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Chapter 2
Genomic Designing for Climate-Smart Tomato

Mathilde Causse, Jiantao Zhao, Isidore Diouf, Jiaojiao Wang, Veronique Lefebvre, Bernard Caromel, Michel Génard and Nadia Bertin

Abstract Tomato is the first vegetable consumed in the world. It is grown in very different conditions and areas, mainly in field for processing tomatoes while fresh-market tomatoes are often produced in greenhouses. Tomato faces many environmental stresses, both biotic and abiotic. Today many new genomic resources are available allowing an acceleration of the genetic progress. In this chapter, we will first present the main challenges to breed climate-smart tomatoes. The breeding objectives relative to productivity, fruit quality, and adaptation to environmental stresses will be presented with a special focus on how climate change is impacting these objectives. In the second part, the genetic and genomic resources available will be presented. Then, traditional and molecular breeding techniques will be discussed. A special focus will then be presented on ecophysiological modeling, which could constitute an important strategy to define new ideotypes adapted to breeding objectives. Finally, we will illustrate how new biotechnological tools are implemented and could be used to breed climate-smart tomatoes.

Keywords Tomato · Breeding · Productivity · Biotic stress · Abiotic stress · Ideotypes · Modeling

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2.1 Introduction

Tomato is the first vegetable consumed worldwide following potato. It has become an important food in many countries. Two main types of tomato varieties are produced, tomatoes for the processing industry, with determinate growth produced only in open field and indeterminate growth varieties for fresh market, which may be grown in very diverse conditions, from open field to greenhouses with controlled conditions.

Tomato, *Solanum lycopersicum* L., is a member of the large Solanaceae family, together with potato, eggplant, and pepper. It is a self-pollinated crop, with a diploid ($2n = 2x = 24$) genome of medium size (950 Mb). A high-quality reference genome sequence was published in 2012 (The Tomato Genome Consortium 2012). Tomato originates from South America along with 12 wild relative species, which can be crossed with the cultivated tomato species. Several large collections of genetic resources exist and more than 70,000 varieties are conserved in these gene banks. The collections also include scientific resources such as collections of mutants or segregating populations.

Tomato is also a model species for genetic analysis since a long time. Many mutations inducing important phenotype variations were discovered and positionally cloned and many disease resistance genes were functionally characterized. Tomato is also a model species for fruit development and physiology. It is easy to transform and it has been the first transgenic food produced and sold (Kramer and Redenbaugh 1994).

In this chapter, we will first present the main challenges to breed climate-smart tomatoes. The breeding objectives relative to productivity, fruit quality, and adaptation to environmental stresses will be presented with a special focus on how climate change is impacting these objectives. In the second part, the genetic and genomic resources available will be presented. Then, traditional and molecular breeding techniques will be discussed. A special focus will then be presented on ecophysiological modeling, which could constitute an important strategy to define new ideotypes adapted to breeding objectives. Finally, we will illustrate how new biotechnological tools are implemented and could be used to breed climate-smart tomatoes.

2.2 Challenges, Priorities, and Breeding Objectives

Tomato crop faces several challenges, which impact its breeding objectives. Breeders will orient their main breeding objectives according to the wide diversity of growth conditions and use them as fresh or processed. These objectives can be classified into (1) productivity, (2) adaptation to growth conditions in terms of response to biotic and abiotic stresses, and (3) fruit quality at both nutritional and sensory levels.

2.2.1 Productivity

From 1988 to 2017, the tomato world production regularly grew from 64 to 182 MT. Since 1995, China increased its production and became the first producer, and since then, its production increased up to 60 MT (Fig. 2.1) covering almost 4,800,000 ha. This growth is due to an increase in the production area, but also due to improvement in productivity and variety breeding.

With an average yield of 37 T/ha, compared to 16 T/ha in 1961, the yield has increased over years but large differences remain according to countries and growth conditions. In south European greenhouses, the average yield is 50–80 T/ha, while it may be more than 400 T/ha in the Netherlands and Belgium, with a crop lasting up to 11 months. Expressed per square meter, the average yield is 3.7 kg/m^2, reaching 50 kg/m^2 in the Netherlands, while it is 5.6 in China where most of the production is in the open field although modern Chinese solar greenhouses are developed (Cao et al. 2019).

Tomato yield is strongly dependent on cultivars and growth conditions. Yield results from fruit number and fruit weight. Cultivars for fresh market are classified based on their fruit size and shape from the cherry tomato (less than 20 g) to beef tomato (fruit weight higher than 200 g). The potential size depends on cell number established in pre-anthesis stage, but the final fruit size mainly depends on the rate and duration of cell enlargement (Ho 1996). Seed number and competition among fruits also affect the final fruit size (Bertin et al. 2002, 2003). Seed and fruit are highly sensitive to biotic and abiotic stresses, which often lead to seed and fruit abortion (Ruan et al. 2012). Fruit number is controlled by the truss architecture but the increase in flower number often leads to abortion (Soyk et al. 2017a, b). Fruit shape varies from flat to long or ovate and is also determined at the carpel development stage.

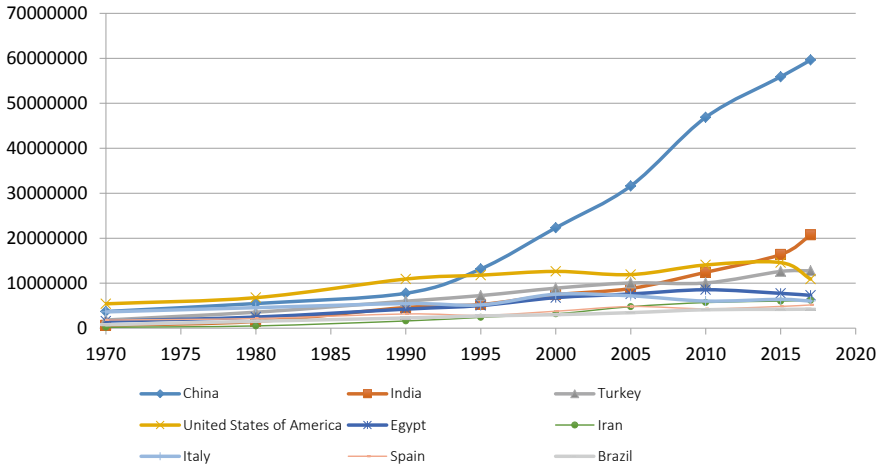

Fig. 2.1 Evolution of tomato production over years in the nine main producing countries

Mutations in four genes explain most of the tomato fruit shape (Rodríguez et al. 2011).

2.2.2 Fruit Quality

2.2.2.1 Nutritional Quality

Tomato consumption has been shown to reduce the risks of certain cancers and cardiovascular diseases (Giovannucci 1999). Its nutritional value is related to fruit composition in primary and secondary metabolites (Table 2.1) but is mostly due to its content in lycopene and carotene (Bramley 2000). Lycopene is responsible for the red fruit color but also acts as a dietary antioxidant. Tomato also constitutes an important source of vitamin C. In spite of considerable efforts in developing cultivars with higher content of carotenoids, or vitamin C, none has reached a commercial

Table 2.1 Average tomato fruit nutritional value and composition (adapted from USDA)

Proximates	Content (per 100 g fresh weight)
Water	94.5 g
Energy	18 kcal
Protein	0.88 g
Lipids	0.2 g
Fibers	1.2 g
Sugars	2.63 g
Acids	0.65 g
Minerals	
Calcium	10 mg
Magnesium	11 mg
Phosphorus	24 mg
Potassium	237 mg
Sodium	5 mg
Fluoride	g
Vitamins	
Vitamin C	14 mg
Choline	6.7 mg
Vitamin A and carotene	0.59 mg
Lycopene	2.57 mg
Lutein and zeaxanthin	123 g
Vitamin K	8 g

(adapted from USDA: https://www.usda.gov/)

importance, in part because of a negative correlation between yield and these traits (Klee 2010).

In addition to these well-known vitamins and antioxidants, other compounds in tomato fruit with antioxidant properties include chlorogenic acid, rutin, plastoquinones, tocopherol, and xanthophylls. Tomatoes also contribute but to a lesser extent to carbohydrates, fiber, flavor compounds, minerals, protein, fats, and glycoalkaloids to the diet (Davies and Hobson 1981). Exhaustive metabolome studies have described the composition of tomato in terms of both primary and secondary metabolites and has shown the wide diversity present among tomato accessions and their wild relatives (Tikunov et al. 2005; Schauer et al. 2006; Rambla et al. 2014; Wells et al. 2013; Tieman et al. 2017; Zhu et al. 2018).

Considerable genetic variation exists in tomato for micronutrients with antioxidant activity or other health-promoting properties (Hanson et al. 2004; Schauer et al. 2005). A number of these micronutrients, particularly carotenoids, have long been the major objectives of breeding programs because of their contribution to the quality of fresh and processed tomato products. Increased recognition of their health-promoting properties has stimulated new research to identify loci that influence their concentration in tomato.

Vitamin A and vitamin C are the principal vitamins in tomato fruit. Tomatoes also provide moderate levels of folate and potassium in the diet and lesser amounts of vitamin E and several water-soluble vitamins. Carotene biosynthesis in tomato has been deciphered and many genes and mutations have been identified (Ronen et al. 1999). More than 20 genes that influence the type, amount, or distribution of fruit carotenoids have been characterized in tomato (Labate et al. 2007).

Vitamin C pathway in plants has been deciphered by Smirnoff and Wheeler (2000). The variation in ascorbic acid content may depend on varieties and growth conditions (Gest et al. 2013) and a few quantitative trait loci (QTLs) controlling its variation have been identified (Stevens et al. 2007). The synthesis pathway of folate is also well characterized and the genes involved were identified (Almeida et al. 2011). One of the major QTLs controlling its variation has been shown to be related to an epigenetic variation (Quadrana et al. 2014).

Glycoalkaloids and their toxic effects are commonly associated with the Solanaceous species. Tomato accumulates the glycoalkaloids α-tomatine and dehydrotomatine which are less toxic than glycoalkaloids in potato (Madhavi and Salunkhe 1998; Milner et al. 2011). Several genes controlling their variations have been identified (Cárdenas et al. 2016; Zhu et al. 2018).

Tomato mineral composition is greatly influenced by plant nutrition (see below), and as a result, has been well characterized in the context of mineral deficiency and the effect of these conditions on plant health. There is a significant genotypic variation for mineral content in tomato fruit. Potassium, together with nitrate and phosphorous, constitutes approximately 93% of the total inorganic fruit constituents (Davies and Hobson 1981).

Flavonoids comprise a large group of secondary plant metabolites and include anthocyanins, flavonols, flavones, catechins, and flavonones (Harborne 1994). Numerous efforts have focused on the manipulation of transgene expression to

enhance fruit flavonoids (Muir et al. 2001; Bovy et al. 2002; Colliver et al. 2002). Willits et al. (2005) identified a wild accession that expressed structural genes of the anthocyanin biosynthetic pathway in the fruit peel and fruit flesh. Introgression of the *S. pennellii* accession into tomato produced progeny that accumulated high levels of quercetin in fruit flesh and peel. The mutation responsible for the lack of accumulation of yellow color flavonoid in the pink tomato has been identified (Adato et al. 2009; Ballester et al. 2016). Phenolic acids form a diverse group. Hydroxycinnamic acid esters of caffeic acid predominate in Solanaceous species and chlorogenic acid is the most abundant (Molgaard and Ravn 1988). Rousseaux et al. (2005) noted large environmental interactions for fruit antioxidants and identified several QTLs for total phenolic concentration in fruit of *S. pennellii* introgression lines.

2.2.2.2 Sensory Quality

Fresh-market tomato breeders improved yield, disease resistance, adaptation to greenhouse conditions, fruit aspect, but have lacked clear targets for improving organoleptic fruit quality. Consumers have complained about tomato taste for years (Bruhn et al. 1991). Nevertheless improving sensory fruit quality is complex as it is determined by a set of attributes, describing external (size, color, firmness) and internal (flavor, aroma, texture) properties.

Flavor is mostly due to sugars and organic acids (Stevens et al. 1977), to their ratio (Stevens et al. 1979; Bucheli et al. 1999), and to the composition in volatile aromas (Klee and Tieman 2013). Sweetness and acidity are related to the content of sugars and acids (Janse and Schols 1995; Malundo et al. 1995). Sweetness seems to be more influenced by the content in fructose than in glucose, while acidity is mostly due to the citric acid, present in higher content than malic acid in mature fruits (Stevens et al. 1977). Depending on the studies, acidity is more related to the fruit pH or to the titratable acidity (Baldwin et al. 1998; Auerswald et al. 1999). Both sugars and acids contribute to the sweetness and to the overall aroma intensity (Baldwin et al. 1998). More than 400 volatiles have been identified (Petró-Turza 1986), a few of them contributing to the particular aroma of tomato fruit (Baldwin et al. 2000; Tieman et al. 2017). Texture traits are more difficult to relate to physical measures or to fruit composition, although firmness in the mouth is partly related to the instrumental measure of fruit firmness (Causse et al. 2002), and mealiness was found related to the texture parameters of the pericarp (Verkerke et al. 1998). Several studies intended to identify the most important characteristics of consumer preferences (Causse et al. 2010).

Although production of high-quality fruits is dependent on environmental factors (light and climate) and cultural practices, a large range of genetic variation has been shown, which could be used for breeding tomato quality as reviewed by Davies and Hobson (1981), Stevens (1986), and Dorais et al. (2001). Causse et al. (2003) showed the importance of flavor and secondarily of texture traits in consumer appreciation. Cherry tomatoes have been identified as a source of flavor (Hobson and Bedford 1989), with fruits rich in acids and sugars. Long shelf life cultivars

have been described as generally less tasty than traditional ones (Jones 1986), with lower volatile content (Baldwin et al. 1991). Furthermore quality has a subjective component and there is not a unique expectation (Causse et al. 2010).

Wild relatives of *S. lycopersicum* may be an interesting source for improving fruit composition. Mutations of enzymes involved in the carbon metabolism were found in *S. chmielewskii* and in *S. habrochaites*, leading to particular sugar compositions: The *sucr* mutation in an invertase gene, in *S. chmielewskii,* provides fruits with sucrose instead of glucose and fructose (Chetelat et al. 1995). In *S. habrochaites*, an allele of the ADP glucose pyrophosphorylase enzyme was identified as much more efficient than the allele of the cultivated species, leading to an increase in the final sugar content of the fruit (Schaffer et al. 2000). Another locus *Fgr* modulates the fructose to glucose ratio in mature fruit, for which an allele from *S. habrochaites* yields higher fructose to glucose ratio (Levin et al.2000). The gene responsible is a sugar transporter of the SWEET family (Shammai et al. 2018). A gene *Lin5* encoding apoplastic invertase has been shown to be a QTL modulating sugar partitioning, the allele of *S. pennellii* leading to higher sugar concentrations than the *S. lycopersicum*one (Fridman et al. 2000). Wild tomato species may also provide original aromas, either favorable to tomato quality (Kamal et al. 2001) or unfavorable (Tadmor et al. 2002). Several genes responsible for the variation of aroma production in tomato have been cloned (Klee 2010; Bauchet et al. 2017a, b; Zhu et al. 2019).

Many efforts for improving fruit quality have failed because of the complex correlations between the various components or between yield or fruit weight and fruit components. The correlation between fruit weight and sugar content is frequently negative (Causse et al. 2001), but may be positive in other samples (Grandillo and Tanksley 1996a). In several studies involving sensory evaluation and fruit composition analyses, sweetness was positively correlated with reducing sugar content and sourness with titratable acidity (Baldwin et al. 1998; Causse et al. 2002). The firm texture is positively correlated with the instrumental firmness (Lee et al. 1999; Causse et al. 2002). Correlations were also detected between fruit size and antioxidant composition (Hanson et al. 2004). High-throughput metabolic profiling allowed getting insight on the whole metabolic changes in tomato fruits during fruit development or in various genotypes (Schauer et al. 2005; Overy et al. 2004; Baxter et al. 2007).

Addressing the demand of the producers and retailers of fresh-market tomatoes, breeders have considerably improved the external aspect and shelf life of tomato fruit. This improvement was obtained either by the use of ripening mutations or by the cumulative effect of several genes improving fruit firmness. Several mutations affecting fruit ripening are known, *rin* (ripening inhibitor) the most widely used, *nor* (non-ripening), and *alc* (alcobaca). Long shelf life cultivars have entered into the tomato market in the 1990s, but consumers have criticized their flavor (Jones 1986; McGlasson et al. 1987). The corresponding genes have been identified and extensively studied (Vrebalov et al. 2002; Ito et al. 2017; Wang et al. 2019). The impact of the enzymes involved in cell wall modifications during ripening on fruit firmness and shelf life has been extensively studied and modifications of polygalacturonase or pectin methylesterase activity were proposed to increase fruit shelf life and texture properties (Hobson and Grierson 1993).

Processing tomato has specific quality attributes. The self-pruning mutation (*sp*), characteristic of all the processing varieties, controls the determinate growth habit of tomato plants. Processing cultivars associate the *sp* mutation with concentrated flowering, fruit firmness, and resistance of mature fruits to overripening, allowing a unique mechanical harvest. The *sp* gene was cloned (Pnueli et al. 1998). This mutation does not only affect plant architecture, but also modulates the expression of genes controlling fruit weight and composition (Stevens 1986; Fridman et al. 2002; Quinet et al. 2011). This gene belongs to a gene family that is composed of at least six genes (Carmel-Goren et al. 2003). Recently, *sp* gene was also shown to be responsible for the loss of day-length-sensitive flowering (Soyk et al. 2017a, b). The jointless mutations, provided by the *j* and *j2* genes, are also useful for processing tomato production. The *j2* mutation has been discovered in a *S. cheesmaniae* accession, and has no abscission zone in fruit pedicel allowing harvest without calyx and pedicel during vine pick-up (Mao et al. 2000; Budiman et al. 2004).

2.2.2.3 Mild Stress as a Tool to Manage Quality

Tomatoes are produced all year round under contrasting environmental conditions, triggering seasonal variations in their sensory quality. Over the tomato growth cycle, different factors such as light intensity, air and soil temperatures, plant fruit load, plant mineral nutrition, or water availability influence the final fruit quality (reviewed in Davies and Hobson 1981; Poiroux-Gonord et al. 2010). Variations in temperature and irradiance during ripening affect carotene, ascorbic acid, and phenolic compound content in the fruit, although acid and sugar content are not modified considerably by these two factors (Venter et al. 1977; Rosales et al. 2007; Gautier et al. 2008). Changes in plant fruit load through trust pruning modify fruit dry matter content and final fruit fresh weight by disrupting the carbon flux entering the fruit (Bertin et al. 2000; Guichard et al. 2005). Water limitation and irrigation with saline water may positively impact tomato fruit quality, mainly through an increase in sugar content in fruit (either by concentration or accumulation effect) and contrasted effects on the secondary metabolite contents (Mitchell et al. 1991; De Pascale et al. 2001; Nuruddin et al. 2003; Johnstone et al. 2005; Gautier et al. 2008; Ripoll et al. 2016). The effects reported on fruit composition are associated or not with large yield loss depending upon the intensity and duration of the treatment and the development stage of the plant (Ripoll et al. 2014; Guichard et al. 2001; Albacete et al. 2015; Osorio et al. 2014).

Thus, the optimization of the growth practice, in particular, water management, is considered in horticultural production as a tool to manage fruit quality while limiting yield losses, offering the opportunity to address simultaneously environmental issues and consumer expectations of tastier fruits (Stikic et al. 2003; Fereres and Soriano 2006; Costa et al. 2007). The genetic variability of tomato response to water limitations and other abiotic constraints and their combination still need to be deciphered to develop genotypes adapted to these practices (Poiroux-Gonord et al. 2010; Ripoll et al. 2014). Large phenotypic variation in response to a wide range of climate and

nutrition conditions exists in the genus *Solanum* at both inter- and intraspecies levels (reviewed in Labate et al. 2007).

Several authors attempted to measure genotype-by-environment (GxE) interactions on tomato fruit quality by repeating the same experiment in different locations or/and under several growing facilities (Auerswald et al. 1999; Johansson et al. 1999; Causse et al. 2003) or by building experimental design to isolate the effect of particular environmental factors on large number of genotypes (see Semel et al. 2007; Gur et al. 2011; Albert et al. 2016a; for water availability and Monforte et al. 1996, 1997a, b for salt stress). In different experiments, the G x E interaction was significant for the fruit quality traits measured (including fruit fresh weight, secondary and primary metabolism contents, and fruit firmness), but generally accounted for a low part of the total variation in comparison to the genotype main effect. Albert et al. (2016a) dissected further the genotype by watering regime interaction in an intraspecific *S. lycopersicum* recombinant inbred line population grown under two contrasting watering regimes in two locations. Besides, they detected large genetic variation and genetic heritabilities under both watering regimes, encouraging the possibility to develop tomato genotypes with an improved fruit quality under mild water stress.

2.2.3 Biotic and Abiotic Stresses

2.2.3.1 Biotic Stresses

Pests and Pathogens of Tomatoes

Pests and pathogens cause great damage to tomato crops in field and in greenhouse. Tomato is afflicted by at least 200 pests and pathogens, from most major classes such as bacteria, fungi, oomycetes, viruses, nematodes, insects, and spider mites (Foolad and Panthee 2012). Insects are as diverse as aphids, thrips, whiteflies, leafminers, fruit borers, caterpillars, leafhoppers; they disturb the foliage development perturbing photosynthesis carbon assimilation, deform fruit appearance, and ultimately reduce the yield. Moreover several of them may transmit viruses. A few viruses may also be transmitted by contact such as Tobamoviruses. Foolad and Panthee (2012) made a compendium of the most important diseases on tomato caused by 21 fungi, 1 oomycete, 7 bacteria, 7 viruses, and 4 nematodes.

Diseases contribute to almost 40% of tomato yield loss in the field worldwide. The occurrence of those diseases varies according to the geographical regions where tomatoes are grown, environmental conditions, and cultural practices. For instance, high relative humidity favors the stem canker and the early blight caused by different species of *Alternaria*, and warm air temperature and damp conditions favor the gray leaf spot caused by different species of *Stemphylium* while low soil temperature favors the corky root rot caused by *Pyrenochaeta lycopersici* and cool air temperature favors the *Fusarium* crown and root rot. Otherwise, high air humidity alternating with

cool night temperature is favorable for the development of late blight caused by the Oomycete *Phytophthora infestans* that can easily destroy up to 100% of field or greenhouse tomato crops.

Impact of Climate Change on Pest and Pathogen Resistance

Climatic prediction models indicate severe weather pattern changes, which will result in frequent droughts and floods, rising global temperatures, and decreased availability of fresh water for agriculture. A great challenge is thus to improve the robustness of plant resistance and tolerance to pests and pathogens, to a wide array of combined biotic and abiotic stress combinations. Tomato crops are exposed to multiple abiotic stresses in fields and greenhouses that could attenuate or enhance the response to biotic stress. Recent studies have revealed that the response of plants to combinations of two or more stress conditions is unique and cannot be directly extrapolated from the response of plants to each stress applied individually. Few studies report the tomato responses to biotic x abiotic stress combinations.

It is well known for a long time that high temperatures (above 30 °C) inhibit plant defense mechanisms making major resistance genes frequently dysfunctional. For instance, the tomato *Mi-1.2* resistance gene to root knot nematode and *Cf-4*/*Cf-9* genes to *Cladosporium fulvum* are inactivated at high temperature (de Jong et al. 2002; Marques de Carvalho et al. 2015). Other abiotic stresses could also modify tomato immunity. For instance, drought stress reduces disease severity to *Botrytis cinerea* and stops the development of *Oidium neolycopersici*. Irrigation with saline water increases disease severity to *Fusarium oxysporum f. sp. radicis-lycopersici* and to *Phytophthora capsici*, does not affect *Botrytiscinerea* infection, and reduces infection by *O. neolycopersici* (Achuo et al. 2006; Dileo et al. 2010). Bai et al. (2018) suggest that salt stress modifies the hormone balance involved in sthe ignaling pathway that could decrease the resistance level conferred by the *Ol-1* gene but has no effect on resistance conferred by *Ol-2* and *Ol-4* genes, those three genes controlling *O. neolycopersici* responsible for tomato powdery mildew. Limited nitrogen or water supplies increase tomato stem susceptibility to *B. cinerea* (Lecompte et al. 2017). Very high environmental pressure caused by elevated ozone concentration eliminates the effect of potato spindle tuber viroid (PSTVd) on biomass reduction in tomato (Abraitiene and Girgzdiene 2013). The few examples cited here mainly focused on the effect of environmental changes on tomato immunity controlled by major resistance genes. Much less publications concern resistance QTLs yet, even if research on the effect of G x E interactions on resistance to biotic stress is increasing. Actually, there is a knowledge gap in the identification of QTLs involved in responses to combined biotic antibiotic stresses.

