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REVIEW

Tobamoviruses: old and new threats to tomato cultivation

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Abstract
Mosaic diseases caused by tobamoviruses have posed significant threats to tomato production. In this review, we overview studies of tomato mosaic diseases published over the past century, which have led to several important discoveries in plant virology, such as the application of attenuated strains. A resistance breeding program established in the 1970s successfully controlled tomato mosaic virus for over 40 years; however, newly emerging tobamoviruses are posing serious challenges in current tomato production. We introduce recent biotechnological attempts to engineer tobamovirus-resistant tomato plants, which offer promising technologies for eradicating the current outbreak.

Keywords Tobamovirus · Tomato mosaic virus · Tobacco mosaic virus · Tomato brown rugose fruit virus · Tomato mottle mosaic virus

Introduction

The first description of a mosaic disease of tobacco (*Nicotiana tabacum* L.) (Mayer 1882) was swiftly followed by the discovery of filterable plant pathogens (Ivanovsky 1892) and the conception of the virus as a "*contagium vivium fluidum*" (Latin: contagious living fluid; Beijerinck 1898). Similar mosaic diseases were later observed on tomato plants (*Solanum lycopersicum* L.) in the USA, with the first description by Woods (1902). Many pathogens that cause mosaic diseases in tobacco and tomato in Europe and America were found to have common characteristics (e.g., Ainsworth 1933; Johnson 1926). In Japan, tomato plants were introduced during the seventeenth century and mainly cultivated for ornamental purposes until the nineteenth century. Tomatoes were first cultivated as garden vegetables in Japan at the beginning of the twentieth century (Kamimura 1980); mosaic diseases spread nationwide soon afterward (Murayama 1936; Nakata and Takimoto 1940).

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Tomato mosaic diseases caused by tobamoviruses

Tomato-infecting tobamoviruses

In the 1920s and 1930s, tobacco mosaic virus (TMV)-like viruses were isolated from tobacco and tomato plants, and back-inoculated plants were found to reproduce mosaic symptoms. During this era, the identification and distinction of virus strains was based only on host susceptibility and symptoms (Stanley 1946), such that typical names included ordinary tobacco mosaic (Johnson 1926), aucuba mosaic of tomato (in distinction from aucuba mosaic of potato) (Smith 1928), and glasshouse streak (after symptoms observed in glasshouse-grown tomato plants) (Ainsworth 1933; Jerrett 1930).

Tobacco mosaic strains mechanically inoculated onto *N. sylvestris* or *N. tabacum* cultivar 'White Burley', which have the *N*′ resistance gene (*N*′ tobacco) caused systemic mosaic disease, whereas strains collected from tomato produced necrotic spots on inoculated leaves, with no systemic infection (Broadbent 1962; Kassanis and Selman 1947; Kunkel 1934). Later studies revealed that in the presence of the *N*′ gene, expression of the coat protein (CP) of the TMV

tomato isolate, but not that of the tobacco isolate, induced a hypersensitive reaction that led to formation of local necrotic lesions and inhibition of virus spread (Knorr and Dawson 1988; Saito et al. 1987; Sekine et al. 2012).

Using this distinction method, Broadbent (1962) investigated TMV strains collected from tobacco and tomato plants in the UK. Among 64 isolates obtained from smoking tobacco plants, 60 exhibited responses similar to tobacco mosaic infection (i.e. systemic mosaic), whereas 187 of 203 strains collected from tomato plants showed responses similar to tomato mosaic infection, including necrotic spots on inoculated leaves with no systemic infection. Thus, different TMV strains appeared to be infecting tobacco and tomato plants. Similarly, *N′* tobacco showed different responses to inoculation with TMV isolates from tomato and tobacco plants in Japan (Komuro et al. 1966; Komuro and Iwaki 1968; Oshima et al. 1964). Following these observations, the first report of the International Committee on Nomenclature of Viruses established two species, *Tobacco mosaic virus* and *Tomato mosaic virus* in the TMV group (Harrison et al. 1971; Wildy 1971). In the 1980s, complete nucleotide sequences were determined for TMV-vulgare and tomato mosaic virus (ToMV)-L (formerly TMV-L), which shared only ~ 80% nucleotide sequence identity (Goelet et al. 1982; Ohno et al. 1984).

TMV and ToMV are presently classified in the genus *Tobamovirus* (family *Virgaviridae*), which includes 37 virus species (Walker et al. 2022). Tomato mosaic diseases caused by tobamovirus infection have been reported worldwide, nearly everywhere that tomato plants are grown (CABI 2021). Geographically and historically, TMV and ToMV are the most prevalent tobamoviruses that infect tomato plants worldwide (Hollings and Huttinga 1976; Panno et al. 2021; Zaitlin 2000; Zitter 2014). Li et al. (2021) performed a field survey in China in 2013–2017, and detected ToMV and another tobamovirus, tomato mottle mosaic virus (ToMMV), in 2.9% and 1.1% of 446 field-grown tomato samples showing virus-like disease symptoms, respectively. This survey showed that ToMV was the fifth most common virus, and that tobamovirus infection rates had declined compared to those reported in previous studies, perhaps due to the application of control measures such as virus-resistant varieties.

A global phylogenetic analysis of 75 ToMV isolates with available CP open reading frame nucleotide sequences subdivided the isolates into three clades (Rangel et al. 2011). Clade I consisted of 71 ToMV isolates with very low genetic diversity, and four isolates were categorized into Clades II and III. The Clade III sequences were identical or similar to the sequence of ToMMV (Li et al. 2013). Considering that these four isolates were found in Brazil, where ToMMV was detected from the sample in 1992 (Nagai et al. 2018), the Clade III viruses may have been unrecognized cases of ToMMV. The phylogeographic history of ToMV in the Eurasian continent was examined using CP gene sequences from a total of 102 ToMV isolates collected in East Asia, Europe, and the Middle East from 1975 to 2020; the results suggested that it first appeared in Europe in ~ 1750 and then was introduced in the Middle East in the 1920s, followed by East Asia (Xu et al. 2021). Notably, ToMV sequences detected by reverse-transcription polymerase chain reaction (RT-PCR) in glacial ice subcores from Greenland generated ~ 140,000 years ago had nucleotide sequences that were nearly identical to those found in the modern age (Castello et al. 1999).

Symptomatology and yield loss associated with tomato mosaic disease

The symptomatology and epidemiology of tomato mosaic disease were studied extensively from the 1950s to the 1970s (reviewed in Broadbent 1976). However, the causal viruses were not properly distinguished until the ~ 1960s, and ToMV was still thought to be a strain of TMV until ~ 1980 (Brunt 1986). In this subsection, we follow the nomenclature of the original literature.

Tomato mosaic diseases caused by ToMV or TMV infection generally do not result in plant death but inhibit the growth of shoots and roots (Broadbent and Cooper 1964) and cause various leaf, stem, and fruit symptoms (Fig. 1). The appearance and severity of symptoms varies considerably depending on many factors such as the combination of virus isolates and host genotypes, timing of infection, light intensity, and temperature (Broadbent 1976; Zitter 2014). Leaves exhibit light and dark green mottling, sometimes accompanied by yellowing, curling, or narrowing (Zitter 2014). Stripe or streak diseases that cause leaf, petiole, or stem necrosis are also produced by some TMV strains (Ainsworth 1933; Ainsworth et al. 1934; Komuro 1963; Komuro et al. 1966).

Tomato plants with mosaic disease may also suffer from fruit abnormalities such as yellow rings (at high temperatures) or uneven ripening, including bronzing, blotchy ripening, graywall, brownwall, and internal browning symptoms, which reduce their quality (Broadbent 1976; Zitter 2014). The appearance of symptoms on the fruit of TMV-infected plants is affected by various factors including light intensity (Murakishi 1960) and the timing of infection (Boyle and Bergman 1967; Boyle and Wharton 1957; Broadbent 1964; Taylor et al. 1969).

TMV infection is also associated with yield reduction (Broadbent and Cooper 1964; Rast 1967). In field-grown, machine-harvested tomatoes in Italy, every 10% increase in the infection rate resulted in a 4.4% decrease in the average yield (Di Candilo et al. 1992). The number of tomato fruit set per cluster temporally decrease after TMV infection (Alexander and Campbell 1959; Komochi et al. 1966).

Fig. 1 Leaf mosaic (left) and fruit abnormalities (right) of glasshouse-grown tomato plants infected with tomato mosaic virus

Transmission of tobamoviruses

Tobamoviruses are readily transmitted from infected plants to healthy plants through mechanical dispersal via contaminated scissors, hands, clothing, and soil (Broadbent 1976). Although birds and bumblebees transmit tobamoviruses among tomato plants (Broadbent 1965a; Levitzky et al. 2019; Okada et al. 2000), they are not major routes of ToMV transmission. By contrast, seed transmission is an important pathway for tobamoviruses. In tomato seeds contaminated with TMV or ToMV, the virus resides mainly on the surface or within the seed coat (testa) and sometimes in endosperm but is absent from the embryo (Broadbent 1965b; Taylor et al. 1961). Seed transmission occurs through infection from lesions mainly formed during transplantation. When highly contaminated tomato seeds were planted, seed transmission was often observed, but in most cases only after transplantation (Taylor et al. 1961). Thus, contaminated seed coats are considered a major source of seed transmission.

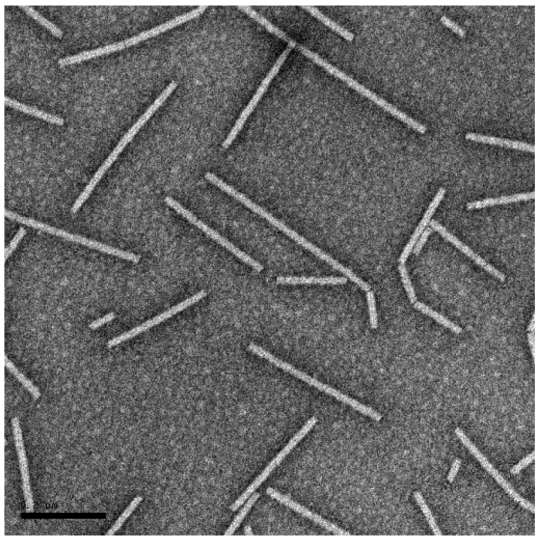

Fig. 2 Electron micrograph of purified virion of the L strain of tomato mosaic virus. Scale bar 200 nm. Photograph by Yasuhiro Tomitaka

Tobamovirus genome organization

Tobamovirus virions are rod-shaped particles of approximately 300 nm in length and 18 nm in diameter (Fig. 2), each containing one genomic RNA and approximately 2,130 CP molecules. The tobamovirus genome is a non-segmented, single-stranded, messenger-sense RNA of approximately 6,400 nucleotides in length. It encodes at least four proteins: a 130-kDa protein, its read-through product of 180 kDa, a 30-kDa protein, and the CP (17.5 kDa) (Ishibashi and Ishikawa 2016) (Fig. 3). The 130-kDa and 180-kDa proteins are produced through the translation of genomic RNA, participate in viral RNA replication (Ishikawa et al. 1986), and are collectively referred to as replication proteins. The 130-kDa protein also acts as a suppressor of RNA silencing (Ding et al. 2004; Kubota et al. 2003). The other two proteins are dispensable in viral RNA replication; each is produced through the translation of subgenomic RNAs synthesized during viral RNA replication. The 30-kDa protein is required for cell-to-cell movement of the virus, and therefore is referred to as a movement protein (MP) (Meshi et al. 1987). The CP is required for systemic infection and virion formation. Replication proteins co-translationally bind the 5′-proximal region of genomic RNA to select a replication

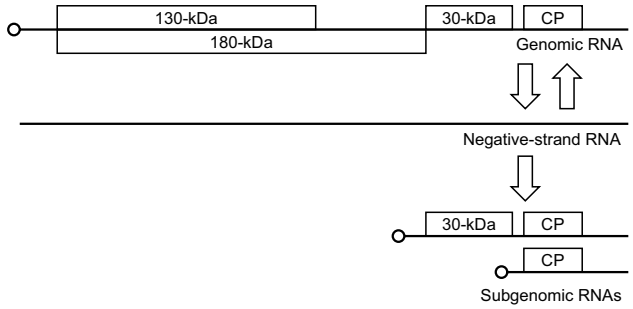

Fig. 3 Schematic representation of tobamovirus genome RNA replication and gene expression via transcription of subgenomic RNAs. Circle indicates a 5′-cap structure. Boxes indicate open reading frames

template, and form a replication complex on intracellular membranes that catalyzes the synthesis of negative-strand RNA, followed by the synthesis of positive-strand genomic and subgenomic RNAs (Ishibashi and Ishikawa 2016).

