Plant Cell Reports (2021) 40:767–782
https://doi.org/10.1007/s00299-020-02650-9

REVIEW

Skin colour, carotenogenesis and chlorophyll degradation mutant alleles: genetic orchestration behind the fruit colour variation in tomato

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Received: 28 September 2020 / Accepted: 4 December 2020 / Published online: 3 January 2021
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Abstract

The genetics underlying the fruit colour variation in tomato is an interesting area of both basic and applied research in plant biology. There are several factors, like phytohormones, environmental signals and epistatic interactions between genes, which modulate the ripe fruit colour in tomato. However, three aspects: genetic regulation of skin pigmentation, carotenoid biosynthesis and ripening-associated chlorophyll degradation in tomato fruits are of pivotal importance. Different genes along with their mutant alleles governing the aforementioned characters have been characterized in detail. Moreover, the interaction of these mutant alleles has been explored, which has paved the way for developing novel tomato genotypes with unique fruit colour and beneficial phytonutrient composition. In this article, we review the genes and the corresponding mutant alleles underlying the variation in tomato skin pigmentation, carotenoid biosynthesis and ripening-associated chlorophyll degradation. The possibility of generating novel fruit colour-variants using different combinations of these mutant alleles is documented. Furthermore, the involvement of some other mutant alleles (like those governing purple fruit colour and high fruit pigmentation), not belonging to the aforementioned three categories, are discussed in brief. The simplified representation of the assembled information in this article should not only help a broad range of readers in their basic understanding of this complex phenomenon but also trigger them for further exploration of the same. The article would be useful for genetic characterization of fruit colour-variants and molecular breeding for fruit colour improvement in tomato using the well-characterized mutant alleles.

Keywords Carotenoid biosynthesis · Flavonoid biosynthesis · Mutant alleles · Ripening-associated chlorophyll degradation · Tomato fruit colour · Tomato skin pigmentation

Introduction

Tomato (*Solanum lycopersicum* L.) is widely consumed as fresh, culinary additive or processed products. The ripe fruits of tomato contain different important pigments and phytonutrients (Schierle et al. 1997; Holloway et al. 2000; Livny et al. 2002; Canene-Adams et al. 2005; Toor and Savage 2005; Perveen et al. 2013; Campestrini et al. 2019). The

Communicated by Wusheng Liu.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00299-020-02650-9.

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major pigments present in tomatoes are the carotenoids that impart the red, orange or yellow colour in the ripe fruits. The carotenoids lycopene and β-carotene provide varied health benefits (Khachik et al. 2002), owing to their antioxidant properties as quenchers of reactive oxygen species (ROS) (Jomova and Valko 2013). Consumption of fresh and processed tomato products reduces the risk of several chronic diseases including cardiovascular diseases and even cancer, where the protective role is attributed to the carotenoids (Fraser and Bramley 2004; Palozza et al. 2011; Burton-Freeman and Sesso 2014; Niranjana et al. 2015; Stajc˘ic´ et al. 2015). The role of lycopene has been recently reviewed to—reduce blood pressure, lower the risk of artery blockage, prevent cholesterol oxidation, lower the risk of lung, prostrate, breast and uterine cancers and have positive effects on the skeletal system, neurodegenerative diseases including Alzheimer's and Parkinson's (Przybylska 2020). Apart from the carotenoids, a few tomato mutants accumulate flavonoids comprising of anthocyanins in ripe fruits. Anthocyanins exert potential health benefits (Tsuda 2012; Gerardi et al. 2018; Campestrini et al. 2019), particularly through anti-inflammatory and anti-atherosclerotic effects (Amin et al. 2015; Olejnik et al. 2016; Blando et al. 2018, 2019). Several experiments on animals and clinical trials on human have confirmed the role of anthocyanins in the prevention of cardiovascular diseases and cancer (Wallace et al. 2016; Lin et al. 2017).