New Emerging Tomato Diseases

Global climate change is supposed to result in the emergence of new pests and pathogens into production areas. Tomato health management is thus challenged by the emergence of new races that overcome resistance genes deployed in cultivars and by novel introductions due to the world's agricultural market and the climate change. Several diseases are reemerging or emerging on tomato crops such as the late blight caused by *P. infestans* (Fry and Goodwin 1997), the leafminer *Tuta absoluta*, and new viruses that increasingly affect tomato crops. The Potexvirus *Pepino mosaic virus* (PepMV), mainly mechanically transmitted, emerged around 2000 and causes now significant problems on glasshouse tomato crops worldwide (Hanssen and Thomma 2010). Recently, the *tomato brown rugose fruit virus* (ToBRFV), a new tobamovirus present in Jordania and Israel, was able to break *Tm-2*-mediated resistance in tomato that had lasted 55 years (Maayan et al. 2018). The emergence of new viruses is often coupled with the proliferation of adapting insect vectors. Tomato production in tropical countries is severely constrained by insects and mites, particularly whiteflies (*Bemisia tabaci*) that could transmit begomoviruses (including TYLCV known for a long time but also many other emergent begomoviruses) and fruit borers that cause serious problems during the reproductive phase of the crop. Deploying host resistance against viruses, when available, is actually the most effective method for controlling viruses and preventing their spread, even if in recent years resistance-breaking strains of viruses have been characterized, against which these resistance genes are no longer effective. For example, the resistance gene *Sw-5* confers resistance to TSWV transmitted by the thrips *Frankliniella occidentalis*, as well as to related orthotospovirus species such as *Groundnut ring spot virus* (GRSV) and *Tomato chlorotic spot virus* (TCSV) recently emerged in the United States and the Caribbean. But it has been overcome by new virulent TSWV strains (Oliver and Whitfield 2016; Turina et al. 2016).

In addition, the bacteria *Clavibacter michiganense* subsp. *michiganensis* (Cmm), causing the bacterial canker disease devastating tomato production worldwide, is considered as a real plague. This bacteria is one of the few pathogens transmitted by seeds. To fight the spread of this disease, Good Seed and Plant Practices (GSPP; https://www.gspp.eu/), adopted by sites or companies working on tomato breeding and plantlet production, prevent tomato seed and plant lots from being infected by Cmm. GSPP-accredited sites or companies are granted the right to market their tomato seeds and young plants with the GSPP logo. The first GSPP seed and plants have been available since July 2011 in France and the Netherlands.

So far, there is no sufficiently sustainable or effective genetic leverage available for tomato breeding programs to combat these new diseases. Their sustainable control is a goal of global importance, which will probably require combining several genetic strategies associated with cultural practices to effectively manage those novel pathosystems.

2.2.3.2 Abiotic Stresses

Tomato domestication and improvement have focused for a long time on agronomic traits associated with productivity, quality, and disease resistance. Crop resilience facing the global climate change nowadays represents one of the most challenging aspects of plant breeding, raising awareness in developing climate-smart crops. It has led to the characterization of new breeding traits related to abiotic stress tolerance. Understanding the complex genetic architecture of plant response to environmental changes appears to be central for the development of new cultivars. Indeed, variations in environmental factors usually induce some disorders at molecular, physiological, and morphological levels that may alter the agronomic performance of crops. Stress adaptation in plants at the molecular level requires generally the activation of multiple stress-response genes that are involved in different metabolic pathways for growth maintenance and which expression is regulated by various transcription factors (TFs). The genomic era facilitated the characterization of such stress-response genes across plant species that were assigned to a diverse family of TFs. The major families of TFs playing significant roles in stress tolerance that were described in the literature include the basic leucine zipper (bZIP), dehydration-responsive element binding protein (DREB), APETALA 2 and ethylene-responsive element binding factor (AP2/ERF), zinc fingers (ZFs), basic helix-loop-helix (bHLH), heat-shock proteins (Hsp), and others (Lindemose et al. 2013). The functions covered by these TFs are very common in the plant kingdom; however, each species presents specificities.

In tomato, Bai et al. (2018) characterized the 83 WRKY genes identified in previous studies and displayed their different roles in response to pathogen infection, drought, salt, heat, and cold stresses. Some genes were highlighted as being altered in their expression by different stress such as drought and salinity stress (*SlWRKY3; SlWRKY3, and SlWRKY33*) pointing pertinent candidates for further investigation. The expression profiles of other tomato stress-response genes were also investigated for a class of genes belonging to the ERFs family (Klay et al. 2018) and Hsp20 gene family (Yu et al. 2017). Examples of single genes involved in tomato tolerance to abiotic stress were also described including the *SlJUB1* promoting drought tolerance; *DREB1A* and *VP1.1* playing a role in salinity tolerance, and *ShDHN, MYB49,* and *SlWRKY39* for tolerance to multi-stress factors (Liu et al. 2015; Sun et al. 2015; Cui et al. 2018).

Tomato is a suitable plant model to study the genetics of plant response to the environment and for deciphering the genotype-by-interaction (GxE) mechanisms, due to the wide range of environmental conditions—from fields to greenhouse cultivation—for its production highlighting its large adaptability.

Water Deficit

Tomato is a high water-demanding crop (Heuvelink 2005) making water resource management one of the key factors essential for the crop. The amount of irrigation

water in tomato production is usually managed according to the reference evapotranspiration (ET_0) and the developmental stage. When water deficit (WD) occurs during the cropping period, morphological and molecular changes are usually observed that hamper the final yield production. Several studies addressed the impact of WD stress on tomato, most of which establishing WD as a percentage of water restriction, according to the optimal water requirement (Albert et al. 2016a, b; Ripoll et al. 2016; Diouf et al. 2018).

From an agronomic point of view, the main consequence of WD on tomato is yield reduction that can be severe when stress occurs during fruit development (Chen et al. 2013). However, all developmental stages are susceptible to WD to a level depending on the cultivar and stress intensity. Seed germination is the first step exposed to environmental stress. In tomato, a delay or even an inhibition of seed germination was observed with the application of osmotic stress (Bhatt and Rao 1987). Water deficit during vegetative and reproductive development negatively affects the overall economic performance of the crop but positive effects on fruit quality are documented. Indeed, Costa et al. (2007) described some trade-off between yield decrease and increase in quality component on fruit trees and vegetables including tomato where enhancement in fruit quality compounds such as vitamin C, antioxidants, and soluble sugars was observed under WD stress (Albert et al. 2016a; Ripoll et al. 2014; Patanè and Cosentino 2010; Zegbe-Domínguez et al. 2003). The two groups of accessions constituted of cherry tomato and large fruit accessions usually show different sensitivity to environmental stresses. For instance, a study using a panel of unrelated lines tested under control and WD conditions revealed that large fruit tomato accessions were more susceptible and had higher responsiveness to WD (Albert et al. 2016b). This study also showed that the increase in the sugar content in fruit under WD is due to a reduction in fruit water content and not due to increased synthesis of sugars. However, Ripoll et al. (2016) found higher fructose and glucose synthesis in tomato fruits submitted to WD stress for different stages of fruit development, indicating that both dilution effect and higher sugar synthesis are responsible for fruit quality enhancement in tomato under WD. The omics approaches allow targeting specific genes and studying their variation in expression level according to different environmental conditions. Some examples of water deficit response genes involved in tomato tolerance to drought are published. This is the case for *SlSHN1* gene that induces tolerance to drought by activating downstream genes involved in higher cuticular wax accumulation on leaves (Al-Abdallat et al. 2014). Tolerance to drought induces early activation of signaling pathways to elicit drought-related genes. Wang et al. (2018) identified a drought-induced gene (*SlMAPK1*) playing an active role in the antioxidant enzyme activities and ROS scavenging leading to higher drought tolerance.

Salinity Stress

Soil salinity has become problematic in agriculture especially in the Mediterranean region where soil aridification and non-sustainable irrigation practices tend

to increase the surface area of salty soils (Munns and Tester 2008). Munns and Gilliham (2015) defined salinity stress (SS) as the level of salinity up to which the energy for plant growth is redirected into defense response. Considering yield as a measure of tolerance to SS, tomato is a crop that can tolerate up to 2.5 dS m^{-1} of salinity and cherry tomatoes are less salt sensitive than large fruit accessions (Scholberg and Locascio 1999; Caro et al. 1991). Over the above-mentioned threshold, a significant yield decrease is observed. Yield reduction under SS in tomato was found to be associated with a reduction in both fruit size and fruit number (Scholberg and Locascio 1999). As for WD, SS also leads to an increase in sugar content in tomato fruits (Mitchell et al. 1991). Besides, SS leads to changes in the cation/anion ratio and the increase in sugar content in fruits of salinized plants likely results from the interaction between reduced fruit water content, increased ion content, and maintained hexose accumulation (Navarro et al. 2005). These changes are the consequences of tomato response to the osmotic adjustment. The threshold for salinity tolerance defined above was set upon the characterization of a few selected tomato cultivars. However, Alian et al. (2000) noticed a high genotypic variability in response to salinity in fresh-market tomato cultivars. This highlights the possibility and the potentiality for the crop to breed salt-tolerant cultivars.

Facing SS, plants deploy a variety of response to rebalance and reestablish the cellular homeostasis. Physiological responses to SS involve the ionic channels transporters as they are highly needed to regulate the ionic imbalance (Apse et al. 1999). In their study, Rajasekaran et al. (2000) screened salinity tolerance in a number of tomato wild relatives and associated salinity tolerance mainly to a higher K^+/NA^+ ratio in roots. High genetic variability was observed in *S. pimpinellifolium* accessions for yield and survival traits in response to SS (Rao et al. 2013). Among yield component traits, fruit number was the most affected trait in both wild and cultivated populations (Rao et al. 2013; Diouf et al. 2018). Breeding salt-tolerant variety thus seems possible by using either physiological traits or agronomic performance under salinity, as sufficient genetic variability is available in several tomato genetic resources.

Temperature Stress

All crop species have an optimal temperature range for growth. Tomato is known as a crop that can grow in a wide range of environments, from elevated areas with low temperatures to tropical and arid zones where high temperatures usually occur. Based on the crop simulation model, Boote et al. (2012) indicated that the optimal growth for tomato and its fruit development is about 25 °C. Temperatures below 6 °C and above 30 °C severely limit growth, pollination, and fruit development and could negatively impact final fruit yield. Studies on different accessions and wild relative species of tomato helped understanding how the crop responds to low and high-temperature stresses.

High-temperature stress

The most visible effect of climate change is the rise in temperature in different areas of the world. The end of the twenty-first century is expected to come with the increase in global warming causing significant yield decrease in major worldwide cultivated crops (Zhao et al. 2017). When plants are exposed to fluctuating high temperatures (HT), ensuing stress is considered as short-term heat stress; when the period of exposure to HT is short or long-term heat stress. if plants experienced the HT for several consecutive days. The latter has more dramatic effects on agronomic performances of crops, especially when it occurs during the entire cropping season. In open field trials, seed germination is more generally impaired by high temperature of the soil and can differ to the effects of elevated air temperatures. However, flowering period is described as the most critical stage under HT stress (Wahid et al. 2007). Severe yield decrease caused by HT stress arises from the hampered reproduction performance with a high impact of HT on reproductive organs (Nadeem et al. 2018). In tomato, HT stress around flowering was shown to inhibit reproduction by altering male fertility at a high degree and female fertility at a lower rate (Xu et al. 2017a, b). In areas where the temperature range could be reliably predicted, managing the sowing date to avoid HT stress around anthesis is an important factor to consider. Tomato male fertility could be considered as the main factor limiting reproduction success under HT stress. This has led some studies to use pollen traits as a measure of heat tolerance instead of only final yield (Driedonks et al. 2018). Male reproductive traits were highly variable among wild species and some accessions showed high pollen viability compared to cultivated cultivars. This opens possibilities for transferring heat-tolerant alleles from wild donors to cultivated tomato. A reduction of fruit setting was also observed in cultivated tomato with a higher rate of parthenocarpic fruits noticed under HT stress at 26 °C in growth chambers (Adams et al. 2001). These authors noticed that fruit maturation is accelerated under higher temperature mostly when fruits are exposed themselves to heating periods, that could alter final fruit quality composition.

Considering the important effect of HT on agriculture, numerous studies successfully tackled and identified several heat-response genes (Waters et al. 2017; Keller and Simm 2018; Fragkostefanakis et al. 2016). Heat-response genes are commonly regulated by the activity of several heat stress transcription factors (HSFs) as described in the literature for different organisms. This has led to the investigation of the roles played by HSFs in thermo-tolerance and majors HSFs depicted across plant species could lead to the development of heat-tolerant tomato via genome editing(Fragkostefanakis et al. 2015).

Chilling and cold stress

Chilling stress (CS) is usually considered when plants are growing in temperature below the optimal growth range and above 0 °C, just before freezing stress. The geographical distribution of wild tomato species includes elevated zones where annual temperatures can be below the optimal growth for cultivated tomatoes (Nakazato et al. 2010). This denotes that adaptation to sub-optimal temperature is possible in tomato.

Adams et al. (2001) observed that at 14 °C, tomato growth was reduced. Lower temperatures equally induce some chilling stress symptoms as reviewed by Ploeg and Heuvelink (2005) who noticed that below 12 °C, almost no growth is observed for tomato. As for HT stress, fruit set is inhibited in tomato mainly due to poorer pollen viability. Reduction in the number of flowers, number of fruits, and final yield was observed with low temperature that also affects the partitioning of photosynthetic products (Meena et al. 2018). Indeed, photosynthesis is highly impacted during CS and several related physiological parameters are described. For example, the relative water content, chlorophyll fluorescence, and accumulation of phenolic compounds are associated to mechanisms inducing cold tolerance (Giroux and Filion 1992; Dong et al. 2019; Khan et al. 2015). By the way, Meena et al. (2018) showed that external application of phenolic compounds—notably salicylic acids—significantly increased tomato tolerance to CS. Low-temperature stress during plant growth and development adversely affects the fruit quality of tomato and reduces non-enzyme antioxidants such as lycopene, β-carotene, and α-tocopherol.

Transcriptome analysis depicted some genes responding to CS in tomato. For example, Zhuang et al. (2019) identified a cold response tomato gene (*SlWHY1*) whose expression is enhanced under 4 °C, playing a role in photosystem II protection and starch accumulation in chloroplast. For several plant species, signal transmission of CS involves the C-repeat binding factor (CBF) (Jha et al. 2017) leading to downstream activation of cold responsive genes for cold tolerance. Major types of CBF are known to regulate cold acclimation in tomato (Mboup et al. 2012). In a recent review, Kenchanmane Raju et al. (2018) showed that genes related to photosynthesis and chloroplast development were consistently repressed in response to low temperature and the most conserved set of genes up-regulated in response to low-temperature stress belonged to the CBFs, WRKYs, and AP2/EREBP transcription factors. These results highlighted some genes and family of transcription factors that could be targeted for breeding tomato adapted to low-temperature conditions.

Mineral Nutrition Deficiency

The positive effect of mineral nutrition on plant growth has long been recognized and mineral elements are usually classified as essential or non-essential; the latter being, however, beneficial for plant development (Marschner 1983). The macronutrients are mostly necessary to stimulate growth and nitrogen (N), potassium (K^+), and phosphorus (P) are among the most important in higher plants. Their use has a significant environmental cost and thus selection for reduced need of fertilizer could be useful for the production of smart crops.

Nitrogen

Nitrogen *(N)* is among the most important limiting nutrient for tomato development. Insufficient N nutrition can cause severe consequences to economically important traits. It was shown that N-deficiency negatively affects the number of fruits, fruit size, storage quality, color, and taste of tomato (Sainju et al. 2003). As evidenced by de

Groot et al. (2004) and Larbat et al. (2012), tomato growth rate is linearly correlated to N supply. Low N supply limits growth in leaves but promotes root development and this activity was mainly linked to variation in cytokinin concentration. An increase in accumulation of phenolic compounds is also a notable consequence of N-deficiency in tomato. Indeed, Larbat et al. (2012) found that sequential limitation of N nutrition resulted in an up-regulation of genes associated with phenolic biosynthetic pathway.

Oversupply of N above the required optimal level is usual in tomato cultivation due to its beneficial effects and the willing to avoid the negative effects of limited N; however, excess of N can overproduce vegetative growth at the expense of fruit development and rapid fruit maturation and inhibits root system development besides its negative effect on groundwater pollution (Du et al. 2018). This highlights the necessity to manage N nutrition in tomato cropping that can be achieved through a good characterization of genes involved in nitrogen use efficiency. Apart from genetic solutions to improve tolerance to N-deficiency, real-time greenhouse management technics are now available with the use of computational intelligence systems and definition of new stress tolerance traits like leaf reflectance as proposed by Elvanidi et al. (2018).

Phosphorus

Phosphorus *(P)* is usually present in the soil in a form that is not accessible for plants. Fertilization is thus required for major crops including tomato. Plant capacity to acquire P present in the soil is associated to root morphological changes and involves variation in plant-hormone levels. Early plant development is very sensitive to P nutrition and sub-optimal P supply in tomato can lead to impaired growth and plant development (Sainju et al. 2003; de Groot et al. 2004). Phosphate deficiency induces modification in root architecture morphology via increased auxin sensitivity leading to the activation of P transporter genes to remobilize P from lipids and nucleic acids (Schachtman and Shin 2007). Long-term adaptation to P starvation appears to be linked to reduced primary root growth at the expanse of lateral root growth that is promoted (Xu et al. 2012). Besides, the net-photosynthesis decreased in the leaves with reduced sucrose content after long exposure to P starvation, while the starch content increased. These authors also identified different genes responding to P starvation that belong to the 14-3-3 gene family encoding phosphoserine-binding proteins involved in protein–protein interactions.

In open field conditions, a larger root system development may be required for greater exploration and acquisition of P present in the soil. For greenhouse production where the P input can be managed, the need is more in the characterization of P-deficiency response genes and their correlation to morphological and physiological response for the development of cultivars with higher P-use efficiency.

Potassium

The importance of *Potassium* (K^+) in plant nutrition has been attested with its involvement in important physiological processes such as photosynthesis, osmoregulation, and ion homeostasis (Marschner 1983; Pettigrew 2008). Yield and quality are known to be impacted by the photosynthesis capacity of the plant and thus could be directly

linked to the K^+ concentration in plant organs. In tomato, positive effects of K^+ supply have been described for vigorous growth, early flowering, fruit number production, and higher rate of titratable acidity (Sainju et al. 2003). Increase in soluble solids, antioxidative capacity, and ascorbic acid were also observed in tomato fruits (Tavallali et al. 2018) with K^+ supply. Alternatively, deficiency in K^+ nutrition induced morphological injuries resulting in brown marginal scorching with interveinal chlorosis and yellowing of tomato leaves. Indeed, plants usually sense external changes in K^+ concentration leading to the activation of signal transduction to reestablish the ion homeostasis. Adaptation to low K^+ supply is achieved through different K^+ movement monitored by different K^+ transporters. The function and role of different transporter channels involved in K^+ movement in plants were described by Wang and Wu (2015) including the *HAK/KUP/KT* family of transporters seemingly crucial for K^+ transport. The transport of K^+ in plants is initiated in the roots and the major impact of K^+ deficiency is on root architecture (Zhao et al. 2018). Improving root system development could then directly alleviate the deleterious effect of K^+ deficiency.

Calcium

Calcium is an important ion involved in diverse metabolic processes central to plant growth and development (Bush 1995). Several reviews regarding the role of this macronutrient on plants pinpoint its involvement in the cell wall rigidity, cell membrane stability, the control of ion transport, and the signaling of abiotic stress (Hepler 2005; Hirschi 2004; Wilkins et al. 2016). Calcium deficiency is associated with changes in the cell ion homeostasis and had been related to nutritional imbalance incidence, among other problems in plants. The diminution of Ca^{2+} nutrition as well as environmental stimuli has been considered as leading changes in the cytosolic concentration of Ca^{2+} mediating some modifications in Ca^{2+} flux through transporter proteins in order to reestablish the ion homeostasis (Bush 1995). Besides, plant response to abiotic stresses is tightly linked to modification in Ca^{2+} homeostasis essential to signaling and subsequent plant tolerance deployment (Rengel 1992; Wilkins et al. 2016). In tomato, Ca^{2+} nutrition under salinity stress, for example, has been shown to alleviate the negative impact induced by salt toxicity on plant and fruit growth (Tuna et al. 2007). This was linked to Ca^{2+} use efficiency upon the availability of sufficient Ca^{2+} concentration in the plant. Calcium-use efficiency is an important characteristic for plant adaptation to environmental stress and this trait is genetically variable indicating the possibility for breeding cultivars with high potentiality of adaptation to low Ca^{2+} input (Li and Gabelman 1990). However, most tomato accessions are susceptible to Ca^{2+} deficiency and among the undesirable effects associated with this stress, a physiological disorder at the fruit named blossom-end rot (BER) has been noticed (Adams and Ho 1993). Other studies correlate BER incidence to differences in genotype capacity to limit oxidative stress by increasing the synthesis of antioxidant metabolites such as ascorbate (Rached et al. 2018) or genotype sensitivity to gibberellin (Gaion et al. 2019) suggesting a non-direct effect of Ca^{2+} depletion in the cells to induce BER symptoms. Moreover, through transcriptomic analyses, de Freitas et al. (2018) identified candidate genes inhibiting BER in tomato

that were mostly associated with resistance against oxidative stress. Tomato BER is thus a complex physiological disorder occurring from the impact of abiotic stresses, genetic, physiological, or agronomic factors with possible interaction between them (Hagassou et al. 2019). However, regarding the tight link between BER and the level of Ca^{2+} in tomato, the characterization of the channel gene families involved in regulation of Ca^{2+} homeostasis under different environmental stimuli could help to disentangle the underlying molecular mechanisms of the interaction between BER incidence and Ca^{2+} concentration.

2.2.3.3 Stress Combination

Plant responses to individual stress at a specific growth stage are well documented and avenues for crop breeding to enhance tolerance to a particular stress were provided. However, observations in the nature and in open field conditions clearly brought to light that stress combination is a common phenomenon, especially with the climate change that has an incidence of co-occurring of environmental stresses such as WD and HT stress. Climate change trend has also an impact on pathogen spreading and new disease appearance and distribution (Harvell et al. 2002). Different scenarios of biotic and abiotic stress combination are then expected to arise, according to the geographical regions and areas of crop cultivation. With different crop species exposed to different stress treatments, Suzuki et al. (2014) presented a stress matrix with the potential positive and negative effects of various patterns of stress combination. The global effect of combined stresses on yield, morphological, and physiological traits on plants can be highly different from those of a single stress. Thus the stress matrix proposed by Suzuki et al. (2014) would be highly useful if specified for tomato, to achieve a global view of how stress combinations could be managed in breeding programs.

Examples of studies conducted in tomato to assess the impact of combined stress on different traits are available in the literature. Zhou et al. (2017) showed that physiological and growth responses to the combined WD and HT stresses had a similar pattern across different cultivars but the response was different from the single heat response. Combination of HT stress and SS on tomato showed, however, less damage on growth than the application of SS alone (Rivero et al. 2014). Besides morphological changes, some studies conducted on the model species *Arabidopsis thaliana* demonstrated that variations in gene expression under stress combination are highly independent of variation induced by single stress application (Rasmussen et al. 2013).

In addition to the combination of different environmental stresses, simultaneous biotic and abiotic stresses, which are usually studied separately, are expected, especially in field conditions. Recently, studies were performed to fill the lack of knowledge about the genetic response to biotic and abiotic stress combination compared to a single stress effect. In tomato, Kissoudis et al. (2015) studied the combined effect of salinity and powdery mildew (*Oidium neolycopersici*) infection and found that salt stress increases the powdery mildew susceptibility in an introgression line

population. Anfoka et al. (2016) showed that long-term HT stress was accompanied with TYLCV accumulation in tomato reducing by the way the HT response efficiency. Some stress responses such as endogenous phytohormone secretion and ROS production are important physiological processes involved in both abiotic and biotic plant responses (Fujita et al. 2006) that could require the action of a group of genes regulating both types of stresses. Some genes were shown to be involved in the simultaneous response to biotic and abiotic stress on tomato such as the *SlGGP-LIKE* gene that Yang et al. (2017) found to be correlated to higher ascorbic acid synthesis, less ROS damage, and higher tolerance to chilling stress, however, its suppression led to higher ROS accumulation and resistance to *P. syringae*. Using genomic data from multiple stress-response genes, Ashrafi-Dehkordi et al. (2018) performed a comparative transcriptome analysis on tomato and found a set of genes the expression of which is altered under simultaneous biotic and abiotic stresses. Single tomato genes involved in responses to both abiotic stresses and *Pseudomonas syringae* (Sun et al. 2015) or *Phytophthora infestans* (Cui et al. 2018) were identified making them suitable targets for breeding. However, up to now, stress combination is mostly addressed in a genomic or metabolomics point of view and few examples of genetic response to combined stress are documented except in *A. thaliana* (Thoen et al. 2017).

The impact of mineral nutrition on plant pathogen is also important: the enhanced phenolic and volatile compounds accumulated with N fertilization have been shown to interact with tomato disease induced by insect attacks such as whitefly, *Bemisia tabaci* (Islam et al. 2017), and leafminer *Tuta absoluta* Han et al. (2015). Interaction between N supply and tomato resistance to *Botrytis cinerea* has also been described (Lecompte et al. 2010). Nitrogen supply not only interacts with biotic tolerance in tomato but has also a different impact according to some abiotic factors.

Among abiotic stresses, salinity is the most important stress in tomato affecting tomato responses. The simultaneous effect of salinity stress and N input was measured by Papadopoulos and Rendig (1983) who showed that the positive effects of N supply on growth and fruit weight were suppressed by salinity stress reaching up to 5 dS m^{-1}.

In an interspecific introgression line (IL) population, (Frary et al. 2011) showed that salinity decreased the leaf Ca^{2+} content by 47% and K^{+} content by 8%. *S. pennellii* alleles were found contributing mostly to higher Ca^{2+} content under both control and salinity stress suggesting this species as a natural resource for salinity and low Ca^{2+} input stress tolerance.

