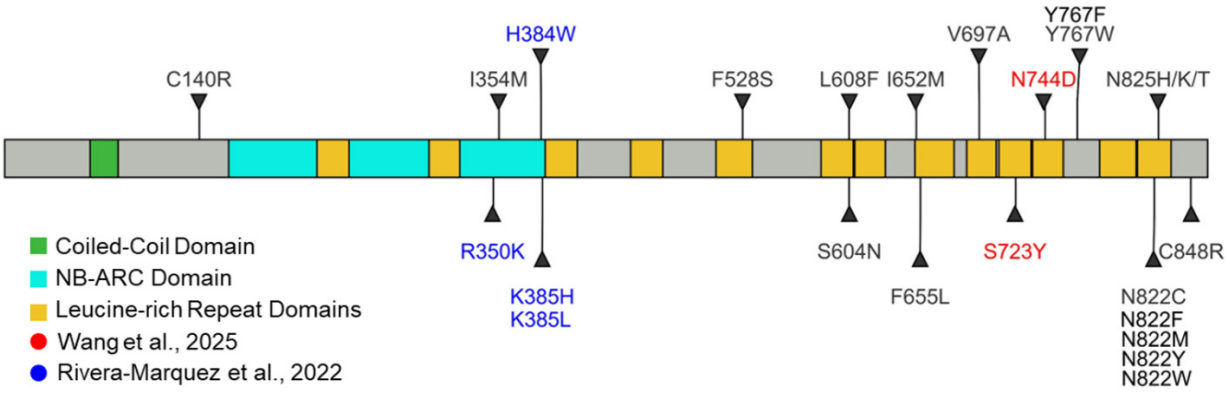


Figure 4. Amino acid polymorphism associated with *Tm-2*^{2}. Green, blue, and yellow regions indicate coiled-coil, NB-ARC, and LRR domains, respectively. Arrow heads indicate different amino acid substitutions reported in the literature. Blue labelled substitutions are associated with bioinformatics analysis of *Tm-2* reported in Rivera-Marquez et al., 2022 [121], and red labelled arrowheads indicate strong HR-inducing alleles in response to ToBRFV infection reported in Wang et al., 2025 [122]. Grey labelled arrow heads indicate polymorphisms reported in patents associated with *Tm-2*.

Chromosome 11 was the focus of 15 patents, and sequence data from 3 of these patents was associated with the *CCA* gene (Solyc11g018810), which was also identified in a GWAS study of ToBRFV resistance [20,124]. Multiple combinations of substitutions, insertions, and deletions in the *CCA* gene are reported in these patents as potentially being responsible for resistance (Table 2). The *CCA* gene encodes an ATP:tRNA nucleotidyltransferase, which adds a cytosine-cytosine-adenosine triplet nucleotide to the 3′ end of tRNA, and is essential in tRNA post-transcriptional maturation [125]. Tobamoviruses contain 3′ tRNA-like structures with a terminal CCA trinucleotide, and *CCA* genes have been suggested to be important for tobamovirus replication [41]. The 3′ UTR of tobamoviruses plays

important roles in enhancing viral protein translation and is critical for negative strand RNA synthesis [41]. Mutants lacking the C-terminal 158 nucleotides failed to produce negative strands for RNA synthesis, and even deletion of the terminal adenosine residue can have drastic effects on RNA synthesis [41,47,126]. However, a recent study of resistance traits from *S. pennellii* suggest that *CCA* was not involved in the high resistance described in this specific study, and another unknown gene could also contribute to ToBRFV resistance [109].