Keeping the health promoting roles of different pigments in mind, attempts have been made to develop tomato lines with improved pigmentation in fruits, through conventional and non-conventional strategies. Several mutant alleles have been identified through the detailed analyses of skin pigmentation, carotenoid biosynthesis (carotenogenesis) and ripening-associated chlorophyll degradation in tomato fruits, the introgression of which can dramatically modify the fruit colour (and nutrient composition) in tomatoes. In this review, we present the different allelic variants of the major genes that govern skin pigmentation, carotenogenesis and ripening-associated chlorophyll degradation in tomato fruits. Moreover, some novel mutants directly or indirectly impacting the tomato fruit colour are also discussed. The detailed characterization of the mutant alleles, as presented here should be quite useful not only in characterizing the colour-variant genetic stocks at the molecular level but also for developing allele-specific robust molecular markers that can be explored in breeding programmes addressing fruit colour and nutritional improvement in tomato.

The ripe fruit colour of tomato

Ripening of tomato fruits is characterized by pigmentation of the skin (exocarp) and increased carotenogenesis coupled with regulated chlorophyll degradation (during chloroplast to chromoplast transition) in flesh (pericarp and placenta), which ultimately turns the unripe green fruits into ripe red tomatoes. Naturally, the major colour-variants result from aberrations in: skin pigmentation, carotenogenesis and ripening-associated chlorophyll degradation. Salient features of the identified and characterized major genes (along with their mutant alleles and available mutant lines) regulating these three processes are summarised in Table 1. Involvement of these mutant alleles in governing fruit colour of tomato is sequentially discussed below.

Tomato skin colour

The skin colour is an important determinant as it interacts with the flesh (pericarp) colour to modify the overall appearance of ripe tomato fruits. For example, the red flesh tomatoes with colourless skin appear as pink tomatoes in comparison to red tomatoes (where red flesh is under the normal yellow skin). The natural yellow skin colour of tomato is due to the presence of the flavonoid naringenin chalcone, which is the predominant pigment accumulated in the tomato peel during ripening (Hunt and Baker 1980). Mutations at the *y* locus cause the absence of naringenin chalcone, resulting in *colourless skin* in tomatoes (Lindstrom 1925; Rick and Butler 1956). The flavonoid biosynthetic pathway transcription factor gene *Solanum lycopersicum* MYB12 (*SlMYB12)* is the candidate gene for the *y* locus governing this *colourless skin* phenotype (Adato et al. 2009; Ballester et al. 2010; Wang et al. 2018). Ballester and co-workers (2010) used pink-fruited wild introgression lines to characterize the *SlMYB12* gene, where the mutant allele contained several polymorphisms including a 72-bp insertion in the 3rd exon and absence of a 53-bp duplication in the 2nd intron. Comparison of the deduced amino acid sequences identified 11 amino acid substitutions, 1 amino acid deletion and a 23 amino acid insertion. Interestingly, all these sequence variations were absent in four natural pink-fruited tomato cultivars and indicated the altered transcriptional regulation of the gene to be responsible for the *colourless skin* phenotype (Ballester et al. 2010). Afterwards, detailed sequence analysis of the *SlMYB12* gene revealed a 603-bp deletion in the upstream region (at − 4865 bp position from the start codon), a transition (C > T) and a 1-bp insertion (TG > T**A**G) in the 2nd exon of the allelic variant (Lin et al. 2014). The sequence deletion in the upstream region justifies transcriptional repression, whereas the transition and insertion mutations lead to introduction of premature stop codons resulting in truncated non-functional protein(s). Subsequently, a pink-fruited hybrid tomato was characterized where both the transition and insertion mutation of the 2nd exon was absent, whereas the 603-bp deletion in the upstream region was present in heterozygous condition (Veerappan et al. 2016). This observation indicated the possibility of another

Table 1 The major genes and their mutant alleles involved in regulating skin colour, carotenoid biosynthesis and ripening-associated chlorophyll degradation in tomato fruits