2.3 Genetic and Genomic Resources for Trait Breeding

2.3.1 Genetic Resources

2.3.1.1 Origin of Tomato and Its Wild Relatives

Genetic resources for food and agriculture are keys to global food security and nutrition (FAO 2015). In crop production, maintaining genetic diversity is an essential strategy not only to breed new varieties, to identify candidate genes of target traits, to dissect the evolutionary history, but also to reduce the effects of biotic and abiotic stresses, etc.

Tomato belongs to the large and diverse Solanaceae family also called Nightshades, which includes more than three thousand species. Among them, major crops arose from Old world (eggplant from Asia) and New world (pepper, potato, tobacco, tomato from South America). The *Lycopersicon* clade (Table 2.2) contains the domesticated tomato (*Solanum lycopersicum*) and its 12 closest wild relatives (Peralta et al. 2005). Charles Rick and colleagues started the first prospections and studies on the tomato wild relatives in the 1940s.

Tomato clade species are originated from the Andean region, including Peru, Bolivia, Ecuador, Colombia, and Chile. Their growing environments range from sea level to 3,300 m altitude, from arid to rainy climate and from Andean Highlands to the coast of Galapagos Islands. Their habitats are often narrow and isolated valleys and they were adapted to many climates and different soil types. The large range of ecological conditions contributed to the diversity of the wild species. This broad variation is also expressed at the morphological, physiological, sexual, and molecular levels (Peralta et al. 2005).

The domestication of tomato is due to a divergence from *S. pimpinellifolium* that occurred several thousand years ago. It probably happened in two steps, first in Peru, leading to *S. lycopersicum cerasiforme* accessions then in Mexico, leading to large fruit accessions (reviewed in Bauchet and Causse 2012) and confirmed by molecular analyses (Blanca et al. 2012; Lin et al. 2014; Blanca et al. 2015). Only a few tomato seeds were brought back from Mexico to Europe, leading, after domestication, to a new genetic bottleneck. The tomato cultivation first slowly spread in southern Europe and it is only after the Second World War that its intentional selection started and that it was spread over the world.

2.3.1.2 Genetic Resources as Sources for Adaptation

There are more than 83,000 tomato accessions stored in different seed banks worldwide (FAO 2015). These seed banks include the Tomato Genetic Resources Center (TGRC) in Davis, USA (https://tgrc.ucdavis.edu/), the United States Department of Agriculture (USDA) in Geneva, USA (https://www.ars.usda.gov/), the World Vegetable Center in Taiwan, (https://avrdc.org/), the Centre for Genetic

Table 2.2 Tomatoes and their wild relative species of the Lycopersicon section according to Peralta et al. 2005 "Lycopersicon group" corresponds to the red- and orange-fruited species). For further details of crossability and other biological parameters of wild tomatoes see Grandillo et al. (2011)

Species	Distribution	Habitat; (elevational range	Section according to Peralta et al. (2005)
Solanum lycopersicum L.	Globally cultivated domesticate	Cultivated; sea level-4000 m	*Lycopersicon* "Lycopersicon group"
Solanum pimpinellifolium L.	Southwestern Ecuador to northern Chile (many northern populations in Ecuador are admixture with *S. lycopersicum*; Peralta et al. 2005; Blanca et al. 2013)	Dry slopes, plains and around cultivated fields; sea level-3000 m	*Lycopersicon* "Lycopersicon group"
Solanum peruvianum L.	Central Peru to northern Chile	Dry coastal deserts and lomas; sea level-3000 m	*Lycopersicon* "Eriopersicon group"
Solanum cheesmaniae (L. Riley) Fosberg	Galápagos Islands	Dry, open, rocky slopes; sea level-1300 m	*Lycopersicon* "Lycopersicon group"
Solanum galapagense S.C. Darwin and Peralta	Galápagos Islands	Dry, open, rocky slopes; seashores; sea level-1600 m	*Lycopersicon* "Lycopersicon group"
Solanum arcanum Peralta	Northern Peru	Dry inter-Andean valleys and in coastal lomas (seasonal fog-drenched habitats); 100–4000 m	*Lycopersicon "Arcanum group"*
Solanum chmielewskii (C.M. Rick, Kesicki, Fobles & M. Holle) D.M. Spooner, G.J. Anderson & R.K. Jansen	Southern Peru and northern Bolivia	Dry inter-Andean valleys, usually on open, rocky slopes; often on roadcuts; 1200–3000 m	*Lycopersicon "Arcanum group"*
Solanum neorickii D.M. Spooner, G.J. Anderson & R.K. Jansen	Southern Ecuador to southern Peru	Dry inter-Andean valleys; 500–3500 m	*Lycopersicon "Arcanum group"*

(continued)

Table 2.2 (continued)

Species	Distribution	Habitat; (elevational range	Section according to Peralta et al. (2005)
Solanum chilense (Dunal)Reiche	Coastal Chile and southern Peru	Dry, open, rocky slopes; sea level-4000 m (B. Igic, pers. comm. Has suggested the higher elevation plants represent a new species)	*Lycopersicon "Eriopersicon group"*
Solanum corneliomulleri J.F. Macbr.	Southern Peru (Lima southwards)	Dry, rocky slopes; 20–4500 m (low elevation populations associated with landslides in southern Peru)	*Lycopersicon "Eriopersicon group"*
Solanum habrochaites S. Knapp and D.M. Spooner	Andean Ecuador and Peru	Montane forests, dry slopes and occasionally coastal lomas; 10–4100 m	*Lycopersicon "Eriopersicon group"*
Solanum huaylasense Peralta	Río Santa river drainage, north-central Peru	Dry, open, rocky slopes; 950–3300 m	*Lycopersicon "Eriopersicon group"*
Solanum pennellii Correll	Northern Peru to northern Chile	Dry slopes and washes, usually in flat areas; sea level-4100 m	*Lycopersicon "Neolycopersicon group"*

Resources, in the Netherlands (https://www.wur.nl/en/Research-Results/Statutory-research-tasks/Centre-for-Genetic-Resources-the-Netherlands-1.htm), and others. These seed banks maintain most of the genetic diversity of tomatoes.

Thanks to the pioneering work of Charles Rick, the Tomato Genetics Resource Center of the University of California, in Davis, maintains the largest collection of wild relative accessions that he prospected during his life. This collection has been an important source of diversity for breeding tomato and for gene discovery. For instance, there is a collection of 46 *S. pennellii* that is only found in Peru, and is particularly adapted to dry conditions (Fig. 2.2).

2.3.1.3 Natural and Induced Mutants

Natural genetic diversity is the main source of adaptation and crop breeding. Natural mutations appeared in cultivated accessions or were introduced from wild relative species, which provide a great source of genetic diversity for many traits, including disease resistance genes and quality trait-related genes (Bauchet and Causse 2012;

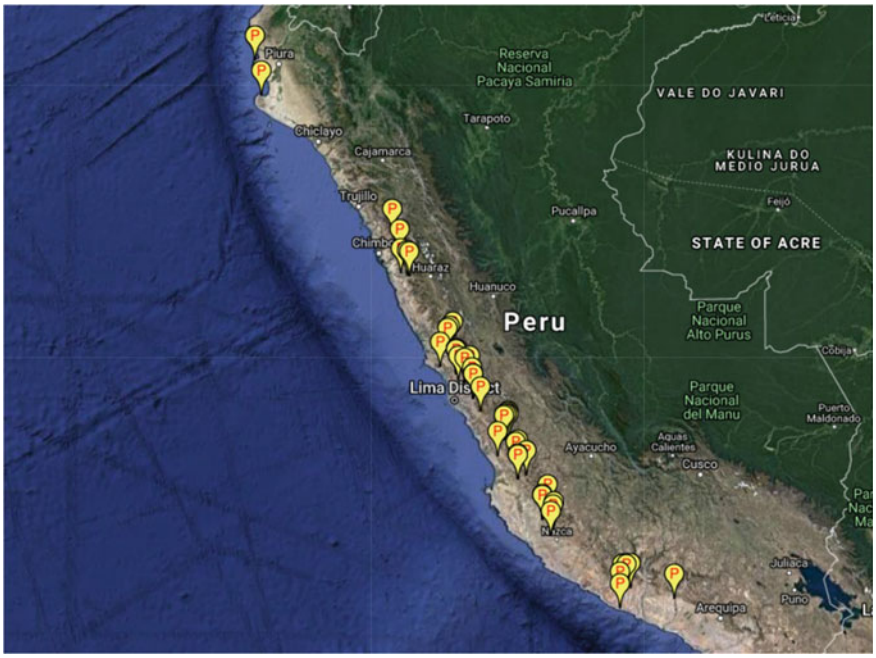

Fig. 2.2 Geographical locations of wild tomato species *Solanum pennellii*. Data were collected from Tomato Genetics Resource Center, University of California, Davis (https://tgrc.ucdavis.edu/Data/Acc/Wildspecies.aspx)

Bauchet et al. 2017a; Rothan et al. 2019). However, the number of cloned genes with detailed functional validations is still limited (Rothan et al. 2019). Some biotechnology tools such as TILLING (Targeting Induced Local Lesions in Genomes; Comai and Henikoff 2006) provide collections of mutants in a specific accession, accelerating functional genomic research and the discovery of interesting alleles at a given locus (Menda et al. 2004; Baldet et al. 2007; Okabe et al. 2011; Mazzucato et al. 2015; Gauffier et al. 2016). This technology typically uses chemical mutagens such as ethyl methanesulfonate (EMS) to generate several base mutations in the genome. There are several TILLING collections worldwide for tomato, such as the UCD Genome Center TILLING laboratory, University of California, USA (http://tilling.ucdavis.edu/index.php/TomatoTilling); The Microtom collection (Okabe et al. 2011); TOMATOMA database, Japan (http://tomatoma.nbrp.jp/); The Repository of Tomato Genomics Resources, University of Hyderabad, India (https://www.uohyd.ac.in/images/index.html); The Genes That Make Tomatoes (http://zamir.sgn.cornell.edu/mutants/index.html); the Tilling Platform of Tomato, INRA, France (http://www-urgv.versailles.inra.fr/tilling/tomato.htm) (Minoïa et al. 2010); LycoTILL database, Metapontum Agrobios, Italy (http://www.agrobios.it/tilling/) (Minoia et al. 2010) and others.

2.3.2 Molecular Markers and Gene/QTL Mapping

2.3.2.1 Evolution of Molecular Markers

Tomato has been used for genetic studies and mutation mapping of interesting traits even before the discovery of molecular markers (Butler 1952). Genes of interest were first mapped thanks to pairs of near-isogenic lines differing only in the region of the interesting gene (Philouze 1991; Laterrot 1996). Nevertheless, until the 1980s, the location of mutations of interest on genetic maps was not precise. The first isozyme markers were limited in number and rapidly replaced by restriction fragment length polymorphism (RFLP) markers. The first high-density genetic map based on RFLP markers was constructed (Tanksley et al. 1992). With more than 1000 loci, spread on the 12 chromosomes, it allowed the localization of several mutations and genes of interest. Then, PCR-based markers, including random amplified polymorphic DNA (RAPD), amplified fragment length polymorphism (AFLP), and microsatellites, were used, but remained limited in polymorphism level and distribution across the genome. Following the identification of PCR markers linked to the gene of interest, specific PCR markers were set up, simplifying the genotyping step for breeders. Nevertheless, PCR markers such as RAPD or AFLP map in majority close to the centromeres, reducing their potential efficiency for gene mapping in tomato (Grandillo and Tanksley 1996a; Haanstra et al. 1999; Saliba-Colombani et al. 2001).

2.3.2.2 Trait Mapping

The construction of genetic maps of molecular markers permitted the dissection of quantitative traits into QTLs (quantitative trait loci) (Paterson et al. 1988; Tanksley et al. 1992). This strategy also opened the way to investigate physical mapping and molecular cloning of genetic factors underlying quantitative traits (Paterson et al. 1991). The first gene cloned by positional cloning was the *Pto* gene, conferring resistance to *Pseudomonas syringae* (Martin et al. 1994). Since then, several interspecific progenies with each wild relative species were studied. Due to the low genetic diversity within the cultivated compartment (Miller and Tanksley 1990), most of the mapping populations were based on interspecific crosses between a cultivar and a related wild species from the lycopersicon group (as reviewed by Foolad 2007; Labate et al. 2007; Grandillo et al. 2011) or from lycopersicoides (Pertuzé et al. 2003) and juglandifolia group (Albrecht et al. 2010). However, maps based on intraspecific crosses have proved their interest notably for fruit quality aspects (Saliba-Colombani et al. 2001). All those populations allowed the discovery and characterization of a myriad of major genes (Rothan et al. 2019) and QTLs involved in various traits (Grandillo and Tanksley 1996b; Tanksley et al. 1996; Fulton et al. 1997; Bernacchi et al. 1998a, b; Chen et al. 1999; Grandillo et al. 1999; Frary et al. 2000; Monforte and Tanksley 2000; Causse et al. 2001; Saliba-Colombani et al. 2001; Causse et al. 2002; Doganlar et al. 2003; Frary et al. 2004; Schauer et al. 2006; Baldet et al. 2007;

Jiménez-Gómez et al. 2007; Cagas et al. 2008; Kazmi et al. 2012a, b; Haggard et al. 2013; Alseekh et al. 2015; Pascual et al. 2015; Ballester et al. 2016; Rambla et al. 2014; Kimbara et al. 2018).

The main results of QTL studies can be summarized:

- QTLs are detected in every case, sometimes with strong effects. A few QTLs explaining a large part of the phenotypic variation, acting together with minor QTLs, are frequently detected. Most of the QTLs act in an additive manner, but a few dominant and even overdominant QTLs were detected (Paterson et al. 1988; DeVicente and Tanksley 1993).
- QTLs can be separated into two types: QTLs stable over the environments, years or types of progeny, and QTLs more specific of one condition (Paterson et al. 1991).
- Some regions involved in the variation of a trait are found in progenies derived from different accessions of a species, or from different species (Fulton et al. 1997; Bernacchi et al. 1998a, b; Chen et al. 1999; Grandillo et al. 1999; Fulton, 2002).
- The dissection of complex traits in relevant components and the QTL mapping of these components allowed the genetic bases of the variability of complex traits to be understood. For example, a map of QTLs controlling several attributes of organoleptic quality in fresh-market tomato revealed relations between QTLs for sensory attributes and chemical components of the fruit (Causse et al. 2002). The analysis of biochemical composition of a trait is also important.
- Fine mapping experiments allowed to precisely map the QTLs in a chromosome region and to verify the existence of several QTLs linked in the same region (Paterson et al. 1990; Frary et al. 2003; Lecomte et al. 2004a). For example, by reducing the size of introgressed fragments from *S. pennellii*, (Eshed and Zamir 1995) identified three linked QTLs controlling fruit weight on a single chromosome arm. Fine mapping is also an important step for cloning QTLs, as first shown by the successes in cloning QTLs controlling fruit weight (Alpert and Tanksley 1996; Frary et al. 2000), fruit shape (Tanksley 2004) and soluble solid content (Fridman et al. 2000, 2004).
- Wild species, in spite of their low characteristics in comparison to cultivars, can carry alleles, which may contribute to the improvement of most of the agronomic traits (DeVicente and Tanksley 1993).

2.3.2.3 Specific Populations to Dissect Phenotypes

Rapidly, molecular breeding strategies were set up and implemented to try to "pyramid" genes and QTL of interest for agronomical traits, notably using advanced backcross QTL method (AB-QTL) (Grandillo and Tanksley 1996b). Using this approach with a *S. lycopersicum x S. pimpinellifolium* progeny, in which agronomical favorable QTL alleles were detected, Grandillo and colleague*s* showed how a wild species could contribute to improve cultivated tomato (Grandillo et al. 1996). Introgression

Lines (IL) derived from interspecific crosses allowed to dissect the effect of chromosome fragments from a donor (usually from a wild relative) introgressed into a recurrent elite line. IL offers the possibility to evaluate the agronomic performance of a specific set of QTL (Paran et al. 1995). IL was used as a base for fine mapping and positional cloning of several genes and QTL of interest. The first IL library was developed between *S. pennellii* and *S. lycopersicum* (Eshed and Zamir 1995; Zamir 2001). QTL mapping power was increased compared to biallelic QTL mapping population, and was again improved by the constitution of sub-IL set with smaller introgressed fragments. This progeny was successful in identifying QTLs for fruit traits (Causse et al. 2004); antioxidants (Rousseaux et al. 2005), vitamin C (Stevens et al. 2007), and volatile aromas (Tadmor et al. 2002). The introgression of a QTL identified in these IL has allowed plant breeders to boost the level of soluble solids (brix) in commercial varieties and largely increased tomato yield in California (Fridman et al. 2004). Complementary genetic resources are now available, including a new backcrossed inbred line (BIL) population generated by repeated backcrosses, followed by selfing (Ofner et al. 2016). This BIL population could be used in combination with ILs for fine mapping QTLs previously identified and to pinpoint strong candidate genes (Fulop et al. 2016). Moreover, the *S. pennellii* ILs have been broken into additional sublines carrying molecular marker-defined introgressions that are smaller than those carried by the original ILs, further facilitating the identification of candidate genes (Alseekh et al. 2013). These sub-isogenic lines are available to the scientific community and have been used to map loci affecting fruit chemical composition (Alseekh et al. 2015; Liu et al. 2016a, b). Such exotic libraries were also designed with other species, involving *S. pimpinellifolium* (Doganlar et al. 2003), *S. habrochaites* (Monforte and Tanksley 2000; Finkers et al. 2007a, b), and *S. lycopersicoides* (Canady et al. 2005).

Introgression lines were also used to dissect the genetic basis of heterosis (Eshed and Zamir 1995). Heterosis refers to a phenomenon where hybrids between distant varieties or crosses between related species exhibit greater biomass, speed of development, and fertility than both parents (Birchler et al. 2010). Heterosis involves genome-wide dominance complementation and inheritance model such as locus-specific overdominance (Lippman and Zamir 2007). Heterotic QTL for several traits were identified in tomato IL (Semel et al. 2006). A unique QTL was shown to display at the heterozygous level improved harvest index, earliness, and metabolite content (sugars and amino acids) in processing tomatoes (Gur et al. 2010, 2011). Furthermore, a natural mutation in the SFT gene, involved in flowering (Shalit et al. 2009), was shown to correspond to a single overdominant gene increasing yield in hybrids of processing tomato (Krieger et al. 2010).

2.3.2.4 Genes and QTLs Controlling Tomato Disease Resistance

The excessive use of chemical fungicides and pesticides was for a long time most common in tomato crops. Because of environmental, consumer, and grower constraints, their elevated costs, and their limited effectiveness, other levers, such as

genetic resistance and various cultural practices, have to be integrated for achieving sustainable agriculture (Lefebvre et al. 2018). However, the development of new cultivars with enhanced resistance or tolerance was often hindered by the lack of genetic diversity within the cultivated *S. lycopersicum* germplasm, because of its narrow genetic diversity due to its domestication history. Screening the tomato-related wild species germplasm collections enabled to discover many sources of disease resistance traits during the last 80 years (Rick and Chetelat 1995). About 40 major resistance traits were discovered in wild tomato species. Those genes confer resistance to diseases of different pest and pathogen classes. Of the 40 major resistance traits, about 20 have been introgressed into cultivated tomato (Ercolano et al. 2012). *S. peruvianum*, *S. habrochaites*, *S. pimpinellifolium,* and *S. chilense* have proved to be the richest sources of resistance genes (Laterrot 2000). The systematic screening of tomato germplasm for disease resistance will probably permit to discover further novel resistance sources and consequently novel resistance loci (major resistance genes and resistance QTLs).

Resistance Gene and QTL Discovery

More than 100 loci underlying the 30 major tomato resistance diseases have been genetically mapped (Foolad and Panthe2012 for review). Molecular markers associated with many resistance genes or QTLs have been reported. Up to now, 26 major resistance genes were isolated (*Asc-1*, *Bs-4*, *Cf-2*, *Cf-4*, *Cf-5*, *Cf-9*, *Hero*, *I* (=*I-1*), *I-2*, *I-3*, *I-7*, *Mi-1.2* (= *Mi* = *Meu*), *ol-2*, *Ph-3*, *pot-1*, *Prf*, *Pto*, *Tm-1*, *Tm-2*, *Tm-2*^{2} (= *Tm-2.2* = *Tm-2*^{a}), *Ty-1, Ty-2*, *Ty-3*, *ty-5*, *Ve-1 (=Ve)*, *Sw-5*) (Table 2.3). Resistance tomato locus has a well-defined nomenclature; written in italic, they are abbreviated by 1–3 letters (the first letter in uppercase for dominant resistance alleles and in lowercase for recessive dominant alleles) and separated of a number by a dash, the number indicating the order of discovery of the gene for the target disease. In a few cases, the last figure is followed by a dot and another number indicating different alleles; alleles could also be indicated by a number or a letter in superscript.

Most of reported major effect resistance genes are dominant, except *pot-1, ty-5,* and *ol-2* conferring resistance to potyviruses (PVY and TEV), *Tomato yellow leaf curl virus* (TYLCV), and to *Oidium neolycoersici*, respectively, that were both cloned (Bai et al. 2008; Lapidot et al. 2015; Ruffel et al. 2005). Another recessive resistance allele *py-1* (also named *pyl*) controlling *Pyrenochaeta lycopersici* responsible for corky root rot was reported but is not cloned yet (Doganlar et al. 1998).

For a few tomato diseases, both major effect resistance genes and resistance QTLs have been identified according to the resistance genitor and the pathogen variant used in the analysis and to environmental conditions. Otherwise, a single major resistance gene was discovered for most tomato diseases. For a few diseases, several major resistance genes have been reported, such as for TSWV, where 6 dominant resistance genes and 3 recessive resistance genes were described (Foolad and Panthee 2012) and for *Meloidogyne* nematodes where several resistance genes have been identified.

Table 2.3 Pest and pathogen resistance genes of tomato molecularly characterized. Genes are classified by pest and pathogen Latin name inside each pest and pathogen class. For each gene, the ITAG gene model(s) and the Genebank accession number are given when available

Locus name (synonym)	Function of cloned gene	Species from which the trait was discovered	Genetic resources carrying this gene	Tomato chromosome	ITAG gene model	Genebank accession number	Literature
Asc (Asc-1)	LAG1 Longevity Assurance Gene Family	*S. pennellii*	VFNT Cherry, LA716	T3	Solyc03g114600	AJ312131	Brandwagt et al. (2000)
Cf-2	Leucine-rich repeat receptor-like protein kinase LRR-RLP	*S. pimpinellifolium*	LA2244, LA3043	T6	Solyc06g008300	U42444	Dixon et al. (1996)
Cf-4	Leucine-rich repeat receptor-like protein kinase LRR-RLP	*S. habrochaites*	LA2446, LA3045, LA3051, LA3267	T1	Solyc01g006550	AJ002235	Takken et al. (1998, 1999)
Cf-5	Leucine-rich repeat receptor-like protein kinase LRR-RLP	*S. lycopersicum*	–	T6	–	AF053993	Dixon et al. (1998)
Cf-9	Leucine-rich repeat receptor-like protein kinase LRR-RLP	*S. pimpinellifolium*	LA3047	T1	Solyc01g005160	AJ002236	Jones et al. (1994)

(continued)

Table 2.3 (continued)

Locus name (synonym)	Function of cloned gene	Species from which the trait was discovered	Genetic resources carrying this gene	Tomato chromosome	ITAG gene model	Genebank accession number	Literature
I (I-1)	Leucine-rich repeat receptor-like protein kinase LRR-RLP	*S. pimpinellifolium*	PI79532	T11	Solyc11g011180		Catanzariti et al. (2017)
I-2	CC-NB-LRR	*S. pimpinellifolium*	PI126915	T11	Solyc11g071430		Ori et al. (1997), Simons et al. (1998)
I-3	S-receptor-like kinase 5 (SRLK-5)	*S. pennellii*	LA716	T7	Solyc07g055640	KP082943	Catanzariti et al. (2015)
I-7	Leucine-rich repeat receptor-like protein kinase LRR-RLP	*S. pennellii*	PI414773, Tristar cultivar	T8	Solyc08g77740	KT185194	Gonzalez-Cendales et al. (2016)
ol-2 (SlMlo1)	Loss-of-function mlo	*S. lycopersicum*	LA1230, KNU-12 cultivar	T4	Solyc04g049090	AY967408	Bai et al. (2008)
Ve-1 (Ve)	RLP-type resistance protein	*S. lycopersicum*	VFN8, Craigella GCR 151, PI 303801	T9	Solyc09g005090	AF272367	Kawchuk et al. (2001), Fradin et al. (2009)
Ph-3	CC-NB-LRR	*S. pimpinellifolium*	LA4285, LA4286, LA1269(= PI365957), L3708	T9	near Solyc09g092280-Solyc09g092310	KJ563933	Zhang et al. (2013, 2014)

(continued)

Table 2.3 (continued)

Locus name (synonym)	Function of cloned gene	Species from which the trait was discovered	Genetic resources carrying this gene	Tomato chromosome	ITAG gene model	Genebank accession number	Literature
pot-1	eukaryotic translation initiation factor 4E (eIF4E)	*S. habrochaites*	PI247087	T3	Solyc03g005870	AY723736	Ruffel et al (2005), Piron et al. (2010)
Tm-1	Inhibitor of tobamovirus RNA replication	*S. habrochaites*	PI126445	T2	Solyc02g062560	AB713135, AB713134	Ishibashi et al. (2007)
Tm-2	CC-NB-LRR	*S. peruvianum*	Craigella GCR236	T9	Solyc09g018220	AF536200	Lanfermeijer et al. (2005)
Tm-2^2 (Tm-2^a)	CC-NB-LRR	*S. peruvianum*	Craigella GCR267	T9	Solyc09g018220	AF536201	Lanfermeijer et al. (2005)
Sw-5	CC-NB-LRR	*S. peruvianum*	PI128654/Stevens cultivar	T9	Solyc09g098130	AY007367	Brommonschenkel et al. (2000)
Ty-1	DFDGD-Class RNA–Dependent RNA Polymerases	*S. chilense*	LA1969	T6	Solyc06g051170, Solyc06g051180, and Solyc06g051190		Verlaan et al. (2013)
Ty-2 (TYNBS1)	CC-NB-LRR	*S. habrochaites*	H9205, TY-Chie, Shurei cultivars	T11	near Solyc11g069660.1 and Solyc11g069670.1	LC126696	Yamaguchi et al. (2018)
Ty-3	DFDGD-Class RNA–Dependent RNA Polymerases	*S. chilense*	LA2279	T6	Solyc06g051170, Solyc06g051180, and Solyc06g051190		Verlaan et al. (2013)

(continued)

Table 2.3 (continued)

Locus name (synonym)	Function of cloned gene	Species from which the trait was discovered	Genetic resources carrying this gene	Tomato chromosome	ITAG gene model	Genebank accession number	Literature
ty-5	messenger RNA surveillance factor Pelota (Pelo)	*S. peruvianum*	Tyking cultivar TY172	T4	Solyc04g009810	KC447287	Lapidot et al. (2015)
Pto	Serine/threonine protein kinase	*S. pimpinellifolium*	LA2396, LA2458, LA3472	T5	Solyc05g013300	U02271	Martin et al. (1993)
Prf	CC-NB-LRR	*S. pimpinellifolium*	LA2396, LA2458, LA3472	T5	Solyc05g013280	U65391	Salmeron et al. (1996)
Bs-4	TIR-NB-LRR	*S. lycopersicum*	Money Maker cultivar	T5	Solyc05g007850	AY438027	Schornack et al. (2004)
Hero	CC-NB-LRR	*S. pimpinellifolium*	LA121	T4	Solyc04g008120	AJ457051	Ernst et al. (2002)
Mi-1.2 (Mi, Meu)	CC-NB-LRR	*S. peruvianum*	Motelle cultivar and most of tomato rootstocks	T6	Several homologs on Chr6	AF039682	Vos et al. (1998), Milligan et al. (1998), Nombela et al. (2001), Rossi et al. 1998, Casteel et al. (2007)

However, generally a single of those genes, such as *Sw-5* and *Mi-1.2*, is currently used in MAS because it confers a broader spectrum resistance than others.

