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Molecular breeding of tomato: Advances and challenges∞

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ABSTRACT

The modern cultivated tomato (*Solanum lycopersicum*) was domesticated from *Solanum pimpinellifolium* native to the Andes Mountains of South America through a "two-step domestication" process. It was introduced to Europe in the 16th century and later widely cultivated worldwide. Since the late 19th century, breeders, guided by modern genetics, breeding science, and statistical theory, have improved tomatoes into an important fruit and vegetable crop that serves both fresh consumption and processing needs, satisfying diverse consumer demands. Over the past three decades, advancements in modern crop molecular breeding technologies, represented by molecular marker technology, genome sequencing, and genome editing, have significantly transformed tomato breeding paradigms. This article reviews the research progress in the field of tomato molecular breeding, encompassing genome sequencing of germplasm resources, the identification of functional genes for agronomic traits, and the development of key molecular breeding technologies. Based on these advancements, we also discuss the major challenges and perspectives in this field.

Keywords: genome editing, genome sequencing, germplasm, molecular breeding, tomato

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INTRODUCTION OF TOMATO

Tomato (*S. lycopersicum* L.), native to the Andes region of South America, was domesticated in Mexico before being introduced into Europe in the 16th century. Since then, it has ascended to become the second most extensively cultivated vegetable crop globally. Tomatoes can be broadly categorized as fresh-market and processing tomatoes. According to Food and Agriculture Organization of the United Nations (FAO) statistics, approximately 190 million tons of tomatoes are produced worldwide each year, with approximately 39 million tons dedicated to processing purposes. China is the largest producer and consumer of tomatoes globally, with an annual production of approximately 67 million tons, 6 million tons of which are processing tomatoes. In recent years, consumers have increasingly criticized the diminished flavor of tomatoes. The loss of tomato flavor can be attributed to a variety of factors, including targeted breeding for traits such as disease resistance, uniform fruit color, and longer shelf life. Therefore, alongside the need to preserve disease resistance and ensure high yield, improving fruit quality has become an urgent and challenging task for tomato breeders. Furthermore, tomato production, particularly for fresh-market tomatoes, is labor intensive. With the escalation of labor costs, the development of new tomato varieties suitable for simplified cultivation practices is also imperative. Undoubtedly, achieving these breeding goals relies heavily on a deeper understanding of the genetic basis and molecular mechanisms underlying these traits.

Owing to its compact genome, short growth cycle, abundant genetic resources, and ease of genetic transformation, tomato is a classic model organism for genetic, genomic, and molecular biology studies (Tomato Genome Consortium, 2012). Tomato is one of the earliest crop plants for which a high-density molecular linkage map was constructed (Tanksley et al., 1992). Through the utilization of tomatoes as a research platform, scientists have made several groundbreaking discoveries: the identification of systemin, the first polypeptide plant hormone (Ryan and Pearce, 1998; Zhou et al., 2024); the cloning of *Pto*, the gene that confers resistance to *Pseudomonas syringae* pv. *tomato* and the first disease-resistance gene discovered in plants that adheres to the "gene-for-gene" hypothesis (Martin et al., 1993); the identification of the first quantitative trait locus (QTL), *Fruit weight 2.2* (*Fw2.2*), in crops (Frary et al., 2000); and the discovery of REGENRATION FACTOR1 (REF1), a key signal that induces plant regeneration after mechanical injury (Yang et al., 2024b). With the rapid development of molecular biology and high-throughput sequencing technologies, particularly the completion of the tomato reference genome sequencing in 2012 and the application of CRISPR/Cas9 gene editing in plants in 2013, research in tomato functional genomics has accelerated significantly. To date, the functions of more than 300 tomato genes have been meticulously analyzed, with a subset of these genes demonstrating significant contributions to trait enhancement and germplasm innovation.

The history of tomato breeding can be divided into four core stages. Breeding 1.0: Domestication breeding, which began approximately 10,000–7,000 years ago, *Solanum pipmpinellifolum* was domesticated into the cultivated tomato through phenotypic selection, and it spread to various parts of the world over 400 years ago. Breeding 2.0: Traditional breeding, from the late 19th century to the early 20th century, scientists uncovered the principles of Mendelian genetics and quantitative genetics. Precise control of hybridization, statistical analysis, scientific experimental design, hybrid breeding, pedigree-based breeding value assessment, and large-scale, high-precision yield measurement have advanced the development of modern tomato breeding systems. Breeding 3.0: Molecular breeding, which emerged approximately 30 years ago, saw the addition of molecular markers driving technologies such as marker-assisted selection (MAS) and linkage map analysis. Genome sequencing and high-throughput genotyping enriched the toolkit of quantitative genetics, enabling deeper analysis of genetic variation in natural populations and precise selection based on genomic breeding values. Currently, we are in the era of Breeding 4.0, and by integrating genetic information and editing the tomato genome, we can precisely select and modify plant genotypes to achieve more efficient and faster breeding goals. In particular, the emergence of genome-editing technologies, such as the CRISPR/Cas9 system, allows breeders to directly edit the genome of crops, precisely altering target traits and accelerating the breeding process. Looking ahead, Breeding 5.0 represents the forefront of future tomato breeding. Breeding 5.0 is characterized by the integration of big data applications, information technology, artificial intelligence, and advanced biotechnologies, making breeding strategies more precise and efficient and enabling the rational combination of desirable genetic variations (Figure 1) (Wallace et al., 2018; Kuriakose et al., 2020).

This review aims to provide a comprehensive overview of the latest research in the field of tomato molecular breeding, providing an in-depth analysis of future directions and challenges and contributing new insights and strategies for the sustainable development of the tomato industry.

GERMPLASM RESOURCES AND GENOMIC RESEARCH

Germplasm resources

Cultivated tomato (*S. lycopersicum* var. *lycopersicum* (SLL)) is an herbaceous plant in the family Solanaceae, genus *Solanum*, and section *Lycopersicon*. In addition to cultivated tomatoes, *Solanum* section *Lycopersicon* includes 12 wild tomato species (tomato relatives): *Solanum pimpinellifolium*, *Solanum cheesemaniae*, *Solanum galapagense*, *Solanum neorickii*, *Solanum chmielewskii*, *Solanum arcanum*, *Solanum peruvianum*, *Solanum chilense*, *Solanum corneliomulleri*, *Solanum huaylasense*, *Solanum habrochaites*, and *Solanum pennellii*. Among these, *S. pimpinellifolium* bears red fruits, while *S. cheesemaniae* and *S.*

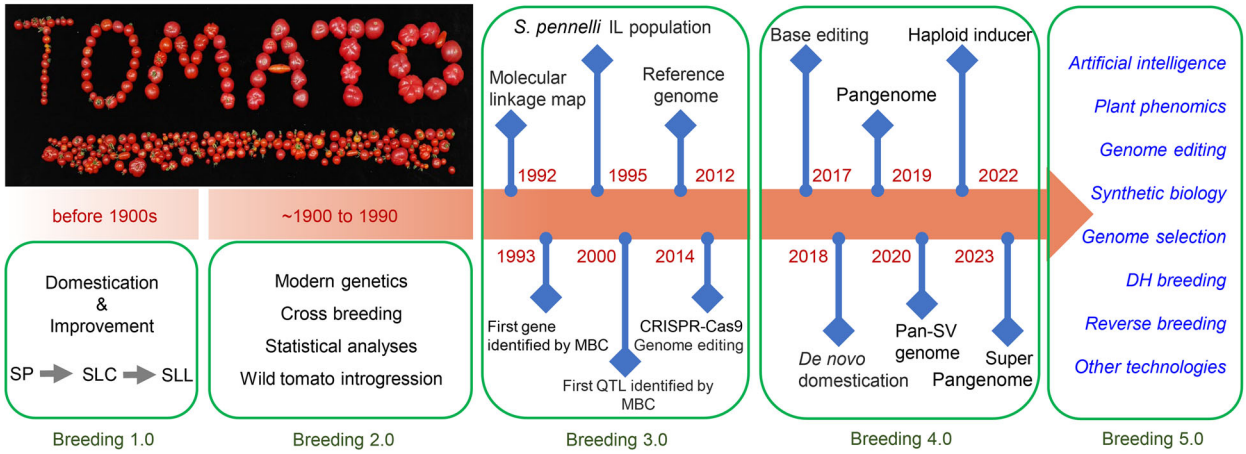

Figure 1. Major progress of tomato molecular breeding in the past 30 years

galapagense bear yellow or orange fruits. The mature fruits of the other wild species are typically green or yellow-green. Additionally, there are four allied species closely related to tomato, belonging to two sections of the genus *Solanum*: *Solanum lycopersicoides* and *Solanum sitiens* from *Solanum* section *Lycopersicoides*, and *Solanum juglandifolium* and *Solanum ochranthum* from *Solanum* section *Juglandifolia*. These four species are evolutionarily positioned between tomato (*Solanum* section *Lycopersicon*) and potato (*Solanum* section *Petota*) (Peralta et al., 2008; Li et al., 2023). All 16 tomato wild species or relatives exhibit significant differences in their reproductive habits compared with those of cultivated tomato accessions (Peralta et al., 2008). Cultivated tomato varieties and certain wild species (such as *S. cheesemaniae*, *S. galapagense*, and *S. neorickii*) are self-compatible (SC), with non-exserted or slightly exserted stigmas, making them primarily autogamous (self-pollinating). By contrast, *S. chilense*, *S. corneliomulleri*, *S. huaylasense*, and the four allied species are self-incompatible (SI) and possess floral structures, such as exserted stigmas, that facilitate cross-pollination (allogamy). The remaining wild tomato species exhibit facultative reproductive habits and can be divided into two categories: (i) SC species that display floral traits conducive to cross-pollination, such as larger floral organs and exserted stigmas (namely, *S. pimpinellifolium* and *S. chmielewskii*); and (ii) mostly SI species, with some SC variants predominantly at the periphery of their population distributions (namely, *S. arcanum*, *S. habrochaites*, *S. pennellii*, and *S. peruvianum*). The SC variants in category (ii) are hypothesized to have arisen from mutations in otherwise SI populations (Li and Chetelat, 2010).

Studies on hybridization compatibility between cultivated tomato and wild tomato species or their relatives have yielded several key insights. First, three cultivated SC species (*S. pimpinellifolium*, *S. cheesemaniae*, and *S. galapagense*) are capable of successful hybridization, producing viable seeds through both direct and reciprocal crosses. Second, five SC species (cultivated tomato, *S. pimpinellifolium*, *S. cheesemaniae*, *S. galapagense*, and *S. neorickii*) can serve as the maternal parent in successful crosses with SI species, although the success rate varies. Conversely, the reciprocal crosses (SI as the maternal parent, and SC as the paternal parent) are unsuccessful, indicating unidirectional hybridization incompatibility. Third, cultivated tomato, *S. pimpinellifolium*, *S. cheesemaniae*, and *S. pennellii* also exhibit unidirectional hybridization incompatibility with the allied species *S. lycopersicoides* (SI). In this case, successful crosses can only occur when *S. lycopersicoides* is used as the paternal parent. Fourth, unidirectional hybridization incompatibility in interspecific tomato crosses adheres to the "SI × SC" principle, wherein the stigma of SI species rejects pollen from SC species; however, there are exceptions: (i) *S. chmielewskii* (SC) accepts its own pollen and that of *S. neorickii* but rejects pollen from all other SC and SI species, and (ii) the stigmas of SI species do not reject pollen from the SC species *S. pennellii* (LA0716) and *S. arcanum* (LA2157) (Figure 2) (Bedinger et al., 2011; Baek et al., 2015, 2016).

Modern cultivated tomato was domesticated from *S. pimpinellifolium* through a two-step process: (i) domestication, which led to the creation of the intermediate subspecies *S. lycopersicum* var. *cerasiforme* (SLC), and (ii) improvement of SLC into large-fruited cultivated tomatoes (Lin et al., 2014). Studies have suggested that the intermediate subspecies SLC was distributed throughout Central and South America, but the final domestication of SLC occurred in Mexico approximately 7,000 years ago, leading to cultivated tomato. In the 16th century, Spanish colonists introduced tomatoes from Mexico into Spain and Portugal, where they were initially cultivated as ornamental plants. By the 18th century, tomato was widely cultivated as a food crop in Southern Europe, eventually spreading worldwide, establishing itself as an important fruit and vegetable crop. It is worth noting that the intermediate subspecies SLC should not be equated to cherry tomatoes (Blanca et al., 2015). SLC accessions produce tomatoes of variable sizes and shapes, ranging from 10 g to over 100 g. The term "cherry tomato" refers to fruits of a smaller size, typically weighing between 10 and 30 g, and includes not only SLC varieties but also modern cultivated varieties and traditional landraces. According to the systematic classification of tomato, cultivated tomato lines are classified into three major categories: traditional varieties, modern processing tomatoes, and fresh-market tomatoes. Traditional varieties refer

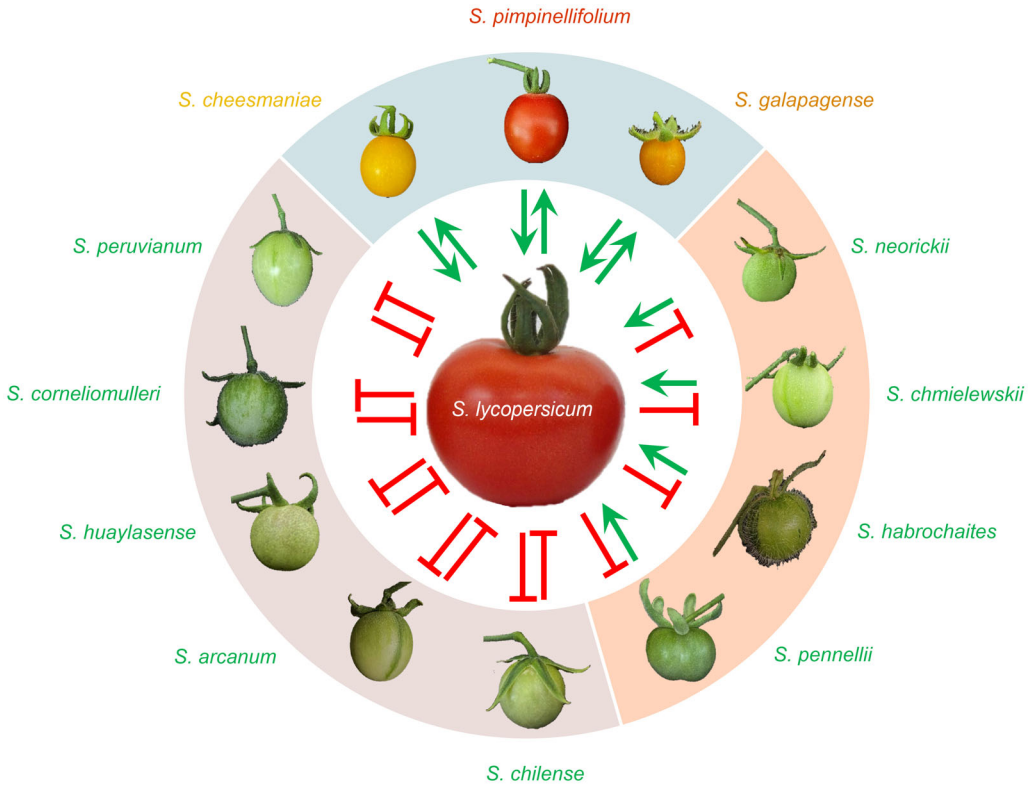

Figure 2. Compatibility between *Solanum lycopersicum* and its wild relatives
Direction of compatible and incompatible crosses (fruits with viable seeds) is indicated by green arrowed and red lines, respectively. Diagram modified based on Baek et al. (2015) and Muñoz-Sanz et al. (2020).

to those cultivated before the initiation of modern breeding practices, and include vintage, landraces, and heirlooms, many of which are still thriving in the gardens of European and American households (Blanca et al., 2022a). Modern processing and fresh-market tomatoes are products of systematic breeding techniques that have been developed since the 20th century to meet different consumer demands (Figure 1). Many of these modern varieties also contain disease-resistance genes incorporated from wild species to enhance their environmental adaptability and yield.

Because of the domestication bottleneck and genetic erosion caused by over 400 years of global dissemination, the present-day cultivated tomato varieties exhibit minimal genetic diversity. However, the substantial genetic variation found in wild species and their close relatives constitutes a crucial genetic resource for functional genomics studies and cultivar improvement. Over the past century, significant success has been achieved in transferring disease resistance, fruit yield and quality traits from the wild germplasm into cultivated genotypes. The rapid advancement of molecular research techniques in the last 30 years has greatly accelerated the exploration and utilization of wild tomato genetic resources. For instance, the development of high-density molecular genetic linkage maps and high-throughput molecular MAS systems have facilitated the development of multiple sets of introgression line (IL) populations derived from wild tomatoes, providing invaluable resources for the study and utilization of key agronomic traits (Eshed and Zamir, 1995). Additionally, naturally occurring or artificially induced mutations serve as important resources for tomato genetic improvement. Discoveries such as *self-pruning* (*sp*), which results in compact plants with uniform fruit ripening; *fruit shape 8.1* (*fs8.1*), which leads to square-shaped, crush-resistant fruits; and *jointless* (*j*), which causes the detachment of the calyx from the fruit, have significantly accelerated the mechanization of processing tomato production (Pnueli et al., 1998; Mao et al., 2000; Zhu et al., 2023a).

Currently, germplasm repositories around the world house extensive collections of tomato genetic resources, encompassing a wide range of wild species, intermediate subspecies, as well as representative varieties, lines, and mutants, representing various stages of domestication and improvement. The primary repositories for tomato germplasm include the C.M. Rick Tomato Genetics Resource Center (TGRC) in the USA, the World Vegetable Center (WVC) in Taiwan, the United States Department of Agriculture (USDA) in the USA, the Leibniz Institute of Plant Genetics and Crop Plant Research (IPK) in Germany, and the Centre for Genetic Resources in the Netherlands. Mexico, Peru, Cuba, Brazil, Japan, Russia, China, France, Italy, and Spain have also established their own germplasm centers. The European Cooperative Programme for Plant Genetic Resources (ECPRG) has established a collaborative network that conserves over 20,000 tomato germplasm resources. Public tomato mutant repositories include TGRC, Genes that Make Tomatoes, LycoTILL, and TOMATOMA (Chaudhary et al., 2019). Unfortunately, with the exception of a few genetic resource centers such as

TGRC that adopt relatively open policies, most national tomato germplasm resources remain primarily accessible to researchers or breeders within their own countries. This restriction undoubtedly impedes the global sharing, preservation, and efficient utilization of valuable genetic resources. Therefore, strengthening international cooperation and promoting open access to germplasm resources to fully leverage their potential are critical priorities that must be addressed to advance global agricultural sustainability.

Genomic research

A high-quality reference genome is a critical foundation for functional genomics research and crop genetic improvement. In 2012, owing to the collaborative efforts of global research teams, the first reference genome sequence of cultivated tomato (Heinz1706) was successfully completed (Tomato Genome Consortium, 2012). Approximately 34,727 genes were identified, 33,840 of which (97.4% genes) were accurately mapped to chromosomes. Subsequent updates to the Heinz1706 genome sequence have improved the data significantly. The latest SL5.0 genome assembly includes 801.8 Mb of sequence data, featuring a larger contig N50 size (41.7 Mb in SL5.0 vs. 5.5 Mb in SL4.0) and fewer gaps (31 in SL5.0 vs. 259 in SL4.0). In addition to the Heinz1706 reference genome, high-quality genome assemblies have been completed for 24 other cultivated tomato varieties. *Solanum pimpinellifolium*, recognized as the progenitor of cultivated tomato, was among the first wild tomato species to have its genome sequenced (Wang et al., 2024e). To date, at least 15 chromosome-level genome assemblies of *S. pimpinellifolium* have been completed, with genome sizes ranging from 739 Mb (LA1589) to 840.3 Mb (LA0400). Additionally, genomes of 10 other wild tomato species have also been sequenced, including *S. habrochaites* (LYC4, LA0407, and LA1777), *S. pennellii* (LA0716 and LA5240), *S. galapagense* (LA0436 and LA0317), *S. chilense* (LA1969 and LA3111), *S. arcanum* (LA2157), *S. peruvianum* (LA0446), *S. corneliomulleri* (LA1331), *S. neorickii* (LA0247), *S. chmielewskii* (LA1028), and *S. lycopersicoides* (LA2951) (Yu et al., 2022; Li et al., 2023; Wang et al., 2024e). These tomato genome sequencing efforts provide a solid foundation for the subsequent discovery of functional genes and investigation of the evolutionary transition from wild to cultivated species, thereby accelerating the application of genomics in tomato breeding.

The limitations of a single genome sequence lie in its inability to represent the entire genetic variation within a species. A pangenome represents the collective sum of all known genomic information of a species and, compared with traditional single-reference genomes, significantly enhances the inclusivity of genetic diversity, effectively mitigating the interference caused by reference genome biases in detecting genetic variations. The first pangenome study of tomato included genomic data from 372 cultivated tomato, 267 SLC, 78 *S. pimpinellifolium*, three *S. cheesemaniae*, and five *S. galapagense* accessions (Gao et al., 2019). The authors identified an additional 4,873 novel protein-coding genes beyond those found in the reference genome, revealing the widespread nature of gene loss during tomato domestication and improvement. In addition, pangenome research has highlighted the role of structural variations (SV) as a crucial driver of gene expression changes and phenotypic diversity. Furthermore, 238,490 structural variants were identified through pan-SV analysis of 100 different cultivated and wild tomato accessions (Alonge et al., 2020). Some of these variants were directly linked to fruit traits such as flavor, size, and yield. For instance, a 50-kb tandem repeat in the *FW3.2* fruit weight QTL region significantly enhanced the expression of *SlKLUH*, thereby increasing fruit weight (Alonge et al., 2020). Through continued research, the boundaries of pangenomes continue to expand. In 2023, a "super-pangenome" was constructed by integrating more diverse tomato resources, including ten wild species and one cultivated tomato accession (Li et al., 2023). This genomic resource not only covered a broad range of genetic diversity within the Solanaceae family but also uncovered 9,320 new genes previously unidentified in earlier pangenome studies. Graph-based pangenomes, which store and display species variation information in the form of nodes and paths, play a crucial role in extending the coordinate system of linear reference genomes to accommodate more genetic diversity. A graph-based pangenome of tomato (TGG1.0) was constructed on the basis of 838 accessions to address the challenges in genetic variation detection and reclaim the "missing heritability" resulting from the incomplete detection of causal genomic variants and genetic heterogeneity. Compared with a single-reference genome, genetic variations based on the graph-based pangenome increased the estimated genetic heritability by 24%, highlighting the marked ability of graph-based pangenomes to enhance the accuracy and depth of genetic variation detection (Zhou et al., 2022b).

Building on a robust foundation of high-quality reference genome sequences, researchers have utilized strategies such as genome resequencing to conduct an in-depth investigation of the domestication history and dispersal trajectories of tomato and to elucidate mechanisms underlying its key agronomic traits. Resequencing data from 360 distinct tomato genotypes confirmed the critical role of SLC as a bridge between *S. pimpinellifolium* and cultivated tomato, strongly supporting the validity of the two-step domestication theory (Lin et al., 2014). Although SLC is recognized as a semi-domesticated tomato, there remains some debate regarding its geographical origin and specific domestication pathways. Notably, SLC fruits originating from South America (especially northern Peru) are significantly larger than the SLC fruits commonly found in Central America. Utilizing genome resequencing and population genomics, it has been proposed that the large-fruited South American SLC accessions might predate the overall tomato domestication process, with the large-fruit traits being lost during the northern migration but later being re-selected and reinforced during the subsequent domestication (Razifard et al., 2020). Conversely, an alternative perspective suggests that the small-fruited SLC accessions from Central America represent a more primitive state, characterized by greater genetic diversity and lower linkage disequilibrium (LD). These materials are believed to have undergone gradual domestication; while *S. pimpinellifolium* is known to

have migrated from the Peruvian desert to the Mexican rainforest, it is possible that small-fruited SLC accessions migrated back to Peru, where they underwent further domestication into large-fruited SLC before eventually moving to Central America and being selected by humans to form the large-fruited cultivated tomatoes we know today (Blanca et al., 2022b). The domestication and improvement of tomato have profoundly influenced traits such as disease resistance, yield, quality, and environmental adaptability. Through the integration of advanced techniques such as genome resequencing and genome-wide association studies (GWAS), researchers have successfully identified a series of key genes and genetic loci that regulates major agronomic traits in tomato and have pinpointed numerous genomic regions subjected to both natural and artificial selection during the domestication and improvement processes (Lin et al., 2014). These valuable findings not only provide insight into the genetic basis of fruit traits, but also lay a solid foundation for future molecular breeding efforts in tomato.

In addition to genome sequencing, the rapid advancement of high-throughput sequencing technologies has significantly accelerated the application of whole-genome transcriptome sequencing (RNA-seq; including conventional transcriptome sequencing, single-cell transcriptome sequencing (scRNA-seq), and spatial transcriptome sequencing), chromatin immunoprecipitation sequencing (ChIP-seq; for transcription factors or histones), chromatin accessibility profiling, DNA methylation sequencing, and RNA methylation sequencing in tomato functional genomics research. For instance, RNA-seq analysis performed on 10 different tissues and five epidermal cell types of tomato fruits harvested at six different developmental stages resulted in the construction of a high-resolution spatiotemporal transcriptome map, representing tomato fruit development and ripening (Shinozaki et al., 2018). By integrating high-resolution spatiotemporal metabolomics and transcriptomics data from 20 samples of MicroTom, representing different growth stages and tissues, a tomato metabolic network (MMN) dataset was generated, aiding in the validation of novel regulatory factors for key metabolic pathways (Li et al., 2020c). The mechanism underlying the amplification of the transcriptional regulatory cascade of jasmonic acid (JA) in response to disease was discovered in tomato through combined ChIP-seq and RNA-seq analyses, offering new perspectives for breeding disease-resistant varieties (Du et al., 2017). *SHOOTBORNE ROOTLESS* (*SBRL*), a super locus that regulates the initiation of aboveground and belowground roots in tomato, was identified using scRNA-seq (Omary et al., 2022). Using various spatial transcriptome analysis methods, researchers have discovered highly heterogeneous cell populations within tomato callus tissue, highlighting the critical role of chlorenchyma cells in the position determination and differentiation of shoot meristem cells (Song et al., 2023). The DNA demethylation function of the *SlDML2* gene was demonstrated through the integration of DNA methylation sequencing and RNA-seq technologies, suggesting that DNA methylation may serve as the third crucial factor, following transcription factors and plant hormones, controlling tomato fruit ripening (Lang et al., 2017). By using RNA methylation (m^6A) sequencing, researchers have revealed the significant role of m^6A modification in tomato fruit maturation and preliminarily established the intrinsic link between DNA and RNA methylation (Zhou et al., 2019). These vast high-throughput sequencing datasets are generally uploaded by researchers to public data platforms, such as NCBI, EMBL-EBI, DDBJ, and the Genome Sequence Archive, facilitating global resource sharing and collaboration. Notably, as early as 2005, the Sol Genomics Network was established by international peers to serve as a genomic data platform for Solanaceae crops. This platform currently houses publicly available tomato genome sequencing, resequencing, and RNA-seq data that can be used by researchers globally to conduct sequence queries, alignments, molecular marker design, and gene expression analyses. However, with the explosive growth of high-throughput, low-cost sequencing data for tomato, the efficient integration, management, and utilization of these data have become a great challenge that needs urgent resolution. Continuous efforts toward ensuring data standardization and quality control, developing data integration platforms, and promoting interdisciplinary collaboration are needed to fully unlock the enormous potential of these data resources and to drive tomato genetic improvement and agricultural production.