One putative resistance quantitative trait locus (QTL) identified on chromosome 9 or 11 interacted with the *Tm-1* gene, and both genes together could result in more effective resistance [10,109,127]. An allele of *Tm-1* from *S. pennellii* was recently reported to provide resistance to ToBRFV, when combined with another locus on Chr. 11 [109]. Other putative resistance genes on Chr. 11 identifiable through patents include a putative disease resistance RPP13-like protein, an LRR repeat-containing protein, an auxin response factor, acetyltransferase, an uncharacterized protein with a DnaJ domain, a heat shock protein, and the F-box protein *CPR1,* which can negatively regulate accumulation of the *R* protein SNC1 [128] (Table 2). Other research identified quantitative trait loci on Chr. 11 and identified two disease resistance gene analogues in the mapping interval corresponding to Solyc11g062150 (TIR-NBS-LRR resistance protein, Toll-Interleukin receptor) and Solyc11g062180 (disease resistance protein, leucine-rich repeat), which are also good candidates for resistance genes [9].

A few patents also referenced genes on chromosomes 1, 3, 4, 6, 7, and 12, including genes with homology to Ring finger proteins, receptor like kinases, and notably the *TOM* genes (Table 2). Six patents were linked to genes containing leucine rich repeat regions, similar to *Tm-2*. Finally, a further 36 patents did not contain any sequence data. These patents provide some information on potential candidate resistance genes and traits being bred into commercial elite cultivars, although the role of any gene in ToBRFV resistance is still speculative.

1.5. Resistance Breakdown, Temperature Sensitivity, and Mechanisms of Resistance

Unfortunately, many of these resistance genes have already been reported to break down over time and under high temperatures, including *Tm-1* and *RGA1* [13,62]. The tobacco *N* gene, when transformed into tomato plants, provided resistance to ToBRFV at 20 °C, but failed to provide resistance at temperatures over 30 °C [53]. ToBRFV resistance from *S. habrochaites* and *S. peruvianum* lineages, which is linked to the *RGA1* gene, also failed at temperatures above 33 °C [13,129]. Elevated temperatures can even reduce the effectiveness of HR reactions, which could further weaken *Tm-2*^{2} like resistance [130,131]. Increased temperatures due to climate change could therefore seriously exacerbate the ongoing ToBRFV pandemic [132].

While many different genes are possibly involved in mediating ToBRFV resistance, there are some clear trends that can allow for grouping of genes into similar mechanisms of action (Figure 5) [100,133,134]. The first major group activates the resistance signaling like some traditional *R* genes that initiate a hypersensitive response (HR) against tobamoviruses. This includes *Tm-2* alleles, the tobacco *N* gene and the pepper *L* alleles [52,135]. The putative resistance gene *RGA1* could also function in a similar way, recognizing a viral avirulence protein, likely the ToBRFV MP, and initiating HR to prevent viral replication. The second major group includes resistance genes and host factors involved in viral replication like *Tm-1*, the *TOM* genes, and potentially *CCA*. Determining the identity of novel resistance genes, understanding their function, and determining their possible additive effects will help to establish the long-term efficacy of these resistance genes against ToBRFV.