A few cloned genes correspond to allelic series such as *Ty-1* and *Ty-3* on chromosome T6 (Verlaan et al. 2013), or *Tm-2* and *Tm-2*^{2} on chromosome T9 (Lanfermeijer et al. 2005), to very tightly linked genes such as *Pto* and *Prf* on chromosome T5 both involved in recognition of *Pseudomonas syringae* pv. *tomato* (Salmeron et al. 1996a, b), or else they belong to clusters of major resistance genes such as *Cf-4* and *Cf-9* on chromosome T1 (Takken et al. 1999) or *Cf-2* and *Cf-5* on chromosome T6 (Dixon et al. 1998). Additionally, while resistance genes are often specific to a pest, a pathogen, or a variant of a species, in rare cases, a same gene can confer resistance to different distantly related pests, such as *Mi-1.2* called also *Meu* that triggers the resistance to root knot nematodes caused by three *Meloigogyne* species (*M. incognita, M. arenaria, M. javanica*), to the aphid *Macrosiphum euphorbiae*, to the whitefly *Bemisia tabaci*, and to the psyllid *Bactericerca cockerelli* (Casteel et al. 2007; Milligan et al. 1998; Nombela et al. 2003; Rossi et al. 1998; Vos et al. 1998).

For many diseases, no major gene has been found yet, or major genes previously discovered were breakdown by virulent pathogen variants. For this reason, several research groups are now willing to focus on quantitative resistance that has the particularity to reduce the development of pests and pathogens rather than to block them totally. Quantitative resistance, also called partial resistance and generally controlled by QTLs, provides in most of the cases a more durable and broad-spectrum resistance (Cowger and Brown 2019); in addition, resistance QTLs are more frequent than major resistance genes in natural genetic resources. Many resistance QTLs have been mapped in the tomato genome, particularly for resistance traits to *P. infestans* (Arafa et al. 2017; Brouwer et al. 2004; Brouwer and St Clair 2004; Foolad et al. 2008; Ohlson et al. 2018; Ohlson and Foolad 2016; Panthee et al. 2017; Smart et al. 2007), *O. lycopersici* (Bai et al. 2003), *Alternaria solani* (Foolad et al. 2002), *Alternaria alternata* (Robert et al. 2001), *Xanthomonas sp.* (Hutton et al. 2010; Sim et al. 2015), *C. michiganensis* (Coaker and Francis 2004; Kabelka et al. 2002), *Ralstonia solanacearum* (Carmeille et al. 2006; Mangin et al. 1999; Wang et al. 2013a, b), *Botrytis cinerea* (Davis et al. 2009; Finkers et al. 2008; Finkers et al. 2007a, b) and *Cucumber mosaic virus* (CMV) (Stamova and Chetelat 2000).

Mainly, three genes were described for controlling resistance to late blight, but *Ph-1* is not effective anymore, due to the emergence of evolved races of *P. infestans*, and *Ph-2* and *Ph-3* have both an incomplete penetrance and evolved races of *P. infestans* have been described on plant material carrying those genes. Due to the breakdown of those three major resistance genes controlling late blight, many efforts are now underway to identify new resistance sources in tomato relatives and within the cultivated tomato germplasm (Caromel et al. 2015 and work in progress at INRA GAFL; Foolad et al. 2014).

An approach to breed for resistance when there are no natural variants, without transformation with foreign DNA, consists to inactivate by TILLING plant dominant susceptibility genes that permit the pathogen to multiply. A proof of concept of such an approach has allowed the de novo creation of resistance to two potyvirus species in tomato (Piron et al. 2010). Similarly, EcoTILLING allows the detection of natural

variability of the allelic variants of a specific gene, an approach that has resulted in the detection in tomato diversity of a new Sw-5 variant controlling TSWV (Belfanti et al. 2015).

Resistance Gene and QTL Architecture

Mapping of resistance loci in the tomato genome highlights several hotspots of resistance genes even if the 12 tomato chromosomes harbor resistance loci (Fig. 2.3). Equally, mapping of the repertoire of major resistance genes evidenced that they are organized in tandem or in clusters (Foolad 2007). It appears that a lot of resistance loci were identified on chromosomes 6 and 9, from the same genitor or from the tomato wild relatives. The chromosome 6 carries major resistance genes to root knot *Meloidogyne* (*Mi-1.2*), *O. neolycopersici* (*Ol-1*, *Ol-3*, *Ol-4*, *Ol-5* and *Ol-6*), *Cladosporium fulvum* (*Cf-2* and *Cf-5*), TYLCV (*Ty-1* and *Ty-3*), *Alfalfa mosaic virus* (*Am*), and resistance QTLs to *Ralstonia solanacearum* and ToMoV (*Tomato mottle virus*) (Agrama and Scott 2006). Identically the chromosome 9 is rich in resistance gene clusters with *Tm-2* and *Tm-2*^{2} controlling the *Tomato mosaic virus* (ToMV) (Pillen et al. 1996) and *Frl* controlling FORL (Vakalounakis et al. 1997) near the centromere, *Sw-5* controlling TSWV (Stevens et al. 1995) and *Ph-3* controlling *P. infestans* (Chunwongse et al. 2002) near a telomere, and *Ve* controlling *Verticillium dahliae* near the other telomere (Kawchuk et al. 2001).

Molecular Basis of Resistance Genes and QTLs

Many resistance traits in tomato are conferred by single dominant genes, encoding proteins that recognize directly or indirectly avirulent proteins of pests and pathogens and trigger the plant defense response. A few correspond to single recessive genes (e.g., *pot-1*, *ol-2*, generally written with lowercase letters). Recessive resistance alleles are due to loss-of-function or absence of susceptibility that hampers the pathogen's development in the plant; conversely, the corresponding susceptible alleles facilitate the development of the pathogen that benefits of the host's machinery. Many major resistance genes have been cloned by forward genetics and map-based cloning approaches (see Sect. 3.6 below) and most of the dominant cloned genes encode conserved NB-LRR proteins. The conserved molecular structure of resistance genes (NB-LRR R-genes, RLP, RLK, etc.) was used to search for genes homologous to genes already isolated in the same species or in related species, and to discover and isolate new resistance alleles or genes (e.g., *Sw-5* and *Mi* that are homolog, the *Cf* serie genes). More recently, the RenSeq technology, using baits designed from 260 NBS-LRR genes previously identified in Solanaceae, helped to pick-up 105 novel nucleoside binding site-Leicin rich repeat (NBS-LRR) sequences within the reference genome of tomato (*S. lycopersicum*) Heinz1706 and 355 novel NBS-LRR novel within the draft of *S. pimpinellifolium* LA1589 genome, to complete the repertoire of genes that encode NB-LRR R-genes in these species (Andolfo et al. 2014).

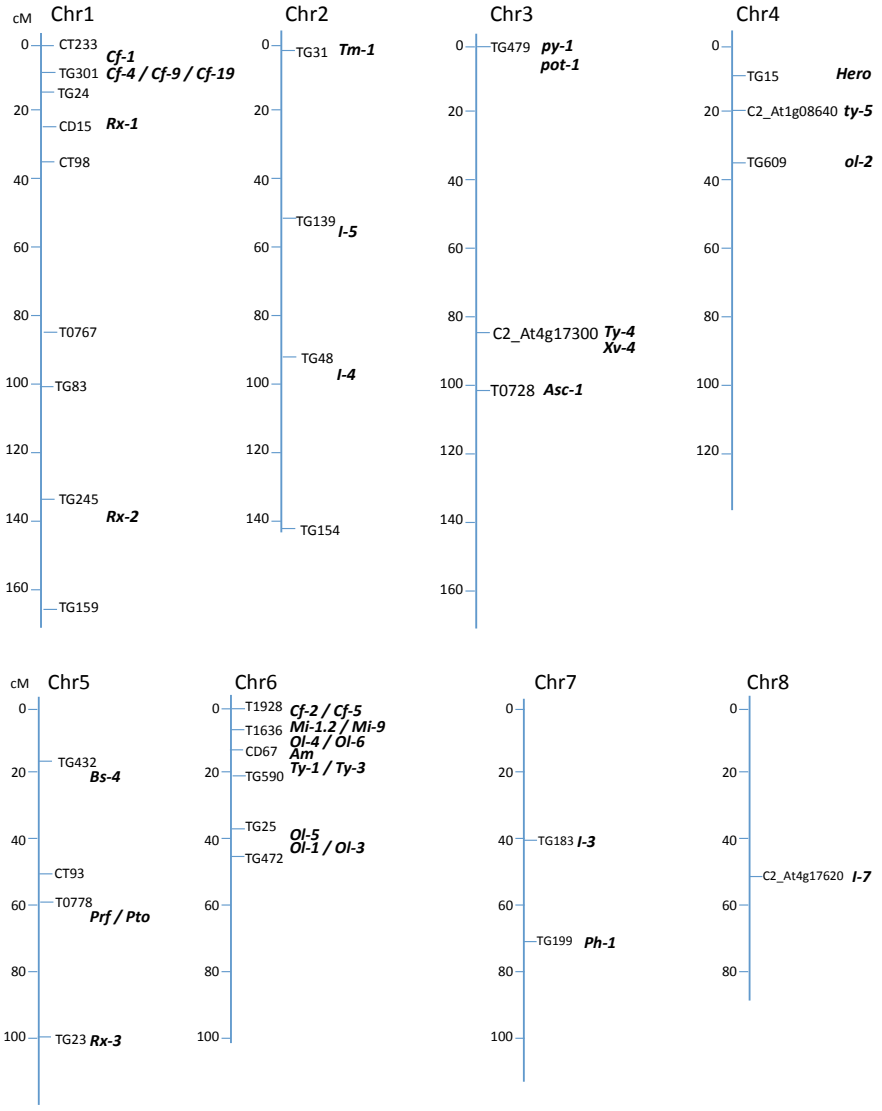

Fig. 2.3 Genetic map of tomato with mapped major resistance genes. Marker names and genetic distances are according to the SGN tomato- EXPEN 2000 map (https://solgenomics.net/). The position of genes is adapted from Foolad (2007), Foolad et al. (2014), Lee et al. (2015), Bai et al. (2018), Gill et al. (2019) and Sharma et al. (2019). When there is no common marker between the publication and the EXPEN 2000 map, the relative position was determined using a blastn search with the linked marker sequences as a query, against tomato chromosomes SL2.50 to identify the nearest marker. Genetic distances (in cM) are indicated on the left of the chromosomes

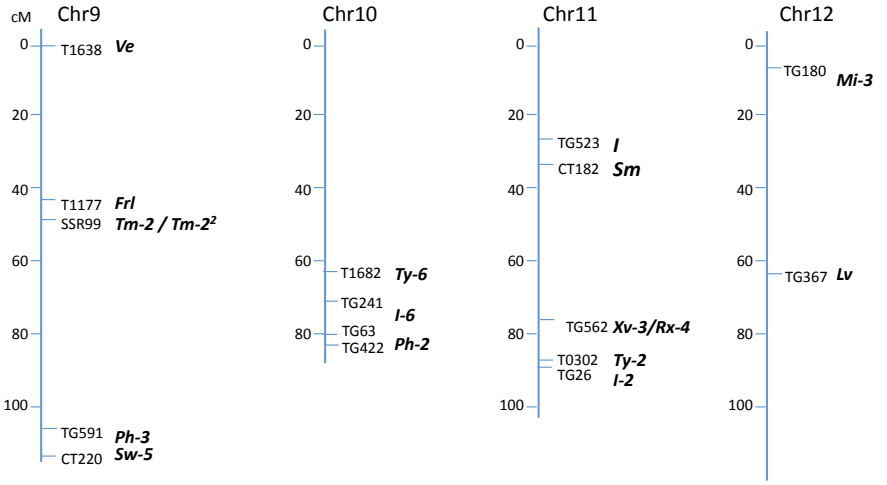

Fig. 2.3 (continued)

Besides those major effect resistance genes, many genes activated during the tomato disease defense response were also characterized. Several are specific of a plant–pathogen interaction. A few are involved in several plant–pathogen interactions, such as the lipase-like protein EDS1 that is involved in defense mechanisms triggered by Cf-4 and Ve proteins. Equally Prf, I-2, and Bs-3 proteins interact with the RAR1, SGT1, and HSP90 proteins. Beside, transcriptional analysis highlighted several genes involved in jasmonate acid or salicylic acid signaling pathway regulation. A few of these genes could correspond to resistance QTLs.

Until now, no QTL determining disease resistance has been cloned in tomato. Quantitative plant resistance loci may correspond to a large array of molecular mechanisms that play a role in partial resistance, they may be genes involved in PAMP recognition responsible for basal defense, genes involved in defense signal transduction, genes regulating the phytoalexin synthesis, weak effect alleles of R-genes, genes regulating developmental phenotypes, or other genes not yet identified (Poland et al. 2009).

2.3.3 Genomic Resources

2.3.3.1 The Reference Genome Sequence

Genomic information greatly promoted our understanding of the genetic architecture and evolutionary history of modern tomato. The tomato genome sequencing project was initiated as part of the International Solanaceae Project (SOL), which was launched on November 3, 2003 at Washington, USA and gathered a consortium

of scientists of 10 countries including China, France, Spain, Italy, USA, UK, the Netherlands, Japan, Korea, and India (Mueller et al. 2005). The main reason why tomato was first chosen as the reference genome for the Solanaceae was due to its high level of macro and micro-synteny among over 3,000 species. This project was first started with conventional sequencing technologies, such as Sanger sequencing. In order to reduce the cost of producing a high-quality reference, bacterial artificial chromosome (BAC)-by-BAC sequencing strategy based on saturated genetic markers was used to select seed BACs within the gene-rich part of the tomato genome for sequencing. However, this process was quite slow and became a serious obstacle, which was greatly accelerated by next-generation sequencing.

The first tomato genome sequence was published in 2012 for the inbred tomato cultivar "Heinz 1706" (*S. lycopersicum*) together with a draft of its closest wild species *S. pimpinellifolium* (accession LA1589) (The Tomato Genome Consortium 2012). In the tomato genome, recombination, genes, and transcripts are substantially located in the euchromatin regions compared to the heterochromatin regions, whereas chloroplast insertions and conserved microRNA genes were more evenly distributed throughout the genome (The Tomato Genome Consortium 2012). The tomato genome was highly syntenic with other Solanaceae species, such as pepper, eggplant, potato, and *Nicotiana*. Tomato had fewer high-copy, full-length long terminal repeat retrotransposons with older insertion ages compared to *Arabidopsis* and Sorghum. Genome annotation showed that there were a total 34,727 protein-coding genes and 30,855 of them were supported by RNA sequencing data. Chromosomal organization of genes, transcripts, repeats, and sRNAs were very similar between tomato and potato. Among all the protein-coding genes, 8,615 genes were common to tomato, potato, *Arabidopsis*, rice, and grape. A total of 96 conserved sRNAs were predicted in tomato, which could be further divided into 34 families, 10 of which being highly conserved in plants. The potato genome showed more than 8% divergence from tomato, with nine large and several smaller inversions (The Tomato Genome Consortium 2012). The *Solanum* lineage has experienced one ancient and one more recent consecutive genome triplication. The genome information provides a basic understanding of the genetic bottlenecks that narrowed tomato genetic diversity (The Tomato Genome Consortium 2012).

Since the first published version, the sequence has been completed, corrected, and re-annotated using new sequence data and new RNAseq data and the genome version today is SL3.0 while the annotation is ITAG3.2.

2.3.3.2 Resequencing Tomato Accessions

Next-generation sequencing technologies made it possible to sequence genomes at large scales (Goodwin et al. 2016). Soon after the availability of the reference tomato genome, the genome of the stress-tolerant wild tomato species *S. pennellii* was published (Bolger et al. 2014). This species is characterized by extreme drought tolerance and unusual morphology. Many stress-related candidate genes were mapped in this wild species. Large gene expression differences were observed between *S.*

lycopersicum cv. M82 and *S. pennellii* (LA716) due to polymorphisms at the promoter and/or coding sequence levels. This wild species and others were further re-sequenced and assembled using long read sequencing platforms complemented with Illumina sequencing (Usadel et al. 2017). After the genome of *S. pennellii*, a panel of diversified tomato accessions and related wild species were sequenced (The 100 Tomato Genome Sequencing Consortium 2014). The allogamous self-incompatible wild species have the highest level of heterozygosity, which was low for the autogamous self-compatible species (The 100 Tomato Genome Sequencing Consortium 2014). Almost at the same time, a comprehensive genomic analysis based on resequencing 360 tomato accessions elucidated the history of tomato breeding (Lin et al. 2014). This study showed that domestication and improvement of tomato mainly involved two independent sets of QTLs leading to fruit size increase. Five major QTLs (*fw1.1*, *fw5.2*, *fw7.2*, *fw12.1,* and *lcn12.1*) contributed to the enlargement of tomato fruit during the domestication process. Then, up to 13 major QTLs (*fw1.1*, *fw2.1*, *fw2.2*, *fw2.3*, *lcn2.1*, *lcn2.2*, *fw3.2*, *fw3.2*, *fw5.2*, *fw7.2*, *fw9.1*, *fw10.1*, *fw11.1*, *fw12.1*, *fw11.3*, *fw12.1,* and *lcn12.1*) contributed to the second improvement of tomato fruit. This study also detected several independent mutations in a major gene *SlMYB12* that changed modern red tomato to pink tomato appreciated in Asia. This study also illustrated the linkage drag associated with wild introgressions (Lin et al. 2014).

Since then, low-depth resequencing or genotyping-by-sequencing has become a common practice and is widely applied in many tomato collections. Up to now, around 900 tomato accessions have been re-sequenced, with the sequence depth ranging from low to high (The Tomato Genome Consortium 2012; Causse et al. 2013; Bolger et al. 2014; Lin et al. 2014; The 100 Tomato Genome Sequencing Consortium 2014; Tieman et al. 2017; Ye et al. 2017; Tranchida-Lombardo et al. 2018). These genomic resources are freely available (https://solgenomics.net) and will greatly facilitate modern breeding of new climate-smart tomato cultivars.

In a recent pan-genome study of 725 phylogenetically and geographically representative tomato accessions, a total of 4,873 genes were newly discovered compared to the reference genome (Gao et al. 2019). Among these, 272 were potential contaminations and were removed from the "Heinz 1706" reference genome. Substantial gene loss and intensive negative selection of genes and promoters were detected during tomato domestication and improvement. During tomato domestication, a total of 120 favorable and 1,213 unfavorable genes were identified, whereas 12 favorable and 665 unfavorable genes were identified during the improvement process.

Disease resistance genes were especially lost or negatively selected. Gene enrichment indicated that defense response was the most enriched group of unfavorable genes during both domestication and improvement. No significantly enriched gene families were found in favorable genes during improvement. A rare allele in the *TomLoxC* promoter was found under selected during domestication. In orange-stage fruit, accessions with both the rare and common *TomLoxC* alleles have high expression compared to those homozygous in modern tomatoes. Taken together with other

findings, this pan-genome study provides useful knowledge for further biological discovery and breeding (Gao et al. 2019).

2.3.4 SNP Markers

2.3.4.1 SNP Discovery

Single nucleotide polymorphisms (SNPs) are the most abundant molecular markers for major crops. SNPs can be detected in any region of the genome, including coding sequences or non-coding sequences of genes, as well as the intergenic regions. Only the non synonymous SNPs in the coding regions of genes change the amino acid sequences of proteins. However, SNPs in the non-coding region are also likely to affect gene expression through different mechanisms (Farashi et al. 2019). Millions of SNPs can be directly generated via genotyping-by-sequencing (GBS) or resequencing of a few lines (Catchen et al. 2011). Next-generation sequencing-based technologies have also accelerated the identification and isolation of genes associated with agronomic traits in major crops (Le Nguyen et al. 2018). There are many GBS methods available, including at least 13 reduced-representation sequencing (RRS) approaches and at least four whole-genome resequencing (WGR) approaches (Scheben et al. 2017). Among them, RNA sequencing and exome sequencing based on transcriptome sequences is an important alternative RRS approach (Haseneyer et al. 2011; Scheben et al. 2017). The sequenced data can be used for expression analysis and also does not require prior genomic sequence information (Wang et al. 2010).

Since the availability of the reference tomato genome, whole-genome resequencing of different tomato accessions could directly generate millions of SNPs, covering the whole tomato genome (Bolger et al. 2014; Lin et al. 2014; Menda et al. 2014; The 100 Tomato Genome Sequencing Consortium 2014; Tieman et al. 2017; Ye et al. 2017; Zhu et al. 2018). The number of SNPs in the wild tomato species exceeds 10 million, which are 20-folds higher than that in most of the domesticated accessions (The 100 Tomato Genome Sequencing Consortium 2014). Once the reference genome was available, it became possible to only sequence chromosome regions of interest to screen for SNP. For example, Ranc et al. (2012) sequenced 81 DNA fragments covering the chromosome 2 at different mapping densities in a core collection of 90 tomato accessions and discovered 352 SNPs.

2.3.4.2 SNP Arrays

SNP arrays is another popular and cost-effective genotyping approach, such as the Solanaceae Coordinated Agricultural Project (SolCAP) (Hamilton et al. 2012; Sim et al. 2012b), the Centre of Biosystems Genomics (CBSG) consortium (Víquez-Zamora et al. 2013) or, the Diversity Arrays Technology (DArTseq) (Pailles et al.

2017). However, RNAseq based SNP arrays, such as SolCAP and ddRAD-Seq (Arafa et al. 2017), have some major limitations: Gene expression is dependent on tissue and time, multiple biases are introduced by library preparation during RNA fragmentation (Wang et al. 2009) and SNP coverage is low in coding regions (Scheben et al. 2017). In tomato, these SNP arrays have been widely used to genotype different tomato collections (Sim et al. 2012a; Víquez-Zamora et al. 2013; Ruggieri et al. 2014; Sauvage et al. 2014; Blanca et al. 2015; Bauchet et al. 2017a, b; Pailles et al. 2017; Albert et al. 2016b).

2.3.4.3 Genotype Imputation

When a large diverse reference panel is available, SNP density can be significantly increased by genotype imputation (Guan and Stephens 2008; Halperin and Stephan 2009; Iwata and Jannink 2010; Marchini and Howie 2010; Pasaniuc et al. 2012; Browning and Browning 2016; Das et al. 2016; Wang et al. 2018). In human and model plant species, there are some very good reference panels suitable for genotype imputation, such as the 1000 Genomes Project (The 1000 Genomes Project Consortium 2015) and the UK10K Project in humans (Danecek et al. 2015; The UK10K Consortium 2015), the 3000 Rice Genome Project (2014; McCouch et al. 2016), and the 1001 Genomes Consortium in *Arabidopsis thaliana* (2016). The marker density of SNP arrays in tomato is quite low and many genomic gaps remain, compared with the whole-genome sequencing (Sauvage et al. 2014; Bauchet et al. 2017b; Zhao et al. 2019). After imputation, the SNP number can be increased up to 30-folds and greatly bridged the genomic gaps and genomic coverage (Fig. 2.4) (Zhao et al. 2019).