Modern breeding relies heavily on genomic information, underscoring the critical importance of genomic research in advancing tomato breeding programs. This paper presents a selection of pertinent genomic studies related to tomatoes; for a more detailed and comprehensive overview, we refer readers to the work by Wang et al. (2024e).

MOLECULAR BASIS OF KEY AGRONOMIC TRAITS

To date, tomato researchers have identified thousands of QTLs and hundreds of genes that control key agronomic traits. In this review, we focus on tomato genes that: (i) were identified through forward genetics; (ii) account for the genetic diversity underlying important agronomic traits; and (iii) are promising candidates for MAS and genome editing (Figure 3; Tables 1, S1).

Plant architecture

Plant architecture influences light absorption and nutrient distribution, ultimately affecting yield and quality (Tieman et al., 2017; Zhu et al., 2018). During tomato production, growers need to regularly adjust plant architecture (e.g., by installing trellises, pruning old leaves, removing branches, and thinning flowers and fruits) to ensure optimal light absorption, nutrient distribution, and yield quality (Xia et al., 2021). Traits related to plant architecture in tomato include growth habit, flowering time, lateral branching, stem and leaf development, plant height, and inflorescence structure.

These traits are primarily influenced by genetic and environmental factors.

Plant growth habit and flowering

Tomato is a typical plant with a sympodial branching pattern, characterized by continually alternating vegetative and reproductive growth phases throughout its life cycle. Depending on their growth habit, tomato genotypes can be classified as indeterminate or determinate. In indeterminate genotypes, after the production of six to 12 leaves during the vegetative growth phase, the upward growth of its main stem is terminated by the formation of the first inflorescence. Subsequently, the axillary meristem (AXM), located in the youngest leaf axil adjacent to the first inflorescence, replaces the apical meristem and continues upward growth. This AXM develops into a sympodial unit consisting of three leaves and one inflorescence (the second inflorescence). The upward growth of this sympodial unit is terminated by the formation of the second inflorescence, leading to the emergence of the next sympodial unit (Périlleux et al., 2014; Périlleux and Huerga-Fernández, 2022). Thus, indeterminate tomatoes have multiple sympodial units, each comprising three leaves and one inflorescence, and the continuous production of sympodial units leads to a higher total number of inflorescences compared with determinate tomatoes. Most fresh-market tomatoes are indeterminate, and these varieties typically require pruning, involving the manual removal of branches, to ensure that nutrients and energy are primarily directed toward the main-stem inflorescences. Indeterminate types also require a larger vertical space for growing. By contrast, the number of leaves in the sympodial units of determinate tomato genotypes gradually decreases and, after producing three to five sympodial units, determinate tomatoes typically form two consecutive inflorescences and terminate growth, resulting in fewer total inflorescences. Determinate varieties usually do not require pruning, and the inflorescences produced by lateral branches contribute to high yields. Therefore, determinate tomatoes exhibit a short, compact, and bushy growth habit, with uniform fruit ripening, making them suitable for mechanized harvesting and for processing tomato production. However, because of the larger area occupied by individual plants, determinate types are less suitable than indeterminate types for the production of fresh-market tomatoes in greenhouses or other facilities. Before 1930, almost all cultivated tomato varieties were indeterminate. In 1914, Bert Croft discovered a determinate

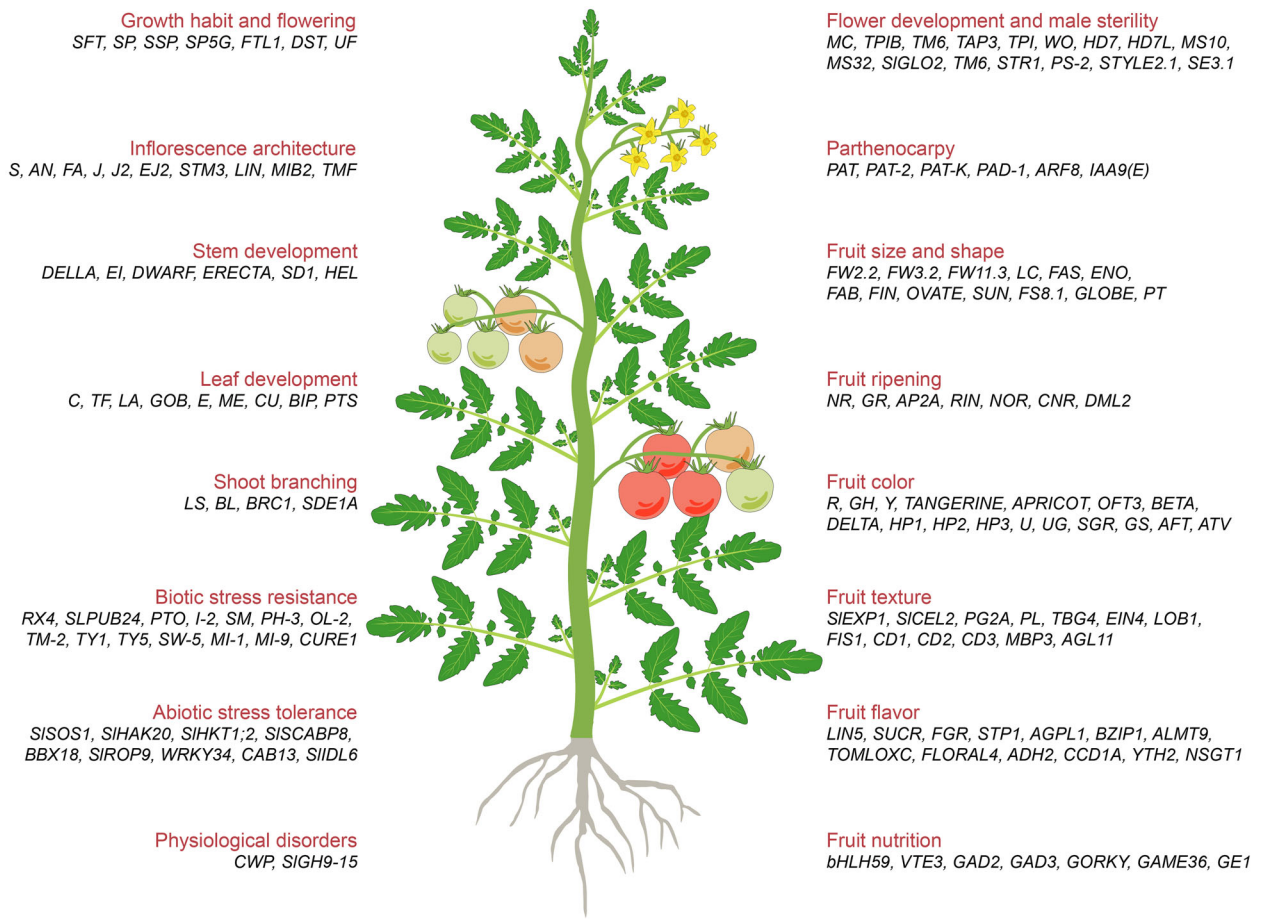

Figure 3. The representative functional genes identified in tomato

Table 1. Representative functional genes identified in tomato

Gene/Locus	Gene ID	Trait	Reference
Plant architecture			
SP	*Solyc06g074350*	Sympodial growth	Pnueli et al. (1998)
SFT	*Solyc03g063100*	Plant architecture; flowering time	Lifschitz and Eshed, 2006
SSP	*Solyc02g083520*	Plant architecture; flowering time	Park et al., 2014
SP5G	*Solyc05g053850*	Flowering time	Soyk et al., 2017b
Bl	*Solyc11g069030*	Shoot branching	Schmitz et al., 2002
Ls	*Solyc07g066250*	Shoot branching	Schumacher et al., 1999
S	*Solyc02g077390*	Inflorescence branching	Lippman et al., 2008
Flower development			
J	*Solyc11g010570*	Abscission zones	Mao et al., 2000
J2	*Solyc12g038510*	Inflorescence architecture	Soyk et al. (2017a)
Ms-10	*Solyc02g079810*	Pollen development	Jeong et al., 2014
Ps-2	*Solyc04g015530*	Anther dehiscence	Gorguet et al., 2009
Ms-15	*Solyc02g084630*	Stamen development	Cao et al., 2019
Style2.1	*Solyc02g087860*	Style length	Chen et al., 2007
SE3.1	*Solyc03g098070*	Style length	Shang et al. (2021)
Pat-2	*Solyc04g080490*	Parthenocarpy	Nunome, 2016
Pat-k	*Solyc01g093960*	Parthenocarpy	Klap et al., 2017
Fruit traits			
Fw2.2	*Solyc02g090730*	Fruit size	Frary et al., 2000
Fw3.2	*Solyc03g114940*	Fruit size	Alonge et al., 2020
Fw11.3	*Solyc11g071940*	Fruit size	Mu et al., 2017
Lc	*Solyc02g083950*	Locule number	Muños et al., 2011
Fas	*Solyc11g071380*	Locule number	Xu et al., 2015
Ovate	*Solyc02g085500*	Fruit shape	Liu et al., 2002
Sun	*Solyc10g079240*	Fruit shape	Xiao et al., 2008
FS8.1	*Solyc08g061910*	Fruit shape	Zhu et al., 2023a
FIS1	*Solyc10g007570*	Fruit firmness	Li et al., 2020a
PL	*Solyc03g111690*	Fruit firmness	Wang et al., 2019c
Nor	*Solyc10g006880*	Fruit ripening	Klee and Giovannoni, 2011
Cnr	*Solyc02g077920*	Fruit ripening	Manning et al., 2006
Rin	*Solyc05g012020*	Fruit ripening	Vrebalov et al., 2002
U	*Solyc10g008160*	Green shoulder	Powell et al., 2012
R	*Solyc03g031860*	Fruit color	Fray and Grierson, 1993
Beta /Old gold	*Solyc06g074240*	Fruit color	Ronen et al. (2000)
Delta	*Solyc12g008980*	Fruit color	Ronen et al. (1999)
Y	*Solyc01g079620*	Fruit color	Ballester et al., 2010
Aft	*Solyc10g086290*	Fruit color	Sun et al., 2020
Lin5	*Solyc09g010080*	Sugar content	Fridman et al., 2004
STP1	*Solyc02g079220*	Sugar content	Wang et al., 2023c
SlCDPK27	*Solyc11g065660*	Sugar content	Zhang et al., 2024b
TomLoxC	*Solyc01g006540*	Apocarotenoid	Gao et al., 2019
TFM6	*Solyc06g072910*	Malate acid	Ye et al., 2017
AAT1	*Solyc08g005770*	Acetate esters	Goulet et al., 2015
Resistance			
Pto	*Solyc05g013300*	Resistance to *Pst*	Martin et al., 1993
Bs4	*Solyc05g007850*	Resistance to bacterial spot	Schornack et al., 2004
I-2	*Solyc11g071430*	Resistance to *F. o. lycopersici* race 2	Ori et al., 1997
Ve1	*Solyc09g005090*	Resistance to *Verticillium alboatrum*	Kawchuk et al., 2001
Ph-3	*Solyc09g092310*	Resistance to late blight	Zhang et al., 2014
Cf4	*Solyc01g009690*	Resistance to *Cladosporium fulvum*	Thomas et al., 1997

Continued

Table 1. Continued

Gene/Locus	Gene ID	Trait	Reference
Cf9	AJ002236	Resistance to *Cladosporium fulvum*	Jones et al., 1994
MLO1/Ol-2	*Solyc04g049090*	Resistance to powdery mildew	Bai et al., 2008
Ty-1/Ty-3	*Solyc06g051190*	Resistance to TYLCV	Verlaan et al., 2013
Ty-5	*Solyc04g009810*	Resistance to TYLCV	Lapidot et al., 2015
$Tm2^2$/Tm-2a	*Solyc09g018220*	Resistance against ToMV	Lanfermeijer et al., 2003
Sw-5	*Solyc09g098130*	Resistance to TSWV	Brommonschenkel et al., 2000
Mi-9	*Sarc_034200*	Resistance to RKNs under high temperatures	Jiang et al., 2023
Ref1	*Solyc04g072310*	Resistance to wounding; shoot regeneration	Yang et al., 2024b

mutant, *self-pruning* (*sp*), in a field in Florida, USA. This mutant exhibited a short, compact, and bushy growth habit. Subsequently, the *sp* trait was introduced by breeders into processing tomatoes, accelerating their mechanization and commercialization (Atherton and Rudich, 1986). *SP* encodes a member of the CENTRORADIALIS/TERMINAL FLOWER 1/Self-Pruning (CETS) protein family (Pnueli et al., 1998), which inhibits flowering by antagonizing the activity of florigen, a protein encoded by *SINGLE FLOWER TRUSS* (*SFT*), another prominent member of the CETS family (Lifschitz et al., 2014). *SFT* is primarily expressed in leaves, and florigen is transported from leaves to the shoot apex, where it induces flower bud differentiation (Molinero-Rosales et al., 2004; Lifschitz and Eshed, 2006). The *sft* mutant exhibits significantly delayed flowering, with the first inflorescence typically forming only after 15–20 leaves have accumulated on the plant. The regular sympodial unit growth pattern is disrupted, which leads to the formation of vegetative inflorescences composed of single flowers and leaves (Lifschitz and Eshed, 2006). As a negative regulatory factor of the SFT-mediated flowering signal, SP primarily controls the vegetative-to-reproductive phase transition during sympodial growth, thereby affecting the aboveground plant architecture and fruit yield. The *sp* mutant has a strong flowering signal at the sympodial growth stage, with a faster transition from vegetative to reproductive growth, which results in fewer leaves in between inflorescences, higher inflorescence density, and premature termination of the main stem. A moderate reduction in the amount of the flowering signal in the *sp* mutant can alter plant architecture, increasing the number of leaves between inflorescences, decreasing inflorescence density, and delaying the termination of plant growth, thereby increasing the number of inflorescences on the main stem (Krieger et al., 2010; Kang et al., 2022). For example, introducing different alleles of *sft* or maintaining *sft* in a heterozygous state in the *sp* mutant background can, in a dose-dependent manner, weaken the flowering signal and partially suppress the premature growth termination phenotype of the *sp* mutant. This results in the production of more sympodial units and inflorescences, significantly increasing yield (Krieger et al., 2010). Similarly, a series of *suppressor of sp* (*ssp*) mutants, exhibiting a weaker flowering signal than *sp*, were generated by the chemical mutagenesis of the *sp* mutant. Among them, *ssp-2129* and *ssp-610* harbor mutations in the homologs of the Arabidopsis flowering transcription factor gene *FLOWERING LOCUS D* (*FD*). In the *ssp-2129 sp* and *ssp-610 sp* double mutants, the self-pruning (determinate growth) phenotype of the *sp* mutant is completely suppressed, which results in indeterminate growth. More importantly, these double mutants have fewer leaves (two leaves) in each sympodial unit compared with the typical indeterminate growth type, ultimately leading to increased inflorescence density and higher yield (Park et al., 2014). It is worth noting that indeterminate growth habit with two leaves between inflorescences has also been reported in wild tomato species such as *S. pennelli* and *S. peruvianum*. Such plant architecture holds great potential for increasing yield and shortening the tomato harvest period. The above research not only confirms the important role of SFT, SP, and SSP in regulating flowering and yield, but also highlights the enormous potential of genetic manipulation in optimizing tomato plant architecture and yield. *Solanum pimpinellifolium* is a short-day plant, that is, it flowers earlier under short-day conditions than under long days (Zhang et al., 2018). Moreover, the biological activities that characterize circadian rhythms, such as leaf movement, stomatal opening and closing, and gene expression, are better adapted to the short-day environment in *S. pimpinellifolium*. Through domestication and improvement, cultivated tomato lines have lost their sensitivity to day length and adaptability to the circadian rhythm, enabling their widespread cultivation and adaptability. *SP5G* and *FTL1*, both of which are *SFT* homologs, regulated the sensitivity of tomatoes to long-day and short-day conditions, respectively, during domestication and improvement. In wild species such as *S. pimpinellifolium*, *S. galapagense*, and *S. pennelli*, the expression of *SP5G* is induced by long-day conditions, which significantly inhibits flowering. However, cultivated tomato accessions exhibit lower sensitivity to day length, because of a 52-bp deletion in the 3′ untranslated region (UTR) of *SP5G* (Soyk et al., 2017b; Zhang et al., 2018). Importantly, under long-day conditions, the *sp5g* mutant exhibits significantly accelerated flowering, indicating its potential value for breeding early-maturing varieties. Conversely, short-day photoperiod has been reported to activate the expression of *FTL1* in wild tomato species, promoting flowering initiation; in cultivated tomatoes, *FTL1* carries a 2-bp deletion and

therefore no longer responds to short-day conditions, allowing cultivated tomato genotypes to flower normally under short-day conditions, thus overcoming the constraints of photoperiod (Song et al., 2020).

In addition to *SFT* and its homologs, the regulatory network controlling flowering in tomato also includes several other key genes, such as *Delayed sympodial termination* (*Dst*) (Meir et al., 2021), *Late termination* (*Ltm*) (Tal et al., 2017), *Flowering Activator 1* (*FAF1*) (Zhang et al., 2024a), *Sucrose Transporter 4* (*SlSUT4*) (Liang et al., 2023), *Flowering of uniflora* (*Uf*) (Dielen et al., 2004), *Ethylene Responsive Factor 36* (*SlERF36*) (Garg et al., 2024), *OPEN STOMATA 1* (*SlOST1*) (Chong et al., 2022), as well as *microRNA156* (*miR156*) (Zhang et al., 2011; Cui et al., 2020). These genes work together through unique mechanisms to ensure the precise and efficient progression of tomato flowering.

Lateral branching and stem development

Axillary meristems, which develop into lateral branches from leaf axils, significantly influence plant architecture and fruit yield in tomato. During the production of fresh-market tomatoes, the removal of lateral branches can ensure that nutrients and energy are primarily directed toward the development of inflorescences on the primary stem, thereby increasing yield. However, for processing tomatoes, more fruit-bearing lateral branches mean higher yields. The development of AXMs is a complex process regulated by multiple factors, including plant hormones (such as auxins) and epigenetic modifications. Key genes known to control the formation of lateral branches in tomato include *LATERAL SUPPRESSOR* (*LS*), *BLIND* (*BL*), *Super determinant 1a* (*Sde1a*), and *BRANCHED1* (*BRC1a/b*). Both *ls* and *bl* mutants exhibit impaired lateral branch development, but the mechanisms underlying the altered branching phenotype differ; in *ls*, the formation of lateral branches is impaired only during the vegetative growth of the primary stem (before the formation of the first inflorescence) whereas, in the *bl* mutant, the establishment of sympodial meristems is also impeded, leading to the abnormal development of sympodial units and cessation of growth after the formation of the first inflorescence. *LS* encodes a GRAS family transcription factor, while *BL* encodes an R2R3-MYB transcription factor. Genetic analysis suggests that *LS* and *BL* regulate the formation of AXMs through different pathways (Schumacher et al., 1999; Schmitz et al., 2002). The *super determinant 1a* (*sde1a*) mutant shows severe defects in lateral branch development. The *Sde1a* gene, encoding a RAWUL domain-containing protein, is primarily expressed at early stages of boundary development in a small group of cells at the center of the leaf-axil boundary. *Sde1a* and *Ls* act in the same genetic pathway to regulate lateral branch development, but unlike the *ls* mutant, the *sde1a* mutant does not show any defects in inflorescence development and branching (López et al., 2021). *BRC1a/b*, homologs of Arabidopsis *BRANCHED1*, encode TCP transcription factors that play important roles in inhibiting the outgrowth of axillary buds. *BRC1a/b* genes are mainly expressed in arrested axillary buds and not in the sympodial meristems, indicating that BRC1a/b primarily control the formation of axillary buds in tomato. Silencing *BRC1b* expression can significantly promote the outgrowth of axillary buds, while the effect of silencing *BRC1a* is relatively limited, possibly because of its lower expression levels in cultivated tomato. The *BRC1a* allele in *S. pennellii* LA0716 is expressed at significantly higher levels than the corresponding allele in the cultivated tomato variety M82, resulting in fewer axillary bud outgrowths (Martín-Trillo et al., 2011). Light and brassinosteroids (BRs) play important roles in lateral branch development. ELONGATED HYPOCOTYL5 (HY5), a core transcription factor in the light signaling pathway controlling plant growth, promotes the growth of tomato axillary buds by directly inhibiting the expression of *BRC1* and activating BR biosynthesis within the axillary buds. Inactivation of the light receptor phytochrome B (phyB) or the absence of cryptochrome 1a (cry1a) leads to a decrease in HY5 protein levels and an increase in BRC1 levels, thereby inhibiting the growth of axillary buds (Dong et al., 2023). Gene loss or pseudogenization that occurred during domestication and improvement is one of the main reasons why cultivated tomato genotypes have fewer branches than their semi-domesticated or wild counterparts. A 244-bp deletion in a cytochrome P450 gene leads to its loss of function and reduces fruit-bearing branches in cultivated tomatoes (Li et al., 2023). It is currently difficult to utilize the known lateral branching-regulating genes in tomato breeding programs. An in-depth analysis of the molecular genetic basis of lateral branch development will provide important genetic and genomic resources for plant architecture regulation and will lead to the development of new, simplified cultivated tomato varieties.

Internode length determines plant height, leaf ventilation, and light penetration, which makes it an important agronomic trait in tomato production. Internode length is mainly regulated by gibberellin (GA) and BR. The *procera* mutant exhibits elongated internodes, because of the loss of function of DELLA proteins, which act as negative regulators of the GA signaling pathway (Bassel et al., 2008). The *Elongated Internode* (*El*) gene encodes the GA metabolic enzyme SlGA2ox7 and shortens internode length in tomato by degrading active GAs (Sun et al., 2019). The GA receptor protein-encoding gene *SlGID1a* is a candidate gene for the *tomato plant height 1.1* QTL (*qtph1.1*), which controls plant height by regulating internode length (Liu et al., 2020c). The *Dwarf* (*D*) gene encodes a key BR biosynthetic enzyme. Mutation of the *D* gene leads to reduced BR levels, contributing to the extreme dwarfism of MicroTom (Li et al., 2016). In addition to the *d* gene, mutations in *miniature* (*mnt*) and *sp* genes also contribute to the extremely dwarf phenotype of MicroTom. Although the *mnt* gene has not yet been cloned, it is speculated to be involved in the GA signaling pathway (Martí et al., 2006). Mutations in *Sl*, a homolog of Arabidopsis *ERECTA*, result in shorter internodes, shorter inflorescences, and a more compact plant architecture. It has been reported that tomato

plants with simultaneously knocked-out *SI*, *SP5G*, and *SP* genes are suitable for urban cultivation (Kwon et al., 2020). Researchers have also cloned a number of genes related to the growth and development of tomato stems, including *Stem diameter 1* (*SD1*), which controls stem thickness, and *Helical* (*HEL*), which controls the helical growth of the plant (Yang et al., 2020; Ye et al., 2020).

Generally, tomato plants can accumulate anthocyanins in their hypocotyls and stems, which gives them a purple coloration. However, some tomato genotypes fail to accumulate anthocyanins in their stems; these genotypes are called green-stem mutants. Green stem is a recessively inherited trait that serves as a morphological marker at the seedling stage and is widely used in tomato breeding. Several green-stem genes have been identified to date. The *Anthocyanin absent* (*Aa*) gene, located on chromosome 2, is closely linked to *Male sterile 10* (*Ms 10*), which controls male sterility in tomato. The *aa* allele is commonly used to assist in the selection of *ms10* male-sterile plants. The *Aa* gene, which encodes the anthocyanin transporter protein SlGSTAA, is lost in the green-stem mutant as part of a large 3.4-kb deletion, ultimately resulting in the formation of green stems (Zhang et al., 2016). In addition to *aa*, other green-stem mutants include *anthocyanin free* (*af*), *anthocyanin reduced* (*are*), *anthocyanin without* (*aw*), *anthocyanin-less* (*a*), and *entirely anthocyanin-less* (*ae*), all of which are caused by mutations of genes in the phenylpropanoid metabolic pathway (Goldsbrough et al., 1994; De Jong et al., 2004; Kang et al., 2014; Maloney et al., 2014). In addition, mutations in *Hoffman's anthocyaninless* (*ah*) gene, which encodes the basic leucine zipper helix–loop–helix (bHLH) transcription factor SlAN1, also result in the green-stem phenotype (Qiu et al., 2016).

Tomato plants sometimes develop adventitious roots on their stems in high-humidity environments. The formation of adventitious roots is related to various environmental factors, such as soil water status and nutrient conditions, and internal signals, including plant hormone levels. The LATERAL ORGAN BOUNDARIES DOMAIN (LBD) family member SHOOT BORNE ROOTLESS (SBRL) plays a significant role in the development of adventitious roots in tomato. Knocking out *SBRL* significantly reduces the formation of adventitious roots on the stem and markedly decreases the number of roots induced under waterlogged and damaged conditions (Omary et al., 2022).