Virus control using attenuated strains

Attenuated ToMV strains

The infection of a plant with a virus strain prevents or delays subsequent infection by another strain of the same virus or a closely related virus. This phenomenon, called cross-protection, was first observed in tobacco plants infected with a light-green mosaic virus that showed tolerance to re-inoculation with a yellow mosaic virus, whereas such protection was not observed when a dark-green mosaic virus was administered as the first inoculant (McKinney 1929). Since then, cross-protection has been widely used to control viral diseases (Ziebell and Carr 2010). For this purpose, the protecting virus must produce milder symptoms than those of common strains. Such isolates have been obtained by selection from natural strains or through artificial treatments with virulent strains, such as infection at higher or lower temperatures, incubation with nitrous acid, or ultraviolet irradiation. The masked strain of TMV was the first artificially produced attenuated strain; it was obtained by incubating tobacco stems at 34˚C following inoculation with a virulent strain (Holmes 1934).

To protect tomato plants from widespread tomato mosaic diseases in Japan (Komuro et al. 1966), Oshima et al. (1965) developed the attenuated strain ToMV-L_{11} (hereafter, L_{11}) by incubating ToMV-L-infected tissues at high temperatures. Infection with L_{11} protected tomato plants from natural infection by ToMV or challenge inoculation by ToMV-L. However, its protection efficiency was insufficient for practical use, partly due to the occurrence of revertants from L_{11} to virulent strains (Goto and Nemoto 1971; Oshima et al. 1965). To improve its stability, L_{11} was further passaged to obtain ToMV-L_{11}A (hereafter, L_{11}A), which showed milder symptoms in tomato plants. Field tests in Chiba and Shizuoka Prefectures in Japan demonstrated that inoculation with L_{11}A led to higher fruit yield than in a non-inoculated control (Aoki and Ogiwara 1974; Oshima 1981). In response to the increased demand for pre-inoculated tomato seedlings from tomato growers, a large-scale spray inoculation technology was developed (Nagai and Takeuchi 1979).

In the 1970s, tomato cultivars harboring the resistance gene *Tm-1* were introduced and cultivated. However, ToMV strains that overcame the resistance were soon found throughout Japan (Noba and Kishi 1979). Because L_{11}A was a derivative of ToMV-L, which was unable to overcome *Tm-1*, L_{11}A was inapplicable for these cultivars. Oshima et al. (1978) conducted repeated inoculation of L_{11}A into *Tm-1* tomato plants and obtained ToMV-L_{11}A237, which multiplies faster than L_{11}A in these plants. L_{11}A237 exhibited much greater protection efficiency than L_{11}A in tomato cultivars with *Tm-1* against challenge inoculation with a virulent *Tm-1* resistance-breaking isolate or natural infection of ToMV in field-grown tomatoes.

L_{11}A was provided to tomato growers and achieved good results in various regions of Japan. Over time, isolates used in Chiba, Akita, and Fukushima Prefectures were observed to have different levels of protection efficiency. L_{11}A-Fukushima was superior, particularly during summer at high temperatures (Matsumoto et al. 1998). L_{11}A-Fukushima accumulation in infected tissues was 2–3-fold higher than that of L_{11}A, which may account for its higher protection efficiency (Matsumoto et al. 2002).

Molecular characterization of attenuated strains

Comparisons of the complete nucleotide sequences of ToMV-L and L_{11}A identified 10 nucleotide substitutions, among which three cause amino acid substitutions in the replication protein (Nishiguchi et al. 1985). Because the first substitution (G1117 to A causing a Cys349 to Tyr substitution in the replication protein) was shared with L_{11}, it was expected to be responsible for symptom attenuation. Around the same time, the reverse genetics system of ToMV was developed, and tomato and tobacco plants inoculated with infectious transcripts from cloned cDNA of ToMV-L and L_{11}A reproduced symptoms similar to those of each parental isolate (Meshi et al. 1986).

The importance of RNA silencing and its suppression by viral suppressors in virus infection has been well established (Jin et al. 2021). Using transgenic tobacco in which green fluorescent protein (GFP) gene expression was spontaneously silenced, ToMV-L infection was shown to suppress GFP silencing, whereas L_{11}A had much weaker suppression activity. A GFP agroinfiltration assay in *N.*

benthamiana identified the 130-kDa protein of ToMV as an RNA silencing suppressor, and showed that the Cys349 to Tyr substitution in the 130-kDa protein is involved in symptom attenuation and deficiency in silencing suppression (Kubota et al. 2003). Thus, the deficient RNA silencing suppression of attenuated tobamovirus strains may explain the observed reduction in virus titer and symptom attenuation. RNA silencing also plays an important role in formation of mosaic symptoms in tobacco by ToMV infection, defining the marginal regions of dark green tissues in a mosaic leaf (Hirai et al. 2008).

Introducing the same mutation into another tobamovirus, pepper mild mottle virus (PMMoV) produced similar attenuated phenotypes (Tsuda et al. 2007). Other amino acid substitutions responsible for symptom attenuation were found also in the replication proteins of tobamoviruses including TMV (Lewandowski and Dawson 1993), ToMV-L_{11}A-Fukushima (Yamamoto et al. 2002), PMMoV (Hagiwara et al. 2002; Ichiki et al. 2005), and cucumber green mottle mosaic virus (CGMMV) (Ali et al. 2016) (Table 1).

Two mutually nonexclusive molecular mechanisms have been proposed for symptom attenuation by amino acid substitutions in the replication proteins of tobamoviruses. Tobamovirus replication proteins bind the small RNA duplex and have been suggested to inhibit formation of the RNA-induced silencing complex (Csorba et al. 2007; Kurihara et al. 2007). Replication proteins of an attenuated strain of CGMMV, CGMMV-SH33b that have the Glu480 to Gly, Ala1124 to Val, Asn1157 to Asp, and Pro1397 to Ser substitutions, exhibited an impaired activity to bind siRNAs (Chen et al. 2020). In contrast, the Cys349 to Tyr substitution alters the subcellular localization of ToMV replication proteins, such that replication proteins of L_{11} tend to be membrane-bound, which causes a shortage of replication proteins in the soluble fraction. The ability to bind the small RNA duplex of a soluble replication protein is similar between mutant and wild-type proteins. Based on this observation, it was proposed that soluble replication protein acts as an RNA silencing suppressor and that mutation affects RNA silencing suppressor activity through a reduction in soluble replication proteins (Hagiwara-Komoda et al. 2008).

Serial inoculation of two ToMV variants tagged with different fluorescent proteins into tobacco protoplasts combined with a mathematical model revealed that a 2 h interval was sufficient for protection against a challenge-inoculated virus and that the occupation of possible replication sites by the pre-inoculated virus in each cell could be a mechanism for cross-protection (Miyashita et al. 2015).

Expanding development and use of attenuated strains

Following the successful application of L_{11}A for the control of tomato mosaic disease, a similar attenuated strain was developed in the Netherlands, through nitrous acid treatment of a virulent TMV strain (Rast 1972). The attenuated virus, MII-16, was widely used in the Netherlands and the UK (Fletcher and Rowe 1975; Rast 1975). In Japan, three attenuated strains of PMMoV, PMMoV-C-1421, Pa18, and TPO-2–19, were obtained independently through heat treatment or natural selection from field-grown pepper plants and showed good protection ability (Goto et al. 1997, 1984; Nagai 1987). Mosaic symptoms and fruit abnormalities in muskmelon plants caused by CGMMV were controlled by the attenuated strain CGMMV-SH33b, which was developed from virulent strain CGMMV-SH through nitrous acid treatment and ultraviolet light irradiation (Motoyoshi and Nishiguchi 1988).

Recent control of tomato mosaic diseases has largely depended on resistant tomato varieties harboring the *Tm-2*^{2} gene; however, occurrences of ToMV with *Tm-2*^{2}-breaking ability have continued in Japan (Kubota 2016; Kuroiwa et al. 2022), and *Tm-2*^{2}-insensitive tobamoviruses have spread worldwide. Moreover, some tomato growers cannot obtain resistant varieties. Therefore, it is likely that the control of viral diseases using attenuated strains is still useful, and the development of superior isolates and new application methods should continue. Recently, L_{11}A was also applied to control tobamovirus diseases in the Chinese lantern plant (*Physalis alkekengi*) (Yoneda et al. 2019).

Table 1 Amino acid substitutions in the replication proteins of attenuated strains of tobamoviruses

Strain	Substitutions	Isolation method
ToMV-L_{11}A	Cys349 to Tyr, Asn760 to Asp, Gly895 to Arg	Heating
ToMV-L_{11}A-Fukushima	Val633 to Ile, Asn760 to Asp, Gly895 to Arg	Spontaneous from L_{11}A
TMV-V36	Ser643 to Phe	Freezing
PMMoV-C1421	Val649 to Ala	Heating
PMMoV-Pa18	Val556 to Thr, Ser760 to Leu	Heating
PMMoV-TPO-2–19	Val556 to Thr, Ser760 to Leu	Natural isolate
CGMMV-SH33b	Glu480 to Gly, Ala1124 to Val, Asn1157 to Asp, Pro1397 to Ser	Nitrous acid, ultraviolet light

Genetic resistance against tobamoviruses

Plants have developed defense systems against diverse pathogens. Any single gene responsible for resistance to specific pathogens is termed a resistance gene. Resistance genes are either dominant or recessive; most dominant resistance genes encode similar proteins containing nucleotide-binding site and leucine-rich repeats (NB-LRR) (de Ronde et al. 2014). An NB-LRR protein elicits a strong defense reaction that often accompanies hypersensitive cell death upon the recognition of a pathogen infection. Recessive resistance genes encode loss-of-function alleles of host susceptibility genes, which are required for pathogen infection (Garcia-Ruiz 2018; Hashimoto et al. 2016). Two dominant resistance genes against tobamoviruses have been identified and introduced into tomato cultivars (Pelham 1966).

Tm-1

Tm-1 is an atypical resistance gene encoding a conserved but uncharacterized protein that binds ToMV replication proteins and inhibits viral RNA replication (Ishibashi et al. 2007; Ishibashi and Ishikawa 2014). Upon binding to replication proteins, Tm-1 inhibits the formation of the ToMV replication complex on host intracellular membranes before negative-strand RNA synthesis (Ishibashi and Ishikawa 2013). A *Tm-1* allele from ToMV-susceptible tomato plants, *tm-1*, inhibits the replication of tobamoviruses that are not adapted to tomato plants (Ishibashi et al. 2009), suggesting that ToMV has adapted to tomato plants through escape from the antiviral protein tm-1. *Tm-1* was derived from the wild tomato species *Solanum habrochaites*. Molecular evolutionary analyses of *Tm-1* alleles in *S. habrochaites* have suggested that a small part of *Tm-1* (encoding the 79th to 112th amino acid residues) is under positive selection, which constitutes an interface of protein–protein interaction with ToMV replication proteins in a crystal structure (Ishibashi et al. 2012, 2014). These findings suggest that *Tm-1* has evolved under the selective pressure of ToMV infection in *S. habrochaites*.

ToMV mutants capable of overcoming *Tm-1* emerged soon after the introduction of the gene into tomato cultivars (Pelham et al. 1970). Key amino acid residues of the resistance-breaking ToMV mutants were identified in the helicase domain of the replication proteins (Meshi et al. 1988; Strasser and Pfitzner 2007). These residues are exposed on the surface of the protein, where Tm-1 binds (Ishibashi et al. 2014; Nishikiori et al. 2012). Amino acid substitutions found in the resistance-breaking mutants weaken the affinity to Tm-1 (Ishibashi et al. 2007, 2014), which explains how ToMV escapes recognition by Tm-1 to break resistance. The conventionally used *Tm-1* gene encodes Ile at the 91st residue, whereas *Tm-1* alleles in several *S. habrochaites* accessions encode Thr. The Tm-1 variant with Thr91 exhibits stronger activity sufficiently inhibiting the RNA replication of a resistance-breaking ToMV mutant (Ishibashi et al. 2012). Thus, *Tm-1* alleles with Thr91 may be a potential source for resistance breeding.

Tm-2

The *Tm-2* locus on chromosome 9 has the dominant ToMV-resistance alleles *Tm-2* and *Tm-2*^{2}, and the recessive ToMV-susceptible allele *tm-2*. *Tm-2* and *Tm-2*^{2} are derived from *Solanum peruvianum* and encode coiled-coil–NB-LRR proteins with four amino acid differences (Lanfermeijer et al. 2003, 2005). Although ToMV infection generally does not induce a hypersensitive reaction in *Tm-2* or *Tm-2*^{2} tomato plants, Tm-2 and Tm-2^2 induce cell death when transiently coexpressed with ToMV MP (Kobayashi et al. 2011). Similarly, systemic necrosis is often induced when *Tm-2*^{2} scion/rootstock is grafted with ToMV-susceptible or *Tm-1* rootstock/scions. Tm-2^2 protein localizes to the plasma membrane and is activated through self-association via the coiled-coil domain upon the recognition of ToMV MP (Chen et al. 2017; Wang et al. 2020).