2.3.5 Diversity Analyses

Molecular genetic markers play an important role in the modern breeding (Ramstein et al. 2018). They also provide a new vision of tomato genetic diversity (Bauchet and Causse, 2012). Overall, modern cultivated tomato accessions present a lower polymorphism level compared to wild species, as shown by different types of markers, such as RFLP (Miller and Tanksley, 1990), AFLP (Suliman-Pollatschek et al. 2002; Park et al. 2004; Van Berloo et al. 2008; Zuriaga et al. 2009), RAPD (Grandillo and Tanksley 1996a; Archak et al. 2002; Tam et al. 2005; Carelli et al. 2006; El-hady et al. 2010; Meng et al. 2010; Length 2011), SSR (Suliman-Pollatschek et al. 2002; Jatoi et al. 2008; Mazzucato et al. 2008; Albrecht et al. 2010; Meng et al. 2010; Sim et al. 2010; Zhou et al. 2015), ISSR (Vargas-Ponce et al. 2011; Shahlaei et al. 2014) and SNPs (Blanca et al. 2012; Sim et al. 2012a; Lin et al. 2014; The 100 Tomato Genome Sequencing Consortium 2014).

Whole-genome sequencing technology made it possible to detect millions of SNPs and it has revealed that the number of SNPs in wild species is over 10 million and is 20-fold higher than that for most domesticated tomato accessions (The

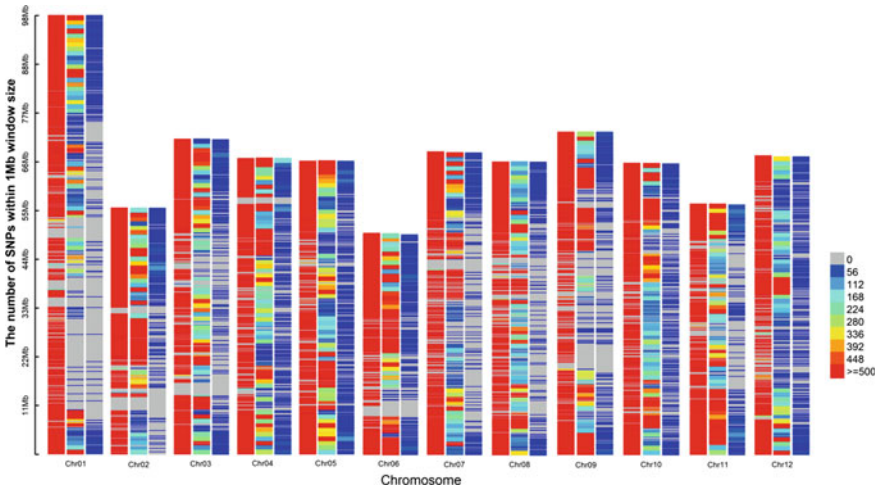

Fig. 2.4 SNP density for the tomato collection reported in Sauvage et al. (2014). Left, middle, and right panels represent the SNP density of the reference panel, after and before genotype imputation, adapted from Zhao et al. (2019)

100 Tomato Genome Sequencing Consortium 2014), which provides clues on the genetic diversity loss during tomato domestication and improvement. A study based on whole-genome sequencing of wild and cultivated tomato species demonstrated that approximately 1% of the tomato genome has experienced a very strong purifying selection during domestication (Sahu and Chattopadhyay 2017). At the expression level, domestication has affected up to 1729 differentially expressed genes between modern tomato varieties and the *S. pimpinellifolium* wild species and also affected about 17 gene clusters. Some gene regulation pathways were significantly enriched, such as carbohydrate metabolism and epigenetic regulations (Sauvage et al. 2017).

Cherry tomato accessions (*S. lycopersicum* var. *cerasiforme*) are intermediate between cultivated and wild species with a moderate genetic diversity (Ranc et al. 2012; Xu et al. 2013; Zhang et al. 2017). The linkage disequilibrium of cherry tomatoes is also intermediate between that of cultivated and wild species (Sauvage et al. 2014; Bauchet et al. 2017a). They could thus be helpful to bridge the gaps between low genetic diversity and high morphological diversity of modern cultivated tomato accessions and wild species which may provide interesting genes but also a strong genetic load. Molecular markers could also link the genetic and morphological diversities together and provide insight into the origin of tomato. By phenotyping 272 genetically and morphologically diverse tomato accessions with the SOLCAP genotyping SNP array, Blanca et al. (2012) revealed that cherry tomato accessions were morphologically and genetically intermediate between modern cultivated tomato accessions (*S. lycopersicum*) and wild accessions (*S. pimpinellifolium*). In addition,

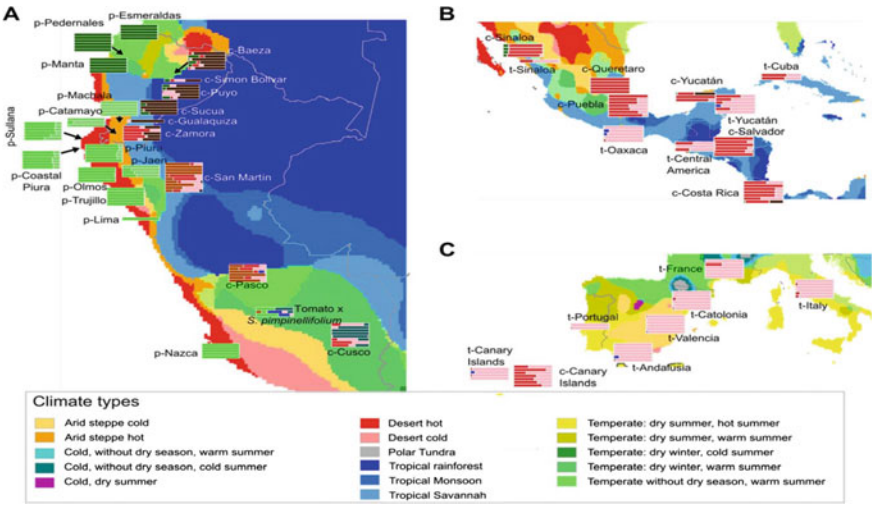

Fig. 2.5 Geographical distributions of the population structure revealed by SOLCAP SNPs, adapted from Blanca et al. (2012). Different colored bars represent the proportion of the population structure

cherry and wild tomato accessions inhabited strikingly different ecological and climatic regions and a clear relationship was found between the population structure and a geographic map based on the climatic classification (Fig. 2.5).

2.3.6 Cloned Genes/QTLs

Tomato is probably one of the crops with the largest number of single mutations used for its breeding (as reviewed by Grandillo and Cammareri (2016), and Rothan et al. 2019). Before the SNP discovery, due to the limited genetic diversity of domesticated tomato accessions, the populations used for linkage mapping have been generated by crosses between a cultivated and a close wild tomato species (Foolad 2007; Foolad and Panthee 2012). Since the development of molecular markers, these segregating populations have become an effective and efficient tool to construct high-density genetic linkage maps (Tanksley et al. 1992), allowing the detection of quantitative trait loci (QTLs). By using different linkage populations and multiple molecular markers, including RFLP, simple sequence repeat, (SSR) and SNPs, hundreds of QTLs have been reported, for different agronomical, morphological, and quality-related traits (Grandillo and Tanksley 1996b; Tanksley et al. 1996; Fulton et al. 1997; Bernacchi et al. 1998a, b; Chen et al. 1999; Grandillo et al. 1999; Fulton et al. 2000; Monforte and Tanksley 2000; Saliba-Colombani et al. 2001; Causse et al. 2002; Doganlar et al. 2003; van der Knaap and Tanksley 2003; Fridman et al. 2004; Baldet et al. 2007; Foolad 2007; Jiménez-Gómez et al. 2007; Cagas et al. 2008; Dal

Cin et al. 2009; Sim et al. 2010; Ashrafi et al. 2012; Haggard et al. 2013; Kinkade and Foolad 2013).

However, among the detected QTLs, only a few have been cloned and functionally validated (Bauchet and Causse 2012; Rothan et al. 2019). The first gene cloned by positional cloning in tomato was the *Pto* gene, conferring resistance to *Pseudomonas syringae* races, with the assistance of RFLP markers (Martin et al. 1994). Based on the same RFLP map, *Fen*, another member of this gene family, was also soon reported (Martin et al. 1994). From then on, different resistance genes were identified and cloned based on RFLP markers, such as *Cf-2*, a leucine-rich repeat protein conferring resistance to *Cladosopum fulvum* strains (Dixon et al. 1996); *Prf*, another resistance gene to *Pseudomonas syringae* pv. tomato (Pst) strains (Salmeron et al. 1996); *Ve* conferring Verticilium wilt resistance, encoding surface-like receptors (Kawchuk et al. 2001); and others. Some other markers were also developed and applied for resistance gene identification, such as *Ph-3* gene from *S. pimpinellifolium* conferring resistance to *Phytophthora infestans*, which was cloned based on cleaved amplified polymorphic sequences (CAPS) or insert/deletion (InDel) markers (Zhang et al. 2014). Sequence-characterized amplified region (SCAR) markers and cleaved amplified polymorphic sequence (CAPS) markers are also applying to map tomato yellow leaf curl virus resistance gene *Ty-2* (Yang et al. 2014).

Some important genes/QTLs involved in developmental processes were also identified and cloned with the assistance of molecular markers. Among them, *fw2.2*, a major QTL controlling tomato fruit weight, was one of the first examples. With the benefits of CAPs markers, a single candidate gene ORFX on chromosome 2 was identified and cloned (Frary et al. 2000), which alters tomato fruit size likely by expression regulation rather than sequence and structure variation of the encoded protein (Nesbitt and Tanksley 2002). Recently, some other major QTLs were functionally validated, such as *fw3.2* (corresponding to a cytochrome P450 gene) (Chakrabarti et al. 2013) and *fw11.2* (corresponding to a cell size regulator) (Mu et al. 2017). Some major QTLs closely related to fruit weight were also reported, such as *OVATE*, a negative regulatory gene causing pear-shaped tomato fruits (Liu et al. 2002); SUN, a retrotransposon-mediated gene (Xiao et al. 2008); locule number *fas* (Huang and van der Knaap 2011) and *lc* (Muños et al. 2011). Other cloned genes related to tomato development are summarized in a recent review paper (Rothan et al. 2019).

Tomato fruits are rich in diverse nutrients and health-promoting compounds, such as sugars, organic acids, amino acids, and volatiles (Goff and Klee 2006; Klee 2013). However, breed tomatoes with high nutrition and strong flavor still remain a major breeding challenge (Tieman et al. 2012; Klee and Tieman 2013; Klee and Tieman 2018; Zhao et al. 2019). *Lin5*, a major QTL modifying sugar content in tomato fruit, was cloned about 20 yearS ago (Fridman et al. 2000). In various genetic backgrounds and environments, the wild-species allele increased glucose and fructose contents compared to cultivated allele (Fridman et al. 2000). In addition, this gene shared a similar expression pattern in tomato, potato, and Arabidopsis (Fridman and Zamir 2003). Recently, a *SWEET* protein, a plasma membrane-localized glucose efflux transporter, was shown to play a role in the ratio of glucose and fructose accumulation (Shammai et al. 2018). A balanced content of sugars and organic acids is crucial for

consumer preference (Tieman et al. 2017). Recently, a major QTL regulating malate content was cloned, corresponding to an *Aluminium Activated Malate Transporter 9* (*Sl-ALMT9*) (Ye et al. 2017). In a new recent study, it was further found that this QTL was also likely regulating the content of citrate in tomato fruits (Zhao et al. 2019). Though only a few QTLs regulating sugars and organic acids have been functionally validated, this knowledge is important for understanding the regulation mechanisms. Several genes involved in the variation of volatile production were also characterized (Tieman et al. 2006; Tikunov et al. 2013; Klee 2010; Klee and Tieman 2018).

2.3.7 New Resources for Gene/QTL Identification

Lin et al. (2014) demonstrated the benefits of whole-genome resequencing of the two extreme bulk populations from an F_2 population of tomato, where many fruit weight QTLs were identified, including *fw2.1*, *fw2.2*, *fw2.3*, *lcn2.1*, *lcn2.2*, *fw9.1*, *fw9.3*, *fw11.1*, *fw11.2,* and *fw11.3*. Whole-genome sequencing of bulked F_2 plants with contrasted phenotypes offers the opportunity to identify the SNPs that are putatively related to the target phenotypes via aligning the sequenced data to the reference genome (Garcia et al. 2016). This approach has been efficient in identifying mutations, especially generated by EMS (Garcia et al. 2016).

However, the genetic diversity of linkage populations is limited to the two parental accessions used for crossing. In order to overcome this limitation, multi-parent advanced generation intercross (MAGIC) populations offer an alternative, which has been generated for different species, such as Arabidopsis (Kover et al. 2009), rice (Bandillo et al. 2013), wheat (Huang et al. 2012; Mackay et al. 2014), faba bean (Sallam and Martsch 2015), sorghum (Ongom and Ejeta 2017), and tomato (Pascual et al. 2015). The first tomato MAGIC population was developed by crossing eight re-sequenced tomato lines and there was no obvious population structure in this population. The linkage map was 87% larger than those derived from bi-parental populations and some major fruit quality QTLs were identified by using this approach (Pascual et al. 2015). Recently, this MAGIC population was also used for identifying QTLs under water deficit and salinity stresses and many stress-specific QTLs were identified (Diouf et al. 2018).

2.3.8 Genome-Wide Association Studies

2.3.8.1 The Conditions for Applying Genome-Wide Association Studies

Association mapping is used to detect associations between a given phenotype and genetic markers in a population of unrelated accessions. If the genetic markers cover the whole genome, it is referred to as genome-wide association studies (GWAS). This technology was first developed in humans. After the demonstration of GWAS

power to analyze human diseases (Klein et al. 2005), it was quickly adopted in major crops (Brachi et al. 2011; Luo 2015; Liu and Yan 2019). In tomato, the first reported association study was performed to identify the SNPs associated with the fruit weight QTL *fw2.2*. However, the authors did not find any positive associated SNP in a small collection of 39 cherry tomato accessions (Nesbitt and Tanksley 2002).

In order to efficiently apply GWAS in tomato, linkage disequilibrium (LD) in different tomato types was assessed using different molecular markers. In general, the LD in cultivated tomato accessions was larger than that of wild species, which could be up to about 20 Mbs, while cherry tomatoes ranged in between (Van Berloo et al. 2008; Mazzucato et al. 2008; Sim et al. 2010; Ranc et al. 2012; Xu et al. 2013; Sauvage et al. 2014; Zhang et al. 2016a, b; Bauchet et al. 2017a). These results also indicated that modern tomatoes lost genetic diversity during tomato domestication and breeding. Admixture of cherry tomatoes with modern cultivars and wild species could help reduce the large LD and overcome the low resolution of association mapping of modern tomato cultivars (Ranc et al. 2012). The average high degree of LD is beneficial in terms of the minimum number of molecular markers needed to cover the whole genome. For example, (Xu et al. 2013) performed an association mapping on 188 tomato accessions with 121 polymorphic SNPs and 22 SSRs. They successfully identified 132 significant associations for six quality traits. Before the availability of large SNP number, molecular markers such as SSRs were popular for GWAS. In particular, (Zhang et al. 2016a, b) genotyped 174 tomato accessions including 123 cherry tomato and 51 heirlooms with 182 SSRs and performed GWAS for fruit quality traits. A total of 111 significant associations were identified for 10 traits and many previously identified major QTLs were located in/near regions of the significant associated markers. The authors further extended the phenotypes to volatiles (Zhang et al. 2016a, b), as well as sugars and organic acids (Zhao et al. 2016). Many significant associations were also identified and some of them were consistent with other GWAS focusing on the same traits that were based on genome-wide SNPs (Sauvage et al. 2014; Bauchet et al. 2017b; Tieman et al. 2017; Zhao et al. 2019).

With the availability of the reference tomato genome (The Tomato Genome Consortium 2012), millions of SNPs became available and allowed the identification of causative polymorphisms. For instance, the causative gene *SlMYB12* conferring pink tomato fruit color was identified in a GWAS using 231 sequenced tomato accessions (Lin et al. 2014). Several mutations were further identified in the protein structure of SlMYB12 and the authors identified three recessive alleles of this gene useful for pink tomato breeding (Lin et al. 2014).

However, whole-genome-sequencing is still quite expensive, especially at a large population scale, which greatly limits the wide applications. SNP arrays were thus developed to overcome this limit (Hamilton et al. 2012; Sim et al. 2012b). Sauvage et al. (2014) genotyped 163 tomato accessions composed of large fruit, cherry, and wild tomato accessions with the SolCAP array, generating a total of 5995 high-quality SNPs. Then they performed GWAS using a multi-locus mixed model (MLMM; (Segura et al. 2012) for 36 metabolites that were highly correlated during two growth periods and identified 44 candidate loci associated with different fruit metabolites

(Sauvage et al. 2014). Among the candidate loci, they identified a gene with unknown function on chromosome 6 that was strongly associated with malate content. This association was further identified in different GWAS and meta-analysis of GWAS based on different populations (Bauchet et al. 2017b; Tieman et al. 2017; Ye et al. 2017; Zhao et al. 2019) and was further validated as an *Al-Activated Malate Transporter 9* (*Sl-ALMT9*) (Ye et al. 2017). In a meta-analysis of GWAS based on three populations, it was further found that this gene was also significantly associated with citrate content in tomato fruits, demonstrating its important role in the regulation of organic acids in tomato (Zhao et al. 2019). In fact, the Al-activated malate transporters are a family of plant-specific proteins, which are important for plant root tissue and function (Delhaize et al. 2007).

Bauchet et al. (2017b) genotyped 300 tomato accessions with both the SolCAP and CBSG arrays, generating a total of 11,012 high-quality SNPs, which were used for GWAS using both MLMM and multi-trait mixed model (MTMM) (Korte et al. 2012). A total of 79 significant associations were identified for 13 primary and 19 secondary metabolites in tomato fruits. Among these, two associations involving fruit acidity and phenylpropanoid content were particularly investigated (Bauchet et al. 2017b). The same population was also characterized for agronomic traits and many QTLs were identified, such as *fw2.2* and *fw3.2*. Within this panel, the authors also demonstrated that intermediate accessions shared different haplotype patterns compared to domesticated and wild tomatoes (Bauchet et al. 2017a). GWAS for similar quality traits were also performed in other collections (Ruggieri et al. 2014; Zhang et al. 2016a, b).

With the fast development of whole-genome-sequencing technology and the reduction of cost per genome, it is possible to sequence hundreds of diverse tomato collections. For instance, (Tieman et al. 2017) sequenced 231 new accessions and combined these data with 245 previously sequenced genomes, generating a total of 476 genome sequences. These data were then used for GWAS for diverse flavor-related metabolites, including 27 volatiles, total soluble solids, glucose, fructose, citric acid, and malic acid. A total of 251 significant associations were detected for 20 traits. Two loci were significantly associated with both glucose and fructose, corresponding to two major QTL *Lin5* and *SSC11.1*. By combining with selection analysis, it was further shown that the negative correlation between sugar content and fruit weight was likely caused by the loss of high-sugar alleles during domestication and improvement of ever-larger tomato fruits (Tieman et al. 2017). In addition, some good candidate genes involved in tomato volatile contents were also identified, such as Solyc09g089580 for guaiacol and methylsalicylate. By combining the three significant associated loci for geranylacetone and 6-methyl-5-hepten-2-one, it was shown that the allelic combinations conferring favorable aromas were progressively lost during domestication and breeding (Tieman et al. 2017).

2.3.8.2 Meta-Analysis

However, with the results of several GWAS in tomato for the same trait, only some significant associations could be identified in different studies, indicating strong cross-study heterogeneity, which refers to the non-random variance in the genetic effects between different GWASs. The main sources of heterogeneity include population structure, linkage disequilibrium, phenotyping measurement methods, environmental factors, genotyping methods, G×E interactions (Evangelou and Ioannidis, 2013). Meta-analysis of GWAS is a new approach to combine different GWAS properly handling the heterogeneity.

Zhao et al. (2019) reported the meta-analysis of GWAS from three tomato populations (Sauvage et al. 2014; Bauchet et al. 2017b; Tieman et al. 2017). Following genotype imputation, a total of 775 tomato accessions and 2,316,117 SNPs were used in the meta-analysis and a total of 305 significant associations were identified for the contents of sugars, organic acids, amino acids, and flavor-related volatiles. By looking at the five loci associated with both fructose and glucose, they showed that sugar contents significantly increased with the number of wild alleles. The authors also demonstrated that domestication and improvement have had an impact on citrate and malate content. In particular, the major QTL *Al-Activated Malate Transporter 9* of malate was also significantly associated with citrate and another malate transporter was identified for citrate content on chromosome 1. This study also identified many new significant associations for flavor-related volatiles. By targeting six significant associations, it was further demonstrated that modern tomato accessions had a limited flavor due to a lower content of pleasant volatiles but also a higher content of unpleasant volatiles compared to cherry tomatoes (Zhao et al. 2019).

2.3.9 Genetic Dissection of Abiotic Stress Tolerance

2.3.9.1 Genetic Control of GxE Interaction

In Sect. 2.3.2 above, the impact of different abiotic stresses on tomato was described. Nevertheless, a large diversity of response has been shown notably between the wild species and the cultivated one, but also across cultivated accessions. Several studies were conducted to understand the genetic mechanisms leading to such variation in tomato response to environmental stresses. Elucidating the genetic determinants of tomato response to abiotic stress was possible thanks to the high genetic diversity present in the *S. lycopersicum* clade.

A large panel of genetic resources is available for the tomato community, including both cultivated and wild species (Sect. 3.1). Screening the genetic diversity in both compartments brought to light high loss of diversity within the cultivated group (Lin et al. 2014) due to extensive directional selection toward agronomic performance traits. However, substantial diversity for environmental response genes remains in the cultivated group that could be attributed to local adaptations during the diversification

for both climatic conditions and growth conditions. This is identified by the presence of substantial genotype-by-environment (GxE) interactions, as observed in different intraspecific experimental tomato populations (Villalta et al. 2007; Mazzucato et al. 2008; Albert et al. 2016a; Diouf et al. 2018).

Besides, wild species constitute a reservoir of specific genes related to abiotic stress tolerance, derived from adaptation to their growing and typically harmful local habitats. For example, the two wild relative species *S. habrochaites* and *S. pennellii* are more tolerant to chilling stress (Bloom et al. 2004) and to drought and salinity stress conditions (Bolger et al. 2014), compared to cultivated species. The presence of tolerance genes in the wild species and the genetic diversity of stress-response genes in cultivated clade give clues to achieve considerable progress in tomato breeding for climate-smart cultivars.

Several studies investigated the genetic nature of tomato response to abiotic stresses since a high-density genetic map was made available. Grandillo et al. (2013) and Grandillo and Cammareri (2016) reported a summary of the QTLs that were identified under different abiotic stress conditions. Table 2.4 summarizes abiotic stress QTLs identified during the last decade only. These QTLs were mapped in different population types and with different mapping methods covering the wide range of mapping strategies available in plant genetics. These studies highlighted several phenotypic traits that were defined to assess tomato response to abiotic factors due to the complexity of stress response mechanisms. For example, Kazmi et al. (2012a, b) used seed quality traits to identify QTLs associated with tomato germination capacity under WD, CS, SS, and HT stress. They identified no less than 90 seed quality QTLs under stress conditions. Physiological parameters under WD and nitrogen-deficiency conditions were mapped in sub-NILs (Arms et al. 2016) and 130 F10 RILs (Asins et al. 2017) populations, respectively. Metabolite variation in tomato seeds under SS was studied by Rosental et al. (2016) and several QTLs were identified in 72 ILs derived from the introgression of chromosome fragments of *S. pennellii* LA716 into the domesticated tomato cultivar M82. A recent study used gene expression data under WD and control conditions and identified some WD interactive eQTLs (Albert et al. 2018). This approach permitted the distinction between *cis* and *trans* regulatory eQTL clarifying the patterns of expression regulation in tomato under WD leading to genotype-by-environment interaction. Combining expression data with QTL analysis thus helped to identify candidate stress-response genes and could be useful for the optimal choice of genetic markers to conduct MAS for stress adaptation.

However, the majority of the studies used agronomic traits instead of physiological parameters or metabolic traits to evaluate the impact of abiotic stress. This has led to the definition of different stress indexes according to breeding objectives (Table 2.4); thus QTL identified for such stress index could be directly used in breeding programs.

Until now, most QTL studies on tomato were conducted on single stress evaluation, achieving a better characterization of genetic loci involved in tomato response to a given abiotic stress. Further studies should target genomic regions that interfere in response to stress combinations. Few examples of such studies are available in plants (Davila Olivas et al. 2017).