Leaf development

Leaf morphology is an important component of plant architecture and, for most cultivated crops, the shape and spatial distribution of leaves affect the efficiency of light utilization, which in turn determines crop yield and quality. Tomato leaves are pinnately compound, with pinnately deep lobes or entire lobes. Typically, the petioles or petiolules bear three or four pairs of primary leaflets, one terminal leaflet, and some intermediate leaflets. Primary leaflets usually have petioles and may bear secondary leaflets. This compound leaf structure allows sufficient light to reach the lower leaves, thereby improving the overall photosynthetic efficiency of the plant. Additionally, both the stems and leaves are covered with abundant trichomes and glandular secretory structures, which release aromatic compounds, reducing the threat of pests and diseases (Yang et al., 2011; Xie et al., 2020). Both wild and cultivated tomato accessions exhibit significant variation in leaf morphology, and cultivated accessions have a wealth of leaf development-related mutants, making tomato an excellent model system for studying compound leaf development. The leaf morphology-related mutants discovered and cloned to date can be broadly categorized into two types: (i) mutants that typically exhibit simplified leaves, reduced leaflet numbers, and smooth leaf margins, including *potato leaf* (*c*), *trifoliate* (*tf*), *Lanceolate* (*La*), *goblet* (*gob*), *entire* (*e*), and *pro*; and (ii) mutants that exhibit increased leaf complexity, that is, leaves with increased leaflet number and more pronounced serrations or lobes, including *Mouse ear* (*Me*), *Curl* (*Cu*), *bipinnata* (*bip*), and *Peteroselinum* (*Pts*).

C and *TF* encode R2R3-MYB transcription factors. *C* is highly homologous to *BL*, which regulates lateral branch formation. Mutations in the *C* gene result in a phenotype similar to that of potato leaves (Busch et al., 2011). Conversely, mutations in the *TF* gene not only affect the formation of leaflets in compound leaves but also inhibit the formation of axillary buds (Naz et al., 2013). The expression of the TCP transcription factor gene *LANCEOLATE* (*LA*) is regulated by *miR319*. Variations in the *miR319* binding site of *LA* result in lanceolate-shaped leaves in tomato (Ori et al., 2007; Burko et al., 2013). Mutations in the NAC transcription factor family gene *Globlet* result in abnormally smooth leaflet margins and fused leaflets, which affects the development of secondary leaflets. Mutations in *Globlet* also cause the cotyledons to fuse abnormally, assuming a distinctive goblet-like shape (Berger et al., 2009). The dominant mutants *Me* and *Cu* exhibit increased leaf complexity, because of abnormal expression of *TKN2*, a member of the *KNOTTED1-LIKE HOMEOBOX I* gene family (Chen et al., 1997; Parnis et al., 1997). The BELL family protein BIPINNATA (BIP) alters the subcellular localization of TKN2 through direct interaction, thereby inhibiting its activity. In the *bip* mutant, *TKN2* gene expression is upregulated, leading to increased leaf complexity (Kimura et al., 2008). Similarly, *Pts*, a dominant mutant with increased leaf complexity, encodes a novel KNOX protein, which increases leaf complexity by inhibiting the TKN2-BIP interaction and thereby upregulating *TKN2* gene expression (Kimura et al., 2008). *Lyrate* (*LYR*) and *Clausa* (*CLAU*) also regulate the development of compound leaves in tomato. *LYR*, which encodes a zinc-finger protein, functions by positively regulating auxin signaling and inhibiting *KNOX I* gene expression, while *CLAU*, encoding a MYB transcription factor, promotes compound leaf differentiation by affecting cytokinin signaling (David-Schwartz et al., 2009; Bar et al., 2016).

Leaf angle, defined as the angle between the leaf and main stem, directly determines ventilation, light penetration,

and space utilization efficiency of plants, which in turn affect plant photosynthetic efficiency and planting density, making it an important trait in tomato breeding. *qLA3.1* is a key regulatory QTL for leaf angle in tomato. It encodes tomato AUXIN RESPONSE FACTOR 11 (SlARF11), which is speculated to regulate the leaf angle by controlling cell elongation and activating auxin and BR signaling genes (Wang et al., 2024c). The erect morphology of leaves ensures more uniform light distribution within the canopy and enhances the photosynthetic efficiency of lower leaves. The erect leaf phenotype of *erectoid leaf* (*erl*) mutant is inherited in a semi-dominant manner. *TILLER ANGLE CONTROL1* (*TAC1*)*-like* is a strong candidate gene for *Erl* (González-Arcos et al., 2019). In tomato, leaf veins typically appear as either clear or dark. The mutation of a C2H2 zinc-finger transcription factor gene *Obscure vein* (*OBV*) results in a dark-vein phenotype (Lu et al., 2021).

Trichomes play a crucial role in helping plants respond to various biotic and abiotic stresses. In tomato, seven distinct types of trichomes have been identified. The regulation of trichomes has also been well understood. The HD-ZIP IV transcription factor Woolly (Wo) is crucial for trichome initiation and polarity regulation in tomato, promoting apical cell division and interacting with SlBRC2a to suppress basal cell division, while other genes such as *LEAFLESS*, *Hair* (*H*), *SPARSE HAIR* (*SH*), and *Hl-2* also play significant roles in regulating different aspects of trichome development and morphology (Yang et al., 2011; Xie et al., 2020; Li et al., 2021a; Wu et al., 2023b, 2024b).

Inflorescence architecture

Like stems, tomato inflorescences also follow a sympodial growth pattern. During inflorescence development, the primary inflorescence meristem (IM) not only initiates the formation of the floral meristem (FM), which gives rise to the first flower, but also produces a lateral sympodial inflorescence meristem (SIM) (Coen and Meyerowitz, 1991). Each SIM has a similar fate, beginning with its differentiation into the FM, followed by the development of the next flower and, simultaneously, the generation of a new SIM. This alternating process of differentiation and growth is repeated multiple times, ultimately leading to the formation of the characteristic zig-zag inflorescence (Coen and Meyerowitz, 1991). During the development of tomato inflorescences, the transition from IM to FM is regulated by a complex and precise genetic regulatory network. Any imbalance in this transition can affect inflorescence development, resulting in excessive branches, fewer flowers, and consequently altered inflorescence morphology.

The *compound inflorescence* (s), *anantha* (*an*), and *falsiflora* (*fa*) tomato mutants exhibit a significant increase in inflorescence branching, but each has distinct characteristics. In the *an* and *fa* mutants, the loss of normal flowering ability causes the lateral SIMs to remain continuously active, leading to the production of cauliflower-like inflorescences and vegetative-type inflorescences, respectively. Conversely, the *s* mutant can still flower normally but exhibits a slower IM to FM transition, taking approximately two to four cycles of lateral SIM formation to produce a flower, which ultimately results in compound inflorescences. Notably, the formation of compound inflorescences in most cultivated tomato is caused by mutations in the *S* gene (Lippman et al., 2008). The *S* gene, which encodes WUSCHEL-RELATED HOMEOBOX 9 (WOX9), is primarily expressed in the IM and controls the induction of the IM-to-FM transition. By contrast, *AN*, encoding the UNUSUAL FLORAL ORGANS (UFO) F-box protein, and *FA*, encoding the LEAFY transcription factor, are both expressed mainly in the FM and control the establishment and development of the FM (Molinero-Rosales et al., 1999; Lippman et al., 2008). Exploration of the genetic regulatory mechanisms underlying tomato inflorescence development led to the discovery of the *jointless* (*j*) mutant, which lacks the pedicel abscission zone (AZ). This phenotype is caused by a mutation in a MADS-box gene, which induces the inflorescence to revert back to vegetative growth after forming one to three flowers rather than continuing to differentiate and form more flowers (Mao et al., 2000; Szymkowiak and Irish, 2006). *J2* and *enhancer-of-jointless2* (*EJ2*), also encode MADS-box transcription factors. The *j2* mutant, like *j*, exhibits jointless pedicel, while the *ej2* mutants have larger sepals. Although neither *j2* nor *ej2* single mutants shows an obvious multi-branched inflorescence phenotype, the *j2 ej2* double mutant displays a pronounced multi-branched inflorescence, indicating that *J2* and *EJ2* redundantly regulate inflorescence branching (Soyk et al., 2017a). Evidence suggests that the $ej2^{w}$ mutant was selected during the early stages of tomato domestication, probably because of its larger sepals and because of the close linkage of the $ej2^{w}$ allele to the fruit weight QTL *fw3.2* (Soyk et al., 2017a). The MADS-box gene *SISTER OF TM3* (*STM3*) promotes inflorescence branching by directly activating the expression of *FUL1* (Wang et al., 2021b). *STM3* and *J2* function antagonistically to regulate inflorescence branching through common target genes (Wang et al., 2021b; Wang et al., 2023b). In addition, the AP2-like transcription factor SlTOE1 inhibits inflorescence branching by repressing the expression of *STM3*. Moreover, *SlTOE1* and *EJ2* regulate tomato inflorescence structure in an additive manner, and the *sltoe1 ej2* double mutant exhibits a more pronounced branching phenotype than the *sltoe1* and *j2* single mutants (Sun et al., 2023). The MADS-box gene *long inflorescence* (*Lin*) also plays an important role in the regulation of inflorescence structure. The *lin* mutant exhibits increased flower numbers and elongated internodes, which affect the overall morphology of the inflorescence (Soyk et al., 2017a). The *dof9* mutant is able to produce a multiflowered inflorescence. *SlDOF9* expression is directly regulated by SlARF5, highlighting the importance of the auxin signaling pathway in regulating inflorescence development (Hu et al., 2022). *bifurcate flower truss* (*bif*) mutant exhibits a mean of 4.1 branches per truss, accompanied by a 3.3-fold increase in flower number. This phenotype is reported to be caused by a leucine to stop codon mutation in the mitogen-activated

protein kinase-encoding gene SlMAPK1 (Silva Ferreira et al., 2018). Tomato inflorescence morphology is also influenced by environmental factors, such as high temperature, which can promote inflorescence branching. The *MIB2* gene, encoding a bHLH transcription factor homologous to Arabidopsis *SPATULA*, plays a key role in regulating inflorescence branching under high-temperature conditions (Sun et al., 2024).

Unlike the inflorescence branching mutants mentioned above, the early-flowering mutant *terminating flower* (*tmf*) exhibits a structurally distinct inflorescence, characterized by a single flower. The *TMF* gene encodes a protein that belongs to the ALOG (Arabidopsis LIGHT-SENSITIVE HYPOCOTYL 1, *Oryza* G1) protein family and is primarily expressed in the shoot apex. The core function of TMF is to maintain the plant in a vegetative growth state, preventing premature flowering initiation and ensuring that the plant has sufficient time for nutrient accumulation and development. In the *tmf* mutant, genes that should be specifically expressed in the FM, such as *AN* and *FA*, are prematurely activated in the SAM, leading to an early transition to reproductive growth and the loss of the ability to form subsequent lateral SIMs (MacAlister et al., 2012). Researchers discovered that the accumulation of hydrogen peroxide in the intercalary meristem induces phase separation of the TMF protein. This phase separation forms a transcriptional condensate that targets *AN* expression, precisely regulating the maturation and flowering of the SAM (Huang et al., 2021b). Similarly, *Uniflora* encodes a bHLH transcription factor, and its mutant line produces only a single flower due to the inability to control the transition between IM and FM (Dielen et al., 2004).

Flower development

Flower organ development

In tomato, floral organs are composed of four whorls: sepals, petals, stamens, and carpels (pistils). The ABCDE model of floral organ development provides a detailed explanation of how floral organ primordia develop into sepals, petals, stamens, and carpels according to a predetermined pattern (Coen and Meyerowitz, 1991; Colombo et al., 1995; Aceto and Gaudio, 2011). According to this model, the development of sepals is controlled by Class A and E genes, petals by Class A, B, and E genes, stamens by Class B, C, and E genes, and carpels by Class C and E genes, while ovule development is determined by Class C, D, and E genes. Most genes in this model encode MADS-box transcription factors. *MACROCALYX* (*MC*), which is homologous to the Arabidopsis Class A gene *AP1*, is responsible for the formation of leaf-like sepals when mutated (Vrebalov et al., 2002). The class B genes in tomato include *GLOBOSA* (*SlGLO*, also known as *TPIB*), *Tomato MADS box 6* (*TM6*), *Tomato APETALA3* (*TAP3*), and *Tomato PISTILLATA* (*TPI*, also known as *SlGLO2*) (Geuten and Irish, 2010). Mutations in *TAP3* result in stamenless phenotypes in tomatoes (Quinet et al., 2014). The class C gene *TOMATO AGAMOUS 1* (*TAG1*) plays an important role in the development of stamens and carpels. Class E genes include *Tomato MADS box 5* (*TM5*) and *Tomato AGAMOUS-LIKE 2* (*TAGL2*) (Pnueli et al., 1994; Busi et al., 2003). Other genes that affect floral organ formation in tomato include *TM4*, *TAGL1*, *TAGL11*, and *TAGL12* (Quinet et al., 2014).

Tomato anthers form a completely closed, barrel-like structure called the anther cone, which fully encloses the style, significantly increasing the fruit set rate. The anther cone is mainly formed by interlocking trichomes that tightly interlock adjacent anthers. In wild tomato species (such as *S. pennellii*), the interlocking trichomes are insufficient to completely close the anther cone. The evolution of the anther cone is closely related to the expression of HD-Zip IV transcription factor genes. HD-Zip IV transcription factors regulate the initiation of interlocking trichomes and the polar elongation of the style through a dosage mechanism (Wu et al., 2024c).

Male sterility

Tomato hybrid varieties outperform conventional varieties in disease resistance, vigor, yield, and uniformity, and thus dominate commercial tomato production. Tomato hybrid seed production relies mainly on manual emasculation (removal of anthers from the plant intended to be used as the female parent) and pollination, which are labor intensive and prone to producing false hybrids. The use of male-sterile lines for hybrid seed production simplifies the seed production process, reduces costs, improves seed purity, and prevents the loss of parent lines. An ideal tomato male-sterile line has the following characteristics: (i) complete male sterility with normal female fertility; (ii) exserted stigma (to avoid emasculation); and (iii) easy maintenance and restoration of male sterility. Male sterility in crops is generally classified into two types: cytoplasmic male sterility (CMS) and nuclear male sterility. Cytoplasmic male sterility has not been found in tomato in nature, but CMS materials have been developed through interspecific hybridization (with wild germplasm), protoplast fusion, and plant transformation (Melchers et al., 1992; Petrova et al., 1999; Sandhu et al., 2007). Of the more than 60 male-sterile mutants identified in nature to date, most are recessive nuclear male-sterile mutants, which exhibit pollen abortion, structural sterility, or functional sterility. Mutants such as *ms-10*, *ms-32*, and *ms-35* exhibit pollen abortion. Among these mutants, *ms-10* and *ms-35* are allelic, and the floral organs of these mutants are generally smaller than those of fertile plants, with yellow-green anthers containing no viable pollen and slightly exposed stigma. *Ms10* encodes a bHLH transcription factor homologous to *Arabidopsis* DYSFUNCTIONAL TAPETUM1 (DYT1), which regulates stamen meiosis and tapetum development (Jeong et al., 2014). As *Ms10* is closely linked to *Anthocyanin absent* (*Aa*), whose mutation causes green stems, the green-stem trait is often used to facilitate the selection of *ms10* plants. *Ms-32* also encodes a bHLH transcription factor that regulates pollen and tapetum development in tomato. A G-to-A mutation in the first exon of the *Ms-32* gene causes premature

termination of translation, leading to a truncated protein, which results in the inability to produce pollen (Liu et al., 2019). CYCLIN-DEPENDENT KINASE 8 (SlCDK8) is crucial for pollen development; its knockout significantly reduces pollen viability, impacting fruit yield and seed number. SlCDK8 interacts with and phosphorylates SlTCP15, enhancing its stability and promoting the expression of *SlDYT1* and *SlMYB103* to regulate pollen development. Proper pollen development is essential for optimal fruit yield, making the SlCDK8–SlTCP15 module a key strategy for ensuring reproductive success and improving tomato breeding (Xu et al., 2024).

Mutants such as *sl*, *sl-2*, *7B-1*, *ms30*, *ms-33*, and *ms-15* exhibit structural sterility, characterized by absent or malformed stamens. *SL* encodes the MADS-box transcription factor TAP3, and mutations in *SL* result in flowers without stamens (Quinet et al., 2014). The *sl-2* mutant has nearly normal petals but deformed stamens and exposed ovules. The *ms-30*, *ms-33*, and *7B-1* mutants, as well as *sl-2*, are allelic and caused by mutations in the B-class MADS-box transcription factor gene *SlGLO2*. The phenotype of *ms-30* is the result of an amino acid substitution caused by a non-synonymous single-nucleotide polymorphism (SNP), while that of *ms-33* is caused by a defective protein that lacks 46 amino acids due to altered gene splicing patterns. The *7B-1* and *sl-2* mutants carry a 4.8-kb transposon insertion (Pucci et al., 2017; Wei et al., 2024). Notably, *7B-1* also exhibits photoperiod-sensitive male sterility, characterized by complete sterility under long-day conditions but normal fertility under short-day conditions (Sawhney, 2004). The *ms-15*^{26} mutant shows abnormal stamen development, often resulting in carpel-like structures. This phenotype of the *ms-15*^{26} mutant is due to the deletion of a 12.7-kb fragment, encompassing the promoter and first four exons of *TM6* (Cao et al., 2019; Fonseca et al., 2024). Given that the *ms-15*^{26} mutant exhibits an exserted stigma phenotype, it is more suitable for breeding applications. As *ms15* is closely linked to *anthocyanin without* (*aw*), which causes green stems, the green-stem trait is often used to assist in the selection of *ms15* plants.

Plants that exhibit functional male sterility have normal pollen grains but are unable to self-pollinate, because of issues such as anther non-dehiscence or abnormal style length. Examples of functional male-sterile mutants include *positional sterility* (*ps*), *ps-2*, *Style2.1*, and *Stigma Exertion 3.1* (*SE3.1*). *ps* was the first functional-sterile mutant reported in tomato; however, the gene harboring the causal mutation has yet to be cloned. *Ps-2* encodes polygalacturonase, and its mutant has indehiscent anthers, thus preventing pollen release (Gorguet et al., 2009). As the *ps-2* mutant can be propagated by assisted self-pollination, it has been applied, to some extent, in tomato production. *Style2.1* and *Se3.1* primarily regulate style length in tomato. Both *Style2.1*, encoding a bHLH transcription factor, and *Se3.1*, encoding a C2H2-type zinc-finger transcription factor, are involved in the transition from exserted stigma (in wild species) to inserted stigma (in cultivated lines) during tomato domestication and improvement (Chen et al., 2007; Shang et al., 2021).

Most of the aforementioned male-sterile mutants exhibit recessively inherited nuclear male sterility. However, not only is the introgression of nuclear male sterility time consuming, but finding effective maintainer lines is also difficult, and both these factors limit the application of nuclear male-sterile lines in tomato hybrid seed production. The traditional method of maintaining recessive nuclear male sterility is to cross heterozygous fertile plants with homozygous male-sterile plants, resulting in a progeny that segregates into 50% heterozygous fertile plants and 50% homozygous sterile plants. However, this process is labor intensive, time consuming, and resource wasting. To overcome these limitations, we previously proposed a strategy for rapidly generating corresponding male-sterile and maintainer lines in the genetic background of elite inbred tomato lines using biotechnology tools and effectively applying them to hybrid seed production. First, the CRISPR/Cas9 gene editing technology was used to specifically knock out the *SlSTR1* gene in the tomato elite inbred line TB0993, creating a male-sterile line within 1 year. Then, the functional *SlSTR1* gene and the *SlANT1* gene, which controls anthocyanin biosynthesis, were fused together and reintroduced into the male-sterile line, thereby obtaining a purple-colored maintainer line with restored fertility. When the male-sterile line is used as the female parent and the heterozygous maintainer line as the male parent, the F_1 progeny segregates into transgenic maintainer lines (purple seedlings) and non-transgenic male-sterile lines (green seedlings) in 1:1 ratio. The non-transgenic male-sterile plants can be easily selected based on seedling color and used for hybrid seed production. This male-sterile seed production system has the following advantages: (i) the male-sterile line is created using a recessive nuclear mutation, theoretically allowing any male-fertile inbred line to serve as a restorer line, thus eliminating restrictions on paternal parent selection in hybrid combinations; (ii) the male-sterile line is created using the CRISPR/Cas9 gene editing technology, enabling rapid and efficient reproduction in multiple inbred lines, saving time and effort and avoiding linkage drag; (iii) crossing the purple-seedling maintainer line with the male-sterile line can produce large quantities of sterile lines, and sterile plants can be accurately identified, based on seedling color, for hybrid seed production; (iv) although the purple-seedling maintainer line is created using transgenic methods, the male-sterile plants used for hybrid seed production contains no transgenic components; and (v) this strategy can be easily replicated and applied to other horticultural crops, such as vegetable and flower crops, and thus has broad application prospects (Du et al., 2020). Similarly, we used the CRISPR/Cas9 technology to simultaneously knock out the closely linked male fertility gene (*Ms15*) and anthocyanin biosynthesis gene (*DFR*), successfully creating a male-sterile line with green stem (green hypocotyl male sterile, GHMS) (Zhou et al., 2023). This green-stem male-sterile line can maintain its sterility in different genetic backgrounds and under different

environmental conditions. It can be selected at the seedling stage, based on its green stem color, thus demonstrating significant application potential.

Parthenocarpy

To ensure stable tomato fruit yield under unfavorable environmental conditions, producers commonly treat the flowers with 2,4-D and GA to induce parthenocarpy. Parthenocarpy refers to the formation of seedless fruits without fertilization. Although parthenocarpy can be artificially induced, plants exhibiting genetically stable parthenocarpic traits are also found in nature. Natural parthenocarpy can be classified into two types: facultative parthenocarpy, which is influenced by both genetic factors and environmental conditions, and obligate parthenocarpy, which is controlled predominantly by genetic factors. In contrast with obligate parthenocarpic genotypes, which exhibit parthenocarpy under all environmental conditions, facultative parthenocarpic genotypes can set fruit without fertilization when conditions are adverse for pollination and fertilization but can produce seeds through hybridization or self-pollination under favorable environmental conditions, making them highly attractive to tomato breeders. To date, nine genetic loci regulating parthenocarpy have been discovered in tomato germplasm: *Pat*, *Pat-2*, *Pat-k*, *Pat3*, *Pat4*, *Pat4.1*, *Pat4.2*, *Pat5.1*, and *Pat9.1*. "Soressi" was the first parthenocarpic tomato genotype to be discovered. Parthenocarpy in "Soressi" is caused by a recessive mutation in the *Pat* gene. Although *pat* mutants exhibit a high fruit set rate, they produce smaller fruits and display typical female sterility characteristics, with abnormal development of stamens and ovules, which renders them unable to produce seeds and thus limits their practical application in tomato production. The *Pat* gene is located on chromosome 3 and encodes the HD-Zip III transcription factor SlHB15A (Beraldi et al., 2004; Clepet et al., 2021). The facultative parthenocarpic phenotype of "Sevenianin" is caused by a 1,034-bp deletion in the *Pat-2* (*Solyc04g080490*) gene, which encodes the zinc-finger transcription factor SlHD31. Genotypes containing the *pat-2* locus exhibit excellent fruit set, with no hollow fruits, under both high-temperature and low-temperature conditions, thus making *pat-2* the preferred locus for applications in parthenocarpic tomato breeding (Nunome, 2016).

The facultative parthenocarpic phenotype of *pat-k* is caused by the loss-of-function mutation of the *AGL6* gene caused by the insertion of a 4,866-bp fragment, containing retrotransposon CopiaSL_37, into its first intron (Klap et al., 2017; Gupta et al., 2021). The *tagl6* mutant shows high and stable parthenocarpic fruit set rates under both normal and stress conditions, highlighting the significant application potential of TAGL6. The parthenocarpic trait of "RP75/79" is thought to be controlled by *pat-3* and *pat-4* genes (Gorguet et al., 2008), which also have considerable breeding potential. The parthenocarpic lines "IVT-1" and "IL5-1" were developed by the hybridization of *S. habrochaites* with cultivated tomato lines, followed by successive backcrosses. "IVT-1" contains two parthenocarpy-related QTLs, *pat4.1* and *pat5.1*, while "IL5-1" contains another two QTLs, *pat4.2* and *pat9.1*. Among these, *pat4.1* and *pat4.2* appear to be allelic, with their candidate gene being *ARF8*, although further verification is needed (Gorguet et al., 2008).

Auxin and GA play particularly crucial roles in parthenocarpy regulation. *SlIAA9* and *SlDELLA* encode transcriptional repressors of auxin and GA signaling, respectively, and their corresponding loss-of-function mutants, *entire* and *procera*, respectively, both exhibit parthenocarpic phenotypes (Zhang et al., 2007; Carrera et al., 2012). ARF transcription factors, have also been reported to participate in the regulation of parthenocarpy (Hu et al., 2018, 2023; Israeli et al., 2023; Hua et al., 2024). Class A ARF transcription factors, represented by SlARF7, interact with SlIAA9 and SlDELLA to mediate the synergistic regulation of fruit development by auxin and GA signaling pathways (Hu et al., 2018). Additionally, mutations in the *Pad-1* gene, which encodes an aminotransferase that regulates auxin homeostasis by catalyzing the conversion of indole-3-pyruvate (IPyA) to tryptophan (Trp), significantly increase auxin concentrations within the ovary, inducing parthenocarpy (Matsuo et al., 2020).

Fruit traits

Tomato serves as an ideal model plant for studying fruit development. Tomato fruits are berries, primarily composed of four parts: pericarp, septa, placenta, and ovules. The ovules are attached to the placenta, and the septa divide the tomato fruit into varying numbers of locules. The development of a tomato fruit from initiation to full maturity takes 5–8 weeks and can be broadly divided into four stages: (i) fertilization and fruit set; (ii) cell division phase, during which the number of cells in the fruit increases rapidly, but the fruit volume grows slowly; (iii) cell expansion phase, characterized by rapid cell volume expansion, during which the tomato fruit grows to its final size; and (iv) fruit-ripening stage, in which significant amounts of ethylene are synthesized, and the fruit experiences a respiratory peak. The fruit-ripening stage involves a series of chemical, structural, and metabolic changes, which led to the formation of final fruit quality traits such as flavor, color, and texture. The processes of maturation and ripening greatly affect fruit quality, which determines the commercial value of tomato fruits. Therefore, fruit-related traits have been subject to stringent selection during domestication and improvement.