Tm-2 and *Tm-2*^{2} have different resistance spectra; *Tm-2*-resistance-breaking ToMV mutants do not overcome *Tm-2*^{2} resistance and vice versa. The MP of *Tm-2* resistance-breaking mutants ToMV-B7 has the Cys68 to Phe and Glu133 to Lys substitutions and ToMV1-2 has Glu52 to Lys and Glu133 to Lys (Meshi et al. 1989; Strasser and Pfitzner 2007), whereas the MP of *Tm-2*^{2}-breaking ToMV-N3 has the Ser238 to Arg and Lys244 to Glu substitutions and ToMV-KMT has Asp240 to Tyr (Kuroiwa et al. 2022; Weber et al. 1993). The emergence of *Tm-2*^{2}-breaking ToMV mutants is sporadic, and *Tm-2*^{2} has long been used to protect tomato plants from ToMV.

Emerging tobamoviruses in tomato crops

Tobamovirus disease in tomato plants has been controlled for more than 40 years, since the introduction of resistant varieties harboring *Tm-2*^{2}. However, new tobamoviruses that affect *Tm-2*^{2} tomatoes have emerged and have caused outbreaks worldwide.

ToMMV

ToMMV was first identified in Mexico (Li et al. 2013) and subsequently reported in the USA (Webster et al. 2014),

Israel (Turina et al. 2016), Spain (Ambrós et al. 2017), China (Li et al. 2017), and Australia (Lovelock et al. 2020). Recent studies have revealed that ToMMV had been present in Brazil since 1992 (Nagai et al. 2018) and was widespread in Europe before 2007 (Schoen et al. 2023). ToMMV-infected tomato plants show leaf distortion, mottling, and necrosis. ToMMV multiplication is strongly suppressed in *Tm-2*^{2}/*Tm-2*^{2} homozygous plants and *Tm-2*^{2}/*Tm-2* heterozygous plants, but it can infect *Tm-2*^{2}/*tm-2* heterozygous tomato plants (Tettey et al. 2023), suggesting that differences in the expression levels of resistant alleles that weakly recognize ToMMV MP may be a determinant of susceptibility to the virus. Because many ToMV-resistant commercial tomato cultivars are *Tm-2*^{2}/*tm-2* heterozygotes, ToMMV can infect these plants to produce symptoms (Nagai et al. 2019).

Tomato brown rugose fruit virus (ToBRFV)

Another emerging tobamovirus, tomato brown rugose fruit virus (ToBRFV), was recently identified in Jordan and Israel (Luria et al. 2017; Salem et al. 2016) (Fig. 4). ToBRFV has caused devastating disease outbreaks, even pandemics, and is currently considered the most serious threat to tomato production worldwide (Salem et al. 2023; Zhang et al. 2022). ToBRFV multiplication is not affected in *Tm-2*^{2}/*Tm-2*^{2} homozygous plants (Hak and Spiegelman 2021). Key amino acid residues in ToBRFV MP for escape from recognition by *Tm-2*^{2} have been identified (Yan et al. 2021b). Interestingly, ToBRFV MP is less functional for viral cell-to-cell transport than TMV MP (Hak and Spiegelman 2021), suggesting that the possible evolution of ToBRFV via adaptation to *Tm-2*^{2} tomato plants may have been associated with a fitness cost.

ToBRFV has been reported in European countries including Albania (Orfanidou et al. 2022), France (Skelton et al. 2022), Germany (Menzel et al. 2019), Greece (Beris et al. 2020), Italy (Panno et al. 2019), the Netherlands (van de Vossenberg et al. 2020), Norway (Hamborg and Blystad 2022), Slovenia (Vučurović et al. 2022), Spain (Alfaro-Fernández et al. 2021), Switzerland (Mahillon et al. 2022), and the UK (Skelton et al. 2019). Cases have also been confirmed in Central America and North America, including Canada (Sarkes et al. 2020), Mexico (Camacho-Beltrán et al. 2019), and the USA (Ling et al. 2019). ToBRFV has even reached countries in Asia, including China (Yan et al. 2019), Iran (Ghorbani et al. 2021), Lebanon (Abou Kubaa et al. 2022), Saudi Arabia (Sabra et al. 2022), Syria (Hasan et al. 2022), and Turkey (Fidan et al. 2019). Temporary ToBRFV infections have also been reported in several countries (https://gd.eppo.int/taxon/ToBRFV/distribution). ToBRFV genomes obtained from samples collected around the world show very limited sequence diversity (Abrahamian et al.

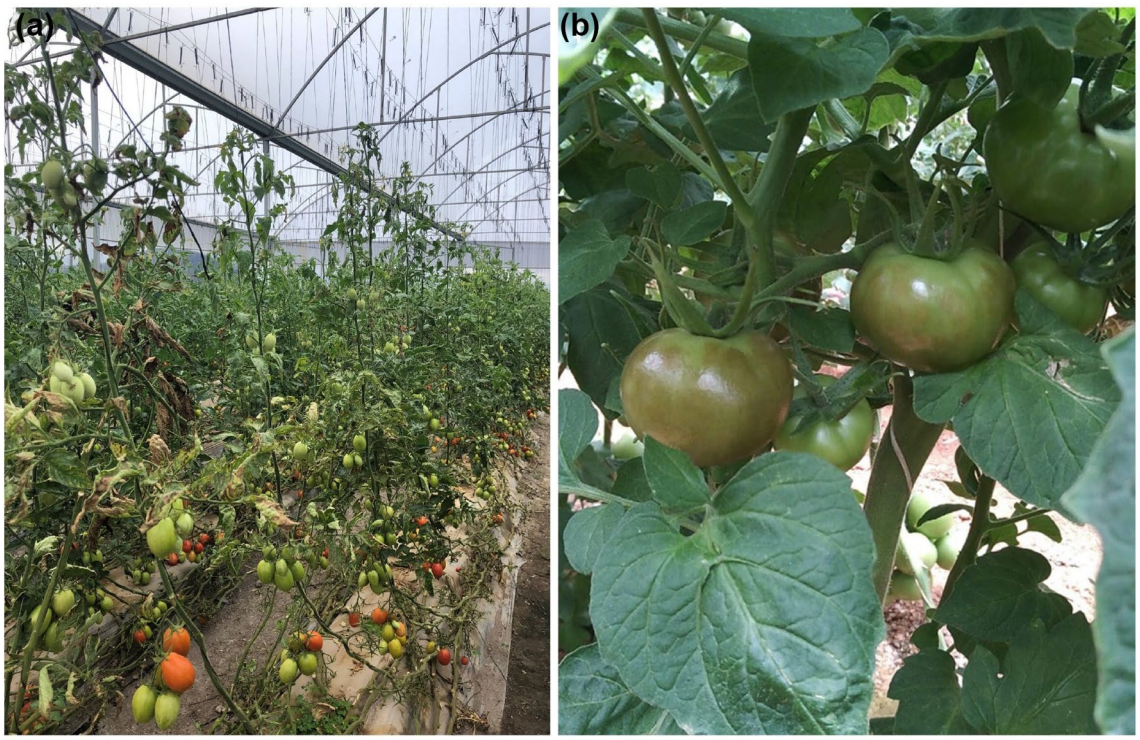

Fig. 4 **a** Tomato brown rugose fruit virus (ToBRFV)-infected greenhouse tomato plants in Mexico. **b** Fruits of ToBRFV-infected tomato plants in Turkey

2022; Çelik et al. 2022), supporting its recent emergence and rapid spread from a single origin.

ToBRFV detection and quarantine of infected plants

The global spread of tobamoviruses including ToBRFV and ToMMV, is thought to occur through untreated or inadequately disinfected contaminated seeds (Dombrovsky et al. 2017). Studies have demonstrated that seeds obtained from plants infected with ToBRFV are indeed contaminated (Davino et al. 2020; Salem et al. 2022). Due to the significant threat posed by ToBRFV to global tomato cultivation, several countries have implemented national seed quarantine systems. For example, the USA issued a federal order regarding the importation and inspection of tomato seeds (https://www.aphis.usda.gov/aphis/ourfocus/planthealth/import-information/federal-import-orders/tobrfv/tomato-brown-rugose-fruit-virus), and the European Union declared a quarantine issue for ToBRFV-infected plants (http://data.europa.eu/eli/reg_impl/2020/1191/oj). Consequently, research institutions and corporations worldwide are actively working to develop rapid detection methods and highly accurate identification techniques for the virus. An increased cost associated with disinfection and phytosanitary measures is another, often overlooked problem associated with the global spread of ToBRFV (Zhang et al. 2022).

Quantitative RT-PCR (qRT-PCR) has emerged as a widely used RNA-based approach for ToBRFV detection. This technique involves converting the viral RNA into complementary DNA (cDNA) through reverse transcription, followed by amplification and quantification using PCR. Numerous primer pairs, probes, and protocols have been developed for this purpose (Caruso et al. 2022). Various advancements in RT-PCR methodology have improved ToBRFV detection capabilities of these techniques (Salem et al. 2023). In particular, multiplex RT-PCR simultaneously detects multiple viruses that may induce similar symptoms in tomato plants, including ToBRFV and other tobamoviruses such as TMV, ToMV, and ToMMV. For example, Yan et al. (2021a) and Tiberini et al. (2022) have developed RT-PCR primers for the efficient simultaneous detection of these tobamoviruses. This multiplexing capability offers a significant advantage in screening and surveillance programs, where multiple viral pathogens must be monitored concurrently.

Another effective method for detecting ToBRFV is the enzyme-linked immunosorbent assay (ELISA) and its variants. ELISA utilizes specific antibodies that bind to viral proteins, allowing the identification and quantification of ToBRFV (Bernabé-Orts et al. 2021). Many reputable commercial providers offer antisera and kits specifically designed for ELISA-based ToBRFV detection. Immunostrips are also available for lateral flow assays for ToBRFV detection. Importantly, these assays may exhibit cross-reactivity with other tobamoviruses such as TMV, ToMV, and ToMMV. However, despite these limitations, the immunostrip method provides rapid, field-deployable assays that deliver results within minutes.

In addition to RT-PCR and ELISA, researchers have explored other innovative techniques for ToBRFV detection. For example, digital droplet PCR (ddPCR) offers increased precision and sensitivity compared to conventional PCR (Vargas-Hernández et al. 2022). This technique partitions the PCR reaction into thousands of individual droplets, allowing for absolute quantification of the target viral RNA molecules. CRISPR-Cas12a is also employed for ToBRFV detection (Alon et al. 2021; Bernabé-Orts et al. 2022). The combination of these and other emerging technologies will facilitate the effective management of evolving tobamoviruses.

In addition to mechanical and seed transmission, tomato fruits and bumblebees may be involved in the spread of ToBRFV (Klap et al. 2020; Levitzky et al. 2019). Addressing potential transmission routes and implementing appropriate measures are essential for safeguarding global tomato cultivation from the threats posed by ToBRFV and other tobamoviruses.

Exploring new resistance resources for ToBRFV

As ToBRFV overcomes *Tm-2*^{2} resistance, the exploration of new genetic resources against ToBRFV is urgently needed. Screening of germplasm resources of cultivated or wild tomato plants for ToBRFV-resistant and tolerant lines has been conducted through inoculation tests (Jewehan et al. 2022a, b; Kabas et al. 2022; Zinger et al. 2021). Various research institutes and seed companies have identified quantitative trait loci (QTLs) and filed patents according to their findings (Ashkenazi et al. 2018, 2020; Hamelink et al. 2019; Kopeliovitch and Gilan 2022; Millenaar et al. 2021). Although some QTLs have been mapped to common chromosomal locations, it remains unclear whether they represent the same allele, different alleles, or adjacent but different genes. Unique resistance genes have also been identified. For example, Ykema et al. (2021) identified a locus from *S. habrochaites* on chromosome 8 encoding an NB-LRR protein. Kalisvaart et al. (2022) introgressed a ToBRFV resistance trait from *S. pimpinellifolium* to *S. lycopersicum* (Hamelink et al. 2019), and identified a QTL region on chromosome 8, along with the most likely candidate gene, *TOM2A*, which is a homolog of a tobamovirus susceptibility gene identified in *Arabidopsis thaliana* (Fujisaki et al. 2008; Tsujimoto et al. 2003). Interestingly, mutated *TOM2A* homologs were also identified as recessive resistance genes for TMV in *N. tabacum*, and artificial knockout of a *TOM2A*

homolog in tomato plants was found to confer resistance to both ToMV and TMV (Hu et al. 2021).

Newly identified genetic materials hold promise as novel sources of ToBRFV resistance and can be utilized in resistance breeding programs. Although claims by various seed companies that trial F_1 tomato plant varieties show resistance to ToBRFV are a positive development for farmers and consumers, excessive patent protection could deviate from their original purpose of addressing the threat of ToBRFV. A balanced approach is needed to ensure that these patents do not strongly hinder new entrants in the field, allowing for the wider dissemination and utilization of ToBRFV-resistant varieties to mitigate the impact of the virus.