Table 2.4 QTL studies on tomato abiotic stress published during the last decade. For each study, the number of genotypes analyzed, the population cross-design, and the number and type of markers used are displayed. The columns "Stress treatment" and "Stress period" present the level of stress applied and the period on which stress was applied. The column "Phenotypes" highlights the phenotypic traits that were evaluated to conduct the QTL/association analysis. The phenotypic traits usually correspond to different traits: Seed quality (germination ability); Fruit quality (SSC, Vitamin C, pH, firmness, organic acids); Plant architecture and vegetative growth (diameter, leaf length, height, dry matter content, specific leaf area, biomass); Phenology (flowering, ripening time); Productivity (yield, fruit weight, number of fruits); Physiological traits (WUE); Model parameters (Maximum cell wall extensibility, membrane conductivity, sugar active uptake, membrane reflection, Pedicel conductivity, soluble sugar concentration, fruit dry weight, fruit water content, xylem conductivity)

Treatment	Number of individuals	Marker types	Stress treatment	Stress period	Cross-design	Phenotypes	Number of QTLs	Reference
Cold stress (CS)								
CS	83 RILs	865 SNP	Cold stress (12 °C)	Seed germination	Bi-parental (Interspecific)	Seed quality	12 QTLs	Kazmi et al. (2012)
CS	146 RILs	120 SSR	Cold stress (11 °C)	Seed germination	Bi-parental (Interspecific)	Germinatin ratio	5 QTLs	Liu et al. (2016a, b)
CS	146 RILs	120 SSR	2 °C for 48 h	4–5 true leaves	Bi-parental (Interspecific)	Chilling injuries	9 QTLs	Liu et al. (2016a, b)
Hight temperature stress (HT)								
HT	192 F2	106 AFLP markers	Minimal/Maximal T° > 25 °C/40 °C	Transplanting—end of the experiment	Bi-parental (Intraspecific)	Fruit set	6 QTLs	Grilli et al. (2007)
HT	160 F2	62 RAPD, ISSR and AFLP markers	Day/Night T° = 37.2 °C/24.7 °C	All growing season	Bi-parental (Interspecific)	Yield; Fruit quality; Reproductive traits	21 QTLs	Lin et al. (2010)

(continued)

Table 2.4 (continued)

Treatment	Number of individuals	Marker types	Stress treatment	Stress period	Cross-design	Phenotypes	Number of QTLs	Reference
HT	83 RILs	865 SNP	Heat stress (35–36 °C)	Seed germination	Bi-parental (Interspecific)	Seed quality	16 QTLs	Kazmi et al. (2012)
HT	180 F2	96 SNP	Day/Night T° = 31 °C/25 °C	From 1st inflorescences appearance	Bi-parental (Intraspecific)	Reproductive traits	13 QTLs	Xu et al. (2017a, b)
HT	98 F8 RILs	727 SNP	37 °C	Seed germination	Bi-parental (Interspecific)	Thermo-tolerance, Thermo-inhibition, Thermo-dormancy	9 QTLs	Geshnizjani et al. (2018)
Salinity stress (SS)								
SS	123 RILs	156 SSR, SCAR markers	125 mM NaCl	15 days after transplanting to the end of the experiment	Bi-parental (Interspecific)	Rootstock induced physiological parameters; Vegetative growth	57 QTLs	Asins et al. (2010)
SS	52 ILs	!!	150 mM NaCl	21 days from the seven true leaf stage	Bi-parental (Interspecific)	Plant architecture; antioxidant content	71 QTLs	Frary et al. (2010)

(continued)

Table 2.4 (continued)

Treatment	Number of individuals	Marker types	Stress treatment	Stress period	Cross-design	Phenotypes	Number of QTLs	Reference
SS	52 ILs	!!	150 mM NaCl	15 days of treatment	Bi-parental (Interspecific)	Plant architecture; Vegetative growth	225 QTLs	Frary et al. (2011)
SS	78 ILs	!!	700 mM $NaCl^+$ 70 mM $CaCl_2$	4 days after transplanting	Bi-parental (Interspecific)	Survival performance	4 QTLs	Li et al. (2011)
SS	90 ILs	!!	700 mM $NaCl^+$ 70 mM $CaCl_2$	4 days after transplanting	Bi-parental (Interspecific)	Survival performance	6 QTLs	Li et al. (2011)
SS	100 RILs	134 SSR, SCAR markers	75 mM NaCl	15 days after transplanting to the end of the experiment	Bi-parental (Interspecific)	Rootstock induced physiological parameters; Vegetative growth	2 QTLs	Asins et al. (2010)
SS	83 RILs	865 SNP	Two levels of SS (−0.3 and −0.5 MPa NaCl)	Seed germination	Bi-parental (Interspecific)	Seed quality	32 (26) QTLs	Kazmi et al. (2012)
SS	124 RILs	2059 SNPs	8.94 dS/m	10 days after the transplanting	Bi-parental (Interspecific)	Yield; Fruit quality; Biomass	54 QTLs	Asins et al. (2015)

(continued)

Table 2.4 (continued)

Treatment	Number of individuals	Marker types	Stress treatment	Stress period	Cross-design	Phenotypes	Number of QTLs	Reference
SS	72 ILs	!!	EC = 6 dS/m	Planting—end of the experiment	Bi-parental (Interspecific)	Seed weight; Seed Germination; Metabolites	131 QTLs	Rosental et al. (2016)
SS	253 MAGIC RILs	1345 SNP	Two levels of SS (Ec = 3.7 dS/m^{-1} and Ec = 6.5 dS/m^{-1})	Transplanting—end of the experiment	MAGIC (Intraspecific)	Fruit quality; Plant architecture and vegetative growth; Phenology; Productivity	35 QTLs	Diouf et al. (2018)
Water deficit stress (WD)								
WD	75 ILs	!!	WD (30 m^3 of water irrigation for 1000 m^2)	Transplanting—end of the experiment	Introgression Line (Interspecific)	Fruit quality; Plant architecture and vegetative growth; Productivity	114 QTL	Gur et al. (2011)
WD	83 RILs	865 SNP	Two levels of Osmotic stress (−0.3 and −0.5 MPa PEG)	Seed germination	Bi-parental (Interspecific)	Seed quality	23 (19) QTLs	Kazmi et al. (2012)

(continued)

Table 2.4 (continued)

Treatment	Number of individuals	Marker types	Stress treatment	Stress period	Cross-design	Phenotypes	Number of QTLs	Reference
WD	119 RILs	679 SNP	WD (40% ETP)	Transplanting—end of the experiment	Bi-parental (Intraspecific)	Fruit quality; Plant architecture and vegetative growth; Phenology; Productivity	36 QTL	Albert et al. (2016a)
WD	141 small-fruit accessions	6100 SNPs	WD (40% ETP)	Transplanting—end of the experiment	GWAS-panel	Fruit quality; Plant architecture and vegetative growth; Phenology; Productivity	100 QTLs	Albert et al. (2016b)
WD	18 sub-NILs	10 markers (SNP; SCAR; CAP)	WD (33%ETP)	Transplanting—end of the experiment	Near-Introgression Line (Interspecific)	Physiological traits; Plant architecture	2 QTLs regions	Arms et al. (2016)
WD	117 F7 RILs	501 SNP	WD (49% ETP)	Transplanting—end of the experiment	Bi-parental (Intraspecific)	Model parameters	8 QTLs	Constantinescu et al. (2016)

(continued)

Table 2.4 (continued)

Treatment	Number of individuals	Marker types	Stress treatment	Stress period	Cross-design	Phenotypes	Number of QTLs	Reference
WD	241 MAGIC RILs	1345 SNP	WD (50% ETP)	Transplanting—end of the experiment	MAGIC (Intraspecific)	Fruit quality; Plant architecture and vegetative growth; Phenology; Productivity	22 QTLs	Diouf et al. (2018)
WD	124 RILs	501 SNP	WD (60% ETP)	Transplanting—end of the experiment	Bi-parental (Intraspecific)	Fruit quality; Plant architecture and vegetative growth; Phenology; Productivity	23 QTLs	Albert et al. (2018)
WD	124 RILs	501 SNP	WD (60% ETP)	Transplanting—end of the experiment	Bi-parental (Intraspecific)	Gene expression level for 274 genes	103 eQTL	Albert et al. (2018)
Other abiotic stress								
Oxidative stress	83 RILs	865 SNP	Oxidative stress (300 mm H_2O_2)	Seed germination	Bi-parental (Interspecific)	Seed quality	17 QTLs	Kazmi et al. (2012)
N-deficiency	130 F10 lines	1899 SNP	N-deficiency (NH_4^+: 0.1 mM and NO_3^-: 1 mM)	Transplanting—1st truss fruit set	Bi-parental (Interspecific)	Vegetative growth, Leaf nitrogen content; Xylème sap hormone content	40 QTLs	Asins et al. (2017)

Genotype-by-environment (GxE) interaction usually occurs in cultivated crops exposed to abiotic stresses. Two strategies are commonly adopted by breeders to deal with GxE: (i) developing some elite cultivars for a specific targeted environment or (ii) breeding stable cultivars for a wide range of environmental conditions. The first strategy will allow to reach high yield in predictable environments (likely controlled environments) while the second strategy will be more efficient for reducing at an optimized level, the yield decrease in unpredictable environments. This has led plant geneticists into the question of genetic control of phenotypic plasticity related to GxE phenomenon. Some studies addressed this question in major crop species and identified different plasticity QTLs. Kusmec et al. (2017), for example, suggested that in maize, genes controlling plasticity for different environments are in majority distinct from genes controlling mean trait variation, assuming a possible co-selection for stability and yield performance concurrently. In tomato, plasticity QTLs were also identified in intraspecific populations under WD and SS conditions (Albert et al. 2016a; Diouf et al. 2018). Extending the environmental range to different stress conditions could be a way to reliably identify multi-stress-response genes that would be useful in the task of breeding climate-smart tomato.

2.3.9.2 Grafting as a Defense Against Stresses

For many plant species specially vegetables and fruit trees, grafting has been considered as a solution to manage soil-borne disease and to improve crop response to a variety of abiotic stresses (King et al. 2010). For stress induced by extreme soil conditions, grafting elite cultivars onto genetic resistant rootstocks is an attractive alternative to introgression from wild resources due to the side effects of linkage drag and the polygenic nature of abiotic stress tolerance. However, grafting requires paying specific attention to the scion x rootstock combination in order to achieve better performance. In tomato, interactions between the scion and the rootstock were detected in different grating operations with alteration in fruit quality components, plant vigor, plant hormonal status, and final yield (Kyriacou et al. 2017). This highlights the necessity to test different combinations of scion-rootstocks in one hand, and in the other hand to have a better understanding of how grafting impacts the targeted breeding traits for efficient utilization of rootstocks under stressful environments.

Different tomato rootstock populations were developed and characterized accordingly. This involves populations generated from interspecific crosses between a cherry tomato accession and two wild relatives from *S. pimpinellifolium* and *S. cheesmaniae* (Estañ et al. 2009). These populations were studied under salinity (Albacete et al. 2009; Asins et al. 2010, 2015, 2013) and N-deficiency stress conditions (Asins et al. 2017). They revealed that grafting could induce variation in leaf hormonal content and ion concentrations correlated to vegetative growth and yield under salinity. The effect mediated by rootstock under salinity has a polygenic nature and is controlled by different QTLs among which one, located on chromosome 7, was related to two HTK candidate genes, involved in ion transport and cell homeostasis regulation. However, while grafting under salinity presents a promising approach to maintain or

increase tomato yield, some drawbacks were recorded concerning higher incidence of BER and delayed fruit ripening.

The hormonal status changes induced by rootstock was also shown as being potentially exploitable to increase tomato WUE (Cantero-Navarro et al. 2016). More generally, Nawaz et al. (2016) reviewed the effect of grafting on ion accumulation within horticultural crops highlighting the need for deeper characterization of rootstock x scion x environment interaction both at phenotype and genetic levels for effective utilization of grafting as a technique to manage extreme soil conditions for crops.

Besides the direct use of genetic control of pests and pathogens, grafting susceptible cultivars onto selected vigorous rootstocks may counteract soil-borne biotic stresses as well as abiotic stresses. Grafting was also proposed for improving virus resistance by enhancing RNA-silencing (Spano et al. 2015). A great challenge is consequently to breed for rootstocks that can withstand combined biotic and abiotic stresses.

2.3.10 Omic Approaches

2.3.10.1 Metabolome Analyses

Metabolomics has an important role to play in characterization of natural diversity in tomato (Schauer et al. 2005; Fernie et al. 2011). Metabolome analysis can be done in a targeted way to better characterize known metabolites (Tieman et al. 2006) or untargeted manner to identify new metabolites (Tikunov et al. 2005). As well, it can boost the biochemical understanding of fruit content and be an enhancer for quality breeding (Fernie and Schauer 2009; Allwood et al. 2011). Metabolome analyses were used to analyze fruit composition at a high-throughput level. Metabolite QTL (mQTL) has been identified for non-volatiles metabolites like sugars, pigments, or volatiles compounds (Bovy et al. 2007; Klee 2010, 2013; Klee and Tieman 2018). This was done on several interspecific populations, notably on *S. pennelli* (Alseek et al. 2015, 2017) and *S. chmielewskii* (Do et al. 2010; Ballester et al. 2016) introgression lines and intraspecific crosses (Saliba-Colombani et al. 2001; Causse et al. 2002; Zanor et al. 2009). The interaction between the tomato plant and thrips was also studied by metabolome profiling (Mirnezhad et al. 2010).

2.3.10.2 Transcriptome Analyses for EQTL Mapping

Several studies analyzed the transcriptome changes along with fruit development (Pattison et al. 2015; Giovanonni et al. 2017; Shinozaki et al. 2018) revealing key changes in gene expression during the different stages. Analysis of the genetic control of such variations in segregating populations was also performed (Ranjan

et al. 2016; Coneva et al. 2017). Characterizing the natural diversity of gene expression across environments is also an important step in understanding genotype-by-environment interactions. Albert et al. (2018) identified some eQTL in response to water stress and showed the large differences between the transcriptome of leaf and fruit under well irrigated and water stress conditions. The authors also studied allele-specific expression (ASE) in the F1 hybrid

To reveal genes deviating from the 1/1 allele ratio expected and showed a large range of genes whose variation exhibited significant ASE-by-watering regime interaction, among which ~80% presented a response to water deficit mediated through a majority of transacting.

2.3.10.3 Multi-omic Approach

Combining metabolome and transcriptome may give clues about the genetic control of fruit composition as underlined by Prudent et al. (2011). Zhu et al. (2018) performed a multi-omic study by integrating data of the genomes, transcriptomes, and metabolomes. Up to 3,526 significant associations were identified for 514 metabolites and 351 of them were associated with unknown metabolites. Correlation analysis between genomes and transcriptomes identified a total of 2,566 cis-eQTL and 93,587 trans-eQTL. Rigorous multiple correction tests between transcriptomes and metabolomes identified 232,934 expression-metabolite correlations involving 820 chemicals and 9,150 genes. By integrating these three groups, a total of 13,361 triple relationships (metabolite-SNP-gene) were further identified, including 371 metabolites, 970 SNPs, and 535 genes. Selection analysis discovered 168 domestication sweeps and 151 improvement sweeps, representing 7.85% and 8.19% of the tomato genome, respectively. A total of 4,095 and 4,547 genes were located within the identified domestication and improvement sweeps. In addition, a total of 46 steroidal glycoalkaloids was identified and five significant associations were located within domestication or improvement sweeps. They also showed that the introgression of resistance genes also introduced significant differences in some metabolites.

2.3.10.4 MiRNA and Epigenetic Modifications

Epigenome is the complete set of epigenetic marks at every genomic position in a given cell at a given time (Taudt et al. 2016). These marks fall into six categories, including DNA modifications, histone modifications, chromatin variants, nucleosome occupancy, RNA modifications, non-coding RNAs, chromatin domains, and interactions (Stricker et al. 2017). Technological advances nowadays make it possible to achieve high-resolution measurements of epigenome variation at a genome-wide scale and great achievements have been made in human, rat, yeast, maize, tomato, Arabidopsis, and soybeans (Taudt et al. 2016; Giovannoni et al. 2017).

Most of epigenome studies in tomato focused on the molecular regulations of fruit ripening and development (Gallusci et al. 2016; Giovannoni et al. 2017).

Among these, histone posttranslational modifications play an important role, which include phosphorylation, methylation, acetylationand mono-ubiquitination of lysine residues (Berr et al. 2011). In Arabidopsis, histone posttranslational modifications are involved in many aspects of plant development and stress adaptation (Ahmad et al. 2010; Mirouze and Paszkowski, 2011).In tomato, at least nine DNA methyltransferases and four DNA demethylases have been identified (Gallusci et al. 2016). Expression patterns of different histone modifiers in some fresh fruits have also been identified, such as histone deacetylases, histone acetyltransferase, and histone methyltransferases (Gallusci et al. 2016). Repression of tomato Polycomb repressive complex 2 (PRC2) components *SlEZ1* altered flower and fruit morphology (How Kit et al. 2010) and *SlEZ2* altered fruit morphology, such as texture, color, and storability (Boureau et al. 2016). These results demonstrated that epigenetic regulations are important for many biological processes.

Very few phenotypes have been associated with epi-mutations. Manning et al. (2006) identified a naturally occurring methylation epigenetic mutation in the SBP-box promoter residing at the colorless non-ripening (*Cnr*) locus, a major component in the regulatory network controlling tomato fruit ripening (Eriksson et al. 2004). Quadrana et al. (2014) identified an epi-mutation responsible of the variation in vitamin E in the fruit. In order to determine whether the process of tomato fruit ripening involves epigenetic remodeling, Zhong et al. (2013) found that tomato ripen prematurely under methyltransferase inhibitor 5-azacytidine. Up to 52,095 differentially methylated regions were identified, representing 1% of the tomato genome. In particular, demethylation regions were identified in the promoter regions of numerous ripening genes. In addition, the epigenome status was not static during tomato fruit ripening (Zhong et al. 2013). Shinozaki et al. (2018) performed a high-resolution spatio-temporal transcriptome mapping during tomato fruit development and ripening. Some tissue-specific ripening-associated genes were identified, such as SlDML2. Together with other analyses, these results indicate that spatio-temporal methylations play an important role during tomato fruit development and ripening (Shinozaki et al. 2018).

Lü et al. (2018) investigated the functional elements of seven climacteric fruit species (apple, banana, melon, papaya, peach, pear, and tomato) and four non-climacteric fleshy fruit species (cucumber, grape, strawberry, and watermelon). By analyzing 361 transcriptome, 71 accessible chromatin, 147 histone, and 45 DNA methylation profiles from the fruit ENCODE data, three types of transcriptional feedback circuits were identified controlling ethylene-dependent fruit ripening (Lü et al. 2018). In particular, H3K27me3, associated with silencing of the flowering regulator FLOWERING LOCUS C and floral homeotic gene AGAMOUS (He 2012), played a conserved role in dry and ethylene-independent fruits by restricting ripening genes and their orthologs.

MicroRNA (miRNAs) is another type of epigenetic regulation. miRNAs are a class of 20- to 24-nucleotide non-coding endogenous small RNAs that are important in transcriptional or post-transcriptional regulation by transcript cleavage and translation repression (Chen 2005, 2009; Rogers and Chen 2013; Sanei and Chen 2015).

miRNAs are encoded by miRNA genes, which contain the TATA-box motif and transcription factor binding motifs, and are regulated by general specific transcription factors (Xie et al. 2005; Megraw et al. 2006; Rogers and Chen 2013; Yu et al. 2017). miRNAs play an important role in many biological processes, including physiological, developmental, defense, and environmental changes both in humans (Calin and Croce 2006; Mendell and Olson 2012; Cui et al. 2017b; Hill and Tran 2018), animals (Ambros 2004; Rajewsky 2006; Grimson et al. 2008) and plants (Rogers and Chen 2013; Won et al. 2014; Sanei and Chen 2015; Cui et al. 2017a; You et al. 2017; Yu et al. 2017). Some regulatory mechanisms of the core components of the dicing complex, such as DICER-LIKE1 (DCL1) and HYPONASTIC LEAVES1 (HYL1) have been uncovered (Manavella et al. 2012; Cho et al. 2014; Zhang et al. 2017). Proteins promoting pre-miRNA processing and reducing miRNA levels have also been identified, such as CAP-BINDING PROTEIN 80 (CBP80), CAP-BINDING PROTEIN 20 (CBP20), STABILIZED1 (STA1), and others (Gonatopoulos-Pournatzis and Cowling 2015; Yu et al. 2017). Some proteins could reduce the accumulation of both mature pre-miRNA and mature miRNA, such as CDC5, NOT2, Elongator, and DDL (Yu et al. 2008; Wang et al. 2013a, b; Zhang et al. 2013; Fang et al. 2015). Though many processes involved in miRNA biogenesis, degradation and activity have been discovered, our knowledge regarding the subcellular locations of these processes is still largely unknown (Yu et al. 2017).

During the tomato genome sequencing, a total of 96 conserved miRNA genes were predicted. Among them, 34 miRNA have been identified and 10 are highly conserved in both tomato and potato (The Tomato Genome Consortium 2012). Several studies focused on the characterizations of miRNAs in tomato during fruit development (Moxon et al. 2008; Zuo et al. 2012; Gao et al. 2015). The dominant sRNAs were 21- to 24-nt sRNAs (Mohorianu et al. 2011; Zuo et al. 2012; Gao et al. 2015). Many ripening-associated gene transcription factors were regulated by certain miRNA families, such as miR156/157, miR159, miR160/167, miR164, miR171, and miR172 families (Moxon et al. 2008; Karlova et al. 2013; Zuo et al. 2013). miRNA precursor genes are also regulated by many transacting factors (Rogers and Chen 2013). Ethylene might be involved in the regulation of miRNA and also their corresponding precursor genes, such as TAS3-mRNA, miR156, miR159, miR160, miR164, miR171, miR172, miR390, miR396, miR4376, and miR5301 (Gao et al. 2015). RIN (ripening inhibitor) regulates tomato fruit ripening-related genes through of the post-transcriptional regulations of related genes via miRNA and ethylene. In addition, the ethylene can also regulate miRNA by modulating the abundance of mRNA (Gao et al. 2015). miRNAs specifically induced in response to biotic or abiotic stresses have also been identified and could be interesting targets for tomato adaptation (Liu et al. 2017). Though epigenome regulation is important during fresh fruit development and ripening, additional investigations about epigenome dynamics during fruit maturation and ripening or under environmental stresses are still needed (Giovannoni et al. 2017).

Table 2.5 Main databases useful for tomato genetics and genomics

Name	Address	Characteristics
Solanaceae Genome Network (SGN)	https://solgenomics.net	Central hub for sol genomics (genome sequences, loci, phenotypes …
Tomato Genetic Resource Center (TGRC)	https://tgrc.ucdavis.edu/	Charles Rick Tomato Genetic Resource Collection in UC Davis
Tomatoma	http://tomatoma.nbrp.jp/	Microtom mutants and genome archive
Mibase Tomato DB	http://www.kazusa.or.jp/jsol/microtom	Microtom genomic resources
SolCAP	http://solcap.msu.edu/	SNP, genotype and phenotypes
Tomato Expression Database	http://ted.bti.cornell.edu/	Gene expression analysis results
Tomato Expression Atlas	http://tea.solgenomics.net/	High-resolution map of gene expression
Tomexpress	http://tomexpress.toulouse.inra.fr/	RNAseq data
Tomato EFP browser	http://bar.utoronto.ca/efp_tomato	Tomato gene expression viewer
Solcyc	http://solcyc.solgenomics.net/	Pathway/genome DB

2.3.11 Databases

Databases are essential to access the wide range of data produced and shared on tomato. Tomato community has benefited for years of the will to gather genetic and later genomic data into one single free access database, known as Solanaceae Genome Network, as the resource concerns several Solanaceae species. Since the first RFLP genetic map, the database hosts information about markers, genes, and QTL and now a genome browser where several genomes and SNP can be found. Several other databases can be useful to tomato geneticists. They describe genetic resources and mutant collections or information about gene expression (Table 2.5).

2.4 Breeding for Smart Tomato

2.4.1 Traditional Breeding

Tomato is a self-pollinated crop. The first varieties were landraces and the intensive breeding started in the 1930s in the USA. As a self-pollinated crop, for years, tomato

has been bred through a combination of pedigree and backcross selection. Very early, introgressions from wild species were proposed to introduce disease resistances but also to improve fruit firmness and other fruit quality traits (Bai and Lindhout 2007). Recurrent selection (successive rounds of selection and intercrossing of the best individuals) also proved efficient to simultaneously increase fruit sugar content and fruit size and break the negative relationship between both traits (Causse et al. 2007a, b).

Although tomato exhibits a low heterosis for yield, F_1 hybrid varieties progressively replaced the pure lines since the 1970s. This was first shown to be interesting for fruit shape and size homogeneity and then for combining several dominant resistance genes. Today F1 hybrids combine 6 to 8 disease resistance genes. For the production of F1 seeds, a set of nuclear recessive male sterility genes have been described, but are not used for a commercial purpose. The use of a functional male sterility gene, controlled by the positional sterile mutation (*ps2*) whose anthers do not naturally open, has been proposed (Atanassova 1999). Nevertheless, due to the difficulty of carrying sterility genes along with the selection schemes and to the rapid turnover of tomato cultivars, F1 hybrids are more frequently produced by hand pollination, in countries with low labor cost.

2.4.2 Marker-Assisted Selection

Many important loci have been mapped and tagged with molecular markers. Marker-assisted selection (MAS) allows breeders to follow genomic regions involved in the expression of traits of interest. The efficiency and complexity of MAS depend on the genetic nature of the trait (monogenic or polygenic). For monogenic traits, marker-assisted backcross (MABC) is the most straightforward strategy, whereas for polygenic traits, various strategies are available.

2.4.2.1 Marker-Assisted Backcross for Monogenic Traits

The principle of MABC for a single gene is simple. First, molecular markers tightly linked to the target gene are identified, allowing the efficient detection of the presence of the introgressed gene ("foreground selection"). Other markers may be also used in order to accelerate the return to the recipient parent genotype at other loci ("background selection"). Background selection is based not only on markers located on the chromosomes carrying the gene to introgress (carrier chromosome), but also on other chromosomes. Markers devoted to background selection on a carrier chromosome allow the identification of individuals for which recombination events took place on one or both sides of the gene, in order to reduce the length of the donor type segment of genome dragged along with the gene (Young and Tanksley 1989). In three generations of MABC, isogenicity is higher than that obtained by classical methods. By comparison, traditional approach would require approximately two more generations

to obtain such an isogenicity (Hospital et al. 1992). Many important genes have been mapped or even cloned and specific markers for favorable alleles developed (Rothan et al. 2019 for a recent review). Today, tomato breeders use molecular markers for the introgression of several monogenic traits such as disease resistances or fruit-specific traits. The reduction of the cost of genotyping allows today the screening of a large number of plants to accelerate the selection process.