Fruit size and shape

Fruit weight (FW) is an important trait in tomato breeding and one that changed significantly during domestication. *Solanum pimpinellifolium* fruits weigh only a few grams, whereas modern fresh-market tomato varieties can produce individual fruits weighing up to 1 kg. Tomato FW is mainly determined by the combined effects of cell division and cell expansion at the early stages of fruit development as well as by the number of locules. Fruit weight is a typical quantitative trait controlled by multiple genes. At present, there are

approximately 10 known major QTLs controlling tomato FW. *fw2.2* was the first FW QTL cloned in tomato and also the first QTL cloned in crops. The *Fw2.2* gene encodes a membrane-localized protein that inhibits cell division and can explain 30% of the difference in FW between wild and cultivated tomato species. The expression level of *fw2.2* is lower in cultivated tomato lines, which enhances the pace of cell division and the size of the placenta and columella (Frary et al., 2000); however, the specific mechanism by which Fw2.2 regulates cell division remains unclear. The *Fw3.2* gene encodes a cytochrome P450 protein SlKLUH belonging to the CYP78A subfamily, which increases fruit size by increasing cell number in the pericarp and septum tissue. A recent study showed that a 50-kb tandem repeat in the genomic region containing the *Fw3.2* gene is a determining factor for increased FW (Alonge et al., 2020). Unlike *fw2.2* and *fw3.2*, the *fw11.3* locus increases FW mainly by increasing cell size in the pericarp. This effect is mainly caused by the deletion of 194 amino acids in the Fw11.3 protein that resulted from a dominant mutation at the 3' end of the *Solyc11g071940* gene in cultivated tomato (Mu et al., 2017).

Locule number is also an important factor affecting fruit size. Wild tomato species have only two locules per fruit, whereas beefsteak tomato varieties can produce fruits weighing up to 1 kg and containing dozens of locules. Locule number is a typical quantitative trait controlled by multiple QTLs (Zielinski, 1948; Lippman and Tanksley, 2001; Barrero and Tanksley, 2004). To date, three QTLs controlling locule number have been cloned, including *locule number* (*lc*), *fasciated* (*fas*), and *excessive number of floral organs* (*eno*). All these three genes regulate locule number by affecting the size of FMs through the CLAVATA-WUSCHEL (CLV-WUS) signaling pathway (Muños et al., 2011; Xu et al., 2015; Yuste-Lisbona et al., 2020). *lc*, located on chromosome 2, is associated with increased locule number and coincides with two SNPs located downstream of the *SlWUS* gene. It is speculated that the *lc* phenotype is related to a slight change in the expression level of *SlWUS* (Muños et al., 2011). The *fas* mutation is attributed to the inversion of a 294-kb chromosomal segment on chromosome 11, which decreases the expression of *SlCLV3* (Xu et al., 2015). As the *fas* mutation often causes irregular fruit shape, it is not commonly used in traditional commercial varieties (Chu et al., 2019). Although both *lc* and *fas* increase fruit size by increasing the locule number, their effects differ. In cultivated tomatoes, *lc* can elevate the number of locules to three to four, while *fas* can increase the number to six, and the combination of these two loci can result in tomatoes with more than eight locules and twice the FW of wild-type fruits (Muños et al., 2011). However, in *S. pimpinellifolium* (wild) tomatoes, the combination of *lc* and *fas* only increases the number of locules to four (van der Knaap et al., 2014), indicating that other loci affect locule number in cultivated tomato. *Eno*, another determinant of the locule number, encodes an AP2/ERF transcription factor that influences the locule number by regulating the expression of *SlWUS*. An 85-bp deletion in the *Eno* promoter is significantly associated with an increase in the number of locules in natural populations (Yuste-Lisbona et al., 2020). *Eno* may correspond to a previously identified QTL (*lcn3.1*) that controls locule number. Furthermore, two additional proteins within the CLV-WUS signaling pathway control the number of locules in tomato fruits: fasciated and branched (Fab) and Fasciated inflorescence (Fin). *Fab* encodes SlCLV1, the receptor kinase of SlCLV3, whereas *Fin* encodes an arabinosyl transferase that can post-translationally modify SlCLV3 (Xu et al., 2015).

In addition to making the fruit larger, domestication and improvement have greatly increased the diversity of fruit shapes. Wild tomato fruits are generally round, while modern cultivated tomatoes exhibit a variety of shapes, including obovoid, ellipsoid, rectangular, heart, long, round, oxheart, and flat. Fruit shape is influenced by locule number, cell division, and cell expansion, and the aforementioned mutations generally increase the number of locules, leading to flatter fruits. The genes *OVATE*, *SUN*, *FS8.1*, and *GLOBE* account for most of the variation in fruit shape among cultivated tomato varieties. *OVATE* is a negative regulator of fruit elongation, and mutation in this gene leads to pear-shaped fruits (Liu et al., 2002). Interestingly, not all *ovate* mutants produce pear-shaped fruits, suggesting that *OVATE* interacts with other loci to regulate the formation of pear-shaped fruits (Wu et al., 2018). *SUN*, which encodes a calmodulin-binding protein of the IQD family, is a positive regulator of fruit elongation, and its effect on promoting fruit elongation is stronger than that of OVATE. A 24.7-kb segmental duplication at the *SUN* locus mediated by the retrotransposon Rider leads to an increase in the expression of the *IQD12* gene (Xiao et al., 2008). Additionally, another member of the IQD/SUN family of calmodulin-binding proteins, SlIQD21, can specifically interact with the microtubule-binding protein SlMAP70 to coordinate the polar elongation of tomato fruit, thereby affecting fruit shape (Bao et al., 2023). The *Fs8.1* gene confers a rectangular shape commonly found in processing tomatoes. *Fs8.1* encodes an atypical Trihelix family transcription factor, which regulates fruit shape by activating the expression of the cell cycle inhibitor gene *KIP-RELATED PROTEIN 2* (*SlKRP2*). The *fs8.1* mutation, caused by a SNP (A857T), leads to the premature termination of protein translation, thereby weakening its inhibitory effect on the proliferation of ovule wall cells, resulting in an increase in cell number and the production of square-shaped fruits (Zhu et al., 2023a). Recently, the *GLOBE* gene, which controls the (round/flat-round) fruit shape, was cloned. *GLOBE* encodes a BR hydroxylase. A 1-bp insertion in the last exon of the *GLOBE* gene causes a frameshift mutation in the encoded protein, leading to a change in tomato fruit shape from flat-round to round (Sierra-Orozco et al., 2021). Additionally, a knockout mutation in *SlMYB3R3* increases the number of cells and elongates the fruit, resulting in a certain proportion of peanut-shaped fruits. These traits of peanut-shaped tomatoes are similar to the traits of tomatoes of other shapes, such as pear-shaped fruits, which are produced by over-

expanded ovaries while being compressed by the surrounding floral organs (Zheng et al., 2022).

A protruded tip gives cherry tomatoes their characteristic appearance and therefore is an important trait. By contrast, in large-fruited cultivated tomatoes, the presence of a tip can negatively affect their appearance. Studies have demonstrated that the presence of a pointed tip is a recessive trait controlled by the *POINTED TIP* (*PT*) gene, which encodes a C2H2-type zinc-finger protein. PT inhibits the formation of a pointed tip by suppressing the expression of *FUL2*, which influences auxin transport. A loss-of-function mutation in *PT* results in the formation of fruits with a pointed tip. During domestication and improvement, genotypes with a loss-of-function *PT* allele were selected, which led to an increased prevalence of fruits with a blossom-end shape in cultivated varieties (Song et al., 2022).

Fruit ripening

The process of tomato fruit ripening is controlled by a series of complex and orderly physiological and biochemical changes that occur during the later stages of fruit development as well as by highly coordinated genetic regulatory mechanisms. During the ripening process, tomato fruit undergoes the accumulation of carotenoids, synthesis of flavor-inducing compounds such as sugars and organic acids, degradation of bitter compounds like tomatine, and a transition in fruit texture from firm to soft. These transformations directly affect the appearance, color, taste, flavor, firmness, and shelf life of the fruit, all of which determine its commercial value. Therefore, the above-mentioned fruit traits are the focus of research and improvement for breeders. Over the past 30 years, numerous genes related to fruit ripening have been identified and cloned in tomato, and extensive research has been conducted to elucidate the genetic regulatory mechanisms of tomato fruit ripening (Klee and Giovannoni, 2011). The research findings have greatly enriched our understanding of the mechanisms of tomato fruit ripening and have promoted the genetic improvement of ripening-related traits.

As a typical climacteric fruit, the ripening process of tomato is strictly dependent on the synthesis and signaling of ethylene. Studies have shown that fruit-ripening mutants, including *Never ripe*, *Green ripe* (*Gr*), and *yellow-fruited tomato 1* (*yft1*), exhibit blocked ethylene signaling, which prevents normal maturation (Gao et al., 2016). The *NR* gene encodes the ethylene receptor LeETR3 (Wilkinson et al., 1995); *GR* encodes a homolog of the Arabidopsis RTE1 protein, which interacts with the ethylene receptor AtETR1 and regulates its activity through post-translational modification (Barry and Giovannoni, 2006); *YFT1* encodes EIN2, a key regulatory factor in the ethylene signaling pathway (Gao et al., 2016). Other genes involved in ethylene synthesis and signaling, such as *ACS2*, *ACS4*, *ACO*, and *EIL1*, also play significant roles in the ripening process of tomato fruit (Klee and Giovannoni, 2011). Additionally, TOMATO AGAMOUS-LIKE1 (TAGL1), FRUITFULL homologs FUL1 and FUL2, the HD-Zip homeobox protein LeHB-1, APETALA2a (AP2a), and a series of ERF transcription factors regulate the ripening process of tomato fruit through the ethylene signaling pathway (Lin et al., 2008; Vrebalov et al., 2009; Chung et al., 2010; Karlova et al., 2011; Bemer et al., 2012; Deng et al., 2022; Pei et al., 2024; Su et al., 2023).

The fruit-ripening mutants *ripening inhibitor* (*rin*), *non-ripening* (*nor*), and *Colorless non-ripening* (*Cnr*) exhibit similar phenotypes, including improper ripening, impaired ethylene synthesis, and insensitivity to exogenously applied ethylene, indicating that the corresponding genes probably function upstream of ethylene, regulating fruit maturation through ethylene-dependent or ethylene-independent signaling pathways. *RIN* encodes a MADS-box transcription factor. The phenotype of the *rin* mutant arises from a partial deletion of the *RIN* coding sequence, resulting in the fusion of the *RIN* gene with the downstream gene *MC*. The resulting RIN-MC fusion protein inhibits the normal ripening process of tomato fruit (Li et al., 2018c). *nor* is a spontaneous mutant resulting from a dominant negative gain-of-function mutation in a *NAC* gene. This mutation disrupts the transcriptional activation domain of the NAC transcription factor, preventing it from activating the expression of ripening-related genes (Gao et al., 2020). The phenotype of the *Cnr* mutant is caused by an epigenetic modification, specifically increased DNA methylation in the promoter region of an *SBP* transcription factor gene (Vrebalov et al., 2002; Manning et al., 2006; Klee and Giovannoni, 2011). In addition to their inability to synthesize ethylene, the aforementioned mutants also show significant abnormalities in fruit softening, carotenoid accumulation, and flavor compound synthesis. ChIP experiments showed that RIN can directly regulate the expression of a series of ripening-related genes, including genes involved in the biosynthesis of ethylene (*ACS2*, *ACS4*, and *ACO1*), carotenoids (*PSY1* and *PDS*), and flavor compounds (*TomLoxC*, *ADH2*, and *HPL*) as well as genes related to cell wall metabolism (*PG2a* and *EXP1*) and genes encoding ripening-related transcription factors (Martel et al., 2011; Qin et al., 2012). It is worth noting that *rin* and *nor* mutants are widely used by breeders to extend the shelf life of tomatoes. Recent studies have shown that CRISPR/Cas9-mediated knockout mutants of the *Rin* gene in tomato could initiate the fruit-ripening process and accumulate carotenoids, suggesting that RIN itself is not essential for the initiation of tomato fruit ripening (Ito et al., 2017; Li et al., 2020b). Moreover, CRISPR/Cas9-mediated *nor* knockout mutants exhibited only partial unripe phenotypes (Gao et al., 2020), unlike the spontaneous *nor* mutant. Additionally, *cnr* knockout mutants generated by CRISPR/Cas9 showed only a 2–3-d delay in fruit ripening, which is significantly different from the fruit ripening phenotypes of the naturally occurring *cnr* mutants and those of *CNR*-silenced plants (Gao et al., 2020). Therefore, the roles of RIN, NOR, and CNR in tomato fruit ripening need to be re-evaluated.

Tomato fruit ripening is also regulated by several other factors, such as other endogenous hormones (ABA) as well

as epigenetic factors (DNA methylation, histone modifications, and non-coding RNAs). Aberrant expression of genes encoding the ABA receptor (*SlRCAR*), ABA synthase (9-*cis*-epoxycarotenoid dioxygenase, *SlNCED1*), and ABA metabolic enzyme (ABA uridine diphosphate glucosyltransferase, *SlCYP707A2* and *SlUGT75C1*) can impact the ripening of tomato fruit (Ji et al., 2014; Sun et al., 2017; Zou et al., 2022). In tomato, whole-genome DNA methylation levels decrease significantly during fruit ripening (Zhong et al., 2013). The tomato *DEMETER-like DNA demethylases 2* (*SlDML2*) gene encodes a DNA demethylase, which regulates the expression of genes related to carotenoid biosynthesis, ethylene biosynthesis, and ethylene signal transduction. The silencing or knocking out of the *SlDML2* gene significantly inhibits the ripening process of tomato fruit (Liu et al., 2015; Lang et al., 2017). Similarly, silencing or knocking out of the histone deacetylase gene *SlHDT3* and long non-coding RNAs (lncRNAs) lncRNA1459 and lncRNA1840 also delays the ripening of tomato fruit and suppresses the accumulation of carotenoids (Zhu et al., 2015; Guo et al., 2017a). By contrast, silencing of histone deacetylase genes *SlHDA1* and *SlHDA3* accelerates fruit ripening (Guo et al., 2017b; Guo et al., 2018). N^6-Methyladenosine (m^6A) is an mRNA modification in eukaryotes, which plays an important role in regulating the stability, splicing, translation efficiency, and nuclear export of mRNAs. In the ripening-defective *Cnr* mutant, the RNA demethylase gene *SlALKBH2* shows reduced expression in the fruit, leading to an overall increase in the m^6A methylation level of genomic transcripts and a reduction in the mRNA abundance of the DNA demethylase gene *SlDML2*, thereby causing a delay in fruit ripening (Zhou et al., 2019).

Fruit color

Color change is one of the key indicators of fruit ripening and an important aspect of fruit appearance/quality. In tomato, ripening fruits display a wide range of colors, including red, pink, yellow, orange, green, white, and purple, over their entire surface or in striped patterns. Tomato fruit color is determined by the type and levels of chlorophylls and carotenoids in the flesh as well as by the flavonoid content of the peel. Among these pigments, carotenoids are the most crucial for tomato fruit coloration. Lycopene and β-carotene are the primary carotenoids in ripe tomatoes, with lycopene accounting for approximately 90% of the total carotenoid content, and β-carotene accounting for approximately 5%–10%. As the tomato fruit matures, chloroplasts are converted into chromoplasts, which leads to the degradation of chlorophyll and the accumulation of carotenoids. This process causes the tomato flesh to change from green to red or other colors.

To date, several mutants related to flesh color variation have been identified in tomato, and the genes responsible for the mutant phenotypes have been successfully cloned (Galpaz et al., 2006). Nine of these mutants carry mutations in genes encoding carotenoid biosynthetic enzymes. The *yellow flesh* (*r*) mutant, which bears yellow-fleshed fruit, harbors a mutation in the phytoene synthase gene *PSY1* (Fray and Grierson, 1993). Fruits of the *tangerine* (*t*) and *carotenoid-deficient* (*fcd1*) mutants exhibit orange flesh, because if mutations in the carotenoid isomerase gene *CRTISO* and the isopentenyl pyrophosphate isomerase gene *IDI1*, respectively (Fray and Grierson, 1993; Pankratov et al., 2016). Recent studies identified two additional mutants carrying allelic mutations in the *IDI1* gene, *apricot* and *oft3*, which not only affect flesh color but also reduce the carotenoid content of floral organs, resulting in pale-yellow petals (Shin et al., 2019; Zhou et al., 2022a). Dominant mutations in two genes, *Beta* and *Delta*, derived from wild tomato species, lead to orange-fleshed fruits. *Beta* encodes lycopene β-cyclase, while *Delta* encodes lycopene ε-cyclase. *Old gold* is an allele of *Beta*, and the *old gold* loss-of-function mutant cannot synthesize β-carotene, resulting in deep-red fruit flesh (Ronen et al., 1999, 2000). Additionally, the knockout mutation of *Beta* not only increases the lycopene content of tomato fruit, but also significantly enhances its cold tolerance and consequently cold-storage capacity (Arruabarrena et al., 2023). The *RZ1AL* gene, which encodes a glycine-rich RNA-binding protein with a zinc-finger domain, regulates carotenoid biosynthesis and influences tomato fruit color. Mutants of *RZ1AL* exhibit lighter fruit color, significantly reduced lycopene content, and incomplete ripening (Li et al., 2022b).

The diversity of tomato fruit color is not only affected by the accumulation of carotenoids but also significantly influenced by chloroplast development and chlorophyll metabolism. Plastids (including chloroplasts and chromoplasts) are the primary sites of chlorophyll and carotenoid synthesis. During tomato fruit development, the size, number, and state of plastids play a critical role in determining fruit color. Notably, the high-pigment mutants *high pigment 1* (*hp1*), *high pigment 2* (*hp2*), and *high pigment 3* (*hp3*) exhibit a significantly increased carotenoid content, which is attributed to an increase in plastid number or size. *HP1* and *HP2* encode UV-damaged DNA-binding protein 1 (DDB1) and DE-ETIOLATED1 (DET1), respectively, both of which act as negative regulators of light signaling, influencing plastid development (Mustilli et al., 1999; Liu et al., 2004). *HP3* encodes zeaxanthin epoxidase (ZEP) (Galpaz et al., 2008), a key enzyme involved in carotenoid and ABA biosynthesis. During the early stages of fruit development, chloroplasts accumulate in the fruit shoulder, resulting in green shoulders. The green shoulders allow the fruit to produce more photosynthetic products, which are ultimately converted into flavor compounds. Therefore, fruits with pronounced green shoulders have a rich flavor, while those without green shoulders tend to have a bland taste. However, fruits with green shoulders often exhibit uneven coloration, which is considered an undesirable trait in terms of appearance. For many years, breeders have pursued uniform fruit coloration, leading to the loss of green shoulders and a subsequent decline in flavor quality. The loss of green shoulders represents a trade-off made by breeders, sacrificing flavor for

improved appearance. The presence or absence of green shoulders is mainly controlled by the *Uniform ripening* (*U*) locus, which encodes the MYB transcription factor Golden 2-like 2 (GLK2). The gradient expression pattern of *GLK2* in the fruit ensures that the shoulder region exhibits dark green coloration. The loss of function of GLK2 in the *u* mutant leads to uniformly pale-green fruit (without dark green shoulders), impaired chloroplast development, reduced pigment and sugar accumulation in the ripe fruit, and significantly diminished flavor (Powell et al., 2012). Similar to *u*, the *uniform gray-green* (*ug*) mutant also lacks green shoulders in unripe fruit. *UG* encodes a KNOX transcription factor TKN4, which regulates the gradient distribution of chlorophyll in the tomato fruit by acting upstream of *GLK2* and *ARABIDOPSIS PSEUDO RESPONSE REGULATOR 2-LIKE* (*SlAPRR2-LIKE*) (Pan et al., 2013; Nadakuduti et al., 2014). Additionally, *Curl* (*Cu*), a gain-of-function mutant of another member of the *KNOX* gene family (*SlTKN2*) produces deep-green fruits with increased chloroplast number and size and elevated chlorophyll content (Nadakuduti et al., 2014). BEL4 and BEL11 also participate in the regulation of chloroplast development and pigment accumulation in the tomato fruit (Meng et al., 2018; Yan et al., 2020). *Lutescent1* and *lutescent2* are tomato mutants with a white-fruit phenotype caused by defective chloroplast development, leading to impaired chlorophyll synthesis or stability (Barry et al., 2012; Liu et al., 2021a). The white-fruit phenotype of *lutescent1* is determined by a mutation in the *SlRCM1* gene, which encodes a chloroplast-targeted metallopeptidase that is highly homologous to Arabidopsis BCM1 and soybean G protein (Liu et al., 2021a). *Lutescent2* encodes a chloroplast-localized zinc metalloproteinase (Barry et al., 2012).

Fruits of the *green flesh* mutant, which carries a mutation in the *STAY GREEN* gene, exhibit incomplete degradation of chlorophyll during ripening (Barry et al., 2008). Consequently, the *green flesh* fruits contain both chlorophyll and lycopene, which leads to a color variation from rust-red to brown. Additionally, changes in the methylation status of the *TAGL1* gene may cause tomato fruits to display green stripes on the fruit peel. Researchers have shown that SNPs in the second intron of the *TAGL1* gene affect its methylation status, which in turn influences the expression of genes related to chlorophyll synthesis and plastid development in the tomato pericarp, ultimately resulting in the formation of green stripes (Liu et al., 2020a).

Tomato fruit color is influenced not only by pigments in the flesh but also by the accumulation of flavonoid compounds in the fruit peel. In red tomatoes, the outer skin appears yellow, because of the accumulation of compounds such as naringenin chalcone. By contrast, pink tomatoes, popular in the Asian market, lack the ability to accumulate these compounds in the fruit peel (colorless), resulting in a pink appearance of the entire fruit. The *Colorless fruit epidermis* (*Y*) gene, encodes the MYB transcription factor SlMYB12, which determines the accumulation of compounds in the fruit peel. Pink tomatoes have a 603-bp deletion in the *SlMYB12* promoter region, leading to reduced gene expression and the absence of naringenin chalcone in the peel (Adato et al., 2009; Ballester et al., 2010; Lin et al., 2014). By knocking out the *SlMYB12* gene, researchers have successfully converted high-quality red tomato varieties into pink tomato varieties (Deng et al., 2018; Yang et al., 2019). Recently, a strategy was proposed for rapidly and simultaneously creating tomato genotypes with seven different fruit colors from red tomato varieties using multiplex gene editing technology. Genes controlling pigment synthesis or metabolism, including the lycopene biosynthesis gene *PSY1*, flavonoid biosynthesis gene *MYB12*, and chlorophyll degradation gene *SGR1*, were knocked out, resulting in a homozygous triple mutant (*psy1 myb12 sgr1*). Because the triple mutant lacks the ability to synthesize lycopene and naringenin chalcone and properly degrade chlorophyll during fruit ripening, its fruits appear green. The triple mutant was backcrossed with a red tomato line, and the resulting progeny was self-pollinated. Different genotypes were selected from the selfed progeny, and seven genotypes, each with a different fruit color, were obtained: *psy1*, *myb12*, and *sgr1* single mutants, with yellow, pink, and brown fruits, respectively; *psy1 myb12*, *myb12 sgr1*, and *psy1 sgr1* double mutants, with light-yellow, pink-brown, and yellow-green fruits, respectively; and *psy1 myb12 sgr1* triple mutant, with light green fruits (Yang et al., 2023).

Anthocyanins are water-soluble flavonoids that, along with chlorophylls and carotenoids, contribute to the diverse colors of plants. Most cultivated tomato varieties do not accumulate anthocyanins in their fruits, while some wild tomato species can accumulate anthocyanins in their fruit peel. This difference between cultivated and wild tomatoes is associated with the presence or absence of a mutation in the *Anthocyanin fruit* (*Aft*) gene. *Aft*, encoding the R2R3-MYB protein SlAN2-like, acts as a master regulator of anthocyanin synthesis in fruits. In cultivated tomato varieties, the *Aft* gene is transcriptionally abnormal and lacks the ability to activate anthocyanin synthesis, because of a mutation in the 5′ splice site of the second exon. *atroviolaceum* (*atv*) encodes the R3-MYB protein *SlMYBATV*, a negative regulator of anthocyanin biosynthesis. The *Aft* and *atv* genes act synergistically to regulate anthocyanin biosynthesis, and the *Aft atv* double mutant shows significantly higher anthocyanin content in the fruit peel compared with the *Aft* single mutant (Sun et al., 2020). In addition to *Aft* and *atv*, the bHLH transcription factor gene *SlAN1* is also a crucial regulator of anthocyanin synthesis. The expression of *SlAN1* is controlled by the *Aft*-encoded protein SlAN2-like, and SlAN2-like forms a complex with SlAN1 to activate the expression of anthocyanin biosynthesis genes (Qiu et al., 2016; Sun et al., 2020). Purple tomatoes with high levels of anthocyanins in both the peel and flesh tissues were first produced through the overexpression of *Ros* (encoding a R2R3-MYB transcription factor) and *Del* (encoding a bHLH transcription factor) from *Antirrhinum majus* using the fruit-ripening-specific *E8* promoter (Butelli et al., 2008). The purple tomato-producing

transgenic line passed the biotechnology regulatory processes of the USDA, FDA, and EPA and is available on the United States market. Similarly, we used the *E8* gene promoter to overexpress the *SlAN2-like* gene in tomatoes, resulting in purple tomatoes with high anthocyanin contents in both the peel and flesh (Sun et al., 2020), which demonstrate significant commercial potential.

Locular gel and placental development

The locular gel of tomato fruit, formed by the outward extension of the placental tissue, is a typical feature of fleshy berries, like tomatoes, and a key determinant of their flavor. The locular gel is the second most abundant tissue in tomatoes after the pericarp, accounting for approximately 23% of the fresh FW, and the main component of tomato juice. The locular gel is rich in sugars, organic acids, vitamins, and volatile flavor compounds, and thus plays a vital role in fruit development, ripening, textural changes, and flavor composition (Moco et al., 2007). In *all-flesh fruit* (*AFF*) tomatoes, the locular tissue remains solid throughout fruit development and ripening, failing to form the gel-like consistency, yet the fruits can develop and mature normally. These fruits exhibit higher firmness and a longer shelf life. The D-class MADS-box transcription factor SlMBP3 is the primary regulator of locular tissue formation in tomatoes. A 416-bp deletion in the *SlMBP3* promoter prevents the formation of juice-like locular tissue, resulting in the all-flesh phenotype (Huang et al., 2021a; Liu et al., 2022a). The *slmbp3* knockout mutant lines show high fruit firmness as early as 10 days after anthesis (10-DAP), and this phenotype persists throughout the ripening process. By contrast, fruits of *SlMBP3* overexpression lines exhibit severe softening and enter a liquefied state after the green-ripe state. Notably, the simultaneous mutation of *SlMBP3* and its homolog *SlAGL11* results in dwarf plants, smaller fruits, and deformed seeds (Huang et al., 2021a), greatly limiting the commercial application potential of the resultant double mutant. Therefore, when breeding for the all-flesh trait, the presence of *SlAGL11* must be considered to avoid the negative effects of simultaneous mutations. Auxin also plays a key role in regulating the development of locular and placental tissues in tomato fruit. Two ARF family transcription factors, SlARF8A and SlARF8B, regulate auxin activity in the fruit by inhibiting the expression of the amido synthetase gene *SlGH3.4*, thus precisely controlling placental tissue development (Hua et al., 2024). This ensures normal fruit growth and ripening as well as the formation of the characteristic flavor of tomato fruit.