As observed in ToMV resistance genes (Cirulli and Ciccarese 1975; Fraser and Loughlin 1982), the new resistant materials may allow increased accumulation of ToBRFV under high-temperature conditions (Jewehan et al. 2022b). The emergence of resistance-breaking mutants is also a concern in the production of resistant varieties. Therefore, sustainable tomato cultivation may require the continuous introduction and screening of new breeding materials.

Genetic engineering of tomato plants for tobamovirus resistance

Biotechnological achievements using transgenic or gene editing technologies include numerous virus-resistant plants. We describe various attempts to develop tobamovirus-resistant tomato plants.

Pathogen-derived resistance

The transgenic expression of parts of viral genomes in plants confers resistance against corresponding viruses. This phenomenon, called pathogen-derived resistance, was first reported by Beachy and colleagues in a TMV–tobacco system (Abel et al. 1986), and found to be applicable to many plant–virus combinations. Nelson et al. (1988) demonstrated that the transgenic expression of TMV CP conferred resistance to TMV and ToMV in tomato plants, and caused no significant yield loss under greenhouse or field conditions; because resistance was positively correlated with CP expression levels, the presence of the CP prior to infection would have perturbed the TMV and ToMV multiplication. However, the expression of non-translatable versions of viral CP mRNA can also induce resistance to the corresponding virus (Lindbo and Dougherty 1992). Further analyses have revealed that post-transcriptional gene silencing occurred in this and many other cases (Waterhouse et al. 1999). Irrespective of the underlying mechanisms, pathogen-derived resistance is useful for protecting crops from viral diseases (Khalid et al. 2017; Lindbo and Falk 2017).

Engineering resistance genes

Engineering existing resistance genes is also promising. Transgenic introduction of the TMV resistance gene *N* from tobacco into tomato confers resistance to TMV, ToMV, and youcai mosaic virus (YoMV) (Whitham et al. 1996). Spiegelman et al. (2022) established a screening system for *Tm-2*^{2} variants that recognized ToBRFV MP and identified three single-nucleotide mutations that allowed the *Tm-2*^{2} gene product to induce resistance against ToBRFV infection. Lindbo (2022) also found that variants or mutants with substitutions in the LRR domain of the Tm-2^2 protein could recognize or bind to the MP of various tobamoviruses, including TMV, ToMV, ToMMV, and ToBRFV. Using molecular docking, in silico 3D structure prediction, and computational affinity methods, Rivera-Márquez et al. (2022) also identified potential amino acid substitutions in Tm-2^2 that conferred resistance to ToBRFV. These engineered *Tm-2*^{2} variants may be used as transgenic or gene-edited plants through targeted mutagenesis of the endogenous gene.

Disruption of susceptibility genes

Genetic engineering for virus resistance can also be achieved through the manipulation of host susceptibility genes that are utilized by viruses for their multiplication. The development of CRISPR-Cas9-mediated gene editing technology has greatly facilitated targeted gene disruption. Host multi-pass transmembrane proteins TOM1 (Yamanaka et al. 2000) and TOM2A (Tsujimoto et al. 2003), and the membrane-associated small GTP-binding protein ARL8 (Nishikiori et al. 2011) are required for efficient tobamovirus multiplication. In *A. thaliana*, the TOM1 protein is encoded by *AtTOM1* and its two homologs, *AtTOM3* and *AtTHH1*. The ARL8 protein is encoded by three homologous genes, *AtARL8a*, *AtARL8b*, and *AtARL8c*. Simultaneous knockout of *AtTOM1* and *AtTOM3* confers strong resistance to tobamoviruses including YoMV and ToMV without appreciable growth defects (Fujisaki et al. 2006; Yamanaka et al. 2002). Similarly, the simultaneous knockout of *AtARL8a* and *AtARL8b* leads to strong tobamovirus resistance with no negative impact on plant vigor (Nishikiori et al. 2011). Knockout of the *TOM2A* gene in *A. thaliana* (*AtTOM2A*) confers resistance to YoMV but has little effect on ToMV multiplication. In either case, the mutant plants are fully susceptible to cucumber mosaic virus of the genus *Cucumovirus*. TOM1 and ARL8 proteins interact with each other and with tobamovirus replication proteins (Nishikiori et al. 2011). TOM1 protein also interacts with TOM2A protein (Tsujimoto et al. 2003). Further analyses have suggested that TOM1 and ARL8 proteins are necessary to activate an enzymatic activity in tobamovirus replication proteins, without which tobamovirus negative-strand RNA synthesis does not occur (Nishikiori et al. 2011).

The tomato genome contains five putative genes that encode proteins with significant amino acid sequence similarity to AtTOM1. These genes have been named differently in three different studies (Ali et al. 2018; Ishikawa et al. 2022; Kravchik et al. 2022) as summarized in Table 2. In this review, we follow the nomenclature of Ishikawa et al. (2022). Among *SlTOM1* genes, the expression levels of *SlTOM1e* are very low. Ali et al. (2018) knocked down *SlTOM1a*, *SlTOM1b*, or *SlTOM1c* genes by expressing inverted repeat RNA of the coding sequences of each gene in the tomato cultivar 'Micro-Tom', and found that these plants showed resistance to ToMV. Tobamovirus-resistant plants developed using this method as well as pathogen-derived resistance are regulated under genetically modified organism legislation, restricting their practical use in many countries.

Ishikawa et al. (2022) knocked out the genes *SlTOM1a–d* using the CRISPR-Cas9 system in tomato cultivar 'GCR26', which is susceptible to ToMV and ToBRFV, and constructed mutant lines carrying homozygous single or multiple *Sltom1* mutations in all combinations. In *Sltom1* single or double mutants, ToMV and ToBRFV CPs accumulated to levels similar to or only slightly lower than those of wild-type non-transgenic plants. In *Sltom1* triple mutant plants, ToMV and ToBRFV CPs accumulated more slowly than in wild-type plants. Neither ToBRFV or ToMV CP accumulation nor disease symptoms were observed in *Sltom1* quadruple-mutant plants, suggesting that the four *SlTOM1* genes contribute in parallel to ToMV and ToBRFV multiplication, in the order $SlTOM1a \geq SlTOM1c > SlTOM1d > SlTOM1b$. In ToBRFV-inoculated *Sltom1acd* triple mutant plants, which showed the strongest resistance among *Sltom1* triple mutants, ToBRFV mutants emerged with more efficient multiplication than wild-type ToBRFV; however, the mutant ToBRFV was unable to multiply in *Sltom1* quadruple mutant tomato plants. Tobamovirus mutants that can multiply in *Sltom1* quadruple mutant plants have not yet emerged, which suggests that this resistance is durable. Loss of *TOM1* function inhibits tobamovirus RNA synthesis, which may help minimize the risk of emergence of mutant viruses that can overcome resistance by the *Sltom1* quadruple mutant. Thus, knockout of the four *SlTOM1* genes is a promising strategy for protecting tomato plants from ToBRFV and other tobamoviruses.

Kravchik et al. (2022) knocked out *SlTOM1a*, *SlTOM1b*, and *SlTOM1c* in tomato cultivar 'M82' using the CRISPR-Cas9 system, and constructed *Sltom1ac* double and *Sltom1abc* triple mutant plants. They found that ToBRFV CP accumulated more slowly in both mutants than in the wild-type plants. ToMV CP accumulation was delayed in the triple mutant plants but not in the double mutant plants. These results are consistent with those of Ishikawa et al. (2022), with minor discrepancies that may have arisen from genetic background differences ('GCR26' vs. 'M82') and/or the conditions of virus multiplication assays.

Recently, Hu et al. (2021) knocked out a tomato homolog of *AtTOM2A* and showed that the plant was resistant to TMV and ToMV. Susceptibility of the *Sltom2a* mutant tomato to ToBRFV has not been reported. The tomato genome contains three genes with significant amino acid sequence similarity to *AtARL8a* and *AtARL8b* (Kravchik et al. 2022). Knockdown or knockout of these genes may also confer resistance against ToBRFV and other tobamoviruses.

Following the development of the GABA-enriched tomato (Waltz 2021), virus-resistant plants created using gene editing technologies are expected to be cultivatable beyond the reach of genetically modified organism legislation in several countries (Tripathi et al. 2020). However, loss-of-function mutations can be generated by other methods such as classical mutagenesis using chemical mutagens, followed by the screening of desired mutants by TILLING or high-throughput sequencing (Henikoff et al. 2004; Rigola et al. 2009). ToBRFV-resistant tomato lines established by these methods could be cultivated globally without any restrictions.

Table 2 Nomenclature of *TOM1* homologs in tomato

SGN* gene ID	GenBank ID	NCBI** Reference Sequence ID	Ali et al. (2018)	Ishikawa et al. (2022)	Kravchik et al. (2022)
Solyc04g008540	AB193041	NP_001234096.1	*LeTH1*	*SlTOM1a*	*SlTOM3*
Solyc01g105270	AB193042	NP_001234100.1	*LeTH2*	*SlTOM1b*	*SlTOM1b*
Solyc02g080370	AB193043	NP_001234306.1	*LeTH3*	*SlTOM1c*	*SlTOM1a*
Solyc01g007900		XP_010315372.1		*SlTOM1d*	*SlTOM1c*
Solyc09g005240				*SlTOM1e*	

*Solanaceae Genomics Network (https://solgenomics.net/)

**National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/)

Conclusions

Tomato plants are cultivated worldwide, and tobamoviruses are found wherever tomatoes are grown. Before the 1970s, approximately 20% of global tomato production was lost by ToMV (Broadbent 1976). Successful resistance breeding with *Tm-2*^{2} has markedly reduced the damage caused by ToMV, such that it is no longer a concern. However, the emergence and subsequent outbreaks of ToMMV and ToBRFV have demonstrated that the arms race between tomato plant cultivation and tobamoviruses has been ongoing. From a virological perspective, the emergence and subsequent spread of ToBRFV, and similarly of SARS-CoV-2, during the high-throughput sequencing era has provided unique opportunities for improving our understanding of viral ecology and epidemiology. The fact that a host susceptibility gene identified in *A. thaliana* ~ 20 years ago is useful for constructing newly emerged tobamovirus-resistant tomato plants highlights the importance of basic research for plant protection. Further understanding of virus–host interactions will provide new tools to combat viruses that may emerge in the future.

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Declarations

Conflict of interest A.K. is employed by Takii and Company, Limited. K.I., A.K., and M.I. are named as inventors on a patent application related to *Sltom1*-knockout tomato plants (JP6810946B1).

References

Abel PP, Nelson RS, De B, Hoffmann N, Rogers SG, Fraley RT, Beachy RN (1986) Delay of disease development in transgenic plants that express the tobacco mosaic virus coat protein gene. Science 232:738–743. https://doi.org/10.1126/science.3457472

Abou Kubaa R, Choueiri E, Heinoun K, Cillo F, Saponari M (2022) First report of tomato brown rugose fruit virus infecting sweet pepper in Syria and Lebanon. J Plant Pathol 104:425. https://doi.org/10.1007/s42161-021-00987-y

Abrahamian P, Cai W, Nunziata SO, Ling K-S, Jaiswal N, Mavrodieva VA, Rivera Y, Nakhla MK (2022) Comparative analysis of tomato brown rugose fruit virus isolates shows limited genetic diversity. Viruses 14:2816. https://doi.org/10.3390/v14122816

Ainsworth G (1933) An investigation of tomato virus diseases of the mosaic "stripe", streak group. Ann Appl Biol 20:421–428

Ainsworth G, Berkeley G, Caldwell J (1934) A comparison of English and Canadian tomato virus diseases. Ann Appl Biol 21:566–580

Alexander LJ, Campbell RE (1959) Concentration of tobacco mosaic virus in tomato plants throughout the growing season of two glasshouse crops and a field crop. Ohio J Sci 59:271–280

Alfaro-Fernández A, Castillo P, Sanahuja E, Rodríguez-Salido MC, Font MI (2021) First report of tomato brown rugose fruit virus in tomato in Spain. Plant Dis 105:515. https://doi.org/10.1094/PDIS-06-20-1251-PDN

Ali ME, Waliullah S, Nishiguchi M (2016) Molecular analysis of an attenuated strain of *Cucumber green mottle mosaic virus* using in vitro infectious cDNA clone: pathogenicity and suppression of RNA silencing. J Plant Biochem Biotechnol 25:79–86. https://doi.org/10.1007/s13562-015-0312-z

Ali ME, Ishii Y, Taniguchi J, Waliullah S, Kobayashi K, Yaeno T, Yamaoka N, Nishiguchi M (2018) Conferring virus resistance in tomato by independent RNA silencing of three tomato homologs of *Arabidopsis TOM1*. Arch Virol 163:1357–1362. https://doi.org/10.1007/s00705-018-3747-4