2.4.2.2 Marker-Assisted Selection for QTLs

Traits showing a quantitative variation are usually controlled by several QTLs, each with a different individual effect. Due to the genetic complexity of such traits, several QTLs with limited effects must be simultaneously manipulated. Depending on their number, the nature and range of their effect, and the origin of favorable alleles, different MAS strategies were proposed.

As for monogenic traits, MABC is the most effective strategy when a small number of QTLs, coming all from the same parent, must be transferred into an elite line. Hospital and Charcosset (1997) determined the optimal number and positions of the markers needed to control the QTLs during the foreground selection step and the maximum possible number of QTLs that could be simultaneously monitored with realistic population sizes (a few hundred individuals). On average, using at least three markers per QTL allows a good control over several generations, providing a low risk to have the donor type alleles at the markers without having the desired genotype at the QTL. However, as the minimum number of individuals that should be genotyped at each generation depends on (i) the confidence interval length, (ii) the number of markers, and (iii) the number of QTLs, it seems illusive to transfer more than four or five QTLs with this simultaneous design unless a very large population can be considered, or the precision of the QTL location is very high.

After the identification of QTL for fruit quality traits (Saliba-Colombani et al. 2001; Causse et al. 2001), several clusters of QTLs were identified. As most of the favorable alleles for quality improvement came from the cherry tomato parental line, a MABC scheme has then been set up in order to transfer the five regions of the cherry tomato genome with the largest effects on fruit quality into three recurrent lines (Lecomte et al. 2004b). The population size allowed a successful transfer of the five segments into each recurrent line, and the MAS scheme allowed reducing the proportion of donor genome on the non-carrier chromosomes under the level expected without selection. Plants carrying from one to five QTLs were selected in order to study their individual or combined effects. Most of the QTLs were recovered in lines carrying one introgression region and new QTLs were detected (Causse et al. 2007a, b). Introgressed lines had improved fruit quality, in comparison to parental lines, promising a potential improvement. Nevertheless, fruit weight in these genotypes was always lower than expected due to the effect of unexpected QTLs, whose effect was masked in the RIL population, suggesting that negative alleles at fruit weight QTLs were not initially detected.

2.4.2.3 Advanced Backcross for the Simultaneous Discovery and Transfer of New Alleles

The advanced backcross QTL analysis is another strategy tailored for the simultaneous discovery and transfer of valuable QTL alleles from unadapted donor lines into established elite inbred lines (Tanksley and Nelson 1996). The QTL analysis is delayed until an advanced generation (BC_3 or BC_4), while negative selection is performed to reduce the frequency of deleterious donor alleles during the preliminary steps. The use of BC_3/BC_4 populations reduces linkage drag by reducing the size of introgressed fragments, limits epistatic effects, and decreases the amount of time later needed to develop near-isogenic lines carrying the QTL (Fulton et al. 1997). Tanksley and colleagues have applied this strategy for screening positive alleles in 5 wild species, *S. pimpinellifolium* (Tanksley et al. 1996), *S. habrochaites* (Bernacchi et al. 1998a), *S. peruvianum* (Fulton et al. 1997), *S. pennellii* (Eshed et al. 1996) et *S. parviflorum* (Fulton et al. 2000). They identified a number of important transgressions potentially useful for processing tomato and demonstrated that beneficial alleles could be identified in unadapted germplasm and simultaneously transferred into elite cultivars, thus exploiting the hidden value of exotic germplasm (Bernacchi et al. 1998b, Tanksley and Nelson 1996).

2.4.2.4 Pyramidal Design

When the number of QTLs to introgress becomes important, Hospital and Charcosset (1997) proposed to use a pyramidal design. QTLs are first monitored one by one by MABC, to benefit from higher background selection intensity, and then the selected individuals are intercrossed, to cumulate favorable alleles at the QTLs in the same genotype. When favorable alleles come from different sources, van Berloo and Stam (1998) proposed an index method to select among recombinant inbred lines those to be crossed and to obtain a single genotype containing as many favorable quantitative trait alleles as possible. Plants showing the optimal index are crossed together. This strategy was shown efficient to obtain transgression in offspring populations of *Arabidopsis* (van Berloo and Stam 1999).

The benefit of MAS for QTL pyramiding was shown but limited by the number of QTLs easily managed (Lecomte et al. 2004b; Gur and Zamir2015; Sacco et al. 2013). This can be overcome by fine mapping experiment and/or validating the QTL effect in other backgrounds (Lecomte et al. 2004a). Today SNP availability and genomic selection open new ways to marker-assisted selection for quantitative traits.

2.4.2.5 Breeding for Resistance to Pests and Pathogens

Despite decades of conventional breeding and phenotypic selection, there are still a large number of pests and pathogens that make tomato production challenging

in various parts of the world. It is why the most prominent issue of tomato breeding remains pest and pathogen resistance. Current advances in tomato genetics and genomics can be combined with conventional plant breeding methods to introgress resistance loci or genes and expedite the breeding process.

Phenotypic (e.g., sensitivity to the Fenthion insecticide linked to resistance to *Pseudomomas syringae* pv. *Tomato* Laterrot and Moretti 1989), enzymatic (e.g., Aps-1^1 linked to rootknot nematode resistance Aarts et al. 1991, Messeguer et al. 1991) and DNA markers tightly linked to resistance loci have long been used for MAS to incorporate resistance loci in new tomato cultivars. MAS is valuable for increasing the efficiency of selection, particularly when it is difficult to perform disease resistance assay, for instance with quarantine pathogens requiring controlled experimental infrastructures, and when disease resistance is controlled by recessive genes, or when genes display a weak penetrance or are strongly influenced by environment. Markers help to carry on a more efficient and precise introgression of the targeted loci, reducing the negative effects of linkage drag. MAS has also permitted to pyramid several resistance loci with other desirable traits. Because most of the resistance genes are clustered on the tomato genome, introgression of resistance traits by phenotyping selection or by using MAS with markers at both sides of the major resistance gene permitted to introgress a kind of cassettes of resistance alleles when they are in coupling linkage and to create multi-resistant cultivars. For instance, most of *Tm-*2^2 tomato cultivars hitchhiked the *Frl* gene responsible for the Fusarium crown and root rot resistance caused by FORL (Foolad and Panthee 2012). Inversely, when resistance alleles are linked in repulsion phase, breeding selection may be hindered by the difficulty to select for homozygous coupling-phase recombinant lines, as illustrated for the association of *Sw-5* and *Ph-3* (Robbins et al. 2010). Thanks to MAS, the rate of improvement has been significantly enhanced in tomato even if many challenges remain.

Nowadays, DNA markers have been made available for about 30 genes controlling single gene inherited resistance traits important for tomato breeding (https://solgenomics.net/; Foolad and Panthee 2012). DNA markers for complex inherited resistance traits are much less abundant and they have rarely been used. MAS is thus routinely employed for selecting major effect resistance genes (*I*, *I-2*, and more recently, *I-3*, *Ve*, *Mi-1.1*/*Mi1.2*, *Asc*, *Sm*, *Pto*, *Tm-*2^2, *Sw-5*) and many commercial cultivars now are resistant to *Fusarium oxysporum f. sp. lycopersici*, *Verticillium dahlia*, *Meloigogyne incognita*, *Alternaria alternata* f.sp. *lycopersici*, *Stemphyllium*, *Pseudomonas syringae* pv. *tomato*, ToMV, and TSWV. Also, markers for *Rx-3* and *Rx-4*, and for *Ty-1*, *Ty-2*, *Ty-3*, *Ty-4* are more and more used to deliver resistant cultivars to *Xanthomonas* spp. and TYLCV.

Although markers have been identified for many disease resistance in tomato, not all of them are useful because of the absence of polymorphism within breeding populations that are often based on intraspecific crosses or because markers are too far from genes or QTLs of interest permitting unwanted crossing-overs. However, advances in next-generation sequencing make possible to identify linked SNPs from which new PCR-based markers can be developed for trait association within breeding populations. The whole plant genome technologies greatly help to identify useful

markers linked to resistance traits within the wild germplasm by ecoTILLING, allele mining, or GWAS. Tomato breeders are thus now able to select the best combinations of genotypes to intercross in order to associate favorable traits and design elite ideotypes.

2.4.3 Genomic Selection

Many traits are controlled by a large number of QTLs with low effect. Both linkage mapping and GWAS have limitations in identifying and quantifying small effect and also rare QTLs or associations that are highly susceptible to environmental conditions (Crossa et al. 2017). In contrast, genomic selection (GS), which has been proposed for about two decades (Meuwissen et al. 2001; Crossa et al. 2017) uses all the genetic information from markers spread over the whole genome, such as SNPs and phenotypic data, in a training population, to predict the genetic estimated breeding values (GEBVs) of unphenotyped individuals in a test population. The main advantages of GS include cost reduction and time saving compared to phenotype-based selection (Crossa et al. 2017).

Several factors influence the accuracy of genomic prediction (GP), including the size, structure, and genetic diversity of the training population, trait heritability, the number and distribution of molecular markers, linkage disequilibrium, prediction method, and number of QTLs (Isidro et al. 2015; Spindel et al. 2015; Duangjit et al. 2016; Kooke et al. 2016; Yamamoto et al. 2016; Boison et al. 2017; Crossa et al. 2017; Minamikawa et al. 2017; Müller et al. 2017; Yamamoto et al. 2017; Crain et al. 2018; Edwards et al. 2019; Mangin et al. 2019; Sun et al. 2019). In order to improve the prediction accuracy, complex GS models were developed in order to handle different factors, such as the multi-trait and multi-environment G×E interactions (Montesinos-López et al. 2016; Fernandes et al. 2018). To date, many models for GS are available and the prediction accuracy varies according to traits and conditions (Heslot et al. 2012; Jonas and de Koning 2013; Yamamoto et al. 2016, 2017).

The first GS test in tomato was focused on a simulation-based breeding design and phenotypic prediction, where a theoretical method was proposed to apply GS to actual breeding schemes of simultaneous improvement of yield and flavor (Yamamoto et al. 2016). Briefly, 96 big-fruited tomato varieties were selected and 20 agronomic traits were measured, which can be divided into four categories, including yield, quality, physiological disorder of fruit, and others, with the broad-sense heritability ranging from 0.10 to 1.00. Seven GP models were compared, including five linear methods, Ridge regression (RR) (Endelman 2011), Bayesian Lasso (BL) (Park and Casella, 2008), extended Bayesian Lasso (EBL) (Mutshinda and Sillanpää 2010), weighted Bayesian shrinkage regression (wBSR) (Hayashi and Iwata 2010), and Bayes C (Habier et al. 2011), and two nonlinear methods, reproducing kernel Hilbert space regression (RKHS) (Gianola and van Kaam 2008) and random forest (RF) (Breiman 2001). The highest prediction accuracy for different traits varied and the accuracy of Bayes C was highest for up to eight traits, ranking the best among all models.

Some individuals with high GEBV of total fruit weight and soluble solid contents were selected as parents to simulate later generations. Simulations demonstrated that after five generations, the simulated GEBVs were comparable with parental varieties. Breeding selections of target traits could also have impact on some non-target traits. In particular, simultaneous selection for yield and flavor resulted in morphological changes, such as the increase in plant height. These results demonstrated the benefits of simulations for real breeding design.

Yamamoto et al. (2017) then used big-fruited F_1 population to construct the GS models to assess its potential for the improvement of total fruit weight and soluble solid content in a practical experiment. By testing six GS models and 10-fold cross-validation, the prediction accuracy for soluble solid content was higher than for total fruit weight. GBLUP and BL had significantly higher predictability compared to other models for soluble solid content. In contrast, RKHS and RF had significantly higher predictability compared to other linear models for total fruit weight. The authors further developed four progeny populations to predict trait segregations and demonstrated that all individuals in the four progeny populations were genetically distinct from each other but intermediate between their parental varieties. However, the genetic diversity within each population was much lower compared to the training population.

Duangjit et al. (2016) investigated the impacts of some key factors on the efficiency of GP, including the size of training population, the number and density of SNPs, and individual relatedness. Based on the analysis of 163 tomato accessions, the optimal size of the training population was 122. The prediction accuracy also increased with the increase of marker density and number, but weakly. Individual relatedness also influenced the prediction accuracy, and predictions were better in closer individual relatedness. However, there are some limitations in this study: (1) it only tested the ridge regression best linear unbiased prediction (rrBLUP) statistical model (Endelman 2011); (2) the number of SNPs was relatively small and the genomic coverage in certain genomic regions was quite limited (Zhao et al. 2019); (3) population structure existed and the number of wild accessions was quite small compared to cherry and large-fruited tomato accessions.

Most of the GS models rely on marker-based information and are unable to exploit local epistatic interactions among markers. Molecular markers can also be combined into haplotypes by combining linkage disequilibrium and linkage analysis to improve prediction accuracy (Clark 2004; Calus et al. 2008; Jiang et al. 2018), which has been recently shown especially in animals (Calus et al. 2008; Cuyabano et al. 2014, 2015a, b; Hess et al. 2017; Karimi et al. 2018). Haplotype-based genome-wide prediction models make it possible to exploit local epistatic effects inside haplotype blocks (Wang et al. 2012; de Los Campos et al. 2013; He et al. 2016; Jiang et al. 2018). The benefits of haplotype-based GS remain to be investigated in major crops (Jiang et al. 2018).

Genomic selection should permit to breed for a combination of traits related to qualitative resistance to biotic stresses as well as quantitative resistance and tolerance to biotic and abiotic stress combinations considering also the genetic architecture of yield and fruit quality-related traits. Both foreground and background

selection should promote a sustained performance under diverse changing environments. Until now, disease quantitative resistance does not seem to be actively pursued by breeders because the complex polygenic control has generally hampered a wide deployment of QTL introgression. The development of post-genomics should help to foster tomato breeding for multiple polygenic traits including multi-resistance to pests and pathogens.

2.5 Designing Ideotypes by Ecophysiological Modeling

Until the 1970s, genetic advances have favored the creation of high-yielding varieties adapted to mechanized and high-input production systems. Since the 90s, the context of global change instigates to renew the breeding goals by taking into account multiple environmental, economic, and social issues. These multidisciplinary and integrative approaches have combined genetics and ecophysiology or agronomy skills, taking into account the mechanisms linking phenotypes to genotypes, and their modulation by the environment (essentially defined by soil, climate, and pests) and cultural practices. Such approaches have allowed for a meaningful assessment of genotype-environment interactions and plant performances in terms of yield, quality, and environmental impact in current production contexts. They have also made it possible to combine genetic information (available through the emergence of genetic and genomic tools) with phenotypic traits that determine variables of agronomic interest. In this context, the notion of ideotype has progressively developed to design plants able to perform in a given production context and finally to define breeding targets. To this end, process-based predictive models have proven their efficiency to unravel the mechanisms behind genetic variability of complex traits (Reymond et al. 2003; Tardieu 2003; Quilot et al. 2005; Struik et al. 2005), to analyze Genotype x Environment x Management (GxExM) interactions (Génard et al. 2010; Bertin et al. 2010; Martre et al. 2011), or to design new ideotypes adapted to specific environments (Kropff et al. 1995; Quilot-Turion et al. 2016; Martre et al. 2015; Génard et al. 2016).

2.5.1 What Is an Ideotype?

The ideotype concept, first proposed for wheat and then extended to several domesticated crops, is "a theoretical biological model which is expected to perform or behave in a predictable manner within a defined environment" (Donald 1968). Martre et al. (2015) extended the ideotype definition, to "the combination of morphological and physiological traits (or their genetic bases) conferring to a crop a satisfying adaptation to a particular biophysical environment, crop management, and end use".

Application for breeding may be straightforward for monogenic traits such as some biotic stress resistance. For instance, Zsögöna et al. (2017) proposed to take

advantage of genome-editing techniques in order to tailor such monogenic traits in cultivated cultivars or, on the opposite, to manipulate yield-related traits in wild relatives harboring polygenic stress resistance. Things are more complicated in case of traits with polygenic basis, for which geneticist has to face major issues. One of them is the complexity of some selection targets, such as yield, quality, nitrogen use efficiency, or adaptation to water deficit. Indeed these traits result from numerous nested processes with feedback effects and therefore, they are controlled by many genes. Another issue lies in the fact that the expression of these characters also depends on the environment and farming practices. This often results in strong GxExM interactions that make genetic work and their breeding application difficult. In a first empirical approach, optimal combinations of traits adapted to one specific environment and production system could be easily designed. For extrapolation to many different contexts, process-based predictive models may play a major role as discussed below (Quilot-Turion et al. 2012; Génard et al. 2016).

2.5.2 Current Process-Based Models of Tomato for the Prediction of GxExM Interactions

The plant and its organs can be seen as complex systems in which many processes interact at different scales under the control of GxExM interactions. Process-based predictive models are formal mathematical descriptions of this system and they have the potential to mimic its complexity in interaction with the environment, by integrating processes at several organizational levels (from cell to plant). The so-called component traits, which are underlying the predicted complex traits, are characterized in terms of model parameters, which instead of the complex trait itself, may subsequently be linked to underlying genetic variations (Struik et al. 2005; Bertin et al. 2010). This usually consists in forward genetics approaches such as QTL mapping, in which one searches for co-localizations between QTL for traits and QTL for model parameters (e.g., Yin et al. 1999; Reymond et al. 2003; Quilot et al. 2005; Prudent et al. 2011; Constantinescu et al. 2016). Thus, a preliminary step is the identification of specific genotype-dependent parameters of the model in opposition to other generic parameters that do not vary among genotypes. Then each combination of genes or alleles is represented by a set of parameters and the phenotype can then be simulated in silico under various environmental and management conditions. In order to extend the range of prediction beyond known genotypes, it is necessary to estimate the values of the genotypic parameters depending on combinations of QTLs (QTL-based models), alleles, or genes (gene-based models) involved in the modeled process (Martre et al. 2015). By formalizing each individual trait as a combination of genotypic and environmental effects, the model-based approach allows to detect more QTL that tends to be more stable than traditional QTL mapping. However, up to date, only a few genotypic parameters (i.e., allelic variants) have been advantageously

introduced into simulation models of tomato (Prudent et al. 2011; Constantinescu et al. 2016).

Several process-based simulation models that predict the processes underlying fruit growth and quality are now available and allow exploring the myriad of GxExM combinations (Génard and Lescourret 2004; Bertin et al. 2010; Martre et al. 2011; Kromdijk et al. 2013). For tomato, several plant models are driven by processes of carbon assimilation and allocation among sinks according to different rules of priority (Heuvelink and Bertin 1994; Jones et al. 1991; Boote 2016; Fanwoua et al. 2013), while only a few models simulate the water transfer and accumulation. For instance, Lee (1990) considers a unidirectional and constant flux of water uptake and transpiration per unit of fruit area. Bussières (1994) developed a model of water import in tomato fruit, based on water potential gradients and resistances. Yet, only rare models of fruit growth integrate both dry matter and water accumulation within the fruit. A virtual fruit model developed for peach (Fishman and Génard 1998) has been adapted to predict processes involved in tomato fruit growth and composition (Liu et al. 2007). This model relies on a biophysical representation of one big cell, in which sugars are transported from the fruit's phloem by mass flow, diffusion, and active transport. Incoming water flows are regulated, in particular, by differences in water potential and growth is effective only when the flow balance induces a sufficient turgor pressure on the cell walls. These models have been further modified and coupled to a stem model to estimate the contribution of xylem and phloem (Hanssens et al. 2015) and evaluate the effect of crop load on fruit growth (De Swaef et al. 2014).

The Virtual Fruit model has been also combined with a structural plant model to predict water and carbon allocation within the plant architecture, as well as the induced gradients of water potential and phloem sap concentration in carbon (Baldazzi et al. 2013). Because the cell level is the elementary level for mechanistic modeling of fruit (Génard et al. 2010), a crucial issue is to model the way cell division and expansion developmentally progress (Baldazzi et al. 2012; Okello et al. 2015). The rare models of tomato fruit, which integrate cell division, cell expansion, and DNA endoreduplication, have been used to better understand the emergence of fruit size and cell distribution (Fanwoua et al. 2013; Baldazzi et al. 2017, 2019). A virtual fruit model that predicts interactions among cell growth processes would be able to integrate subcellular models (Beauvoit et al. 2018), such as the ones proposed for tomato fruit to describe metabolic shifts during fruit development (Colombié et al. 2015, 2017) and pericarp soluble sugar content based on enzyme activity and compartmentation (Beauvoit et al. 2014). Indeed, except for sugar metabolism (Prudent et al. 2011), there is still a lack of predictive models of fruit composition, which is a major issue for fruit quality. For instance, no mechanistic model predicts the main compounds involved in tomato health value, like carotenoids, polyphenols, or vitamins, which deserve further development. Such models exist for peach acidity (Lobit et al. 2003, 2006) and could be tailored to tomato.

Such integrated models centered on the fruit, integrating cellular processes and connected to a plant model open major perspectives to integrate information on the molecular control of fruit growth and composition regulations and to analyze the

effects of GxExM interactions on yield and quality (Martre et al. 2011). Indeed, integrated models are important tools to phenotype plant in silico. They do not only allow to predict plant and organ traits such as yield or fruit composition, but also to asses physiological variables that are not easily measured on large panels such as xylem and phloem fluxes, active sugar transport… (Génard et al. 2010). So, process-based models enable to better understand genetic variability and identify candidate genes. They can also assist breeders to identify the most relevant traits and appropriate developmental stages to phenotype plants, and provide necessary links between genotype and phenotype in a given environmental context (Struik et al. 2005).

2.5.3 Process-Based Models Design of Tomato Ideotypes

An important issue of simulating GxExM interactions is the in silico design of ideotypes, i.e., combinations of QTL/genes/alleles relevant to optimize fruit growth and quality under specific conditions, by multi-criteria optimization methods (Quilot-Turion et al. 2016). Therein lies the interest of process-based predictive models for developing breeding strategies.

A process-based model breeding program could break down into 3 successive steps (Fig. 2.6): the first step consists of determining the values of the genetic coefficients of the model that makes it possible to obtain the desired characters for the ideotypes (virtual phenotype), in a given context of production (for instance low water supply, plant pruning…). The second step is to assess the values of the genetic coefficients from the genetic point of view (virtual genotypes), which requires identifying the combinations of alleles associated with each genetic coefficient. The last step is either to search among the existing genotypes for those that are the closest to the ideotype defined for a given environment, or to propose breeding strategies to obtain new genotypes on the basis of these ideotypes. For this last step, process-based models can be coupled with genetic models accounting for the genetic architecture of the genetic coefficients to simulate the genotypic changes that are expected to occur during the breeding program. Quilot-Turion et al. (2016) further proposed to add genetic constraints to improve ideotype realism and to optimize directly the alleles controlling the parameters, taking into consideration pleiotropic and linkage effects. This approach enabled reproducing relationships between parameters as observed in a real progeny and could be very useful to find out the best combinations of alleles in order to improve fruit phenotype in a given environment.

Despite clear benefits and perspectives, only a few tomato ideotypes have been designed through modeling. Using a static functional structural plant model, Sarlikioti et al. (2011) looked for optimal plant architecture of greenhouse-grown tomato with respect to light absorption and photosynthesis. They concluded that an ideotype with long internodes and long and narrow leaves would improve crop photosynthesis. A second example based on the virtual fruit model of tomato described above, (Constantinescu et al. 2016) suggested that a successful strategy to maintain yield

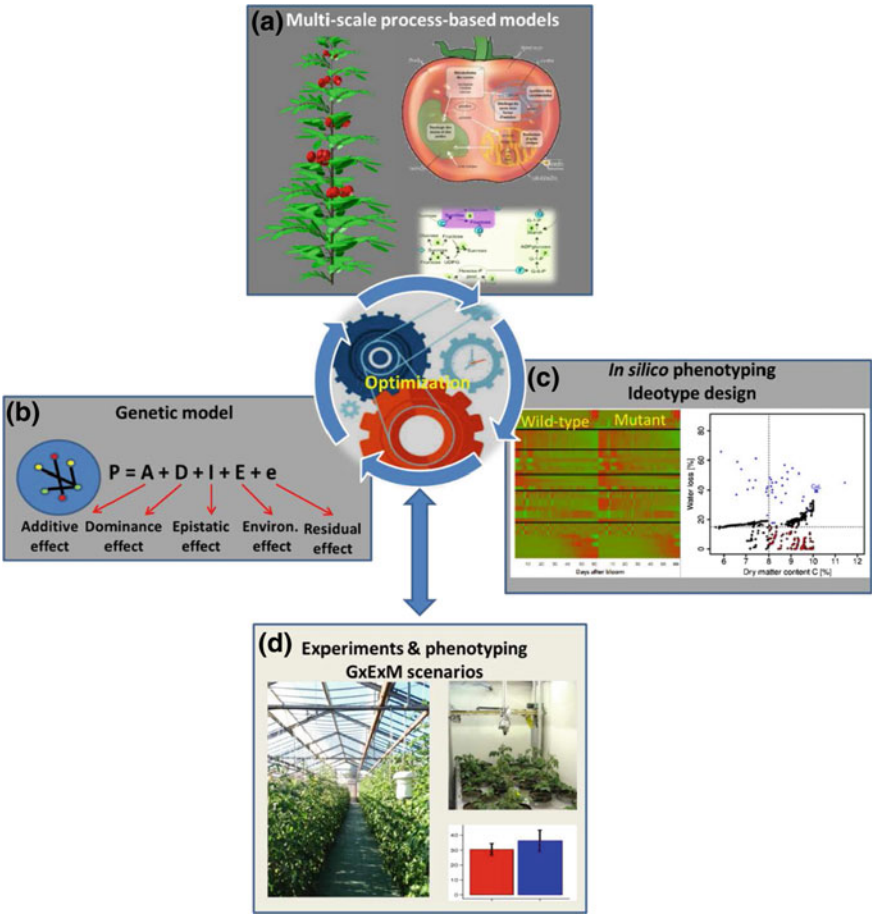

Fig. 2.6 Overall scheme of the process-based design of tomato ideotypes. Plant and organ phenotypes measured in a controlled environment or phenotyping platforms under different GxExM combinations (**d**) can be predicted by coupling process-based models that describe water and carbon fluxes in the plant, growth processes, and primary and secondary fruit metabolism (**a**). On the right, figure (**c**) illustrates the use of the coupled model for phenotyping plants and fruits and for designing ideotypes. The heatmap shows the effect on all the simulated processes of a virtual mutation controlling one genetic parameter of the model, while the plot shows the position of ideotypes generated by the model according to fruit dry matter content and fruit water loss due to water deficit. On the left (**b**), the genetic model is dependent on several effects, which control the genotypic parameters of the process-based models in (**a**). The genetic model enables to predict the genotype of ideotypes selected in (**c**). The optimization procedure applies both to estimate the genotypic parameters of the models and to design the ideotypes

and quality of large fruit genotypes under water deficit conditions could be to combine high pedicel conductance and high active uptake of sugars. Through the model calibration, the authors could identify some genotypes of the studied population, which were close to the ideotypes and thus, which may bring interesting traits and alleles for breeding plant adapted to low water supply.