Fruit quality

Tomato fruit is rich in soluble sugars, organic acids, carotenoids, vitamins, and numerous volatile flavor compounds, giving it a sweet and acidic taste with a rich flavor (Pereira et al., 2021). Compared with traditional varieties, modern cultivated tomatoes often have a bland taste and less intense flavor. These undesirable characteristics of modern tomatoes could be attributed to several key factors: linkage drag associated with the introduction of disease-resistance loci from wild accessions into cultivated lines; negative effects of extending the shelf life of the tomato fruit; and the widespread application of the *uniform ripening* trait, which has led to the loss of green shoulders. Improving fruit flavor through cultivation practices (such as water, temperature, light, and soil salinity management, fertilizer application, and exogenous hormone treatments) and by altering storage conditions and methods is currently a hot topic in research. In recent years, the QTLs related to tomato quality traits and the genes underlying those QTLs have been researched extensively, revealing the genetic components of tomato flavor. Furthermore, through genome sequencing, transcriptomic, and metabolomic analyses, scientists have gained deeper insight into the evolutionary history of tomato fruit development, genomic fixation during tomato breeding, and the evolution of metabolites. Elucidation of the molecular and genetic bases of tomato flavor has laid a strong foundation for future tomato flavor breeding and improvement.

Flavor quality

Flavor quality, including sweetness, acidity, and aroma, is associated with soluble sugars, organic acids, amino acids, and volatile aromatic compounds in the fruit. Soluble sugars in tomato fruit are primarily derived from the assimilation and transport of photosynthetic products. While 20% of the photosynthetic products in tomato fruit are derived from photosynthesis in the fruit, 80% are transported from source organs such as leaves (Powell et al., 2012). Sucrose is the primary photosynthetic product and the primary form in which photosynthetic products are transported. During fruit development, photosynthetic products are transported from leaves to fruits in the form of sucrose via the phloem through symplastic and apoplastic pathways. In the fruit, these products are metabolized by various enzymes. In mature cultivated tomatoes, the main soluble sugars are glucose and fructose, while in some wild species like *S. peruvianum*, *S. chmielewskii*, and *S. habrochaites*, sucrose is the predominant sugar in mature fruits. The soluble solids content (SSC) or Brix, which represents the percentage of solutes in the fruit juice, is an important indicator of tomato flavor quality. Researchers have made significant progress in studying SSC-related metabolites, especially soluble sugars. *Lin5* and *SUCR* encode apoplastic and vacuolar invertases, respectively, whose main function is to hydrolyze sucrose into fructose and glucose (Fridman et al., 2004). *Lin5* was initially identified in an IL population derived from a cross between *S. pennellii* line LA0716 and cultivated tomato line M82 and was named *Brix9-2-5*. The allele from *S. pennellii* can increase glucose and fructose levels in tomato fruit by 28% and 18%, respectively, significantly enhancing SSC. The *sucrose accumulator* (*sucr*) gene, identified in *S. chmielewskii* line LA1028, controls sucrose levels in mature fruit. While the *sucr* allele of *S. chmielewskii* has been shown to increase the levels of sucrose, total sugar, and SSC in mature fruit, the absence of this gene is thought to be a primary factor

contributing to sucrose accumulation in mature fruits of other wild species (Chetelat et al., 1993, 1995). Additionally, sugar transporters play an essential role in the transport of sugar from photosynthetic tissues to the fruit. The *Fructose-to-glucose ratio* (*Fgr*) gene encodes a SWEET transporter, and its high expression increases the fructose-to-glucose ratio in tomato fruit (Shammai et al., 2018). The *STP1* gene also encodes a sugar transporter, and its mutation significantly reduces the SSC in tomato fruit. A zinc-finger transcription factor, ZAT10-LIKE, activates *STP1* expression by binding to its promoter. During the development of large-fruited tomatoes from SLC, the *STP1* promoter underwent a 21-bp deletion encompassing the ZAT10-LIKE binding site, which led to a reduction in SSC in cultivated tomatoes (Wang et al., 2023c). Furthermore, the *AGPL1* gene, which encodes the large subunit of ADP-glucose pyrophosphorylase, was identified in *S. habrochaites* LA1777. AGPL1 significantly increases starch content in immature fruit and SSC in mature fruit (Petreikov et al., 2006). Recently, two calcium-dependent protein kinase (CDPK)-encoding genes, *SlCDPK27* and *SlCDPK26*, have been identified. These genes function as sugar brakes by phosphorylating sucrose synthase, thereby promoting its degradation. Gene-edited knockout lines of *SlCDPK27* and *SlCDPK26* resulted in a significant increase in glucose and fructose contents, with levels rising by up to 30%. This enhancement in sugar content boosts perceived sweetness without adversely affecting FW or yield (Zhang et al., 2024b). *SlbZIP1* encodes a positive regulator of soluble sugar synthesis, and its overexpression significantly increases the level of hexose in tomato fruit (Sagor et al., 2016). Recent studies have indicated that the translation of the SlbZIP1 protein is regulated by a sucrose-inducible upstream open reading frame (uORF) in the 5′UTR region of the *SlbZIP1* gene. CRISPR/Cas9-mediated knockout of this uORF significantly increases SlbZIP1 translation efficiency, thus enhancing the hexose content in tomato fruit (Nguyen et al., 2023).

The primary organic acids in tomato fruit are malic acid and citric acid, which influence the acidity of the fruit. *Tomato Fruit Malate 6* (*TFM6*) is the major regulatory locus controlling malic acid accumulation in tomatoes. *TFM6* encodes an aluminum-activated malate transporter protein (ALMT9), which acts as a positive regulator of malic acid accumulation. A 3-bp insertion–deletion (InDel) in the W-box motif, the binding site of SlWRKY42, in the *ALMT9* promoter reduces the binding and consequently the inhibitory effect of WRKY42 on *ALMT9* expression, ultimately leading to increased malic acid content in tomato fruit (Ye et al., 2017). Genome-wide association studies were performed to identify genomic loci controlling malic acid content in tomatoes, and 15 high-confidence candidate genes were predicted. Subsequently, the optimal combination of variants regulating malic acid accumulation in tomato fruit was identified, providing valuable information for genome-based breeding (Gai et al., 2023). Similarly, through LD and genotype analyses, researchers identified 11 high-confidence candidate genes regulating citric acid content in tomato fruit, with three genes likely to act as positive regulators and eight genes as negative regulators of citric acid accumulation (Gai et al., 2024).

The production of volatile aromatic compounds in tomato fruit involves complex metabolic pathways, such as the isoprenoid/MEP pathway and the lipid-derived volatile biosynthesis pathway (Goulet et al., 2012). Several genes involved in the biosynthesis of fatty acid-derived volatile flavor compounds have been identified in tomato. Among these genes, *TomLoxC* encodes a lipoxygenase that catalyzes the biosynthesis of C6 and C5 aromatic volatiles and also influences the synthesis of carotenoid-derived volatiles. A recent study has shown that a rare genome sequence variation in the promoter region of *TomLoxC* was subjected to negative selection during tomato domestication, possibly contributing to the loss of tomato flavor (Gao et al., 2019). *HPL* encodes hydroperoxide lyase, which controls the synthesis of lipid-derived volatiles. Increased expression of the *SlAAT1* gene promotes the production of volatile ester compounds in tomato fruit (Distefano et al., 2022). Volatile compounds such as phenylacetaldehyde, 2-phenylethanol, and methyl salicylate are derived from phenylalanine through the shikimate pathway, catalyzed by enzymes such as aromatic amino acid decarboxylase (AADC), phenylacetaldehyde reductase (PAR1), 2-phenylethanol acetyltransferase (PPEAT), and carotenoid cleavage dioxygenase (FLORAL) (Burbidge et al., 1997; Baldwin et al., 2000; Tieman et al., 2017; Çolak et al., 2020). *FLORAL4* is a key gene influencing the biosynthesis of phenylalanine-derived volatiles in tomato, significantly affecting the production of phenylacetaldehyde, 2-phenylethanol, and 1-nitro-2-phenylethane. The expression of *SlTNH1* and *SlFMO1* influences the biosynthesis of nitrogen-containing volatile compounds in tomato (Cheng et al., 2021). ALCOHOL DEHYDROGENASE 2 (ADH2) significantly impacts the biosynthesis of aldehyde and alcohol volatile compounds in tomato fruit (Tieman et al., 2010). Apocarotenoids, such as α-ionone and 6-methyl-5-hepten-2-one (Houle et al., 2010), contribute to the unique fruity and floral aromas of tomatoes. In tomato, aromatic apocarotenoids are synthesized from β-carotene and lycopene by CAROTENOID CLEAVAGE DIOXYGENASE enzymes, SlCCD1A and SlCCD1B (Ilg et al., 2014; Wei et al., 2016). *SlYTH2* encodes an m^6A reader protein that regulates the m^6A modification of its target genes, affecting their protein translation efficiency. It was found that knocking out *SlYTH2* significantly accelerated the translation of its target genes such as *SlHPL* and *SlCCD1B*, leading to increased production of aroma-related volatiles (Bian et al., 2024). Phenylpropanoid volatile compounds (PhP-Vs), such as guaiacol and methyl salicylate, negatively affect tomato flavor. Glycosyltransferase Non-Smoky Glucosyl Transferase 1 (NSGT1) and methylesterase play important roles in this process (Tikunov et al., 2013; Alonge et al., 2020; Sapkota et al., 2023). These findings not only enhance our understanding of the mechanisms underlying tomato aroma formation but also lay a solid foundation for improving tomato flavor through breeding.

Nutritional quality

Lycopene is the primary carotenoid in mature tomato fruits, typically accounting for 80%–90% of the total carotenoid content, while other carotenoids, including β-carotene and lutein, make up approximately 5%–10% of the total carotenoid content (Ronen et al., 1999). Lycopene and its derivatives are positively correlated with the synthesis of many important nutrients and aromatic compounds in tomato fruit. Carotenoids not only serve as essential pigments, but are also vital nutrients in tomatoes. Mutations in genes encoding carotenoid biosynthesis enzymes and fruit ripening-related proteins can alter the synthesis and accumulation of carotenoids in tomato fruit, thereby altering the fruit's nutritional quality, as discussed earlier. Notably, the *old gold* (*og*) and *old-gold crimson* (*ogc*) mutants, carrying loss-of-function mutations in the *Beta* gene, exhibit elevated lycopene accumulation, which imparts a deep-red color to the fruit flesh (Ronen et al., 1999, 2000). These mutants hold significant value for tomato breeding. However, the *og* and *ogc* mutant alleles are primarily found in processing tomatoes and, because of the tight linkage between *SP* and *OG*, introducing these traits into fresh-market tomatoes through traditional breeding is time consuming and labor intensive. These limitations, however, can be overcome using gene editing technologies (Arruabarrena et al., 2023).

Both the HD-Zip I transcription factor SlHZ24 and bHLH transcription factor bHLH59 positively regulate the accumulation of ascorbic acid (vitamin C) in tomato fruit by controlling the expression of ascorbic acid biosynthesis genes such as *SlGMP3*, *GME*, and *GGP* (Hu et al., 2016; Ye et al., 2019). An 8-bp InDel mutation in the 5′UTR of *SlbHLH59* is completely linked to the ascorbic acid content in the tomato fruit (Ye et al., 2019). Additionally, ascorbic acid biosynthesis is regulated by light signals. The C2H2 zinc-finger transcription factor SlZF3 interacts with the negative regulator of light signaling, CSN5B, to prevent CSN5B-mediated degradation of VTC1, thereby enhancing ascorbic acid accumulation (Li et al., 2018e). Mutation of the *7-dehydrocholesterol reductase* (*7-DR2*) gene induces the accumulation of 7-dehydrocholesterol (7-DHC), a vitamin D_3 precursor, in tomato fruits and leaves. Thus, this genetically modified tomato could potentially become a new dietary source of vitamin D_3, offering health benefits to the public. Furthermore, *VTE3*, which influences vitamin E content in tomato fruits, has also been cloned (Quadrana et al., 2014). Glutamate decarboxylase (GAD) is responsible for synthesizing γ-GABA. Researchers used genome editing to remove the auto-inhibitory domain of *GAD2* and *GAD3* genes, producing high-GABA tomatoes (Nonaka et al., 2017). The high-GABA tomato passed relevant assessments and was first sold commercially in 2022. Additionally, targeting GABA metabolic enzyme-encoding genes, such as *GABA-TP1*, *GABA-TP2*, and *GABA-TP3* (which encode GABA transaminases) and *CAT9* and *SSADH* (which encode succinate semialdehyde dehydrogenases), can significantly increase GABA content in tomato fruits (Li et al., 2018b).

Tomatine is a bitter-tasting glycoalkaloid that accumulates in the stems, leaves, and unripe fruits of Solanaceae crops, including eggplant, potato, and tomato. Although tomatine serves as a defense barrier against pathogen and insect invasions in plants, it is considered an anti-nutritional factor, because of its negative effects on human health. The concentration of tomatine in tomato fruits decreases significantly during maturation, which prevents ripe tomatoes from tasting bitter. The tomatine content of tomato underwent strong negative selection during domestication and improvement, which has effectively reduced the concentration of tomatine in cultivated tomatoes, thereby minimizing their potential toxicity and bitterness and making them more palatable. Many genes associated with the tomatine content of fruit have been identified, such as *GORKY*, *GAME9* (*GLYCOALKALOID METABOLISM 9*), and *GAME36* (Yu et al., 2020; Akiyama et al., 2021; Kazachkova et al., 2021; Sonawane et al., 2023). *GORKY* encodes an NPF transporter, which facilitates the transfer of α-tomatine and other steroidal alkaloids from the vacuole to the cytosol during fruit ripening, aiding in the conversion of tomatine into the non-bitter compound esculeoside A (Kazachkova et al., 2021). *GAME9* encodes an AP2/ERF transcription factor, which acts as a key regulator of tomatine biosynthesis (Cárdenas et al., 2016). *GAME36* encodes a BAHD acyltransferase, which mediates the degradation of α-tomatine, reducing its accumulation in tomato fruits and thereby decreasing fruit bitterness (Sonawane et al., 2023). A recent study has shown that the expression of *GAME* genes is regulated by a distal enhancer called *GAME Enhancer 1* (*GE1*). Hi-C sequencing analysis revealed that *GE1* and the *GAME* gene cluster on chromosome 7 are associated in a large chromatin loop, regulating the expression of *GAME1*, *GAME17*, and *GAME18*, thus influencing tomatine metabolism. During tomato domestication, a weak allele of *GE1* was selected, leading to a significant reduction in the tomatine content of cultivated tomatoes (Bai et al., 2024).

Fruit texture

In contemporary tomato breeding programs, there has been a pronounced emphasis on enhancing transportability and shelf life, resulting in a significant increase in fruit firmness. Although this improvement effectively enhances the fruit's durability during transportation and storage, it has also led to a decline in sensory quality for consumers. Consequently, fruit firmness could also be a critical sensory quality trait of tomato.

During tomato ripening, the decrease in fruit firmness is primarily caused by the degradation of cell wall polymers by a series of cell wall hydrolases. These enzymes include polygalacturonase (PG), pectin lyase (PL), pectin esterase, pectin methylesterase (PME), β-galactosidase (TBG), and xyloglucan endotransglycosylase (XET). Known genes that regulate fruit firmness include *SlExp1*, *SlCel2*, *PG2a*, *PL*, and *TBG4* (Brummell et al., 1999; Uluisik et al., 2016; Su et al., 2024). *SlExp1*, encoding the expansin protein, and *SlCel2*,

encoding endo-β-1,4-glucanase, exhibit the same spatial expression patterns in the tomato fruit. While the individual knockout of *SlExp1* or *SlCel2* does not significantly alter fruit firmness, simultaneous knocking out of both genes can enhance fruit firmness without affecting fruit quality (Su et al., 2024). PL, a member of the pectinase family, primarily cleaves pectin β-1,4-galacturonan residues through a β-elimination mechanism, affecting cell wall disintegration, cell separation, and fruit softening. Recent studies have indicated that *pl* mutant fruits generated by CRISPR/Cas9 technology exhibit significantly increased firmness, highlighting the critical role of PL in tomato fruit softening. EIN4, a regulatory factor in the ethylene signaling pathway, negatively regulates fruit firmness by affecting the size and density of pericarp cells. Knocking out *EIN4* significantly increases fruit firmness at the red-ripe stage and extends the shelf life of tomatoes, whereas *EIN4* overexpression has the opposite effect (Zhang et al., 2024c).

Recently, a QTL affecting tomato fruit firmness, *qFIRM SKIN 1* (*qFIS1*), was identified. *FIS1* encodes a GA2-oxidase, and a mutation in *FIS1* results in increased levels of bioactive GAs, enhanced cutin and wax biosynthesis, increased fruit firmness, and extended fruit shelf life (Li et al., 2020a). As the outermost protective barrier, the cuticle prevents excessive water loss and pathogen invasion. The cuticle is primarily composed of cutin and wax, with cutin accounting for 40%–80% of the total cuticle weight. Cutin is a polymer of C16 and C18 oxygenated fatty acids linked by ester bonds (Peschel et al., 2007), while wax is a mixture of hydrophobic compounds, including long-chain and very-long-chain fatty acids and flavonoids (Kolattukudy, 1980). The composition and thickness of the cuticle directly affect the shelf life, brightness, and texture of fruits. Although fruits with thinner cuticles have a shorter shelf life, thin cuticle is a favorable trait, as it leads to increased gloss, reduced separation between the flesh and skin, and improved texture (Isaacson et al., 2009). Therefore, selecting varieties with appropriate cuticle thickness to balance shelf life, disease resistance, fruit brightness, and edibility is an important consideration in tomato breeding. Recessive mutants with defects in cutin synthesis, such as *cd1*, *cd2*, and *cd3*, show significantly reduced cutin content, thinner exocarp, and increased fruit gloss (Isaacson et al., 2009). *CD1* (also known as *GDSL1*) encodes a GDSL-motif esterase/lipase family protein that catalyzes the synthesis of linear cutin oligomers. *GDSL1* is primarily expressed in epidermal cells adjacent to the cuticle membrane, and silencing of *GDSL1* decreases the thickness and density of the cuticle as well as the proportion of cutin monomers in the cuticle (Yeats et al., 2012). Mutations in *GDSL2* lead to changes in the content and composition of wax and cutin in the fruit as well as alterations in cuticle thickness (Petit et al., 2014). *CUTIN DEFICIENT 2* (*CD2*), encoding an HD-Zip IV transcription factor, is primarily expressed in the epidermal cell layer of the tomato fruit. In *cd2* mutant fruit, cutin content in the cuticle is reduced by 95%–98%, leading to increased surface stiffness and sensitivity to fungal infections. The *Sticky peel* (*pe*) mutant, which is allelic to *cd2*, exhibits traits such as reduced separation between the peel and flesh and improved texture (Nadakuduti et al., 2012). *CD3* encodes a cytochrome P450 protein of the CYP86A subfamily and is highly expressed in the outer pericarp of mature green fruits. Silencing *CD3* expression leads to a significant reduction in the content of cutin and wax in the cuticle (Shi et al., 2013).

Responses to biotic and abiotic stresses

Biotic stress resistance

Plant diseases and pests are one of the primary causes of crop yield reduction globally. Developing disease-resistant and pest-resistant varieties is the most effective and environmentally friendly way to control these biotic stressors and ensure high and stable crop yields. Tomato production is challenged by a diverse array of diseases, including bacterial diseases, such as bacterial speck, bacterial wilt, and bacterial spot; fungal diseases, such as *Fusarium* crown and root rot (FCRR), *Fusarium* wilt, stem rot, *Verticillium* wilt, gray leaf spot, early blight, late blight, leaf mold, gray mold, and powdery mildew; and viral diseases, such as tomato yellow leaf curl virus disease, tobacco mosaic virus disease, tomato spotted wilt virus disease, tomato chlorosis virus disease, tomato leaf curl New Delhi virus disease, and tomato brown rugose fruit virus disease. Over thousands of years of domestication and improvement, the ability of cultivated tomatoes to counteract invading pathogens and insect pests has been lost in the pursuit of higher yields. To address this issue, breeders have turned to wild tomato species, because they are genetically highly diverse and harbor abundant disease-resistance genes. Using hybridization strategies, disease-resistance loci from wild relatives have been introgressed into cultivated tomato varieties, making them resistant to specific diseases. To date, approximately 30 different resistance genes (*R* genes) have been cloned, most of which encode Nucleotide Binding Site-Leucine Rich Repeat (NBS-LRR) proteins.

Bacterial diseases

Tomato bacterial speck is caused by *Pseudomonas syringae* pv. *tomato*. The *Pto* and *Prf* genes, which confer resistance to bacterial speck, are closely linked. *Pto* was the first plant resistance gene cloned that fit the “gene-for-gene” hypothesis (Salmeron et al., 1996). Tomato bacterial wilt is a soil-borne disease caused by *Ralstonia solanacearum* and also one of the most serious diseases in tomato-producing areas in southern China. After infecting tomato roots, *R. solanacearum* secretes the extracellular polygalacturonase PehC to suppress the plant immune response induced by disease-associated molecular patterns and utilizes the galacturonic acid hydrolysis products as a carbon source for pathogen growth. Tomatoes have evolved a receptor-like kinase to recognize PehC and trigger an immune response to limit the spread of the pathogen in the plant (Ke et al., 2023). There is a lack of bacterial wilt resistance resources in

cultivated tomatoes, and the known resistance loci are mostly derived from *S. pimpinellifolium*. Although several bacterial wilt resistance loci have been identified (Kim et al., 2018), the specific resistance genes still need to be explored. Tomato bacterial spot is a bacterial disease caused by pathogens in the *Xanthomonas* genus. *Bs4* was the first bacterial spot resistance gene to be cloned; however, *Bs4* confers resistance only to *Xanthomonas* strains carrying the effector AvrBs4, which cause pepper bacterial spot, and not to *Xanthomonas vesicatoria* strains, which cause tomato bacterial spot (Schornack et al., 2004). Therefore, *Bs4* has not been utilized in tomato breeding. In contrast with *Bs4*, both *Rx4* and *SlPub24* have shown effective resistance against the *X. euvesicatoria* pv. *perforans* T3 strain (Liu et al., 2021b; Zhang et al., 2021b).

Fungal diseases

Tomato FCRR and *Fusarium* wilt are both caused by the fungus *Fusarium oxysporum*, which infects the vascular bundles and leads to vascular blockage, browning, and decay. FCRR is caused by *F. oxysporum* f. sp. *radices-lycopersici* (FORL), whereas *Fusarium* wilt is primarily caused by *F. oxysporum* f. sp. *lycopersici* (FOL). Resistance to FCRR is associated with a genomic region on chromosome 9 containing the *Frl* gene, which originates from *S. peruvianum* and shows dominant inheritance. *Frl* is closely linked to *Tm-2*, and the specific gene conferring resistance to FCRR remains to be cloned and verified (Devran et al., 2018). The *I-2* resistance gene from *S. pimpinellifolium* confers resistance to both physiological races 1 and 2 of FOL (Ori et al., 1997; Simons et al., 1998), whereas the resistance genes *I-3* and *I-7* from *S. pennellii* exhibit resistance to race 3 (Catanzariti et al., 2015; Gonzalez-Cendales et al., 2016). The *I-2* and *I-3* genes have been widely used in tomato breeding. Tomato *Verticillium* wilt is caused by the soil-borne pathogen *Verticillium dahliae*. Both *Ve1* and *Ve2* impart resistance against *Verticillium* wilt, but they function independently to confer resistance to race 1 of *V. dahliae* (Kawchuk et al., 2001). The tomato gray leaf spot disease, which primarily damages leaves, is caused by *Stemphylium lycopersici*. The occurrence and spread of *S. lycopersici* are influenced by temperature and relative humidity. The *S. pimpinellifolium* gene *Sm* is the only known gene with high resistance to gray leaf spot. This gene has been introduced from *S. pimpinellifolium* into the cultivated tomato variety Motelle and is widely used in the breeding of resistant varieties (Yang et al., 2022b). Late blight of tomato is caused by the fungus *Phytophthora infestans*, which mainly infects the leaves and green fruits of tomato plants. This disease has occasionally been reported in southern China and can affect tomato cultivation in greenhouses. *Solanum pimpinellifolium* is a rich resource of resistance genes for late blight, among which *Ph-3* is a partially dominant resistance gene that shows resistance to multiple physiological races of *P. infestans* (Zhang et al., 2014). *Ph-3* and another *S. pimpinellifolium* gene, *Ph-2*, have been widely used in tomato breeding, and the combination of these two genes further enhances resistance to late blight. Tomato leaf mold, which severely affects photosynthesis in tomato leaves, is caused by *Cladosporium fulvum*. *C. fulvum* has many physiological races and mutates continuously, presenting a significant challenge in the control of leaf mold. The *Cf* gene, which encodes a transmembrane receptor-like protein (RLP) lacking a transcription activation domain, can confer resistance to *C. fulvum* in tomato. At least 24 tomato leaf mold resistance genes (*Cf-1* to *Cf-24*) have been identified in SLC, *S. pimpinellifolium*, *S. peruvianum*, *S. pennellii*, and *S. habrochaites* (Jones et al., 1994; Dixon et al., 1996; Thomas et al., 1997; Dixon et al., 1998). However, with the application and promotion of resistant varieties, new physiological races of leaf mold continue to emerge, and some of these races have developed mechanisms to suppress Cf-mediated defense. The tomato gray mold disease, caused by *Botrytis cinerea*, mainly occurs during flowering and fruit ripening and causes severe postharvest losses. During the fruit ripening process, the ethylene signaling regulator EIL activates the expression of the *CYP94C1* gene, which is involved in the metabolism of JA, a defense-related phytohormone. The degradation of active JA by CYP94C1 reduces the resistance response to *B. cinerea*, which explains why mature fruits are more sensitive to gray mold than immature fruits. While no effective genetic resource for gray mold resistance has been found to date, knocking out *CYP94C1* expression has been shown to significantly enhance the resistance of tomato fruits to *B. cinerea* (Yang et al., 2024a). Tomato powdery mildew, caused by *Oidium neolycopersici*, primarily infects tomato leaves, reducing photosynthesis. To date, six dominant resistance genes (*Ol-1*, *Ol-3*, *Ol-4*, *Ol-5*, and *Ol-6*) and one recessive resistance gene (*ol-2*) effective against powdery mildew have been identified in wild tomato species such as *S. chilense*, *S. habrochaites*, and *S. peruvianum* (Bai et al., 2008).