Alon DM, Hak H, Bornstein M, Pines G, Spiegelman Z (2021) Differential detection of the tobamoviruses tomato mosaic virus (ToMV) and tomato brown rugose fruit virus (ToBRFV) using CRISPR-Cas12a. Plants 10:1256. https://doi.org/10.3390/plants10061256

Ambrós S, Martínez F, Ivars P, Hernández C, de la Iglesia F, Elena SF (2017) Molecular and biological characterization of an isolate of *Tomato mottle mosaic virus* (ToMMV) infecting tomato and other experimental hosts in eastern Spain. Eur J Plant Pathol 149:261–268. https://doi.org/10.1007/s10658-017-1180-2

Aoki H, Ogiwara S (1974) Studies on control of tobacco mosaic virus by interference of attenuated virus on greenhouse tomatoes (in Japanese). Bull Chiba Agric Exp Stn 14:135–143

Ashkenazi V, Rotem Y, Ecker R, Nashilevitz S, Barom N (2018) Tolerance in plants of *Solanum lycopersicum* to the tobamovirus tomato brown rugose fruit virus (TBRFV). EP3409106A1, 5 December 2018

Ashkenazi V, Rotem Y, Ecker R, Nashilevitz S, Barom N (2020) Resistance in plants of solanum lycopersicum to the tobamovirus tomato brown rugose fruit virus. WO2020249996A1, 17 December 2020

Beijerinck M (1898) Über ein contagium vivum fluidum als Ursache der Fleckenkrankheit der Tabaksblätter. Verh Kon Akad Wetensch 5:3–21 [English translation published in 1942: Concerning a contagium vivum fluidum as cause of the spot disease of tobacco leaves. Phytopathol Classics 7:33–52]

Beris D, Malandraki I, Kektsidou O, Theologidis I, Vassilakos N, Varveri C (2020) First report of tomato brown rugose fruit virus infecting tomato in Greece. Plant Dis 104:2035. https://doi.org/10.1094/PDIS-01-20-0212-PDN

Bernabé-Orts JM, Torre C, Méndez-López E, Hernando Y, Aranda MA (2021) New resources for the specific and sensitive detection of the emerging tomato brown rugose fruit virus. Viruses 13:1680. https://doi.org/10.3390/v13091680

Bernabé-Orts JM, Hernando Y, Aranda MA (2022) Toward a CRISPR-based point-of-care test for tomato brown rugose fruit virus detection. PhytoFrontiers 2:92–100. https://doi.org/10.1094/PHYTOFR-08-21-0053-TA

Boyle JS, Bergman EL (1967) Factors affecting incidence and severity of internal browning of tomato induced by tobacco mosaic virus. Phytopathology 57:354–362

Boyle JS, Wharton DC (1957) The experimental reproduction of tomato internal browning by inoculation with strains of tobacco mosaic virus. Phytopathology 47:199–207

Broadbent L (1962) The epidemiology of tomato mosaic: II. Smoking tobacco as a source of virus. Ann Appl Biol 50:461–466. https://doi.org/10.1111/j.1744-7348.1962.tb06041.x

Broadbent L (1964) The epidemiology of tomato mosaic: VII. The effect of TMV on tomato fruit yield and quality under glass. Ann Appl Biol 54:209–224. https://doi.org/10.1111/j.1744-7348.1964.tb01185.x

Broadbent L (1965a) The epidemiology of tomato mosaic IX. Transmission of TMV by birds. Ann Appl Biol 55:67–69. https://doi.org/10.1111/j.1744-7348.1965.tb07868.x

Broadbent L (1965b) The epidemiology of tomato mosaic XI. Seed-transmission of TMV. Ann Appl Biol 56:177–205. https://doi.org/10.1111/j.1744-7348.1965.tb01227.x

Broadbent L (1976) Epidemiology and control of tomato mosaic virus. Annu Rev Phytopathol 14:75–96. https://doi.org/10.1146/annurev.py.14.090176.000451

Broadbent L, Cooper AJ (1964) The epidemiology of tomato mosaic: VI. The influence of tomato mosaic virus on root growth and the annual pattern of fruit production. Ann Appl Biol 54:31–43. https://doi.org/10.1111/j.1744-7348.1964.tb01168.x

Brunt AA (1986) Tomato mosaic virus. In: Van Regenmortel MHV, Fraenkel-Conrat H (eds) The plant viruses: the rod-shaped plant viruses. Springer, Boston, pp 181–204

CABI (2021) Tomato mosaic virus (tomato mosaic). CABI Compend. https://doi.org/10.1079/cabicompendium.54063

Camacho-Beltrán E, Pérez-Villarreal A, Leyva-López NE, Rodríguez-Negrete EA, Ceniceros-Ojeda EA, Méndez-Lozano J (2019) Occurrence of *Tomato brown rugose fruit virus* infecting tomato crops in Mexico. Plant Dis 103:1440. https://doi.org/10.1094/PDIS-11-18-1974-PDN

Caruso AG, Bertacca S, Parrella G, Rizzo R, Davino S, Panno S (2022) Tomato brown rugose fruit virus: a pathogen that is changing the tomato production worldwide. Ann Appl Biol 181:258–274. https://doi.org/10.1111/aab.12788

Castello JD, Rogers SO, Starmer WT, Catranis CM, Ma L, Bachand GD, Zhao Y, Smith JE (1999) Detection of tomato mosaic tobamovirus RNA in ancient glacial ice. Polar Biol 22:207–212. https://doi.org/10.1007/s003000050411

Çelik A, Coşkan S, Morca AF, Santosa AI, Koolivand D (2022) Insight into population structure and evolutionary analysis of the emerging tomato brown rugose fruit virus. Plants 11:3279. https://doi.org/10.3390/plants11233279

Chen H, Ino M, Shimono M, Wagh SG, Kobayashi K, Yaeno T, Yamaoka N, Bai G, Nishiguchi M (2020) A single amino acid substitution in the intervening region of 129K protein of cucumber green mottle mosaic virus resulted in attenuated symptoms. Phytopathology 110:146–152. https://doi.org/10.1094/PHYTO-12-18-0478-FI

Chen T, Liu D, Niu X, Wang J, Qian L, Han L, Liu N, Zhao J, Hong Y, Liu Y (2017) Antiviral resistance protein Tm-2^2 functions on the plasma membrane. Plant Physiol 173:2399–2410. https://doi.org/10.1104/pp.16.01512

Cirulli M, Ciccarese F (1975) Interactions between TMV isolates, temperature, allelic condition and combination of the Tm resistance genes in tomato. Phytopathol Mediterr 14:100–105

Csorba T, Bovi A, Dalmay T, Burgyán J (2007) The p122 subunit of *Tobacco mosaic virus* replicase is a potent silencing suppressor and compromises both small interfering RNA- and microRNA-mediated pathways. J Virol 81:11768–11780. https://doi.org/10.1128/jvi.01230-07

Davino S, Caruso AG, Bertacca S, Barone S, Panno S (2020) *Tomato brown rugose fruit virus*: seed transmission rate and efficacy of different seed disinfection treatments. Plants 9:1615. https://doi.org/10.3390/plants9111615

de Ronde D, Butterbach P, Kormelink R (2014) Dominant resistance against plant viruses. Front Plant Sci 5:307. https://doi.org/10.3389/fpls.2014.00307

Di Candilo M, Faccioli G, Grassi G, Faeti V (1992) Effect of tomato mosaic virus (ToMV) on yield of machine-harvested processing tomatoes. Phytopathol Mediterr 31:32–36

Ding XS, Liu J, Cheng N-H, Folimonov A, Hou Y-M, Bao Y, Katagi C, Carter SA, Nelson RS (2004) The *Tobacco mosaic virus* 126-kDa protein associated with virus replication and movement suppresses RNA silencing. Mol Plant Microbe Interact 17:583–592. https://doi.org/10.1094/MPMI.2004.17.6.583

Dombrovsky A, Smith E, Dombrovsky A, Smith E (2017) Seed transmission of tobamoviruses: aspects of global disease distribution. In: Advances in seed biology. IntechOpen, pp 233–260

Fidan H, Sarikaya P, Calis O (2019) First report of *Tomato brown rugose fruit virus* on tomato in Turkey. New Dis Rep 39:18. https://doi.org/10.5197/j.2044-0588.2019.039.018

Fletcher JT, Rowe JM (1975) Observations and experiments on the use of an avirulent mutant strain of tobacco mosaic virus as a means of controlling tomato mosaic. Ann Appl Biol 81:171–179. https://doi.org/10.1111/j.1744-7348.1975.tb00533.x

Fraser RSS, Loughlin SAR (1982) Effects of temperature on the *Tm-1* gene for resistance to tobacco mosaic virus in tomato. Physiol Plant Pathol 20:109–117. https://doi.org/10.1016/0048-4059(82)90029-7

Fujisaki K, Ravelo GB, Naito S, Ishikawa M (2006) Involvement of *THH1*, an *Arabidopsis thaliana* homologue of the *TOM1* gene, in tobamovirus multiplication. J Gen Virol 87:2397–2401. https://doi.org/10.1099/vir.0.81942-0

Fujisaki K, Kobayashi S, Tsujimoto Y, Naito S, Ishikawa M (2008) Analysis of tobamovirus multiplication in *Arabidopsis thaliana* mutants defective in *TOM2A* homologues. J Gen Virol 89:1519–1524. https://doi.org/10.1099/vir.0.2008/000539-0

Garcia-Ruiz H (2018) Susceptibility genes to plant viruses. Viruses 10:484. https://doi.org/10.3390/v10090484

Ghorbani A, Rostami M, Seifi S, Izadpanah K (2021) First report of *Tomato brown rugose fruit virus* in greenhouse tomato in Iran. New Dis Rep 44:e12040. https://doi.org/10.1002/ndr2.12040

Goelet P, Lomonossoff GP, Butler PJ, Akam ME, Gait MJ, Karn J (1982) Nucleotide sequence of tobacco mosaic virus RNA. Proc Natl Acad Sci U S A 79:5818–5822. https://doi.org/10.1073/pnas.79.19.5818

Goto H, Itai T, Sato S (1997) Selection of attenuated viruses for control of sweet pepper mosaic disease caused by tobacco mosaic virus pepper strain and cucumber mosaic virus, and their effects (in Japanese with English summary). Bull Oita Prefect Agric Res Cent 27:79–122

Goto T, Nemoto M (1971) Studies on control of plant virus diseases by interference of attenuated virus. Selection of TMV attenuated strain and influence on various plants inoculated with the attenuated strain (in Japanese with English summary). Hokkaido Natl Agric Exp Stn Bull 99:67–76

Goto T, Iizuka N, Komochi S (1984) Selection and utilization of an attenuated isolate of pepper strain of tobacco mosaic virus (in Japanese with English abstract). Jpn J Phytopathol 50:221–228. https://doi.org/10.3186/jjphytopath.50.221

Hagiwara K, Ichiki TU, Ogawa Y, Omura T, Tsuda S (2002) A single amino acid substitution in 126-kDa protein of *Pepper mild mottle virus* associates with symptom attenuation in pepper; the complete nucleotide sequence of an attenuated strain, C-1421. Arch Virol 147:833–840. https://doi.org/10.1007/s007050200030

Hagiwara-Komoda Y, Hirai K, Mochizuki A, Nishiguchi M, Meshi T, Ishikawa M (2008) Overexpression of a host factor TOM1 inhibits tomato mosaic virus propagation and suppression of RNA silencing. Virology 376:132–139. https://doi.org/10.1016/j.virol.2008.03.020

Hak H, Spiegelman Z (2021) The tomato brown rugose fruit virus movement protein overcomes *Tm-2*^{2} resistance in tomato while attenuating viral transport. Mol Plant Microbe Interact 34:1024–1032. https://doi.org/10.1094/MPMI-01-21-0023-R

Hamborg Z, Blystad D-R (2022) First report of tomato brown rugose fruit virus in tomato in Norway. Plant Dis 106:2004. https://doi.org/10.1094/PDIS-10-21-2208-PDN

Hamelink R, Kalisvaart J, Rashidi H (2019) Tbrfv resistant tomato plant. WO2019110130A1, 13 June 2019

Harrison BD, Finch JT, Gibbs AJ, Hollings M, Shepherd RJ, Valenta V, Wetter C (1971) Sixteen groups of plant viruses. Virology 45:356–363. https://doi.org/10.1016/0042-6822(71)90336-9

Hasan ZM, Salem NM, Ismail ID, Akel EH, Ahmad AY (2022) First report of tomato brown rugose fruit virus on greenhouse tomato in Syria. Plant Dis 106:772. https://doi.org/10.1094/PDIS-07-21-1356-PDN