As seen above, predictive models used for the design of ideotypes are expected to be highly mechanistic and detailed, therefore very complex, often combining different scales of description. Model parameters are ideally measured through adequate phenotyping, or more currently estimated through model calibration. Yet, a major difficulty is their parameterization based on extensive and heavy experiments on large genetic panels, which is rather prohibitive (Cournède et al. 2013). Similarly, the prediction of model parameters from QTL, alleles, or genes relies on a calibration step that also suffers from the relatively limited number of parameterized genotypes (Letort et al. 2008; Migault et al. 2017). Instead of measuring extensive sets of physiological traits on all genotypes of the studied population, one can select a set of genotypes that well represents the genetic diversity and then predict the parameters for the whole selection of genotypes by QTL or genomic prediction models (van Eeuwijk Fred et al. 2019). Alternatively, a representative training set of genotypes can be selected based on relevant morpho-physiological traits for estimating model parameters, as done in Constantinescu et al. (2016). From the mathematical point of view, the design of ideotypes is complex and relies on multi-objective optimization methods, which are complex due to dimensional problem (increasing number of genotypes and variables) and to the fact that ideotypes usually combine antagonistic nonlinear traits, such as yield and quality for tomato fruit. To solve the optimization problems, large panels of meta-heuristics exist, based on different algorithms that can provide satisfactory solutions in a reasonable amount of time (Ould-Sidi and Lescourret 2011). These methods can also apply to the model calibration step.

Our ability to phenotype large panels has increased in the last decades, with the emergence of high-throughput genotyping and phenotyping platforms that generate large datasets on plant morphology and physiology at high temporal and spatial resolution. The way phenotyping information can be advantageously incorporated in different classes of genotype-to-phenotype models has been recently illustrated for field crops (van Eeuwijk Fred et al. 2019). However, in the case of tomato and other horticultural plants, the range of phenotyped traits should go well beyond the traits that are routinely measured on such platforms, for instance by including fruit growth and composition alongside with plant and fruit development.

2.5.4 Prospects on the Use of Model-Based Plant Design

Model-based design of plants offers promising opportunities for both crop management and breeding of plants able to cope with different environments and to answer multiple objectives. Tomato is particularly relevant for such approach. Its sequenced

genome, the large number of genetic resources, available process-based models integrating process-networks at different organization levels, strong societal demand for high-quality fruits are all key-assets for the successful design of tomato ideotypes. Yet, some progress is still necessary. The integration of cellular and molecular levels can help refine plant models, and shed light onto the complex interplay between different spatial and temporal scales that control the traits of interest. For this, small networks of genes involved in the modeled processes might be helpful, as they could boost our capacity to link process-based model parameters to their genetic basis.

While the proof of concept is validated, it is clear that up to date, rare or no plant improvement has grounded in in silico design of ideotypes. To this end, closer collaborations among modelers, agronomists, geneticists, and breeders are necessary to combine approaches and in particular to couple process-based models and genetic models of tomato. Furthermore, the development of new process-based sub-modules predicting important tomato quality traits such as texture, carotenoid, polyphenol, and vitamin contents will be essential.

Finally, we could question the dominant paradigm according to which genetic improvement relies on gene pyramiding. Indeed, stacking multiple genes in one variety might efficiently increase multiple resistances to biotic stresses, but may fail for other traits depending on the number of genes and their genetic architecture, the nature of germplasm, etc. (Kumar et al. 2016). Instead, a new issue could be to bet on multi-genotype crops to stabilize their performances and reduce the inputs. This will require better understanding of interactions among genomes within a population.

2.6 Biotechnology and Genetic Engineering

2.6.1 A Brief History of Genetic Engineering in Tomato

According to the annual report of ISAAA (International Service for the Acquisition of Agri-biotech Applications) of 2017, 17 million farmers in 24 countries planted 189.8 million hectares biotech/GM crops. In 22 years, the planted area increased over 100 times. Nowadays there is no genetic engineered tomato available in market, whereas the first genetically engineered and commercialized food has been tomato, with a cultivar named FLAVR SAVR^{TM}, which was approved by FDA (USA) on May 18, 1994, and just 3 days later, was available in two stores. It was created by scientists in Calgene company via antisense RNA of polygalacturonase (PG), one of the most abundant proteins that had long been thought to be responsible for softening in ripe tomatoes (Kramer and Redenbaugh 1994). FLAVR SAVR^{TM} showed 99% decrease of PG protein and significant decrease in softening during storage, and increased resistance to fungi, which normally infects ripe fruits, thus providing a longer shelf life. Scientists expected that this tomato could be vine-ripened for enhanced flavor, and still suitable for the traditional distribution system (Kramer et al. 1992). At the same year, Zeneca commercialized a tomato puree made from tomatoes silenced PG with sense gene, with improved viscosity and flavor, and reduced waste (Grierson

Table 2.6 Transgenic tomato varieties approved for commercialization, reproduced from Gerszberg et al (2015)

Event	Developer	Traits	Year	Approved for	Country
FLAVR SAVR	Calgene	Delayed softening(developed by additional PG gene expressed)	1994	All uses in USA; Japan, and Mexico for feed and for environment	USA
1345-4	DNA Plant Technology Corporation	Delayed ripening (developed by a truncated aminocyclopropane cyclase synthase gene)	1994	All uses in USA; food in Canada and Mexico	USA
Da,V,F tomato	Zeneca Seeds	Delayed ripening (developed by additional PG gene expressed)	1994	All uses in USA; food in Canada and Mexico	USA
8338	Monsanto Company	Delayed ripening (developed by introduction of 1-aminocyclopropane-1-carboxylic acid deaminase (accd) gene)	1995	All uses in USA	USA
351 N	Agritope	Delayed ripening (developed by introduction the S-adenosylmethionine hydrolase (SAMK) gene)	1995	All uses in USA	China
Huafan No 1	Huazhong Agricultural University	Delayed ripening (developed by introduction antisense EFE gene)	1996	Data not available	China
5345	Monsanto Company	Insect resistant (developed by introduction of one cry1Ac gene)	1997	All uses in USA; food in Canada	USA
PK-TM8805R (8805R)	Beijing University	Delayed ripening	1999	Food, feed, cultivation in China	China

2016). The success was not as expected. FLAVR SAVR was removed from the market in 1999. Later a dozen of genetic engineering events were registered up to 1999, but none of them were commercialized (Table 2.6). Since 2000, not any new transgenic tomato was registered (http://www.isaaa.org/gmapprovaldatabase/default.asp).

2.6.2 Toolkit for Genetic Engineering Tomato

Tomato genetic transformation was initially established in the 1980s (McCormick et al. 1986). The primary mode of transformation is *Agrobacterium*-mediated procedures by incubating with tomato explants such as leaf, hypocotyl, or cotyledon, followed by the regeneration of plants via shoot organogenesis from callus. Based

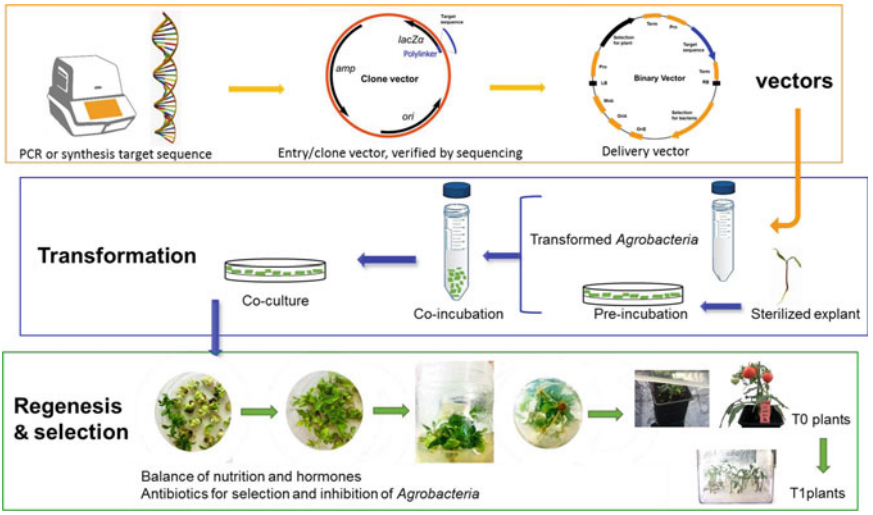

Fig. 2.7 A general workflow for transformation based on widely used protocols. The target sequence could be obtained by PCR or commercial synthesis, and then different cloning methods used to transfer it into the clone vector. After verifying the clone vector, target sequence could be transferred to delivery vector, which is adapted for agrobacteria transformation. Tomato seeds are germinated in sterilized medium. When cotyledons appear, they are cut for pre-culture. After pre-culture, cotyledons (or other explants) are co-incubated with Agrobacteria that carry delivery vector and Ti plasmid, following a short period (such as 2 days) for co-culture. Then explants are transferred to a medium suitable for regeneration and selection. For different steps of regeneration, different nutrition and hormones are needed. When roots appear, transgenic plants are introduced to greenhouse. For T0 plants, the insertion of exogenous modules should be checked. The seeds of T0 plants are planted on medium with selection antibiotic for selecting the transgenic plants

on reported protocols and the review by Bhatia et al. (2004), a general genetic engineering program for tomato requires (Fig. 2.7):

(1) Vectors to deliver engineering modules into agrobacteria and plants;
(2) Integration of the introduced engineering modules into the genome for stable transformation;
(3) In vitro regeneration and selection of transformed plants.

The effective transformation and regeneration are prerequisite steps for utilizing genetic engineering. Transformation efficiency is strongly dependent on the genotype, explant, and plant growth regulators in the medium (reviewed by Gerszberg et al. 2015).

Successful transformation can also be performed either by dipping developing floral buds in the *Agrobacterium* suspension or by injecting *Agrobacterium* into the floral buds. Yasmeen et al. (2009) observed a high transformation frequency, 12–23% for different constructs, while for Sharada et al. (2017), a much lower transformation efficiency (0.25–0.50%) was obtained on floral dips/floral injections. Unlike in

Arabidopsis, for which flower-dipping method became a widely used transformation way (Clough and Bent 1998), in tomato, this methodology has not been efficient.

Gene silencing or expression of heterologous genes in tomato has been used for decades in research. Different from those two conventional genetic engineering methods, genome editing based on CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats) was first proposed on tomato a few years ago (Brooks et al. 2014), but rapidly showed a large potential and wide application for functional gene characterizing, breeding, and domestication.

2.6.2.1 Gene Silencing and Homologous/Heterologous Expression

Gene silencing is usually obtained via antisense (as for FLAVR SAVR), sense, or RNA interfering (RNAi). Scientists have used it to inhibit the unfavorable ripening/softening after tomato harvesting and during a long distance transportation, to remove compounds stimulating allergies (Le et al. 2006), or block seed production resulting in parthenocarpic fruit (Schijlen et al. 2007). Inhibition or better control of fruit ripening and softening is still one of the major challenges for breeders and scientists for commercial perspectives. This purpose was achieved to different degrees by silencing different genes, including those coding pectin methylesterase (Tieman and Handa 1994), expansin protein (Brummell et al. 1999), beta-galactosidase (Smith et al. 2002), ACC synthase (Gupta et al. 2013), transcription factor SlNAC1 (Meng et al. 2016), pectate lyase (Uluisik et al. 2016).

Different from gene silencing strategies which aim to downregulate endogenous genes of tomato, over expression of endogenous or exogenous genes can also be manipulated to study promoters and gene expression, enhance tolerance to biotic/abiotic stresses, and increase the accumulation of secondary metabolites… Promoters (endogenous or exogenous) can be fused with GUS or florescent protein to follow the gene expression pattern. Fernandez et al. (2009) generated novel Gateway destination vectors based on the detailed characterization of series promoters' expression patterns during fruit development and ripening, facilitating tomato genetic engineering. Redox sensitive GFP (roGFP) was also developed to better study the in vivo redox state in tomato (Huang et al. 2014).

Researchers who work on perennial trees such as apple, peach, banana, etc, often used tomato to do heterologous expression of target genes to *in vivo* study the gene function, since the transformation and regeneration techniques are difficult to apply on those species and even when possible, it is time-consuming to pass juvenile phase to obtain fruit phenotypes. In return, the genes from other species, which showed a phenotype on tomato, can be interesting resources for genetic engineering. For instance, apple vacuolar H+ -translocating inorganic pyrophosphatase (MdVHP1) overexpressed in tomato, improved tolerance to salt and drought stress (Dong et al. 2011). Overexpression of banana MYB TF MaMYB3 inhibited starch degradation and delayed fruit ripening (Fan et al. 2018).

Fusing abiotic-driven promoter with functional TF responding to abiotic stress was a promising strategy for improving stress tolerance. Transgenic plants with

the transcription factor CBF driven by ABA-responsive complex (ABTC1) showed enhanced tolerance to chilling, water deficit, and salt stresses without affecting the growth and yield under normal growing conditions (Lee et al. 2003).

The metabolism flux can also be altered to improve fruit qualities, such as volatiles and nutrition compounds. Domínguez et al. (2010) overexpressed genes coding ω-3 fatty acid desaturases, FAD3, and FAD7, resulting in an increase in the 18:3/18:2 ratio in leaves and fruit, and a significant alteration of (Z)-hex-3-enal/hexanal ratio. At MYB12 under the fruit-specific E8, promoter was inserted into tomato genome, activating the genes related to flavonol and hychoxycinnamic ester biosynthesis, leading to accumulation as much as 10% of fruit dry weight (Zhang et al. 2015a, b).

In addition to those remarkable progresses of genetic engineering since 1980s, the most notable progress has been made since the emerging and development of genome-editing tools, such as CRISPR/Cas9.

2.6.2.2 Genome Editing

Unlike genome-editing tools, Zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), which are based on protein–DNA recognition, CRISPR/Cas9 relies on simple RNA–DNA base pairing and the PAM (protospacer adjacent motif) sequence recognition (Gaj et al. 2013). All these tools result in DNA double-strand breaks (DSBs), but CRISPR/Cas9 showed higher efficiency than ZFN and TALEN (Adli 2018). DSB can be repaired either by error-prone non-homology end joining (NHEJ) or homology-directed repair (HDR). Organisms recruit NHEJ or HDR repairing system to induce indel mutations or precise substitution, resulting in knockout or precise-genome editing, respectively. Besides studying the mechanism of CRISPR/Cas9 genome-editing system, scientists also showed enthusiasm for re-engineering CRISPR/Cas9 tools to make them more flexible and increase their fidelity, via making Cas9 nucleases smaller, expanding the targeting scope, and decreasing the off-target rate.

In 2014, the first CRISPR/Cas9 case was reported in tomato (Brooks et al. 2014) and later scientists have explored CRISPR-based engineering on several topics. As CRISPR/Cas9 system can efficiently introduce knockout mutation, it is a useful method to characterize candidate genes from forward genetics or natural mutation. An elegant case of using CRISPR/Cas9 was the production of RIN-knockout mutant, shedding light on an old topic. Tomato *rin* mutants remain firm after harvest and fail to produce red pigmentation and ethylene, thus RIN has long been believed to be indispensable for the induction of ripening. Ito et al. (2017) used CRISPR/Cas9 gene editing to obtain RIN-knockout mutant, which showed moderate red coloring, different from *rin*'s completely fail-to-ripening phenotype. Moreover, using CRISPR/Cas9 to edit *rin* mutant allele partially restored the induction of ripening. Therefore, they showed that RIN is not essential for the initiation of ripening and is a gain-of-function mutation producing a protein actively repressing ripening, rather than a null mutation. This technology has also been used on methylation/demethylation study. A DNA demethylase gene of tomato SlDML2 was mutated by CRISPR/Cas9

to generate loss-of-function mutants, showing a critical role of SlDML2 in tomato fruit ripening possibly via active demethylation of ripening induced genes and the inhibition of ripening-repressed genes (Lang et al. 2017).

Second generation of CRISPR gene-editing tools includes base editing, CRISPR-mediated gene expression regulation, and CRISPR-mediated live cell chromatin imaging (Adli 2018). The probability of gene insertion was increased by the production of landing pad (Danilo et al. 2018) as well as gene knock-in by precise base mutations (Danilo et al. 2019; Veillet et al. 2019). All these strategies are based on manipulation of Cas9, by turning nuclease Cas9 to nickase Cas9 (nCas9) or dead Cas9 (dCas9, catalytically inactive Cas9), but still keeping the capability to recognize specific sequences. The engineered Cas9 can be fused with other enzymes or proteins to enable base editing, gene regulation, or chromatin imaging.

Shimatani et al. (2017) generated marker-free plants with homozygous heritable DNA substitutions by using D10A mutant nCas9At fused with either a human codon-optimized PmCDA1 (nCas9At-PmCDA1Hs) or a version codon-optimized for Arabidopsis (nCas9At-PmCDA1At). It should be mentioned that the offspring of T0 generation also revealed indels, moreover, the rate of substitution was much lower than the rate of indel mutation. It demonstrated the feasibility of base editing for crop improvement even though with a lower rate. Dreissig et al. (2017) showed visualization of telomere repeats in live leaf cells of *Nicotiana benthamiana* by fusing eGFP/mRuby2 to dCas9, and also DNA–protein interactions in vivo via combining CRISPR-dCas9 with fluorescence-labeled proteins. Researchers developed CRISPR interference (CRISPRi) approach with dCas9 binding activity blocking the transcriptional process and thus downregulating gene expressions (Qi et al. 2013).

CRISPR/Cas9 and related second-generation genome-editing tools increase the feasibility and enlarge the applicable scope of biotechnology. With those progresses and the conventional transgenic tools (RNAi, overexpression, and so on), it allows comprehensive breeding to face multiple challenges toward increasing population and climate changes.

2.6.2.3 Comprehensive Genomic Engineering on Tomato

Rodriguez-Leal et al. (2017) focused on three major productivity traits in tomato: fruit size, inflorescence branching, and plant architecture, and used CRISPR/Cas9 to do genome editing of promoters to generate several cis regulatory alleles. They evaluated the phenotypic impact of those variants and provided an efficient approach to select and fix novel alleles controlling the quantitative traits.

Genome editing can also accelerate domestication, as shown by two groups. Li et al. (2018) selected four stress-tolerant wild tomato accessions to introduce desirable traits by using multiplex CRISPR/Cas9 editing. They targeted coding sequences, cis regulatory regions, or upstream open reading frames of genes associated with morphology, flower and fruit production, and ascorbic acid synthesis. The progeny of

edited plants showed domesticated phenotypes yet retained parental disease resistance and salt tolerance. At the same time, Zsögön et al. (2018) chose wild *S. pimpinellifolium* as the starting material to combine agronomically desirable traits with useful wild line traits via editing of six loci that are important for yield and productivity. Engineered tomatoes showed a remarkable increase in fruit size, number, and lycopene content. As the researchers said, those impressive de novo domestication cases pave the way to exploit the genetic diversity present in wild plants.

Genome-editing tools also show big potential for achieving tomato ideotype, for which the concept and design strategies have been explained in Chap. 5. Recently Naves et al. (2019) proposed to engineer tomato to be the biofactory of secondary metabolites, such as capsaicinoids (the metabolites responsible for the burning sensation of hot pepper). Considering that tomato genome presented all the necessary genes for capsaicinoid production, two strategies, transcriptional activator-like effectors (TALEs) or genome engineering for targeted replacement of promoters were suggested to be used in tandem to activate capsaicinoid biosynthesis in the tomato (Naves et al. 2019).

2.6.3 Genetic Engineering for Improving Pest and Pathogen Resistance

A few tomato diseases remain orphan, that is to say, that no natural resistance genes or QTLs have been discovered yet. Moreover, although available from crop wild relatives, breeders may be unable to fully utilize the resistance genes from genetic diversity because of interspecific barriers or because of linkage drag associated to an introgression from a distant species. In that case, resistance might be engineered through biotechnology.

To circumvent the absence of natural resistance, transgenic technologies relying on RNA interference or expression of pathogen-derived sequence have been used to engineer resistance to a number of pathogens. Besides, the ectopic expression of resistance gene could enhance resistance as shown with the introgression of *pvr1*, a recessive gene from *Capsicum chinense*, in tomato that results in dominant broad-spectrum potyvirus resistance (Kang et al. 2007). Nekrasov et al. (2017) also created a transgene-free powdery mildew resistant tomato by genome deletion.

The CRISPR/Cas technology is also expected to accelerate the breeding of cultivars resistant to diseases. Recently, CRISPR/Cas9 system has been used to engineer tomato plants that target the TYLCV genome with Cas9-single guide RNA at the sequences encoding the coat protein (CP) or replicase (Rep) resulting in immunity against TYLCV (Tashkandi et al. 2018). In addition, although still in its infancy, gene editing by CRISPR-nCas9-cytidine deaminase technology might be used to design de novo synthetic functional resistance alleles in tomato, using knowledge about the natural evolution of resistance genes in related species, as demonstrated by Bastet et al. (2019) in *Arabidopsis thaliana*.

2.6.4 Regulatory Status of Gene Edited Plants

Since 2013, CRISPR/Cas9 systems allowed considerable progress in plant genome editing, giving access to cost-effective and efficient transformation compared with previous technologies and making it rapidly accessible to many researchers. However, this emerging method is still developing and scientific efforts continue to be made in order to realize the full potential of the technology. It offers great opportunities, but also creates regulatory challenges. Concerns have been raised over the status of the plants produced by gene editing and classical genetically modified organisms (GMOs) as the technology generates transgene-free plants. Many plant breeders and scientists consider that gene-editing techniques such as CRISPR/Cas9 should be considered as mutagenesis, and thus be exempt from the GMO directive, because they can induce only changes of DNA sequences and not the insertion of foreign genes. But people opposed to GM organisms contend that the deliberate nature of alterations made through gene editing means that they should fall under the GMO directive. In the U.S.A., Canada, and several other countries, CRISPR/Cas induced mutations are exempt from GMO laws and regarded as equivalent to traditional breeding. In Europe, on 25 July 2018, the European Court of Justice (ECJ) ruled that gene edited crops should be subject to the same regulations as conventional GMOs (Callaway 2018). This may have strong consequences on the breeding developments in different countries.

2.7 Conclusion and Prospects

Tomato is a crop widely adapted to very different conditions. Subsequently, it has to respond to many stresses. Molecular markers have permitted the dissection of the genetic bases of complex traits into individual components, the location of many genes/QTLs on chromosomes, which became accessible to selection. Molecular markers have also allowed breeders to access to wild species in a more efficient way than in the past. Exotic libraries, which consist of marker-defined genomic regions taken from wild species and introgressed onto the background of elite crop lines, provide plant breeders with an important opportunity to improve the agricultural performance of modern varieties. Several research consortiums (for genome sequencing, but also for the valorization of genetic resources and traditional varieties) were gathered to study tomato diversity and adaptation.

Since the availability of the reference genome, many new resources (genome sequences, millions of SNPs), tools (databases, methodological tools), and methods (genome editing, crop modeling, and genomic selection) became available and thus breeding should be more efficient.

Better knowledge of physiological processes, metabolic pathways, genes involved as well as the genetic variability of candidate genes, mutant identification, and translational genetics may be used to go further. New growth conditions such as urban horticulture must be taken into account.

It will be important to combine the empirical approach of breeders based on an intimate knowledge of the tomato crop with the power of biotechnologies. Integration of related disciplines will be more and more important to (1) develop more efficient methods to evaluate the impact of environment on the crop, (2) enhance knowledge of the biochemical and molecular bases of the traits, and (3) better understand G x E and to increase the adaptation of new varieties to new conditions.

Some complex questions remain for research: how several stresses interact, how to deal with new pathogens and pests, root x rootstock interaction, reduction of fertilizers. Finally, modeling can help taking into account these aspects and designing new ideotypes optimized to the adverse variable or optimal conditions.

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