Viral diseases

Tomato Yellow Leaf Curl Virus (TYLCV) is a DNA virus transmitted by whitefly. TYLCV has been one of the catastrophic diseases in tomato production in recent years. Known resistance genes against TYLCV include *Ty-1*, *Ty-2*, *Ty-3*, *Ty-3a*, *Ty-4*, *Ty-5*, and *Ty-6*. Among these, *Ty-1* and *Ty-3*, derived from *S. chilense*, are allelic and currently the most thoroughly studied and widely applied resistance genes (Verlaan et al., 2013). *Ty-2* originates from *S. habrochaites*; *Ty-3a* and *Ty-4* from *S. chilense*; and *Ty-5*, a recessive resistance gene, from *S. peruvianum*. It is noteworthy that by pyramiding different *Ty* genes in tomato breeding, the resistance of plants to TYLCV can be significantly enhanced by *Ty* gene pyramiding, that is, introgressing different *Ty* genes into a single tomato genotype (Verlaan et al., 2013; Lapidot et al., 2015; Yamaguchi et al., 2018). Tomato mosaic virus disease is caused by the single-stranded RNA virus Tobacco mosaic virus (TMV). The resistance genes effective against were initially discovered in *S. habrochaites*, and *S. peruvianum*. Known TMV resistance genes include *Tm-1*, *Tm-2*,

and *Tm-2a* (also known as *Tm-2*^{2}), all of which exhibit dominant inheritance. *Tm-2* and *Tm-2a* are alleles and exhibit strong resistance to TMV. *Tm-2* encodes a CC-NLR immune receptor protein and is induced by ethylene (Lanfermeijer et al., 2003). Researchers have developed several molecular markers flanking the *Tm-2* gene to aid in the molecular breeding of TMV resistance in tomato. The tomato spotted wilt virus (TSWV) disease is caused by a representative species of the genus *Orthotospovirus* in the family *Tospoviridae*, order *Bunyavirales*. TSWV is listed among the top 10 most destructive plant viruses in the world. *Sw-5*, a resistance gene from *S. peruvianum*, is a member of a loosely clustered gene family in the telomeric region of chromosome 9, with the *Sw-5b* gene showing significant resistance to TSWV (Brommonschenkel et al., 2000). *Sl5R-1*, a newly identified resistance gene, encodes an NBS-LRR protein, which provides resistance to TSWV when *Sw-5*-mediated resistance is compromised (Qi et al., 2022). Other viral pathogens that pose a serious threat to tomato production include tomato chlorosis virus, tomato leaf curl New Delhi virus, and tomato brown rugose fruit virus. Although some wild tomato resources for resistance to these viruses have been identified, information on the disease-causing mechanisms of these pathogens and the corresponding resistance genes is still insufficient; therefore, further research is needed.

Nematodes

Root-knot nematode (RKN) is a major pest that causes substantial economic losses in tomato production annually. *Mi-1* is currently the only RKN resistance gene commercially utilized in tomato. *Mi-1* limits parasitism and the reproduction of RKNs in the roots of host plants, reducing the formation of root knots (Milligan et al., 1998). However, the *Mi-1* gene loses its function when the soil temperature exceeds 28°C, and populations of virulent RKNs that can overcome the resistance induced by *Mi-1* have appeared in the field. *Mi-9* is a novel, heat-stable RKN resistance gene identified in *S. arcanum* line LA2157. Cultivated tomato lines have lost the *Mi-9* gene (Jiang et al., 2023); therefore, the *Mi-9* gene from *S. arcanum* LA2157 has significant application value. The *Hero* gene is a broad-spectrum resistance gene effective against potato cyst nematodes that imparts a high level of resistance to all pathotypes of *Gobodera rostochiensis* and partial resistance to *Gobodera pallida* (Ernst et al., 2002). In addition to the *Mi* genes, JA also plays an important role in resistance to RKNs in tomato. *SlWRKY45* acts as a negative regulator of resistance to southern RKNs by binding to the promoter of the JA biosynthesis gene *SlAOC* and suppressing its expression (Huang et al., 2022). When tomato roots are infected by RKNs, they produce an electric signal dependent on *GLR3.5* and an apoplastic reactive oxygen species (ROS) signal dependent on *RBOH1*. These two signals interdependently transmit the signal to leaves, thus, activating MPK1/2 to induce the synthesis of JA and its transport to the roots, enhancing resistance to RKNs (Wang et al., 2019d). Autophagy regulates tomato resistance to RKNs by modulating the JA signaling pathway. Specifically, autophagy degrades JAM1 and stimulates the JA-ERF1 branch through a positive feedback loop, thereby promoting JA-mediated defense responses and enhancing plant resistance to RKNs (Zou et al., 2023).

Parasitic plants

Parasitic plants insert their haustoria into the host tissue to connect to the vascular systems and absorb water and photosynthetic products as well as other organic and inorganic compounds from the host, ultimately damaging the host plant. *Cuscuta* is a stem parasite with a wide host range, including legumes, grasses, and solanaceous plants. Notably, cultivated tomato is one of the few plants capable of resisting *Cuscuta* parasitism. *CUSCUTA RECEPTOR 1* (*CuRe1*) encodes an LRR-RLP (Hegenauer et al., 2020), which can perceive the cell wall protein CrGRP of *Cuscuta* spp., thereby initiating a resistance response (Hegenauer et al., 2020). Leafminers and borers are among the most destructive quarantine pests globally. In tomato, these pests can cause damage to the aboveground plant parts at any stage of plant growth. These pests mine leaf tissues, bore into fruits, and also attack shoot tips and young shoots, drilling into tender stems and severely impacting tomato production. However, resistance genes for these pests remain largely unexplored.

Abiotic stress tolerance

Abiotic stressors, including saline–alkaline soils, extreme temperatures, drought, and excessive or low light, significantly limit tomato production. Notably, with the intensification of global climate change, the frequency and intensity of abiotic stress are increasing, posing a major threat to tomato cultivation. Elucidating the molecular mechanisms used by tomato plants to survive and grow under abiotic stress conditions can provide theoretical guidance for tomato variety improvement and cultivation technology innovation. In contrast with biotic stress resistance, the resistance to abiotic stress is typically associated with quantitative traits, and research progress in this area is lagging, particularly in regard to the knowledge of practically applicable genes. Exploring new genes in wild tomato species represents an important direction in the study of abiotic stress resistance. Through long-term natural selection, wild tomato species have evolved various mechanisms to adapt to adverse environmental conditions. Analysis of the genetic diversity of wild tomato germplasm and identification of genes or QTLs associated with abiotic stress resistance will enable the breeding new of tomato varieties with strong stress resistance capabilities.

Saline–alkaline stress

Soil salinization and alkalization inhibit the growth of tomato plants and severely impact their yield, causing significant losses in tomato production. Salt stress can trigger

secondary stresses such as ion toxicity, osmotic stress, and oxidative damage, with ion toxicity primarily referring to the imbalance in sodium ion (Na^+) and potassium ion (K^+) concentrations within plant cells. Plants mainly regulate the balance of Na^+ and K^+ within cells through Na^+–K^+ transporters and channels to mitigate salt stress. Research shows that the salt tolerance of tomato, which sharply decreased during the domestication process, is controlled by multiple loci. The *Salt Overly Sensitive 1* (*SOS1*) gene encodes a Na^+/H^+ antiporter. In tomato, constitutive silencing of *SlSOS1* resulted in salt sensitivity, whereas tissue-specific silencing of *SlSOS1* in the stem vascular bundles significantly enhanced salt tolerance (Olías et al., 2009). Genetic analysis indicates that nucleotide sequence variations in the *SlSOS1* promoter are significantly associated with the Na^+/K^+ ratio in tomato roots. Further studies have found that variations in the promoter of *SlSOS1* in cultivated tomato lines led to a significant reduction in gene expression, which may explain the loss of salt resistance in cultivated tomato (Wang et al., 2021c). Another SOS gene, *SlSOS2*, also contributes to the reduced salt tolerance of cultivated tomato, due to a 53-bp insertion in its promoter region. This insertion contains the binding site of the salt-responsive transcription factor ABI4, which suppresses *SOS2* expression, thereby reducing the salt tolerance of cultivated tomatoes (Hong et al., 2023). Genomic analysis indicates that *SlHAK20*, which encodes a Na^+–K^+ transporter, has undergone strong selection during domestication. A 6-bp deletion downstream of the start codon of *SlHAK20* results in reduced SlHAK20 protein activity, leading to a significant decrease in salt tolerance in cultivated tomato (Wang et al., 2020). *kc7.1* is a major salt tolerance locus in tomato by regulating leaf Na^+/K^+ balance. The *kc7.1* locus contains two potassium transporter genes, *HKT1;1* and *HKT1;2*. Silencing the *SlHKT1;2* gene increases the Na^+/K^+ ratio in transgenic plants, resulting in a salt-sensitive phenotype, whereas silencing the *SlHKT1;1* gene does not cause any significant changes in the leaf Na^+/K^+ ratio, suggesting that *SlHKT1;2* is likely to be the gene responsible for the *kc7.1*-associated salt tolerance phenotype of tomato plants (Jaime-Pérez et al., 2017). *LeNHX2* encodes an endomembrane K^+/H^+ antiporter, and its overexpression in tomato can enhance K^+ absorption under salt stress, thereby improving plant salt tolerance (Huertas et al., 2013). Proline plays a crucial role in osmotic regulation in plants. Abiotic stresses such as drought and salinity can activate the expression of genes such as *SlP5CS1/2* and *SlP5CR* by inducing nitric oxide (NO) production and can enhance the enzymatic activity of SlP5CR through the *S*-nitrosylation modification. *SlP5CS1/2* and *SlP5CR* encode key proline synthesis enzymes in tomato, and their increased gene expression and enhanced enzymatic activity promote proline synthesis, thereby improving tomato resistance to drought and salinity stresses (Liu et al., 2024b). The aforementioned studies primarily focus on the response and tolerance mechanisms of tomato to salt stress; however, our understanding of the combined stresses of salinity and alkalinity is relatively insufficient. By simulating salinity–alkalinity stress using $NaHCO_3$ treatment, researchers have identified a regulatory gene that enhances salinity–alkalinity stress resistance in tomato, namely, *SlSOS3-like Calcium Binding Protein 8* (*SlScaBP8*). Alleles of *SlScaBP8* derived from *S. pimpinellifolium* exhibit stronger saline–alkaline stress tolerance than the cultivated tomato allele. Variations in the promoter region of *SlScaBP8* led to differences in its expression levels between *S. pimpinellifolium* and cultivated tomatoes, resulting in their differing levels of resistance to salinity and alkalinity (Liu et al., 2024c).

Drought stress

Drought stress can lead to abnormal root development in tomato, resulting in stomatal closure, reduced photosynthesis, and ROS accumulation, ultimately slowing down plant growth and development, adversely affecting flowering and fruit ripening, and, in severe cases, even causing plant death. Drought stress triggers a series of defense responses within the plant, such as the induction of antioxidant systems to maintain redox homeostasis, enhanced synthesis of metabolites like mannitol and proline to maintain cellular osmotic potential and ion balance, and activation of mechanisms to protect the integrity of biological membranes (Xie et al., 2024). Furthermore, drought stress can activate signaling pathways involving plant hormones, such as ABA and GA, to better respond to drought stress. *CPK27* encodes a calcium-dependent protein kinase, which acts downstream of the ABA signaling pathway and induces the accumulation of soluble sugars through the phosphorylation of the monosaccharide transporter TST2, thereby enhancing drought resistance of tomato plants (Zhu et al., 2024). *SlROP9* encodes a Rho protein that regulates the production of ROS by modulating the activity of respiratory burst oxidase homolog (RBOH) in tomato. The *rop9* mutant exhibits elevated ROS levels in guard cells and increased stomatal closure, which enhances water use efficiency without affecting yield; these physiological changes indicate significant breeding potential for this mutant (Puli et al., 2024). *SlCIPK7* negatively regulates ABA-mediated stomatal closure, and knocking out this gene in tomato significantly improves drought tolerance (Liu et al., 2024a). A recent study has shown that a mutant allele of the *BBX18* gene carrying a SNP ($BBX18^{TT}$) may be associated with increased sensitivity to drought stress during tomato domestication. Furthermore, knocking out *BBX18* expression could significantly enhance drought tolerance, which holds important implications for breeding drought-resistant tomato varieties (Li et al., 2024d).

Temperature stress

Temperature is one of the key environmental factors influencing plant growth and development. Tomato, a vegetable crop sensitive to temperature changes, frequently encounters low-temperature stress during greenhouse production in the winter. During the reproductive phase of tomato, low temperatures can lead to pollen abortion, flower and fruit

drop, and parthenocarpy; conversely, high temperatures can cause excessive stem elongation and pollen inactivation, significantly impacting fruit set rates. *Solanum habrochaites* and *S. lycopersicoides*, which originated in the Andean Mountains in South America, exhibit exceptional cold tolerance due to their long-term growth in high-altitude environments, making them invaluable genetic resources for improving the cold tolerance of tomato. *WRKY34*, a cold resistance gene isolated from *S. habrochaites*, confers cold tolerance by interfering with the CBF cold response pathway at both the transcriptional and translational levels, thereby regulating cold resistance in tomato. During the evolution of tomato, a 60-bp InDel variation in the promoter region of *WRKY34* resulted in differences in transcriptional levels and cold resistance levels among various tomato cultivars (Guo et al., 2024). Plant hormones such as ABA and JA play crucial roles in the response of tomato to extreme temperatures. Under low-temperature stress, the tetratricopeptide repeat protein SlREDUCED CHLOROPLAST COVERAGE2 (SlREC2) promotes ABA accumulation and induces the expression of CBF pathway genes by interacting with β-RING carotenoid hydroxylase 1b (SlBCH1b), thereby enhancing cold resistance in tomato (Zhang et al., 2023). SlWRKY50 positively regulates the cold stress response in tomato by cooperating with JA in a feedback loop (Wang et al., 2024b). In addition to hormones, various bioactive compounds also participate in the regulation of temperature stress resistance in tomato. As a growth regulator commonly found in animals and plants, 5-aminolevulinic acid (ALA) can induce the expression of the glutathione *S*-transferase gene *SlGSTU43* under cold stress, effectively scavenging excess ROS and enhancing cold tolerance. MYB transcription factors SlMYB4 and SlMYB88 activate the expression of *SlGSTU43* by binding to its promoter, thereby participating in the ALA-mediated cold stress tolerance response in tomato (Zhang et al., 2024d). Moreover, the non-protein amino acid GABA has been shown to significantly enhance the cold tolerance of tomato seedlings, when applied exogenously at a concentration of 55 mM. Overexpression of the GABA biosynthesis gene *SlGAD2* can increase endogenous GABA levels, mitigate cold-induced damage to cell membranes, and enhance antioxidant enzyme activity and ROS scavenging capacity, thereby improving cold resistance in tomato plants. Conversely, SlTHM27 negatively regulates cold tolerance in tomato by inhibiting the expression of *SlGAD2* (Wang et al., 2024a). B-box proteins (BBX) play important roles not only in light-dependent plant development but also in the integration of light and temperature signals. Studies have shown that the disruption of *SlBBX7*, *SlBBX9*, and *SlBBX20* severely inhibits the photosynthetic response of tomatoes under low-temperature stress, thereby impairing cold tolerance (Bu et al., 2021). SlBBX31 can modulate cold-induced expression of several ERF TFs including *CBF2* and DREBs, and SlHY5, the key regulator of light signaling, can directly bind to the *SlBBX31* promoter to activate *SlBBX31* transcription (Zhu et al., 2023b). High temperatures can inhibit the allocation of carbon assimilated from source organs to sink organs, leading to flower and fruit abscission, uneven fruit size and low sugar content. Further research has revealed that the primary cause of this phenomenon is the suppression of cell wall invertase (CWIN) expression. To address this issue, a 10-bp heat-shock element (HSE) was precisely inserted into the promoter of the CWIN gene, *LIN5*, in tomatoes. Under normal agricultural conditions, this method can increase tomato yield by 14%–47%. Under high-temperature stress, the genetically modified tomato germplasm shows a 26%–33% higher yield compared with controls, recovering 56.4%–100% of the yield loss caused by heat stress. Moreover, the improved tomatoes exhibit significantly better uniformity in fruit size and sugar content under corresponding conditions (Lou et al., 2024). High-temperature environments may also lead to increased branching or morphological changes in tomato inflorescences, affecting the normal opening of floral organs and pollen development, which in turn reduces fruit set rates and yield. During the pollen tube growth phase, exposure to high-temperature stress significantly diminishes tomato fruit biomass and seed set. In contrast, thermotolerant varieties exhibit superior pollen tube growth under elevated temperatures, leading to substantially improved fruit sets compared with thermosensitive varieties. Research has identified enhanced ROS homeostasis and increased synthesis and deposition of callose in pollen tubes as critical factors contributing to reproductive thermotolerance in thermotolerant varieties (Ouonkap et al., 2024). Furthermore, elevated ambient CO_2 levels can activate the glucose (Glc)-RGS1 (Regulator of G protein signaling 1)-GPA1 (G protein α subunit) signaling pathway in tomatoes, thereby enhancing their resistance to high temperatures through the regulation of photosynthesis and photoprotection pathways (Wang et al., 2024g).

Light stress

Light is essential for the normal growth and development of plants and is also one of the key determinants of the quality and yield of protected horticultural crops. In winter, inadequate light and smoggy weather can easily result in a weak light environment inside the facilities used for vegetable cultivation. Additionally, old plastic films and high-density cultivation can result in decreased light transmittance and canopy shading within the facilities. Excessive shading not only causes excessive vegetative growth but can also lead to premature fruit drop, significantly reducing tomato yield. Research has shown that under low-light conditions, the supplementation of trace amounts of ultraviolet (UV) light can lead to robust seedling growth and effectively inhibit etiolation, a process that relies on the UV receptor UVR8 (Liu et al., 2020d). Additionally, BBX20/21 inhibits the etiolation of tomato seedlings under low-light conditions by activating the expression of *HY5*, thereby promoting root vigor (Zhang et al., 2022; Yang et al., 2022a). Conversely, auxin and ethylene play crucial roles in regulating the abscission of tomato flowers and fruits, which typically occurs in the AZ. Low light

activates the SlCLV3–SlWUS signaling module in the AZ, inducing the expression of *SlKD1* and *SlFUL2*, which disrupts the auxin response gradient in the AZ and increases ethylene release, ultimately leading to the abscission of tomato floral organs (Cheng et al., 2022). The BEL transcription factor-encoding gene *SlBEL11* is highly expressed in the fruit AZ, and its expression levels continuously increase during fruit development. SlBEL11 can induce the accumulation of auxin transport inhibitors, specifically flavonoids, through SlMYB111, thereby regulating the efflux of auxin from the fruit and preventing premature fruit drop in tomato (Dong et al., 2024). *SlIDA-Like 6* (*SlIDL6*) encodes a small peptide that regulates the activity of cell wall hydrolases, thereby controlling the abscission of floral organs under low-light conditions in tomato (Li et al., 2021b). Additionally, the tonoplast intrinsic protein SlTIP1;1, a member of the aquaporin family, mediates the abscission of floral organs by regulating the cytosolic concentration of hydrogen peroxide (H_2O_2) and osmotic water permeability (Wang et al., 2021a). The HD-ZIP transcription factor-encoding gene *HOMEOBOX 15A* (*SlHB15A*) is abundantly expressed in the pedicel AZ, where it suppresses the expression of the jasmonic acid-isoleucine (JA-Ile) biosynthesis gene *JASMONATE-RESISTANT 1* (*SlJAR1*), thereby reducing JA-Ile levels in the tomato pedicel AZ and inhibiting floral organ drop (Liu et al., 2022b). Artificial light allows longer photoperiods; however, continuous light injures the leaves of tomato plants. *CAB13* derived from *S. neorickii* LA2131, which encodes the type III light-harvesting chlorophyll *a/b* binding protein, confers tolerance to continuous light and results in up to 20% yield increase in tomato (Velez-Ramirez et al., 2014).

Physiological disorders

Adverse growth conditions can trigger various physiological disorders in tomato, such as blossom-end rot (BER), malformed fruit, fruit cracking, yellow shoulder, and yellow sepals. These disorders can severely impact the yield, appearance, and marketability of tomato fruits. BER primarily affects the fruit but can also affect other organs such as flowers and leaves. Symptoms of BER typically manifest at the blossom end of the fruit, presenting as water-soaked lesions that subsequently develop into brown necrotic areas. In severe cases, BER can lead to extensive fruit damage and can increase susceptibility to secondary pathogens. Blossom-end rot was first described as a physiological disorder caused by irregular watering and the disruption of calcium ion homeostasis. Additionally, high concentrations of monovalent cations and plant growth regulators may exacerbate BER. A positive correlation between fruit size and BER incidence was recently reported, with elongated fruits being more susceptible than round fruits (Topcu et al., 2022). Genetic analyses identified at least five loci associated with BER, providing significant insights for molecular breeding efforts (Topcu et al., 2021).

Malformed tomato represents a significant physiological disorder characterized by various irregular fruit shapes, primarily including multiloculed and non-multiloculed malformed tomato (such as zipper fruit and finger-like fruit). These deformities typically arise from abnormal flower bud differentiation and development and are influenced mainly by the plant genotype and environmental conditions. Notably, low temperatures and GA are critical factors inducing the formation of multiloculed tomatoes (Li et al., 2019, 2021b). Exposure to low nighttime temperatures during flower bud differentiation can adversely affect the uptake of nutrients by roots, particularly nutrients closely associated with flower bud differentiation, such as zinc and calcium. A deficiency of these nutrients can impair carpel development, subsequently resulting in multiloculed and zipper fruits. Zipper fruit typically occurs when the stamens fail to separate correctly from the ovary during flowering. The stamens adhere tightly to the ovary during flowering, and as the fruit enlarges, the stamens become embedded in the fruit, forming longitudinal sutures on the fruit surface. Research has shown that low nighttime temperatures can promote the accumulation of active forms of GA (GA_1 and GA_4) by inhibiting the expression of *SlGA2ox*, thereby enhancing carpel cell division and increasing the number of fruit locules. However, low-temperature treatment did not significantly alter the expression levels of *SlWUS*, suggesting that the effect of low temperature on locule number may not be mediated by the WUS–CLV3 pathway (Li et al., 2019). Other studies have indicated that low-temperature treatment can lead to increased expression of the *SlWUS* gene, resulting in multiloculed fruits (Wu et al., 2023a). Malformed tomato can also be caused by high-temperature stress. During tomato flower development, transient high temperatures can aberrantly upregulate the expression of *SlWUS*, preventing timely termination of stem cell differentiation in the FM, thus causing fruit deformities. SlCRCa, conversely, suppresses the expression of *SlWUS*, thereby reducing the proportion of malformed tomatoes (Wu et al., 2024a). Plant hormones such as auxins, GA, and cytokinins play crucial roles in regulating the number of locules in tomato fruits (Wu et al., 2024a). Plant growth regulators like 2,4-D and ABA are also widely used to preserve flowers and fruits; however, improper use of these growth regulators (such as excessive amounts or inappropriate timing of application) can easily lead to malformed tomatoes.

Fruit cracking is typically caused by unsuitable environmental conditions, leading to excessive stretching and rupture of the fruit peel. Tomato cracking includes circumferential cracking, striped cracking, radial cracking, and netted cracking. Traits such as fruit hardness and cuticle thickness, which are controlled by genetic actors, as well as cultivation practices, also influence tomato fruit cracking. Cracking usually occurs in mature fruits and is associated with the degradation of cell walls (Jiang et al., 2019; Santos et al., 2023). Fruit cracking not only affects fruit appearance but can also lead to fruit rot, impacting the commercial quality and edibility of the fruit. Compared with cracking-resistant tomatoes, cracking-susceptible tomatoes exhibit higher cellulase activity and lower cellulose content during

maturation. *FRUIT-NETTED-CRACKING* (*FNC*) is a candidate gene controlling the netted-cracking trait in tomato. IL4-4 exhibits a netted-cracking phenotype, which is dominantly inherited. *ORF5* (*Solyc04g082540.1.1*), identified by map-based cloning, is an allele of the previously cloned *Cuticular Water Permeability* (*CWP*) gene, which encodes a DUF833 domain-containing protein and regulates the process of dehydration in fruits. The *CWP* gene is silenced in cultivated tomato varieties as well as in the wild tomato species *S. pimpinellifolium*, and *S. cheesmanii*; however, it is expressed in the wild tomato species *S. pennellii* and *S. harbrochaites* (Hovav et al., 2007; Chechanovsky et al., 2019; Zhang et al., 2021a). A recent study has shown that low temperatures upregulate *CWP* expression and modify its splicing patterns, exacerbating micro-cracking in tomato fruits (Chechanovsky et al., 2019). *SlGH9-15* is a critical candidate gene regulating tomato fruit cracking, and shows higher expression levels in cracking-susceptible genotypes than in cracking-resistant genotypes (Lin et al., 2023). Abiotic stress and stress-related hormones (such as ethylene and ABA) can induce fruit cracking. Additionally, lncRNAs regulate tomato fruit cracking by coordinating the expression of genes related to auxin, ethylene, and ROS signaling and cell wall metabolism (such as *EXP*, *PG*, and *XTH*), which together comprise the hormone–redox–cell wall network (Xue et al., 2020). Silencing of *PG*/*EXP* genes in tomato results in harder fruits with denser cell walls, thicker cuticles, and greater cracking resistance (Jiang et al., 2019). As fruit cracking is a physiological disorder, it cannot be controlled using chemicals such as pesticides. Under greenhouse cultivation conditions, the strict regulation of temperature, humidity, and light through controlled heating, ventilation, and supplemental lighting, along with regular watering and fertilization to maintain soil moisture and fertility levels, can effectively reduce the incidence of fruit cracking.