Hashimoto M, Neriya Y, Yamaji Y, Namba S (2016) Recessive resistance to plant viruses: potential resistance genes beyond translation initiation factors. Front Microbiol 7:1695. https://doi.org/10.3389/fmicb.2016.01695

Henikoff S, Till BJ, Comai L (2004) TILLING. Traditional mutagenesis meets functional genomics. Plant Physiol 135:630–636. https://doi.org/10.1104/pp.104.041061

Hirai K, Kubota K, Mochizuki T, Tsuda S, Meshi T (2008) Antiviral RNA silencing is restricted to the marginal region of the dark green tissue in the mosaic leaves of *Tomato mosaic virus*-infected tobacco plants. J Virol 82:3250–3260. https://doi.org/10.1128/jvi.02139-07

Hollings M, Huttinga H (1976) Tomato mosaic virus. Descriptions of Plant Viruses, No. 156, Association of Applied Biologists. https://www.dpvweb.net/dpv/showdpv/?dpvno=156. Accessed 9 June 2023

Holmes FO (1934) A masked strain of tobacco-mosaic virus. Phytopathology 24:845–873

Hu Q, Zhang H, Zhang L, Liu Y, Huang C, Yuan C, Chen Z, Li K, Larkin RM, Chen J, Kuang H (2021) Two *TOBAMOVIRUS MULTIPLICATION 2A* homologs in tobacco control asymptomatic response to tobacco mosaic virus. Plant Physiol 187:2674–2690. https://doi.org/10.1093/plphys/kiab448

Ichiki TU, Nagaoka EN, Hagiwara K, Uchikawa K, Tsuda S, Omura T (2005) Integration of mutations responsible for the attenuated phenotype of *Pepper mild mottle virus* strains results in a symptomless cross-protecting strain. Arch Virol 150:2009–2020. https://doi.org/10.1007/s00705-005-0551-8

Ishibashi K, Ishikawa M (2013) The resistance protein Tm-1 inhibits formation of a tomato mosaic virus replication protein-host membrane protein complex. J Virol 87:7933–7939. https://doi.org/10.1128/JVI.00743-13

Ishibashi K, Ishikawa M (2014) Mechanisms of tomato mosaic virus RNA replication and its inhibition by the host resistance factor Tm-1. Curr Opin Virol 9:8–13. https://doi.org/10.1016/j.coviro.2014.08.005

Ishibashi K, Ishikawa M (2016) Replication of tobamovirus RNA. Annu Rev Phytopathol 54:55–78. https://doi.org/10.1146/annurev-phyto-080615-100217

Ishibashi K, Masuda K, Naito S, Meshi T, Ishikawa M (2007) An inhibitor of viral RNA replication is encoded by a plant resistance gene. Proc Natl Acad Sci 104:13833–13838. https://doi.org/10.1073/pnas.0703203104

Ishibashi K, Naito S, Meshi T, Ishikawa M (2009) An inhibitory interaction between viral and cellular proteins underlies the resistance of tomato to nonadapted tobamoviruses. Proc Natl Acad Sci 106:8778–8783. https://doi.org/10.1073/pnas.0809105106

Ishibashi K, Mawatari N, Miyashita S, Kishino H, Meshi T, Ishikawa M (2012) Coevolution and hierarchical interactions of *Tomato mosaic virus* and the resistance gene *Tm-1*. PLOS Pathog 8:e1002975. https://doi.org/10.1371/journal.ppat.1002975

Ishibashi K, Kezuka Y, Kobayashi C, Kato M, Inoue T, Nonaka T, Ishikawa M, Matsumura H, Katoh E (2014) Structural basis for the recognition–evasion arms race between *Tomato mosaic virus* and the resistance gene *Tm-1*. Proc Natl Acad Sci 111:E3486–E3495. https://doi.org/10.1073/pnas.1407888111

Ishikawa M, Meshi T, Motoyoshi F, Takamatsu N, Okada Y (1986) *In vitro* mutagenesis of the putative replicase genes of tobacco mosaic virus. Nucleic Acids Res 14:8291–8305. https://doi.org/10.1093/nar/14.21.8291

Ishikawa M, Yoshida T, Matsuyama M, Kouzai Y, Kano A, Ishibashi K (2022) Tomato brown rugose fruit virus resistance generated by quadruple knockout of homologs of *TOBAMOVIRUS MULTIPLICATION1* in tomato. Plant Physiol 189:679–686. https://doi.org/10.1093/plphys/kiac103

Ivanovsky D (1892) Über die Mosaikkrankheit der Tabakspflanze. St Petersb Acad Imp Sci Bull 35:67–70 [English translation published in 1942: Concerning the mosaic disease of tobacco. Phytopath Classics 7:25–35]

Jerrett PH (1930) Streak—a virus disease of tomatoes. Ann Appl Biol 17:248–259

Jewehan A, Kiemo FW, Salem N, Tóth Z, Salamon P, Szabó Z (2022a) Isolation and molecular characterization of a tomato brown rugose fruit virus mutant breaking the tobamovirus resistance found in wild *Solanum* species. Arch Virol 167:1559–1563. https://doi.org/10.1007/s00705-022-05438-2

Jewehan A, Salem N, Tóth Z, Salamon P, Szabó Z (2022b) Evaluation of responses to tomato brown rugose fruit virus (ToBRFV) and selection of resistant lines in *Solanum habrochaites* and *Solanum peruvianum* germplasm. J Gen Plant Pathol 88:187–196. https://doi.org/10.1007/s10327-022-01055-8

Jin Y, Zhao J-H, Guo H-S (2021) Recent advances in understanding plant antiviral RNAi and viral suppressors of RNAi. Curr Opin Virol 46:65–72. https://doi.org/10.1016/j.coviro.2020.12.001

Johnson J (1926) Mosaic diseases of differential hosts. Phytopathology 16:141–149

Kabas A, Fidan H, Kucukaydin H, Atan HN, Kabas A, Fidan H, Kucukaydin H, Atan HN (2022) Screening of wild tomato species and interspecific hybrids for resistance/tolerance to *Tomato brown rugose fruit virus* (ToBRFV). Chil J Agric Res 82:189–196. https://doi.org/10.4067/S0718-58392022000100189

Kalisvaart J, Ludeking DJW, Roovers AJM (2022) Gene leading to TOBRFV resistance in *S. lycopersicum*. WO2022013452A1, 20 January 2022

Kamimura S (1980) History of the production of tomatoes for processing in Japan. Acta Hortic 100:75–86. https://doi.org/10.17660/ActaHortic.1980.100.10

Kassanis B, Selman IW (1947) Variations in the reaction of white burley tobacco to the tomato aucuba mosaic virus and to some other strains of tobacco mosaic virus. J Pomol Hortic Sci 23:167–170. https://doi.org/10.1080/03683621.1947.11513665

Khalid A, Zhang Q, Yasir M, Li F (2017) Small RNA based genetic engineering for plant viral resistance: application in crop protection. Front Microbiol 8:43. https://doi.org/10.3389/fmicb.2017.00043

Klap C, Luria N, Smith E, Bakelman E, Belausov E, Laskar O, Lachman O, Gal-On A, Dombrovsky A (2020) The potential risk of plant-virus disease initiation by infected tomatoes. Plants 9:623. https://doi.org/10.3390/plants9050623

Knorr DA, Dawson WO (1988) A point mutation in the tobacco mosaic virus capsid protein gene induces hypersensitivity in *Nicotiana sylvestris*. Proc Natl Acad Sci 85:170–174. https://doi.org/10.1073/pnas.85.1.170

Kobayashi M, Yamamoto-Katou A, Katou S, Hirai K, Meshi T, Ohashi Y, Mitsuhara I (2011) Identification of an amino acid residue required for differential recognition of a viral movement protein by the *Tomato mosaic virus* resistance gene *Tm-2*^{2}. J Plant Physiol 168:1142–1145. https://doi.org/10.1016/j.jplph.2011.01.002

Komochi S, Goto T, Oshima N (1966) Studies on the control of plant virus diseases by vaccination of attenuated virus. III. Reduction in fruit setting infection as a shock reaction resulting from infection of tomato plants with TMV (in Japanese with English summary). J Jpn Soc Hort Sci 35:67–74. https://doi.org/10.2503/jjshs.35.269

Komuro Y (1963) On the causal viruses of tomato streak in Japan (in Japanese with English abstract). Ann Phytopathol Soc Jpn 28:40–48. https://doi.org/10.3186/jjphytopath.28.40

Komuro Y, Iwaki M (1968) Strains of tobacco mosaic virus contained in cigarettes, with especial reference to the infection source for mosaic disease (in Japanese with English abstract). Jpn J Phytopathol 34:98–102. https://doi.org/10.3186/jjphytopath.34.98

Komuro Y, Iwaki M, Nakahara M (1966) Viruses isolated from tomato plants showing mosaic and/or streak in Japan, with special reference to tomato strain of tobacco mosaic virus (in Japanese with English abstract). Ann Phytopathol Soc Jpn 32:130–137. https://doi.org/10.3186/jjphytopath.32.130

Kopeliovitch E, Gilan I (2022) A tomato plant comprising dominant resistance genes to tomato brown rugose fruit virus. WO2022018734A1, 27 January 2022

Kravchik M, Shnaider Y, Abebie B, Shtarkman M, Kumari R, Kumar S, Leibman D, Spiegelman Z, Gal-On A (2022) Knockout of *SlTOM1* and *SlTOM3* results in differential resistance to tobamovirus in tomato. Mol Plant Pathol 23:1278–1289. https://doi.org/10.1111/mpp.13227

Kubota K (2016) Recent occurrence of resistant breaking strains of Tomato mosaic virus in Japan (in Japanese). Plant Prot 70:797–800

Kubota K, Tsuda S, Tamai A, Meshi T (2003) Tomato mosaic virus replication protein suppresses virus-targeted posttranscriptional gene silencing. J Virol 77:11016–11026. https://doi.org/10.1128/JVI.77.20.11016-11026.2003

Kunkel LO (1934) Studies on acquired immunity with tobacco and aucuba mosaic. Phytopathology 24:437–466

Kurihara Y, Inaba N, Kutsuna N, Takeda A, Tagami Y, Watanabe Y (2007) Binding of tobamovirus replication protein with small RNA duplexes. J Gen Virol 88:2347–2352. https://doi.org/10.1099/vir.0.82994-0

Kuroiwa M, Handa S, Gyoutoku Y, Moriyama M, Neriya Y, Nishigawa H, Natsuaki T (2022) Characterization of a ToMV isolate overcoming *Tm-2*^{2} resistance gene in tomato. Virus Genes 58:478–482. https://doi.org/10.1007/s11262-022-01921-9

Lanfermeijer FC, Dijkhuis J, Sturre MJG, de Haan P, Hille J (2003) Cloning and characterization of the durable tomato mosaic virus resistance gene Tm-2(2) from *Lycopersicon esculentum*. Plant Mol Biol 52:1037–1049. https://doi.org/10.1023/a:1025434519282

Lanfermeijer FC, Warmink J, Hille J (2005) The products of the broken *Tm-2* and the durable *Tm-2*^{2} resistance genes from tomato differ in four amino acids. J Exp Bot 56:2925–2933. https://doi.org/10.1093/jxb/eri288

Levitzky N, Smith E, Lachman O, Luria N, Mizrahi Y, Bakelman H, Sela N, Laskar O, Milrot E, Dombrovsky A (2019) The bumblebee *Bombus terrestris* carries a primary inoculum of *Tomato brown rugose fruit virus* contributing to disease spread in tomatoes. PLoS ONE 14:e0210871. https://doi.org/10.1371/journal.pone.0210871

Lewandowski DJ, Dawson WO (1993) A single amino acid change in tobacco mosaic virus replicase prevents symptom production. Mol Plant-Microbe Interact 6:157–160

Li R, Gao S, Fei Z, Ling K-S (2013) Complete genome sequence of a new tobamovirus naturally infecting tomatoes in Mexico. Genome Announc 1:e00794-e813. https://doi.org/10.1128/genomeA.00794-13

Li Y, Wang Y, Hu J, Xiao L, Tan G, Lan P, Liu Y, Li F (2017) The complete genome sequence, occurrence and host range of *Tomato mottle mosaic virus* Chinese isolate. Virol J 14:15. https://doi.org/10.1186/s12985-016-0676-2

Li Y, Tan G, Xiao L, Zhou W, Lan P, Chen X, Liu Y, Li R, Li F (2021) A multiyear survey and identification of pepper- and tomato-infecting viruses in Yunnan Province, China. Front Microbiol 12:623875. https://doi.org/10.3389/fmicb.2021.623875

Lindbo J (2022) Tomato plants resistant to TOBRFV, TMV, TOMV and TOMMV and corresponding resistance genes. WO 2022/117884 A1, 9 June 2022

Lindbo JA, Dougherty WG (1992) Untranslatable transcripts of the tobacco etch virus coat protein gene sequence can interfere with tobacco etch virus replication in transgenic plants and protoplasts. Virology 189:725–733. https://doi.org/10.1016/0042-6822(92)90595-G