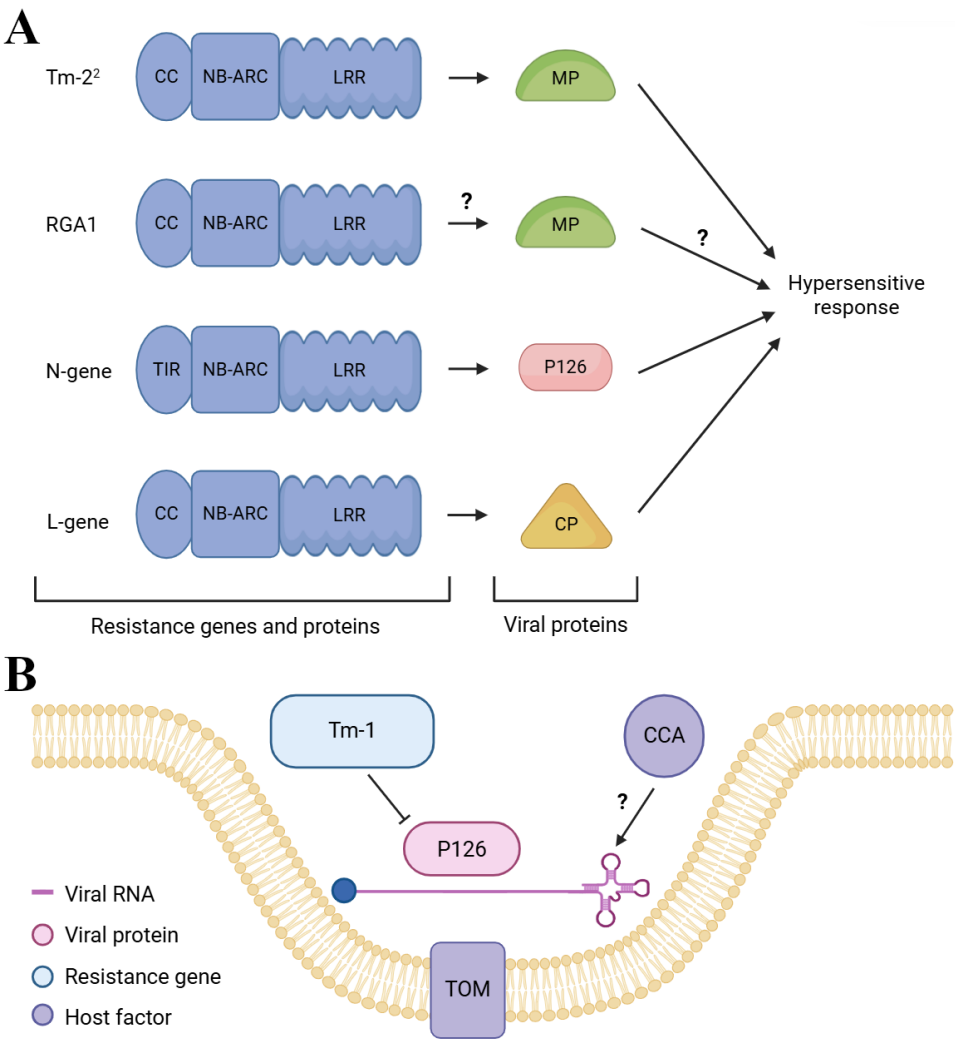


Figure 5. Tobamovirus resistance mechanisms and shared pathways. (**A**) HR-mediated resistance genes and pathways. (**B**) Resistance genes and host factors involved in viral replication. Question mark indicates the role of RGA1 is still uncertain.

2. Conclusions

The rapid worldwide spread of ToBRFV has forced many changes to tomato greenhouse production, resulting in increased costs and reduced fruit production. Similar to other tobamoviruses, ToBRFV is highly resistant to chemical decontamination approaches, and genetic resistance is the optimum approach for controlling ToBRFV. Substantial research has been conducted on the identification of novel sources of resistance. However, early reports already suggest that many of these new resistance genes are not durable, making the identification and understanding of resistance mechanisms to ToBRFV critical. Many putative resistance genes still require characterization. Introgression of resistance genes from wild tomato species can also have negative effects on fruit yield and quality, which can also affect production efficiencies. Finally, the breakdown of resistance under elevated temperatures raises further concerns for food production in the context of global warming [136].

While natural sources of resistance have been thoroughly screened, alternative approaches to resistance, including mutagenesis, could yield new sources of resistance. Allelic combinations between *Tm-1* and other putative resistance genes like *RGA1* could provide more durable resistance. Genome editing could also be applied to putative host factors to rapidly identify and introduce novel resistance traits [30,116]. Similarly, the development

of ToBRFV infectious clones or other RNAi-based control approaches will allow for more precise investigation of virus-resistance gene interactions [137–140]. The ongoing ToBRFV pandemic is a serious issue and managing this unusual aggressive tobamovirus requires a highly coordinated, multi-layered approach, including genetics, molecular biology, and cultural practices.

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