Yellow shoulder is characterized by uneven fruit coloring, which significantly affects the appearance and market quality of tomatoes. This physiological disorder typically occurs in tomato cultivars with the *Uniform ripening* gene and is often attributed to low levels of K in the fruit. Factors such as overcast or rainy weather, as well as variations in root development, can influence the uptake of K^+ from the soil, making tomatoes more susceptible to yellow shoulder. Foliar applications of potassium sulfate or potassium phosphate after flowering can enhance the K^+ content of the tomato plants, effectively mitigating the occurrence of yellow shoulder in the fruit.

MOLECULAR BREEDING: PROGRESS AND CHALLENGES

Fundamentally, crop breeding is the process of combining multiple superior genomic sequence variations from different germplasm into one or a few genotypes. This process involves the discovery, creation, and recombination of superior sequence variations related to agronomic traits. Traditional breeding methods, such as hybrid breeding, mutation breeding, and polyploid breeding, have made significant contributions to the development of new varieties; however, these methods are time consuming, labor intensive, and exhibit a high degree of randomness, heavily relying on the skill of the breeder. Over the past 30 years, innovative technologies such as MAS, genomic sequencing, and gene editing have been integrated with traditional breeding methods to form a new theoretical and methodological framework for crop genetic improvement known as molecular breeding. Molecular breeding can significantly enhance the efficiency of the discovery, creation, and recombination of genetic variations, thereby shortening the breeding cycle and potentially leading to significant improvements in yield, quality, and biotic and stress resistance, making it the preferred method of cultivar development and improvement in the modern era (Figure 4).

Rapid identification of beneficial variants using multi-omics technologies

The establishment of a molecular breeding plan largely depends on our understanding of the genetic factors and molecular mechanisms underlying agronomic traits in crops. The identification and cloning of genes controlling important agronomic traits can lead to the development of markers for molecular marker-assisted breeding and for identifying candidate genes for genome editing. A comprehensive understanding of the regulatory networks governing complex agronomic traits facilitates targeted molecular design breeding. The identification of genes has primarily been carried out by traditional forward and reverse genetics approaches. The main reverse genetics techniques include RNA interference (RNAi), ectopic transgene expression, and Targeting Induced Local Lesions in Genomes (TILLING). Among these methods, TILLING, using high-throughput detection methods, allows the rapid identification of specific point mutations in genes induced by chemical mutagens such as ethyl methanesulfonate in plant populations. Recent advancements in high-throughput genome sequencing technologies have transformed TILLING into a chip-based method (Wang et al., 2012). It is undeniable that most genes were identified and functionally characterized using reverse genetics methods; however, these genes often cannot be directly applied to practical breeding. By contrast, forward genetics approaches, such as QTL mapping and map-based cloning, enable the discovery of key genes and favorable allelic variations that control important agronomic traits, thus facilitating the direct application of these genetic variations in breeding practices.

Traditional QTL mapping requires precise phenotyping and extensive genotyping of segregating populations, followed by linkage analysis to locate target QTLs (Mir et al., 2012). While widely utilized in tomato research, this approach is time consuming and labor intensive. The advent of high-throughput, low-cost, genomic sequencing technologies has significantly accelerated the QTL mapping process. Next-generation sequencing (NGS) has enabled the large-scale development of molecular markers, particularly SNPs, while the combination of NGS with bulked segregant analysis (BSA) has led to the development of a series of rapid gene mapping methods, such as BSA-seq (for

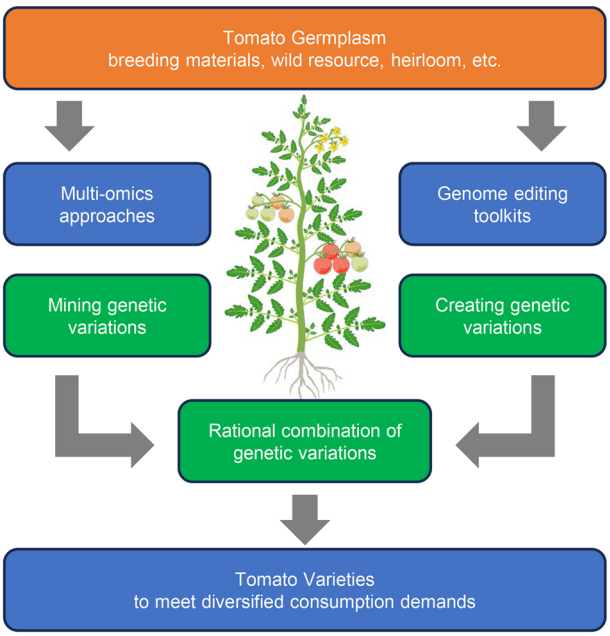

Figure 4. A systematic overview of breeding tomato varieties using various technological tools

qualitative traits), QTL-seq (for quantitative traits), and MutMap (for mutant phenotypes generated during mutagenesis). These gene mapping methods, when integrated with other omics approaches such as RNA-seq and metabolomics, have become mainstream techniques for gene identification. For instance, BSA-seq analysis of an F_2 population showing variation in branching phenotypes facilitated the mapping of genes controlling inflorescence branching, *J2* and *EJ2*, to chromosomes 3 and 12, respectively. Subsequent candidate gene prediction and RNA-seq analyses confirmed that both the *J2* and *EJ2* genes encode MADS-box transcription factors (Soyk et al., 2017a). Similarly, QTL-seq analysis of an F_2 population derived from a cross between *S. galapagense* and a cultivated tomato line led to the identification of the *SP5G* gene, which determines the flowering time in *S. galapagense* by regulating its sensitivity to day length (Soyk et al., 2017b).

The limitations of linkage analysis-based QTL mapping primarily stem from: (i) the limited genetic diversity of parental hybrid segregating populations, where each locus contains only two alleles; (ii) the restricted number of crosses during population construction, leading to fewer recombination events and larger mapping intervals, necessitating subsequent fine mapping to narrow down the mapping intervals. To overcome these limitations, GWAS based on LD analysis was introduced for QTL mapping (Singh et al., 2017). Genome-wide association studies enable the identification of genomic loci associated with phenotypic traits by examining the significance of associations between genome-wide genetic markers and phenotypic variation in large-scale samples, typically derived from natural germplasm collections, thereby elucidating the genetic basis of traits at the population level. Association analysis leverages historical recombination in natural populations (Yu and Buckler, 2006), providing opportunities for higher resolution mapping and the simultaneous identification of QTLs controlling different agronomic traits. Additionally, the sources of genetic variation are more diverse, often allowing for the identification of more trait-associated loci than those found in parental mapping populations. Owing to the presence of LD, when variations that cause phenotypic differences exist in the genome, genetic markers near these variations are also likely to be associated with the phenotype, thereby detecting chromosomal regions containing genes that control phenotypic variation. It is noteworthy that the degree of LD and population structure may lead to false associations between genotype and phenotype. Tomato exhibits significant LD and a strong population structure, which is consistent with its self-pollinating habit and its evolutionary and domestication history. The reconstruction of nested association mapping (NAM) and multi-parent advanced generation intercross (MAGIC) populations can mitigate the effects of strong population structure and allow the stringent selection of candidate genes based on the estimated effects of causal polymorphisms, thereby enhancing the positive rate of GWAS (Yano et al., 2016). Therefore, careful experimental design considering confounding effects, along with robust statistical methods or models, will maximize the ability to identify genes in GWAS (Liu et al., 2016, 2020b). Genome-wide association studies have played a crucial role in the identification of genes controlling important agronomic traits in tomato. For instance, by analyzing 231 tomato germplasms through genome resequencing and GWAS, researchers identified a strong correlation between tomato fruit color (red vs. pink) and a 603-bp InDel variation upstream of the *MYB12* gene (Lin et al., 2014). In addition, *SE3.1*, a key gene controlling style length, was also identified through the GWAS of 277 tomato genotypes (Shang et al., 2021).

The rapid advancement of high-throughput sequencing technologies has enabled the construction of detailed genetic variation maps (variomes) for various tomato cultivars and the development of extensive gene expression blueprints (transcriptomes) across different tissues, environmental conditions, and developmental stages. Concurrently, innovations in metabolite detection technologies, such as liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS), along with the continuous optimization of analytical tools, have led to an astonishing expansion in metabolomics data, ushering in the unprecedented era of big data. The deep integration of these multi-omics data will provide a powerful boost for functional genomics research and breeding in tomato. This integration not only facilitates the precise identification of functional genes but also profoundly reveals the complex regulatory networks governing phenotypes. Early exploratory work, which linked metabolomics and transcriptomics data with a limited number of

genetic variants (such as specific mutants and RILs), has preliminarily demonstrated the close relationship between specific gene expression patterns and metabolite levels (Osorio et al., 2012; Alseekh et al., 2015). Subsequently, an in-depth analysis of over 300 tomato varieties, combined with more than 10,000 SNP loci and gene expression data, successfully uncovered 79 significant association signals underlying more than 30 metabolites (Bauchet et al., 2017). Notably, research focusing on the flavor characteristics of tomato fruit across approximately 400 varieties, in conjunction with detailed sensory evaluations by consumers, accurately identified 28 metabolites that have a decisive impact on flavor traits and consumer preferences (Tieman et al., 2017). Utilizing widespread genetic variations revealed by whole-genome resequencing, researchers conducted a genome-wide metabolic association study (eGWAS) to successfully locate genetic loci affecting the above 28 key flavor metabolites, providing valuable genetic markers for precision breeding. Particularly noteworthy is the comprehensive analysis of a large dataset spanning 399–610 different tomato varieties (Zhu et al., 2018), which not only encompassed comprehensive variome, transcriptome, and metabolome information but also identified 3,526 mGWAS signals, 2,566 *cis*-expression quantitative trait loci (*cis*-eQTL), 93,587 trans-expression quantitative trait loci (trans-eQTL), and 232,934 expression-metabolite correlations. This profound insight from a multi-omics perspective not only elucidates the reshaping effect of the breeding process on the tomato metabolome but also provides a solid theoretical foundation and practical guidance for optimizing fruit quality and cultivating tomato varieties according to consumer preferences.

The multi-omics-based gene mining strategy has been, and will continue to be, applied in the functional genomics research and breeding of tomatoes. It is noteworthy that omics datasets are not limited to genomics, transcriptomics, and metabolomics; the burgeoning fields of epigenetics, proteomics, and phenomics are continuously generating deeper and larger-scale datasets. To effectively harness this data deluge and perform a comprehensive analysis of multi-omics data, we urgently need to make breakthrough advancements in algorithms, tools, and statistical models, particularly in the application of advanced technologies such as machine learning and deep learning (Ballard et al., 2024). The optimization and innovation of these technologies will provide robust support for elucidating the complex mechanisms of the tomato genome. At the same time, we must acknowledge a significant shortcoming in the current functional gene mining efforts in tomato; despite notable achievements in yield enhancement and disease resistance, research on quality improvement and abiotic stress response remains insufficient. This knowledge gap needs to be addressed urgently through increased investment in genetic resources and targeted research, with the aim of achieving breakthrough advancements in the future.

Precise creation of variants using genome-editing technologies

Long-term domestication and improvement have led to a reduction in the genetic diversity and adaptability of tomato. Artificially induced mutations allow the introduction of new allelic variations, providing novel genetic resources for gene function discovery and cultivar improvement. Traditional methods of artificial mutation induction involve the construction of mutant libraries using physical mutagens (such as X-rays, γ-rays, ion beams, and fast neutrons), chemical mutagens (such as EMS, sodium azide, and colchicine), and biological mutagens (such as transposons and T-DNA insertions). With the emergence of various innovative technologies, artificially induced mutant libraries have shown broad application prospects in functional gene identification and plant breeding. On the one hand, reverse genetics techniques such as TILLING can be used to rapidly identify specific allelic mutations using the mutant library; on the other hand, forward genetics strategies like MutMap can facilitate rapid gene mapping and cloning in mutants exhibiting specific phenotypes. Over the past few decades, various mutant libraries have been developed in different tomato varieties, such as M82, Red Setter, and MicroTom (Saito et al., 2011). For instance, a mutant library comprising 13,000 M2 families was created on the M82 genetic background using EMS and fast neutron mutagenesis. The M2 mutants could be categorized into 15 major classes and 48 subclasses, based on their phenotypes. Most mutations in this library led to pleiotropic phenotypes, and the associated phenotypic data can be accessed on the “Genes that Make Tomatoes” website (Menda et al., 2004). However, the construction of mutant libraries is a labor-intensive and time-consuming process, and mutagenesis treatments often result in multi-locus mutations in the genome, with mutation sites being random. This randomness can deter researchers from constructing mutant libraries, thus limiting the creation of new allelic mutations for crop genetic improvement.

In recent years, genome-editing tools, represented by CRISPR/Cas9, have emerged as powerful technologies for creating allelic mutations. Genome editing refers to the precise and targeted modification of the genome, marking one of the most significant advancements in the field of molecular biology. Traditional transgenic techniques also involve modifications at the genomic level and can be considered a form of genome editing; however, their core focus is on introducing functional exogenous gene fragments into organisms, with the insertion sites often being random. By contrast, genome-editing tools such as CRISPR/Cas9 can induce insertions and deletions at specific genomic loci. Although this technology also involves the introduction of foreign DNA, its insertion sites are generally not linked to the target editing sites in the genome. Once the target genomic region has been successfully edited, the inserted foreign DNA fragments can be eliminated through subsequent hybridization, making these edited plants essentially non-transgenic. Moreover, compared with traditional backcross

breeding, genome editing can rapidly and precisely improve target traits without linkage drag, thereby opening new avenues for plant breeding and genetic improvement. Furthermore, while the application of CRISPR/Cas9 is limited by its requirement for a specific protospacer adjacent motif (PAM) sequence featured by a 5′-NGG-3′ pattern, the discovery of Cas variants such as Cas12a (also known as Cpf1), which recognize a distinct 5′-TTTN-3′ PAM sequence, has significantly broadened the scope and versatility of genome-editing applications (Gao et al., 2017). Due to its significant simplicity and applicability compared with the previous two generations of genome-editing tools (ZFN and TALEN), the CRISPR/Cas system has quickly become a superstar among genome-editing tools (Zhang et al., 2019).

In recent years, CRISPR/Cas9 gene editing technology has demonstrated extensive application potential for the validation of gene function and optimization of target traits in tomato. The most commonly employed approach involves introducing frameshift mutations in the coding region of target genes to achieve gene inactivation (i.e., gene knockout). In tomato, CRISPR/Cas9-mediated knockout of the *MLO1* gene conferred significant resistance to powdery mildew (Nekrasov et al., 2017), while the knockout of the *SlDMR6-1* gene conferred broad-spectrum disease resistance (Thomazella et al., 2021). Furthermore, CRISPR/Cas9-mediated knockout of *SlAGL6* induced parthenocarpy in tomato, thereby enhancing fruit yield under high-temperature conditions (Klap et al., 2017). Moreover, CRISPR/Cas9 has also been utilized to enhance the nutritional value of tomatoes. Japanese researchers introduced frameshift mutations in the self-inhibitory domain of *SlGAD3*, significantly increasing the GABA content of tomato fruits by 7- to 15-fold, thereby providing a potential avenue for developing tomato products with antihypertensive and stress-relief functions (Nonaka et al., 2017). Researchers knocked out the gene encoding 7-dehydrocholesterol reductase, resulting in the accumulation of 7-dehydrocholesterol (7-DHC), a precursor of vitamin D_3, in tomato fruits and leaves. The gene-edited tomato variety is expected to become a new dietary source of vitamin D_3, offering potential health benefits to humans (Li et al., 2022a). Additionally, CRISPR/Cas9-mediated knockout of *CRTISO* and *PSY1* genes, which are involved in the carotenoid biosynthesis pathway, resulted in plants with orange and yellow tomatoes, respectively (Dahan-Meir et al., 2018). In our previous work, we used a CRISPR/Cas9-mediated multiplex gene editing system to target and knock out *PSY1*, *MYB12*, and *SGR1* genes in red-fruited tomato varieties, successfully obtaining seven different fruit colors in the hybrid progeny of edited plants, thereby achieving precise creation of fruit colors (Yang et al., 2023). In another study, simultaneous knocking out of *SlExp1* and *SlCel2* not only enhanced cell adhesion and firmness, but also stabilized tomato flavor quality during the ripening process, paving the way for breeding new tomato varieties capable of maintaining fruit taste and quality during storage and transport (Su et al., 2024). Additionally, CRISPR/Cas9 has been used to create male-sterile lines and haploid induction lines, providing robust technical support for modern tomato breeding (Du et al., 2020). In summary, the CRISPR/Cas9 gene editing system has profoundly transformed the landscape of tomato breeding and functional gene research, injecting new vitality into agricultural production and food safety. Furthermore, CRISPR/Cas9 technology can also be utilized for high-throughput gene knockout. By designing and synthesizing a plasmid library containing 4,379 sgRNAs targeting 990 transcription factors, a tomato transcription factor mutant library was successfully created in M82 (Bi et al., 2023).

As previously mentioned, the primary application of genome editing lies in the generation of loss-of-function mutants by targeting gene coding regions. Loss-of-function mutants possess unique advantages in characterizing gene functions; however, for genetic improvement, the loss of function of important genes does not always yield phenotypes of agricultural value (Zhu and Qian, 2020). Mutations that arise during the domestication process often fall into the categories of “weak alleles” or “quantitative alleles,” and the phenotypes of such alleles can be achieved by fine tuning gene expression levels rather than complete gene inactivation. To achieve this goal, scientists have shifted their focus from editing gene coding sequences to editing gene regulatory regions containing *cis*-regulatory elements (CREs). For instance, using the CRISPR/Cas9 system, researchers could precisely target a CArG regulatory element, a MADS-box transcription factor binding site, downstream of the *SlWUS* gene. A 4-bp deletion was created within this CArG element, resulting in an edited line, with 10% of the fruits exhibiting the three-locule phenotype (Rodríguez-Leal et al., 2017). This phenotypic change is moderate compared with the severe developmental defects observed in the knockout mutants of *SlWUS*, highlighting the advantages of fine tuning gene expression. Furthermore, using CRISPR/Cas9 multiplex gene editing, the promoter activity of several genes, including *SlCLV3*, *S*, and *SP*, could be precisely modified. This strategy successfully produced a series of weak-allele mutants targeting key agronomic traits such as fruit locule number, inflorescence branching pattern, and shoot architecture, thereby opening new avenues for crop genetic improvement. To achieve crop genetic enhancement, many key trait-related regulatory genes need to be manipulated, with the aim of improving gene expression or protein translation efficiency rather than reducing or abolishing gene function (Reis et al., 2019). uORFs present in the 5′UTRs of many eukaryotic mRNAs play a crucial role in translation regulation, as they can inhibit the translation initiation of the subsequent main open reading frames (mORFs) (Kurihara, 2020). Based on this finding, scientists have proposed an innovative strategy to finely regulate translation efficiency by precisely editing uORFs, thereby optimizing target traits. For example, by editing a uORF involved in translation repression upstream of *SlbZIP1*, researchers could significantly enhance the sugar and amino acid contents of tomato fruits (Nguyen et al., 2023).

It is important to note that research into the precise editing of CREs and uORFs using the CRISPR/Cas system is still limited, primarily because of a lack of understanding of the transcription and translation mechanisms of important trait-related genes. Certain CREs and uORFs have been identified using the recently developed omics approaches, such as DNase-seq, ATAC-seq, and ribo-seq. Further in-depth investigation of the role of CREs and uORFs in gene expression and translation regulation will undoubtedly broaden the application prospects and potential of genome-editing technologies.

In addition to inducing InDels via the NHEJ repair mechanism triggered by DNA DSBs, the CRISPR/Cas system can also achieve precise editing through the homology-directed repair (HDR) mechanism. After the creation of DSBs, if a donor DNA template containing sequences homologous to the target site is present, the intrinsic HDR mechanism can facilitate the insertion or replacement of large DNA fragments at the target site. However, the probability of HDR is much lower than that of NHEJ; therefore, optimizing the HDR experimental conditions is crucial for improving gene editing efficiency. So far, HDR has been used to induce base substitution in tomato. The CRISPR/Cas-mediated HDR technology was used to precisely replace the *ALC* gene, resulting in a new tomato germplasm with a longer shelf life (Yu et al., 2017). Derivative tools of CRISPR/Cas, such as base editors (BEs) and prime editors, can induce specific base changes without causing DSBs, providing an efficient, simple, and universal strategy for nucleotide substitutions at target sites (Zong et al., 2018; Vu et al., 2022). The principle of base editing is to fuse a catalytically inactive Cas protein (such as deactivated Cas (dCas)) or a Cas protein with single-strand nickase activity (such as nickase Cas (nCas)) to a deaminase that acts on single-stranded DNA (ssDNA), enabling base substitution at the target site. Currently, BEs are divided into two types, depending on the base-modifying enzyme: cytosine base editors (CBEs) and adenine base editors (ABEs). Without generating DSBs, CBEs and ABEs, respectively, can use cytosine deaminase or a modified adenine deaminase to perform the deamination of cytosine (C) or adenine (A) within a certain range of the target site. Eventually, through DNA repair or replication, precise C→T or A→G substitutions are achieved (Zong et al., 2018). A CBE was first applied to tomato in 2017 to edit two hormone signaling genes, *DELLA* and *ETR1*, using target-activation-induced cytidine deaminase (Target-AID), with editing efficiencies ranging from 26.2% to 53.8% (Shimatani et al., 2017). Specific amino acid substitutions in acetolactate synthase can increase the resistance to acetolactate synthase-inhibiting herbicides. Researchers used the CBE system to target the tomato acetolactate synthase gene *ALS1* for base substitution and successfully created tomato plants resistant to chlorsulfuron herbicide, due to the amino acid substitution at proline-186 in ALS1 (Veillet et al., 2020).

PEs are another type of CRISPR/Cas-derived tool that emerged after the BEs. PEs can induce arbitrary base substitutions and precise small-fragment deletions and insertions without causing DNA DSBs, representing a major revolution in the field of genome editing. The prime editing system has been proven to be effective in plants such as rice, wheat, corn, tomato, potato, tobacco, and Arabidopsis. In tomato, a modified prime editing system was successfully used to improve the content of total soluble solids (TSSs) in tomato fruits and to improve fruit yield under both normal and high-temperature conditions (Vu et al., 2022; Lou et al., 2024; Wang et al., 2024f). However, currently, the editing efficiency of PEs is relatively low, and there are significant differences in editing efficiencies at different loci; therefore, further optimization of PEs is required.

In summary, the CRISPR/Cas genome-editing technology has shown revolutionary application potential in the precise genetic improvement of tomato. In 2022, Sanatech Seed Company (Japan) launched the world's first tomato variety edited by CRISPR/Cas9 technology, “Sicilian Rouge.” The uniqueness of Sicilian Rouge tomatoes lies in their high GABA content, which is four to five times higher than the GABA content of ordinary tomatoes, bringing consumers unprecedented health benefits. However, the promotion of gene-edited products is challenging, especially in countries with stringent regulatory policies surrounding the commercialization of gene-edited plants. In the European Union, strict genetically modified organism supervision will be applied to targeted genome-editing tools, even if the final product does not contain any genetically modified ingredients. Compared with genome editing based on traditional transgenic technologies, genome editing without transgenic steps can effectively reduce the risks of off-target effects and cytotoxicity and can provide a new practical path for the commercialization of edited plants to avoid complex transgenic supervision.

Utilization of wild resources for enhancing genetic diversity

Modern cultivated tomatoes are domesticated from *S. pimpinellifolium*. Various types of tomato varieties have been selected through the processes of domestication and breeding to meet consumer requirements. However, owing to the domestication bottleneck and long-term artificial selection, the genetic diversity of cultivated tomato varieties has been greatly reduced, resulting in the loss of many excellent agronomic traits, including tolerance to biotic and abiotic stresses. The narrow genetic background of tomato has become a major limiting factor restricting breakthrough research in tomato breeding. Unlike cultivated tomato, *S. pimpinellifolium* and other wild species have not been subjected to strict artificial selection. After a long period of evolution, wild tomato species have retained a large number of allelic variations, related to important agronomic traits, in their different ecological environments, showing extensive genetic and phenotypic diversity and representing an important genetic resource for tomato breeding. Therefore, the utilization of wild resources is an important way to restore the

genetic diversity of cultivated tomato and overcome the breeding bottleneck.

Over the last 100 years, the utilization of wild resources has greatly promoted the process of tomato breeding. The most successful example is the identification and transfer of disease-resistance and pest-resistance genes from wild germplasm into cultivated varieties. Cultivating disease-resistance and pest-resistant varieties is the most economical, safe, and efficient means of controlling diseases and pests. Modern cultivated tomato varieties can generally resist 5–10 diseases. Most of the disease-resistance genes or loci are derived from wild species. Humans tried to transfer the leaf mold resistance gene from *S. pimpinellifolium* into cultivated tomato as early as 1917. To date, more than 40 disease and pest-resistance sources have been found among wild tomato species. Among them, *S. chilense*, *S. peruvianum*, *S. habrochaites*, *S. pennellii*, and *S. pimpinellifolium* have been confirmed as the richest reservoirs of resistance genes (Foolad et al., 2003). So far, at least 30 disease and pest-resistance loci have been identified in these wild species and transferred into cultivated tomato varieties (Ji et al., 2007). While this process depends on traditional backcrossing and transfer breeding, it also integrates MAS, mainly because disease-resistance and pest-resistance traits are mostly qualitatively controlled by single genes or major loci. During the transfer, disease-resistance genes are accompanied by flanking DNA sequences, making the introgressed chromosomal fragments extremely large. For example, the chromosomal introgression fragments containing the tomato mosaic virus resistance gene *Tm-2a* (derived from *S. peruvianum*), TYLCV resistance gene *Ty-1* (derived from *S. chilense*) and RKN resistance gene *Mi-1* (derived from *S. peruvianum*) were approximately 51 Mb, 30 Mb, and 26 Mb in length, respectively, and occupied at least 50% of the whole chromosome (Lin et al., 2014). As *Ty-1* and *Mi-1* were both transferred to chromosome 6, with almost a complete overlap between their introgression fragments, achieving homozygous alleles for both these genes simultaneously in one genetic background is extremely difficult. The extra-long length of introgression fragments may be caused by factors suppressing chromosomal crossover, such as chromosomal inversion. These ultra-long fragments from wild species often carry deleterious alleles, resulting in the so-called linkage drag. For example, the *Fusarium* wilt resistance gene *I-3* derived from *S. pennellii* increased the susceptibility of cultivated tomato to bacterial spot, primarily because of the negative effects of the large DNA sequences flanking the *I-3* locus (Li et al., 2018a). The key to avoiding linkage drag is to introduce the target gene accurately while eliminating the closely linked, potentially deleterious genes. The realization of this goal depends on the detailed study of the linkage-drag genomic map, wide application of high-density genotyping technology, and continuous innovation and development of intelligent breeding systems. This will allow the accurate tracking of recombination events in the breeding population, thus eliminating linkage drag. For example, the construction of a large inversion map based on multiple diploid potato genome assemblies has provided insight for eliminating potential linkage drag (Tang et al., 2022). The mention of CRISPR/Cas9 technology is particularly noteworthy, as it has been used to modify the structure of plant chromosomes by mediating large-scale inversions in the target region (Schwartz et al., 2021) or inducing chromosomal translocations between heterologous chromosomes (Beying et al., 2020), thus providing strong technical support for accurately manipulating genetic linkage and breaking or repairing undesirable linkage structures in plants.