Lindbo JA, Falk BW (2017) The impact of "coat protein-mediated virus resistance" in applied plant pathology and basic research. Phytopathology 107:624–634. https://doi.org/10.1094/PHYTO-12-16-0442-RVW

Ling K-S, Tian T, Gurung S, Salati R, Gilliard A (2019) First report of tomato brown rugose fruit virus infecting greenhouse tomato in the United States. Plant Dis 103:1439. https://doi.org/10.1094/PDIS-11-18-1959-PDN

Lovelock DA, Kinoti WM, Bottcher C, Wildman O, Dall D, Rodoni BC, Constable FE (2020) *Tomato mottle mosaic virus* intercepted by Australian biosecurity in *Capsicum annuum* seed. Australas Plant Dis Notes 15:8. https://doi.org/10.1007/s13314-020-0378-x

Luria N, Smith E, Reingold V et al (2017) A new Israeli tobamovirus isolate infects tomato plants harboring *Tm-2*^{2} resistance genes. PLoS ONE 12:e0170429. https://doi.org/10.1371/journal.pone.0170429

Mahillon M, Kellenberger I, Dubuis N, Brodard J, Bunter M, Weibel J, Sandrini F, Schumpp O (2022) First report of *Tomato brown rugose fruit virus* in tomato in Switzerland. New Dis Rep 45:e12065. https://doi.org/10.1002/ndr2.12065

Matsumoto T, Furuya H, Tairako K, Yamamoto H (1998) Cross protection of spontaneous mutants derived from an attenuated tomato strain of tobacco mosaic virus TMV-L11A (in Japanese with English abstract). Jpn J Phytopathol 64:213–216. https://doi.org/10.3186/jjphytopath.64.213

Matsumoto T, Nara Y, Furuya H, Takahashi H, Tairako K, Yamamoto H (2002) Characteristics for practical use of attenuated isolate UA-Fukushima of *Tomato mosaic virus*. J Gen Plant Pathol 68:382–384. https://doi.org/10.1007/PL00013107

Mayer A (1882) Over de mozaïkziekte van de tabak; voorloopige mededeeling (English translation: On the mosaic disease of tobacco; preliminary communication.). Tidschr Landbouwk 2:359–364

McKinney HH (1929) Mosaic diseases in the Canary Islands, West Africa and Gibraltar. J Agric Res 39:577–578

Menzel W, Knierim D, Winter S, Hamacher J, Heupel M (2019) First report of *Tomato brown rugose fruit virus* infecting tomato in Germany. New Dis Rep 39:1. https://doi.org/10.5197/j.2044-0588.2019.039.001

Meshi T, Ishikawa M, Motoyoshi F, Semba K, Okada Y (1986) *In vitro* transcription of infectious RNAs from full-length cDNAs of

tobacco mosaic virus. Proc Natl Acad Sci U S A 83:5043–5047. https://doi.org/10.1073/pnas.83.14.5043
Meshi T, Watanabe Y, Saito T, Sugimoto A, Maeda T, Okada Y (1987) Function of the 30 kd protein of tobacco mosaic virus: involvement in cell-to-cell movement and dispensability for replication. EMBO J 6:2557–2563. https://doi.org/10.1002/j.1460-2075.1987.tb02544.x
Meshi T, Motoyoshi F, Adachi A, Watanabe Y, Takamatsu N, Okada Y (1988) Two concomitant base substitutions in the putative replicase genes of tobacco mosaic virus confer the ability to overcome the effects of a tomato resistance gene, *Tm-1*. EMBO J 7:1575–1581. https://doi.org/10.1002/j.1460-2075.1988.tb02982.x
Meshi T, Motoyoshi F, Maeda T, Yoshiwoka S, Watanabe H, Okada Y (1989) Mutations in the tobacco mosaic virus 30-kD protein gene overcome *Tm-2* resistance in tomato. Plant Cell 1:515–522. https://doi.org/10.1105/tpc.1.5.515
Millenaar F, Vredenbregt P, Altena J, Mammella MA, Verbakel H (2021) *Solanum lycopersicum* plants having improved tobamovirus resistance. WO2021213892A1, 28 October 2021
Miyashita S, Ishibashi K, Kishino H, Ishikawa M (2015) Viruses roll the dice: the stochastic behavior of viral genome molecules accelerates viral adaptation at the cell and tissue levels. PLOS Biol 13:e1002094. https://doi.org/10.1371/journal.pbio.1002094
Motoyoshi F, Nishiguchi M (1988) Control of virus diseases by attenuated virus strains, comparison between attenuated strains of cucumber green mottle mosaic virus and tobacco mosaic virus. Gamma Field Symp Inst Radiat Breed Natl Inst Agrobiol Resour 27:91–109
Murakishi HH (1960) Comparative incidence of graywall and internal browning of tomato and sources of resistance. Phytopathology 50:408–412
Murayama D (1936) Studies on the mosaic disease of tomato (in Japanese with English summary). J Soc Agric for Sapporo Jpn 133:215–277
Nagai A, Duarte LML, Chaves ALR, Alexandre MAV, Ramos-González PL, Chabi-Jesus C, Harakava R, Dos Santos DYAC (2018) First complete genome sequence of an isolate of tomato mottle mosaic virus infecting plants of *Solanum lycopersicum* in South America. Genome Announc 6:e00427–e00518. https://doi.org/10.1128/genomeA.00427-18
Nagai A, Duarte LML, Chaves ALR, Peres LEP, dos Santos DYAC (2019) *Tomato mottle mosaic virus* in Brazil and its relationship with *Tm-2*^{2} gene. Eur J Plant Pathol 155:353–359. https://doi.org/10.1007/s10658-019-01762-7
Nagai Y (1987) Production of C-1421, an attenuated mutant of pepper strain of tobacco mosaic virus (in Japanese with English abstract). Jpn J Phytopathol 53:168–174. https://doi.org/10.3186/jjphytopath.53.168
Nagai Y, Takeuchi T (1979) Practical seedling inoculation with the attenuated strain of TMV as a means of controlling the mosaic disease of tomatoes (in Japanese). Bull Chiba Agric Exp Stn 20:57–69
Nakata K, Takimoto S (1940) Studies on the "yellow tobacco mosaic" or "aucuba mosaic" of tomato (in Japanese with English summary). Sci Bull Fac Agr Kyushu Univ 9:167–178
Nelson RS, McCormick SM, Delannay X, Dubé P, Layton J, Anderson EJ, Kaniewska M, Proksch RK, Horsch RB, Rogers SG, Fraley RT, Beachy RN (1988) Virus tolerance, plant performance of transgenic tomato plants expressing coat protein from tobacco mosaic virus. Bio/technology 6:403–409. https://doi.org/10.1038/nbt0488-403
Nishiguchi M, Kikuchi S, Kiho Y, Ohno T, Meshi T, Okada Y (1985) Molecular basis of plant viral virulence; the complete nucleotide sequence of an attenuated strain of tobacco mosaic virus. Nucleic Acids Res 13:5585–5590. https://doi.org/10.1093/nar/13.15.5585
Nishikiori M, Mori M, Dohi K, Okamura H, Katoh E, Naito S, Meshi T, Ishikawa M (2011) A host small GTP-binding protein ARL8 plays crucial roles in tobamovirus RNA replication. PLOS Pathog 7:e1002409. https://doi.org/10.1371/journal.ppat.1002409
Nishikiori M, Sugiyama S, Xiang H, Niiyama M, Ishibashi K, Inoue T, Ishikawa M, Matsumura H, Katoh E (2012) Crystal structure of the superfamily 1 helicase from *Tomato mosaic virus*. J Virol 86:7565–7576. https://doi.org/10.1128/JVI.00118-12
Noba K, Kishi K (1979) Studies on the strains of tobacco mosaic virus isolated from tomato plants. I TMV strains in tomato and their distribution in Japan (in Japanese with English summary). Bull Veg Ornam Crops Res Stn Ser A 6:147–159
Ohno T, Aoyagi M, Yamanashi Y, Saito H, Ikawa S, Meshi T, Okada Y (1984) Nucleotide sequence of the tobacco mosaic virus (tomato strain) genome and comparison with the common strain genome. J Biochem (tokyo) 96:1915–1923. https://doi.org/10.1093/oxfordjournals.jbchem.a135026
Okada K, Kusakari S, Kawaratani M, Negoro J, Ohki ST, Osaki T (2000) *Tobacco mosaic virus* is transmissible from tomato to tomato by pollinating bumblebees. J Gen Plant Pathol 66:71–74. https://doi.org/10.1007/PL00012924
Orfanidou CG, Cara M, Merkuri J, Katis NI, Maliogka VI (2022) First report of tomato chlorosis virus in tomato in Albania. J Plant Pathol 104:1177–1177. https://doi.org/10.1007/s42161-022-01148-5
Oshima N (1981) Control of tomato mosaic disease by attenuated virus. JARQ 14:222–228
Oshima N, Goto T, Sato R (1964) A strain of tobacco mosaic virus (TMV-L) isolated from tomato (in Japanese with English summary). Res Bull Hokkaido Natl Agric Exp Stn 83:87–99
Oshima N, Komochi S, Goto T (1965) Study on control of plant virus diseases by vaccination of attenuated virus (1). Control of tomato mosaic disease (in Japanese with English summary). Hokkaido Natl Agric Exp Stn Bull 85:23–33
Oshima N, Osawa T, Morita H, Mori K (1978) A new attenuated virus L11A237 (in Japanese with English abstract). Ann Phytopathol Soc Jpn 44:504–508. https://doi.org/10.3186/jjphytopath.44.504
Panno S, Caruso AG, Davino S (2019) First report of tomato brown rugose fruit virus on tomato crops in Italy. Plant Dis 103:1443–1443. https://doi.org/10.1094/PDIS-12-18-2254-PDN
Panno S, Davino S, Caruso AG, Bertacca S, Crnogorac A, Mandić A, Noris E, Matić S (2021) A review of the most common and economically important diseases that undermine the cultivation of tomato crop in the Mediterranean Basin. Agronomy 11:2188. https://doi.org/10.3390/agronomy11112188
Pelham J (1966) Resistance in tomato to tobacco mosaic virus. Euphytica 15:258–267. https://doi.org/10.1007/BF00022331
Pelham J, Fletcher JT, Hawkins JH (1970) The establishment of a new strain of tobacco mosaic virus resulting from the use of resistant varieties of tomato. Ann Appl Biol 65:293–297. https://doi.org/10.1111/j.1744-7348.1970.tb04590.x
Rangel EA, Alfaro-Fernández A, Font-San-Ambrosio MI, Luis-Arteaga M, Rubio L (2011) Genetic variability and evolutionary analyses of the coat protein gene of *Tomato mosaic virus*. Virus Genes 43:435–438. https://doi.org/10.1007/s11262-011-0651-3
Rast ATB (1967) Yield of glasshouse tomatoes as affected by strains of tobacco mosaic virus. Neth J Plant Pathol 73:147–156. https://doi.org/10.1007/BF02000454
Rast ATB (1972) M II-16, an artificial symptomless mutant of tobacco mosaic virus for seedling inoculation of tomato crops. Neth J Plant Pathol 78:110–112. https://doi.org/10.1007/BF01980475
Rast ATB (1975) Variability of tobacco mosaic virus in relation to control of tomato mosaic in glasshouse tomato crops by resistance breeding and cross protection. Agric Res Rep 834:1–76

Rigola D, van Oeveren J, Janssen A, Bonné A, Schneiders H, van der Poel HJA, van Orsouw NJ, Hogers RCJ, de Both MTJ, van Eijk MJT (2009) High-throughput detection of induced mutations and natural variation using KeyPoint™ technology. PLoS ONE 4:e4761. https://doi.org/10.1371/journal.pone.0004761

Rivera-Márquez K, Núñez-Muñoz LA, Calderón-Pérez B, De La Torre-Almaraz R, Vargas-Hernández BY, Ruiz-Medrano R, Xoconostle-Cázares B (2022) Bioinformatic-based approach for mutagenesis of plant immune Tm-2^2 receptor to confer resistance against tomato brown rugose fruit virus (ToBRFV). Front Plant Sci 13:984846. https://doi.org/10.3389/fpls.2022.984846

Sabra A, Amer MA, Hussain K, Zakri A, Al-Shahwan IM, Al-Saleh MA (2022) Occurrence and distribution of tomato brown rugose fruit virus infecting tomato crop in Saudi Arabia. Plants. https://doi.org/10.3390/plants11223157

Saito T, Meshi T, Takamatsu N, Okada Y (1987) Coat protein gene sequence of tobacco mosaic virus encodes a host response determinant. Proc Natl Acad Sci 84:6074–6077. https://doi.org/10.1073/pnas.84.17.6074

Salem N, Mansour A, Ciuffo M, Falk BW, Turina M (2016) A new tobamovirus infecting tomato crops in Jordan. Arch Virol 161:503–506. https://doi.org/10.1007/s00705-015-2677-7

Salem NM, Sulaiman A, Samarah N, Turina M, Vallino M (2022) Localization and mechanical transmission of tomato brown rugose fruit virus in tomato seeds. Plant Dis 106:275–281. https://doi.org/10.1094/PDIS-11-20-2413-RE

Salem NM, Jewehan A, Aranda MA, Fox A (2023) Tomato brown rugose fruit virus pandemic. Annu Rev Phytopathol. https://doi.org/10.1146/annurev-phyto-021622-120703

Sarkes A, Fu H, Feindel D, Harding M, Feng J (2020) Development and evaluation of a loop-mediated isothermal amplification (LAMP) assay for the detection of *Tomato brown rugose fruit virus* (ToBRFV). PLoS ONE 15:e0230403. https://doi.org/10.1371/journal.pone.0230403

Schoen R, de Koning P, Oplaat C, Roenhorst A, Westenberg M, van der Gaag DJ, Barnhoorn R, Koenraadt H, van Dooijeweert W, Lievers R, Woudt B, Tavares CP, Botermans M (2023) Identification of tomato mottle mosaic virus in historic seed accessions originating from France, the Netherlands and Spain, indicates a wider presence before its first description. Eur J Plant Pathol. https://doi.org/10.1007/s10658-023-02677-0

Sekine K-T, Tomita R, Takeuchi S, Atsumi G, Saitoh H, Mizumoto H, Kiba A, Yamaoka N, Nishiguchi M, Hikichi Y, Kobayashi K (2012) Functional differentiation in the leucine-rich repeat domains of closely related plant virus-resistance proteins that recognize common Avr proteins. Mol Plant Microbe Interact 25:1219–1229. https://doi.org/10.1094/MPMI-11-11-0289

Skelton A, Buxton-Kirk A, Ward R, Harju V, Frew L, Fowkes A, Long M, Negus A, Forde S, Adams IP, Pufal H, McGreig S, Weekes R, Fox A (2019) First report of *Tomato brown rugose fruit virus* in tomato in the United Kingdom. New Dis Rep 40:12. https://doi.org/10.5197/j.2044-0588.2019.040.012

Skelton A, Gentit P, Porcher L, Visage M, Fowkes A, Adams IP, Harju V, Webster G, Pufal H, McGreig S, Ward R, Fox A (2022) First report of *Tomato brown rugose fruit virus* in tomato in France. New Dis Rep 45:e12061. https://doi.org/10.1002/ndr2.12061

Smith H (1928) Experiments with a mosaic disease of tomato. Ann Appl Biol 15:155–167

Spiegelman Z, Hak H, Ezra JL, Sherman Y (2022) Tobamovirus-resistant tomato plants. WO2022/091104A1, 5 May 2022

Stanley WM (1946) The isolation and properties of crystalline tobacco mosaic virus. In: Nobel Lect. https://www.nobelprize.org/uploads/2018/06/stanley-lecture.pdf

Strasser M, Pfitzner AJP (2007) The double-resistance-breaking Tomato mosaic virus strain ToMV1-2 contains two independent single resistance-breaking domains. Arch Virol 152:903–914. https://doi.org/10.1007/s00705-006-0915-8

Taylor GA, Lewis GD, Rubatzky VE (1969) The influence of time of tobacco mosaic virus inoculation and stage of fruit maturity upon the incidence of tomato internal browning. Phytopathology 59:732–736

Taylor RH, Grogan RG, Kimble KA (1961) Transmission of tobacco mosaic virus in tomato seed. Phytopathology 51:837–842

Tettey CK, Mu X-Q, Ma H-Y, Chen X-Y, Geng C, Tian Y-P, Yan Z-Y, Li X-D (2023) The role of different innate and environmental factors in *Tm-*2^2-mediated resistance to tomato mottle mosaic virus. Phytopathol Res 5:8. https://doi.org/10.1186/s42483-023-00162-4

Tiberini A, Manglli A, Taglienti A, Vučurović A, Brodarič J, Ferretti L, Luigi M, Gentili A, Mehle N (2022) Development and validation of a one-step reverse transcription real-time PCR assay for simultaneous detection and identification of tomato mottle mosaic virus and tomato brown rugose fruit virus. Plants 11:489. https://doi.org/10.3390/plants11040489

Tripathi L, Ntui VO, Tripathi JN (2020) CRISPR/Cas9-based genome editing of banana for disease resistance. Curr Opin Plant Biol 56:118–126. https://doi.org/10.1016/j.pbi.2020.05.003

Tsuda S, Kubota K, Kanda A, Ohki T, Meshi T (2007) Pathogenicity of *Pepper mild mottle virus* is controlled by the RNA silencing suppression activity of its replication protein but not the viral accumulation. Phytopathology 97:412–420. https://doi.org/10.1094/PHYTO-97-4-0412

Tsujimoto Y, Numaga T, Ohshima K, Yano M, Ohsawa R, Goto DB, Naito S, Ishikawa M (2003) *Arabidopsis TOBAMOVIRUS MULTIPLICATION (TOM) 2* locus encodes a transmembrane protein that interacts with TOM1. EMBO J 22:335–343. https://doi.org/10.1093/emboj/cdg034

Turina M, Geraats BPJ, Ciuffo M (2016) First report of *Tomato mottle mosaic virus* in tomato crops in Israel. New Dis Rep 33:1. https://doi.org/10.5197/j.2044-0588.2016.033.001

van de Vossenberg BTLH, Visser M, Bruinsma M, Koenraadt HMS, Westenberg M, Botermans M (2020) Real-time tracking of Tomato brown rugose fruit virus (ToBRFV) outbreaks in the Netherlands using Nextstrain. PLoS ONE 15:e0234671. https://doi.org/10.1371/journal.pone.0234671

Vargas-Hernández BY, Ramírez-Pool JA, Núñez-Muñoz LA, Calderón-Pérez B, De La Torre-Almaráz R, Hinojosa-Moya J, Xoconostle-Cázares B, Ruiz-Medrano R (2022) Development of a droplet digital polymerase chain reaction (ddPCR) assay for the detection of *Tomato brown rugose fruit virus* (ToBRFV) in tomato and pepper seeds. J Virol Methods 302:114466. https://doi.org/10.1016/j.jviromet.2022.114466

Vučurović A, Brodarič J, Jakomin T, Pecman A, Benko Beloglavec A, Mehle N (2022) First report of *Tomato brown rugose fruit virus* in tomato in Slovenia. New Dis Rep 45:e12079. https://doi.org/10.1002/ndr2.12079

Walker PJ, Siddell SG, Lefkowitz EJ et al (2022) Recent changes to virus taxonomy ratified by the International Committee on Taxonomy of Viruses (2022). Arch Virol 167:2429–2440. https://doi.org/10.1007/s00705-022-05516-5

Waltz E (2021) GABA-enriched tomato is first CRISPR-edited food to enter market. Nat Biotechnol 40:9–11. https://doi.org/10.1038/d41587-021-00026-2

Wang J, Chen T, Han M, Qian L, Li J, Wu M, Han T, Cao J, Nagalakshmi U, Rathjen JP, Hong Y, Liu Y (2020) Plant NLR immune receptor Tm-2^2 activation requires NB-ARC domain-mediated self-association of CC domain. PLOS Pathog 16:e1008475. https://doi.org/10.1371/journal.ppat.1008475

Waterhouse PM, Smith NA, Wang M-B (1999) Virus resistance and gene silencing: killing the messenger. Trends Plant Sci 4:452–457. https://doi.org/10.1016/S1360-1385(99)01493-4

Weber H, Schultze S, Pfitzner AJ (1993) Two amino acid substitutions in the tomato mosaic virus 30-kilodalton movement protein confer the ability to overcome the Tm-2(2) resistance gene in the tomato. J Virol 67:6432–6438. https://doi.org/10.1128/JVI.67.11.6432-6438.1993

Webster CG, Rosskopf EN, Lucas L, Mellinger HC, Adkins S (2014) First report of tomato mottle mosaic virus Infecting tomato in the United States. Plant Health Prog 15:151–152. https://doi.org/10.1094/PHP-BR-14-0023

Whitham S, McCormick S, Baker B (1996) The *N* gene of tobacco confers resistance to tobacco mosaic virus in transgenic tomato. Proc Natl Acad Sci U S A 93:8776–8781. https://doi.org/10.1073/pnas.93.16.8776

Wildy P (1971) Classification and nomenclature of viruses: first report of the International Committee on Nomenclature of Viruses. Monog Virol 5:1–81

Woods A (1902) Observations on the mosaic disease of tobacco. Univ Dept Agric Bur Plant Ind Bull 18:1–24

Xu Y, Zhang S, Shen J, Wu Z, Du Z, Gao F (2021) The phylogeographic history of tomato mosaic virus in Eurasia. Virology 554:42–47. https://doi.org/10.1016/j.virol.2020.12.009

Yamamoto H, Abe T, Ueda K, Inoue M, Matsumoto T (2002) A missense mutation in *Tomato mosaic virus* L11A-fukushima genome determines its symptomless systemic infection of tomato. J Gen Plant Pathol 68:385–389. https://doi.org/10.1007/PL00013108

Yamanaka T, Ohta T, Takahashi M, Meshi T, Schmidt R, Dean C, Naito S, Ishikawa M (2000) *TOM1*, an *Arabidopsis* gene required for efficient multiplication of a tobamovirus, encodes a putative transmembrane protein. Proc Natl Acad Sci U S A 97:10107–10112. https://doi.org/10.1073/pnas.170295097

Yamanaka T, Imai T, Satoh R, Kawashima A, Takahashi M, Tomita K, Kubota K, Meshi T, Naito S, Ishikawa M (2002) Complete inhibition of tobamovirus multiplication by simultaneous mutations in two homologous host genes. J Virol 76:2491–2497. https://doi.org/10.1128/jvi.76.5.2491-2497.2002

Yan Z-Y, Ma H-Y, Han S-L, Geng C, Tian Y-P, Li X-D (2019) First report of tomato brown rugose fruit virus infecting tomato in China. Plant Dis 103:2973–2973. https://doi.org/10.1094/PDIS-05-19-1045-PDN

Yan Z-Y, Zhao M-S, Ma H-Y, Liu L-Z, Yang G-L, Geng C, Tian Y-P, Li X-D (2021a) Biological and molecular characterization of tomato brown rugose fruit virus and development of quadruplex RT-PCR detection. J Integr Agric 20:1871–1879. https://doi.org/10.1016/S2095-3119(20)63275-0

Yan Z-Y, Ma H-Y, Wang L, Tettey C, Zhao M-S, Geng C, Tian Y-P, Li X-D (2021b) Identification of genetic determinants of tomato brown rugose fruit virus that enable infection of plants harbouring the *Tm-2*^{2} resistance gene. Mol Plant Pathol 22:1347–1357. https://doi.org/10.1111/mpp.13115

Ykema M, Verweij CW, Bentem SDLFV, Perefarres FMP (2021) Tomato plant resistant to tomato brown rugose fruit virus. US20210238627A1, 5 August 2021

Yoneda E, Ishimatsu T, Tomitaka Y (2019) Cross protection effect of attenuated strains of tomato mosaic virus and tobacco mild green mosaic virus against mosaic and necrosis diseases of Chinese Lantern plants (*Physalis alkekengi* L. var. franchetii M) (in Japanese). Kyusyu Plant Prot Res 65:11–17. https://doi.org/10.4241/kyubyochu.65.11

Zaitlin M (2000) Tobacco mosaic virus. Descriptions of Plant Viruses, No. 370, Association of Applied Biologists. https://www.dpvweb.net/dpv/showdpv/?dpvno=370. Accessed 9 June 2023

Zhang S, Griffiths JS, Marchand G, Bernards MA, Wang A (2022) *Tomato brown rugose fruit virus*: an emerging and rapidly spreading plant RNA virus that threatens tomato production worldwide. Mol Plant Pathol 23:1262–1277. https://doi.org/10.1111/mpp.13229

Ziebell H, Carr JP (2010) Cross-protection: a century of mystery. Adv Virus Res 76:211–264. https://doi.org/10.1016/S0065-3527(10)76006-1

Zinger A, Lapidot M, Harel A, Doron-Faigenboim A, Gelbart D, Levin I (2021) Identification and mapping of tomato genome loci controlling tolerance and resistance to *Tomato brown rugose fruit virus*. Plants 10:179. https://doi.org/10.3390/plants10010179

Zitter T (2014) Tobacco mosaic virus and tomato mosaic virus. In: Jones J, Zitter T, Momol T, Miller S (eds) Compendium of tomato diseases and pests, 2nd edn. APS Press, St. Paul, MN, pp 90–91