Wild tomato species have also been widely used for the improvement of fruit traits, such as fruit quality, in cultivated tomato. For example, the $AgpL1^{H}$ allele derived from *S. habrochaites* LA1777 increased the starch content of immature fruits and the SSC of mature fruits (Petreikov et al., 2006). A recessive locus from *S. chmielewskii* LA1028, *sucr*, was used to increase the sucrose content, total sugar content, and SSC of mature fruits (Chetelat et al., 1995). *Brix9-2-5*, a QTL from *S. pennellii* LA0716 that controls the fruit SSC, increased the glucose and fructose contents of tomato fruits by 28% and 18%, respectively (Fridman et al., 2004). In addition, the allele of the *Fgr* gene derived from *S. habrochaites* LA1777 increased the ratio of fructose to glucose in tomato fruits (Shammai et al., 2018). Wild tomato species also show tolerance to different abiotic stresses and adaptability to extreme environmental conditions. For example, *S. chilense* can thrive in arid desert environments by virtue of its deep main root and wide-reaching secondary roots. *Solanum pennellii* can survive drought conditions due to its excellent water use efficiency. Similarly, *S. cheesmanii* and *S. peruvianum* are able to survive in saline–alkaline coastal areas, because of the unique adaptation mechanisms of their root systems. In addition, some *S. habrochaites* and *S. lycopersicoides* accessions also have excellent cold tolerance (Guo et al., 2024).

There are many obstacles that discourage the transfer of genetic material from wild species into cultivated germplasm, such as hybridization incompatibility between wild and cultivated species, infertility of F_1 hybrids, infertility of segregating populations, and linkage drag. Therefore, wild resources are mainly used to improve simple traits in cultivated lines, that is, traits controlled by single genes such as disease and pest resistance; improving the yield, quality, and abiotic stress resistance of the cultivated germplasm using wild resources is challenging, because these traits are genetically complex are influenced by QTL–QTL and QTL–environment interactions, making it difficult to infer genotypes based on phenotypes, thus reducing selection efficiency. Introgression line populations are generated by crossing the donor (wild species) with the recipient (cultivated species), followed by multiple backcrosses. An ideal IL population is one in which all plants collectively cover the entire genome of the donor and each individual plant only contains a single chromosomal fragment of the donor. Tomato is the first crop with a single-segment IL population, constructed using MAS, and also the

crop with the most in-depth application of ILs for QTL research and utilization of wild resources. The first IL population in tomato was constructed using *S. pennellii* LA0716 as the donor and the cultivated tomato variety M82 as the recipient (Eshed and Zamir, 1994). This IL population initially consisted of 50 ILs, and each IL contained a single chromosomal fragment from *S. pennellii* LA0716 (Eshed and Zamir, 1994). Furthermore, 26 new ILs were decomposed from these 50 lines again. The *S. pennellii* IL population, now comprising 76 ILs, has been widely used for mapping QTLs related to yield, fruit quality, biotic and abiotic stress tolerance, and other traits. For example, researchers used a population of 504 high-generation backcross inbred lines (BILs) and 76 ILs derived from a cross between M82 and LA0716 to conduct multi-angle analysis of tomato fruits, including RNA-seq of tomato fruits at different developmental stages, mass spectrometry-based metabolomics, and pathogen susceptibility analysis. The massive data generated were used for multi-level QTL analysis to determine the causal relationship between genomic sequence variation and gene expression and metabolite level changes in tomato fruits and to determine the final phenotypic changes in fruit quality and *B. cinerea* resistance levels (Szymański et al., 2020). In addition, several other IL or BIL populations generated by hybridization between cultivated tomato lines and wild tomato species (such as *S. habrochaites*, *S. chmielewskii*, *S. lycopersicoides*, *S. pimpinellifolium*, and *S. sitiens*) have been constructed using MAS methods (Monforte and Tanksley, 2000; Canady et al., 2005; Do et al., 2010; Barrantes et al., 2014; Chetelat et al., 2019; Torgeman et al., 2024). In recent years, people have begun to consider multi-parent advanced generation intercross MAGIC populations for mining the superior traits of wild tomatoes and expanding the genetic diversity of cultivated tomatoes. A MAGIC population is generated by pairwise hybridization of multiple parents, followed by several generations of inbreeding or selfing to produce a stable population. Theoretically, the genetic information of each individual in the progeny represents the genomic information of all parents. Therefore, the main advantages of MAGIC populations include the large number of allelic variations and the ability to detect the genetic effects of different locus combinations. The genetically superior lines selected from the MAGIC population can be used as intermediate materials for breeding and can also be flexibly applied to the accurate mapping of QTLs. The first MAGIC population in tomato was constructed from four cultivated varieties and four SLC accessions and contained 397 MAGIC families. This population has been used to map heat tolerance and FW QTLs in tomato (Pascual et al., 2015; Bineau et al., 2021). Subsequently, a MAGIC population containing 400 families was constructed from seven cultivated tomato germplasms and *S. cheesmaniae* LA1407, with the aim of identifying unique diseases and pest resistance, stress tolerance, and high adaptability traits in LA1407 (Campanelli et al., 2019). Recently, a MAGIC population comprising 354 families was constructed using four SLC and four *S. pimpinellifolium* accessions for mapping fruit size-related, leaf morphology-related, and earliness-related QTLs (Arrones et al., 2024).

Introducing excellent traits from wild tomato species into cultivated tomato germplasm through traditional hybridization takes many years and is often accompanied by linkage drag. Based on the in-depth understanding of the genetic basis of tomato domestication, the *de novo* domestication of wild tomato species through the precise manipulation of several key domestication genes using the CRISPR/Cas9 genome-editing technology was proposed. Researchers selected *S. pimpinellifolium*, which exhibits resistance to saline–alkaline stress conditions and bacterial spot disease, as the basic material and targeted the coding regions of genes controlling photoperiod sensitivity and plant architecture (*SP* and *SP5G*), the CREs of genes controlling fruit size (*SlCLV3* and *SlWUS*), and the uORF of the gene encoding vitamin C synthase (*SlGGP1*) using CRISPR/Cas9 gene editing technology. In total, 140 independent gene-edited lines were obtained. Genotypic and phenotypic analyses of these edited lines revealed that the experiment was successful. Editing of the *SP* and *SP5G* genes eliminated the photoperiod sensitivity of wild tomato, overcoming the geographical range limitations of cultivation, and transformed the indeterminate plant architecture, late flowering habit, and sparse fruit setting of *S. pimpinellifolium* into a compact double determinate plant architecture with improved fruit setting rate, synchronized ripening, and enhanced harvest index. Editing the CREs of *SlCLV3* and *SlWUS* and the uORF of *SlGGP1* increased the size and vitamin C content of wild tomato fruits. Thus, researchers accurately introduced yield and quality traits into the wild species *S. pimpinellifolium*, without sacrificing its natural resistance to saline–alkaline conditions and bacterial spot disease, accelerating the artificial domestication of wild tomato species (Li et al., 2018d). In another study, scientists produced newly domesticated tomato plants with altered fruit number, size, shape, nutritional content and plant architecture by simultaneously editing six genes in *S. pimpinellifolium*. The fruits of edited lines contained fivefold more lycopene than those of widely cultivated varieties (Zsögön et al., 2018). The above two studies represent the first reports of the rapid domestication of wild tomato species through gene editing, providing a new strategy for the utilization of wild germplasm. With advancements in genome editing, genome design, or synthetic biology methods and in our understanding of the genomic basis of tomato domestication, knowledge-driven re-domestication of wild tomatoes will prove to be a reliable and efficient genetic improvement tool.

Utilization of innovative technologies for accelerating the combination of genetic variation

The development of new crop varieties relies primarily on hybridization, self-pollination, and selection. Selecting individual plants, families, or populations that contain combinations of beneficial genetic variations is a crucial step for

crop improvement. Traditional conventional breeding involves direct selection based on phenotype, often referred to as empirical breeding; however, this process is time consuming, labor intensive, and sensitive to environmental factors, resulting in low selection efficiency. With a deeper understanding of the genetic basis of important agronomic traits, researchers use closely linked molecular markers to directly select plant genotypes with the target traits (MAS). MAS achieves the transition from phenotypic selection to genotypic selection, offering significant advantages over traditional breeding in both selection efficiency and precision. To date, MAS has been widely applied to the breeding of superior tomato varieties, with notable efficacy in the selection of qualitative traits controlled by single genes or major loci (such as disease resistance). For instance, by integrating MAS and phenotypic evaluation methods, researchers pyramided genes conferring resistance to late blight (*Ph-2* and *Ph-3*), TYLCV (*Ty-2* and *Ty-3*), bacterial wilt (*Bwr-12*), *Fusarium* wilt (*I2*), TMV (*Tm-2a*), and gray leaf spot (*Sm*), thus obtaining breeding lines resistant to six diseases (Hanson et al., 2016). With the rapid development of high-throughput molecular marker detection technology, genomic resequencing, and biostatistical analysis methods, MAS has become indispensable for modern breeding. In addition to being directly applied in the breeding process (such as gene pyramiding and backcross breeding), MAS also shows great potential in genetic diversity analysis, hybrid vigor prediction, seed purity and authenticity testing, DNA fingerprinting, and IL population construction.

For qualitative traits with known major genes or QTL information, MAS is more efficient when selecting based on one or a few closely linked markers. However, for complex traits with low heritability and unclear major genes, the effectiveness of MAS is low. In contrast with MAS, Genomic Selection (GS) generates predictive models using high-density molecular markers covering the entire genome to estimate breeding values. This approach allows accurate predictions of complex traits, especially traits that exhibit low heritability, that are controlled by multiple genes, and are difficult to measure, truly enabling genomic technology to guide breeding practices. Genomic Selection estimates the effect values of different chromosomal segments or individual markers from a large number of genetic markers across the whole genome, and then sums up the segment or marker effect values across the whole genome of an individual to obtain the Genomic Estimated Breeding Value. This process is based on the theoretical assumption that, among the high-density molecular markers distributed across the entire genome, at least one marker is in LD with the QTL affecting the target trait, allowing the effect of each QTL to be reflected through molecular markers. GS requires two populations: a training population, with phenotypic and genotypic data for estimating marker effect values and building a reference model; and a prediction population, with only genotypic data for obtaining estimated breeding values using the reference model, thereby predicting phenotypes and facilitating individual selection. GS can shorten the breeding cycle, accelerate the breeding process, reduce costs, and facilitate modern breeding, with precision and high efficiency, through the early prediction and selection of individuals. GS has been applied in the tomato breeding process. For example, using genome resequencing data as well as yield and SSC data obtained from an F4 segregating population grown under high-temperature conditions, Cappetta et al. (2021) constructed a GS prediction model, with accuracies of 0.729 for yield and 0.715 for SSC under high-temperature conditions, indicating the significant potential of GS in breeding tomato lines with high stress tolerance levels. However, the application of GS is limited by the vast amounts of genotypic and phenotypic data required for model prediction and the complexity of data management and analysis. New statistical models and algorithms represented by artificial intelligence and machine learning provide new methods for dealing with complex and high-dimensional genotypic and phenotypic data. Therefore, processing big data based on efficient and accurate machine learning models and algorithms, effectively eliminating environmental noise to improve the accuracy of breeding prediction, is the key to crop improvement in the future.

The tomato varieties currently used in production are mainly hybrids, making the generation of parental inbred lines a critical step in breeding. Traditional methods of obtaining tomato inbred lines generally require multiple generations of self-pollination, which is time consuming and inefficient. DH breeding, a method that involves inducing haploid plants (through inducer lines or anther culture) and then doubling the chromosome number (naturally or through chemical treatment) to restore the normal chromosome number, can produce genetically pure lines within a short period (two generations). Thus, DH breeding accelerates the selection of superior varieties. Despite the ongoing efforts to establish rapid haploid breeding systems in dicot crops such as tomato, breakthroughs have been limited. Previous studies have demonstrated that microspore cultivation could serve as a potential method for obtaining haploids in tomato, however, no reliable and efficient methodology was established (Sharp et al., 1971; Marin-Montes et al., 2022). Recently, by knocking out the *SlDMP* gene, a homolog of the key inducer gene *ZmDMP* in maize, Zhong and colleagues created tomato plants that can produce seeds with a certain proportion of maternal haploids in both hybrid and self-pollinated offspring. This demonstrates that the mutation of *SlDMP* in tomato possesses independent haploid induction capability, named DMP-HI. High-throughput sequencing of the haploids generated by hybridization confirmed that these haploids do not carry any chromosomes from the paternal parent, indicating that the DMP-HI system induces pure maternal haploids. To overcome the technical bottleneck of haploid plant identification, the authors have successively established methods for the rapid identification of haploids in tomato based on fluorescence marking and seedling color marking. Using these methods, the tomato haploid inducer

line (as the male parent) was crossed with dozens of materials, successfully producing maternal haploids with an induction rate ranging from 0.5% to 3.7% and averaging at 1.9% (Zhong et al., 2022; Wang et al., 2023a). This indicates that the DMP-HI-based tomato haploid induction system does not show significant genotype dependence. The research results not only played a foundational and leading role in the development of rapid haploid breeding technology in tomato but also paved a new way for creating a universal cross-species haploid breeding system and improving the utilization of hybrid vigor in other crops. However, compared with the high induction rate of maize haploid inducer lines (>10%), the current induction rate of DMP-HI is relatively low. Future studies should focus on developing tomato haploid inducer lines with higher induction rates.

The role of haploid inducer lines extends beyond the rapid creation of parental inbred lines. Recently, scientists innovatively integrated haploid induction with genome-editing technology to develop a breeding technique that simultaneously achieves trait improvement and inbred line creation in commercial hybrid varieties within a short time period; this method is named Haploid Inducer-Mediated Genome Editing (IMGE) or HI-edit. IMGE involves the introduction of CRISPR/Cas9 gene editing vectors aimed at improving target traits into haploid inducer lines. The resulting haploid inducer lines carry a CRISPR/Cas9 cassette targeting a desired agronomic trait to pollinate an elite inbred line and to generate genome-edited haploids in the elite background. The chromosome number of haploid plants is then doubled to produce DH inbred lines with improved traits (Kelliher et al., 2019; Wang et al., 2019a). However, it should be noted that the currently developed IMGE or HI-edit technology is based on haploid induction mediated by *MATRILINEAL* (*MATL*) or *CENH3* mutations, which operate through the elimination of the paternal genome after fertilization. The haploid induction mechanism mediated by *DMP* mutations may differ; therefore, whether this technology can be generalized to tomato DMP-HI inducer lines remains to be tested. DH breeding also has great potential for future reverse breeding (Dirks et al., 2009). Traditional hybrid breeding focuses on selecting new hybrid varieties with excellent traits from carefully formulated homozygous self-pollinated lines. By contrast, reverse breeding opens a new pathway, starting with the identification of highly heterozygous individual plants with excellent traits in hybrid varieties or breeding populations that exhibit good performance, aiming to reverse the operation for obtaining homozygous lines that can be used to reconstruct these heterozygous genotypes. The key steps in implementing reverse breeding for the reconstruction of heterozygous genotypes include: (i) suppressing recombination between homologous chromosomes in heterozygous plants through plant transformation, VIGS, or chemical treatments; (ii) using haploid inducer lines to induce a large number of haploids, the chromosome numbers of which are then doubled to produce DH lines; (iii) analyzing the genetic composition of each DH line using genome resequencing or high-throughput genotyping techniques; and (iv) selecting complementary DH lines for crossing to reconstruct the genetic makeup of the original hybrids or excellent heterozygous individual plants. Although reverse breeding heralds a potential revolution in the field of crop breeding, its technical details are not yet fully mature and are largely confined to theoretical discussions and proof-of-concept studies.

Apomixis is a phenomenon that allows plants to produce seeds that are genetically identical to the maternal genotype. Thus, apomixis has been hailed as the “asexual reproduction revolution” in hybrid breeding and holds significant potential for fixing hybrid vigor, improving breeding efficiency, and reducing seed production costs. In recent years, a series of important advancements has been made to artificially induce apomixis (Wang et al., 2019b; Vernet et al., 2022; Xiong et al., 2023). Two elements must be satisfied to induce apomixis artificially: (i) transformation of meiosis into a mitosis-like process for producing functional gametes that are genetically identical to the maternal genotype, known as clonal gametes; and (ii) independent development of the egg cell without normal fertilization, a phenomenon known as parthenogenesis, by inducing the production of maternal haploids. In rice and Arabidopsis, simultaneously mutating three genes involved in meiotic regulation, including *PAIR1*, *REC8*, and *OSD1*, can convert meiosis into mitosis (Mitosis instead of Meiosis (MiMe)), producing clonal gametes. Combining MiMe with parthenogenesis can yield seeds through apomixis, successfully creating asexual reproduction. For instance, the CRISPR/Cas9-mediated simultaneous knocking out of the *PAIR1*, *REC8*, *OSD1*, and *MTL* genes in the rice variety “Chunyou 84” resulted in the development of Fix (Fixation of hybrids) material capable of apomictic reproduction (Wang et al., 2019b). In tomato, *MiMe* mutants that can bypass meiosis were also obtained by simultaneously knocking out *SPO11-1*, *REC8*, and *TAM* (Wang et al., 2024d). To confirm that *MiMe* mutants can produce cloned diploid gametophytes, researchers conducted phenotypic and genotypic analyses of F_1 hybrids, F_2 progeny, and the selfed progeny of *MiMe* mutants. The results showed that, compared with the genetically diverse F_2 population, tetraploid plants produced by *MiMe* mutants did not undergo recombination and exhibited consistent phenotypic characteristics. More interestingly, by crossing different *MiMe* mutants, entirely new tetraploid genotypes, with four sets of grandparental genomes, were obtained. This highlights the immense potential of *MiMe* in polyploid genome design breeding in tomato; for example, integrating the complete genomes of wild tomato species into a tetraploid genetic background to enhance the biotic and abiotic stress tolerance of cultivated tomato varieties.

PERSPECTIVES

As outlined above, tomato breeding has evolved through four stages, and we are currently in a transitional period from Breeding 4.0 to Breeding 5.0. Undoubtedly, the advent of

Breeding 5.0 will usher in a transformative era for tomato breeding programs, which will largely rely on multi-omics data and artificial intelligence technologies. Additionally, it will integrate biotechnologies including gene editing and synthetic biology.

An important objective of crop genomics and other omics approaches is to enhance our understanding and predictive capabilities regarding crop phenotypes. However, the measurement of crop phenotypes is more complex compared with genomics or other omics fields, primarily due to the high plasticity of crop phenotypes: the same genotype may exhibit diverse phenotypes under different environmental conditions. Furthermore, breeding goals with commercial value, such as yield enhancement, involve the combined effects of plant physiology, morphology, anatomy, and chemical properties. Consequently, numerous phenotypic measurements focus on analyzing one or more of these constituent elements, such as photosynthesis efficiency, root system structure, or aboveground biomass, and further predict yield using crop models (Parent and Tardieu, 2014). The rise of high-throughput phenomics provides unprecedented opportunities for accurately capturing crop phenotypic traits (Houle et al., 2010). The application of drones, field robots, and various sensors enables automated collection of phenotypic and environmental data, which not only significantly reduces the workload, improves data accuracy, but also accelerates research on gene–environment interactions (GxE) (Yang and Jostins-Dean, 2022).

Artificial intelligence (AI) has become an indispensable and powerful tool in the field of precise phenotypic analysis. In recent years, "deep" machine learning methods, especially algorithms based on the Artificial Neural Network, have achieved breakthroughs in the field of image analysis. These technologies greatly enhance the accuracy of plant feature recognition, such as precise localization of root tips (Pound et al., 2017), automatic counting of leaf numbers (Ubbens et al., 2018), and efficient derivation of vegetation indices from RGB images (Khan et al., 2018). Additionally, AI has driven innovations in plant disease detection technologies (Mahlein, 2016; Mohanty et al., 2016; Fuentes et al., 2017) and in-depth analysis of plant stress phenotypes (Ghosal et al., 2018). Beyond phenotypic analysis, AI holds significant potential for mining biological information from massive omics data. As AI technology continues to advance, it will enable the deep mining of omics data from various plants, facilitating the analysis of gene regulatory networks, guiding precise gene editing, and significantly accelerating the plant breeding process.

The rapid development of synthetic biology has made it possible to create novel biological functions or modules in plant genomes. Plant synthetic biology (PSB) aims to comprehensively reconstruct plant systems and their biological components using engineering principles (Meng and Ellis, 2020), holding great potential to reshape the agricultural sector (Nemhauser and Torii, 2016). For example, through complex engineering of the carotenoid pathway, scientists successfully synthesized the high-value pigment "ketocarotenoid" in tomato fruits (Nogueira et al., 2017). The integration of synthetic biology, AI, and gene editing technologies holds extraordinary potential to reshape plant structural behavior and revolutionize crop breeding. Deep learning technologies are particularly well suited for capturing the complex relationships between DNA sequences and molecular functions, making them ideal for guiding the *de novo* synthesis or assembly of superior alleles. By leveraging the design principles of synthetic biology, scientists can create protein-coding sequences with exceptional biochemical properties or promoters with special transcriptional regulatory functions, and integrate them into crop genomes using genome-editing or transgene technologies, thereby enabling the emergence of new traits in crops (Chen et al., 2019). In summary, the vigorous development and deep integration of technologies such as AI, multi-omics analysis, information technology, synthetic biology, and genome editing are transforming tomato breeding into a truly modern science.

Whether through domestication or modern breeding, both processes involve searching for beneficial alleles and aggregating multiple target alleles (Meyer and Purugganan, 2013). After long-term artificial selection, tomatoes have achieved the aggregation of traits such as high yield, disease resistance, and high quality, but genetic diversity has decreased, and breeding for complex stress-tolerant traits has encountered a genetic bottleneck, making it difficult to adapt to future climate change and frequent extreme weather. Wild tomatoes, which have undergone long-term natural selection and environmental adaptation, possess valuable traits for stress tolerance and environmental resilience. Consequently, they serve as an important genetic resource for breeding stress-tolerant tomato varieties. Plants can also adapt to environmental changes through collaboration with microorganisms. In response to these environmental fluctuations, the rhizosphere microbiome, which is a host property, plays a crucial role in enhancing crop resilience against various stresses. Intriguingly, microbiota-mediated effects are dependent on the host genotype (Oyserman et al., 2022). For example, the tomato variety Hawaii 7996, which is resistant to the soil-borne pathogen *Ralstonia solanacearum*, can specifically recruit a flavobacterium, named TRM1, to protect themselves from infection. This indicates that elucidating the role of host genetics in plant-microbiome assembly is key to unlocking the breeding and engineering potential of the microbiome for sustainable tomato production (Kwak et al., 2018).

Since tomatoes were domesticated from their wild ancestors thousands of years ago, increasing their yield has been a core objective of breeding programs. With the economic and social development and the continuous upgrading of the tomato industry, tomato breeding faces more challenges and exhibits new development trends. At the production level, increasing pests and diseases, as well as unstable climatic conditions, pose significant pressures on

cultivation. In response to the escalating pest and disease problems in tomatoes, varieties need to be not only resistant to multiple major pests and diseases but also need to cope with the constant emergence of new diseases, such as the recent outbreaks of Tomato Brown Rugose Fruit Virus (ToBRFV) and FCRR diseases. Enhancing tomato adaptability to environmental stressors like cold, heat, low light, and drought is also a crucial objective in breeding efforts. Additionally, the production of fresh-market tomatoes often necessitates labor-intensive practices, including regular pruning, vine lifting, removal of lateral branches, and thinning of flowers and fruits. With the decline in the rural labor force and rising labor costs, there is an urgent need for new varieties that are suited to simplified and mechanized cultivation methods. At the consumption level, as people's living standards improve, high fruit quality has become one of the core directions in tomato breeding. By optimizing tomato fruit traits such as sugar and acid content, aroma, taste, nutrition, color, firmness, and shelf life, the overall quality of tomatoes can be enhanced. Although China is the world's largest producer and consumer of fresh tomatoes, in recent years, the demand for processed tomato products, including tomato paste, canned tomatoes, diced tomatoes, tomato juice, dried tomatoes, and tomato powder, has also been increasing in China. Developing new tomato varieties suitable for different processing purposes is also an important direction for future tomato breeding. In summary, tomato breeding is moving toward specialization and diversification, which will enrich the variety of types of tomatoes on the market, meeting the planting needs of different regions and seasons, and providing consumers with more diversified choices. It is necessary to use large-scale multi-omics data mining to identify key genes and superior variations affecting traits, and construct gene regulatory networks for various tomato traits. Based on rich gene–phenotype association information, AI methods can be used to create precise design breeding models (Figure 4). Combining these with innovative breeding technologies will accelerate the efficient and accurate selection and development of new tomato varieties to meet the diversified demands of tomato.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

M.D., C.S., C.L., and C.-B.L. drafted the manuscript. M.D. and C.S. drew the figures. M.D., C.S., C.L., C.-B.L., L.D., M.Z., J.L., Y.D., Z.Y., S.H., T.L., and J.Y. discussed and revised the manuscript. All authors read and approved the contents of the final version of this paper.

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SUPPORTING INFORMATION

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Table S1. Cloned genes for key agronomic traits in tomato