	Gene	Accession number	Mutant phenotype	Available mutant lines at TGRC[a]	Mutant allele(s) with Reference
Skin pigmentation	*SlMYB12*	*Solyc01g079620*	*colourless skin (loss-of-function)*	LA3189, LA1088	(1) 603-bp deletion in the upstream promoter region (Lin et al. 2014) (2) C to T transition in the 2nd exon (Lin et al. 2014) (3) A addition (TG to TAG) in the 2nd exon (Lin et al. 2014) (4) G to T transversion at 2nd intron splicing site (Veerappan et al. 2016) (5) Genomic deletion from the 3rd intron of the gene (Fernandez-Moreno et al. 2016) (6) G to A transition in the 3rd exon (Jung et al. 2017) (7) G to A transition in the 3rd exon (Jung et al. 2017) (8) Deletion of ~ 45 kb genomic region containing the entire gene (Jung et al. 2017)
Carotenogenesis	*IDI1*	*Solyc04g056390*	*fruit carotenoid deficient (fcd)/ apricot (loss-of-function)*	LA3535, LA2998, LA0215	(1) Transition (G to A) in the 4th exon (Pankratov et al. 2016) (2) Transition (G to A) in the 5th exon (Pankratov et al. 2016) (3) Deletion of TGG in the 5th exon (Pankratov et al. 2016) (4) Insertion of T in the 6th exon (Pankratov et al. 2016; Shin et al. 2019)
	PSY1	*Solyc03g031860*	*yellow flesh (loss-of-function)*	LA3003, LA3532, LA2997, LA2056, 2–141, LA0353	(1) Insertion of Rider transposon in the 1st exon (Fray and Grierson 1993; Jiang et al. 2012) (2) Short deletion in the 3′ end (Fray and Grierson 1993; Jiang et al. 2012) (3) Transition (G to A) in the 2nd exon (Kachanovsky et al. 2012) (4) Transition (A to G) in the 4th intron (Yuan et al. 2008; Kang et al. 2014; Chen et al. 2019) (5) Transition (C to T) in the 3rd exon (Gady et al. 2012) (6) Transition (G to A) in the 3rd exon (Gady et al. 2012) (7) Large insertion in the 1st exon (Kang et al. 2017) (8) Deletion of 691 bp in the upstream promoter region (Shin et al. 2019) (9) T to A transversion mutation in the 6th exon (Shin et al. 2019)

Table 1 (continued)

	Gene	Accession number	Mutant phenotype	Available mutant lines at TGRC[a]	Mutant allele(s) with Reference
	CrtISO	*Solyc10g081650*	*tangerine (loss-of-function)*	LA3183, LA0030, LA3002, LA0351	(1) 348-bp deletion in the upstream promoter region (Isaacson et al. 2002) (2) 282-bp deletion from the gene (Isaacson et al. 2002) (3) Insertion of T in the 2nd exon (Kachanovsky et al. 2012) (4) Transition (G to A) in 3rd exon (L241K) (Kachanovsky et al. 2012) (5) Transition (G to A) in the 11th exon (G520R) (Kachanovsky et al. 2012) (6) Transition (G to A) in the 11th exon (G546E) (Kachanovsky et al. 2012) (7) Insertion of A in the 8th exon (Yoo et al. 2017) (8) C to T transition mutation in the 7th exon (Yoo et al. 2017)
	CYC-B	*Solyc06g074240*	*Beta (gain-of-function)/ old-gold (loss-of-function)/ old-gold crimson (loss-of-function)*	***Beta*** = LA2374, LA3898, LA3899, LA3000 ***old gold*** = LA4026, LA0348, LA0500, LA4025 ***old gold crimson*** = LA0806, LA3179	(1) Transversion G to T at − 77 position (*Beta*) (Hwang et al. 2016) (2) A to ATA mutation (*old gold*) (Ronen et al. 2000) (3) Deletion of A (*old gold crimson*) (Ronen et al. 2000) (4) Transversion (A to C) (Mohan et al. 2016) (5) Transition (G to A) (Mohan et al. 2016) (6) Insertion of 256 bp at upstream promoter region (Mohan et al. 2016)
	LCY-E	*Solyc12g008980*	*Delta (gain-of-function)*	LA4099, LA2996A, LA2921	(1) Insertion of 1,014 bp at upstream promoter region (Yoo et al. 2017)
Chlorophyll degradation	*SGR*	*Solyc08g080090*	*green flesh (loss-of-function)*	LA2071, LA3534, LA2999, LA4449, LA4450, LA4451, LA4452	(1) Transversion (A to T) in the 3rd exon (Barry et al. 2008; Barry and Pandey 2009) (2) Addition of A in the 3rd exon (Barry and Pandey 2009) (3) Deletion of 2 bp in the 2nd exon (Barry and Pandey 2009) (4) Transition (C to T) in the 2nd exon (Barry and Pandey 2009) (5) Deletion of 1163 bp from the gene (Barry and Pandey 2009) (6) Transition (T to C) in the last base of the 3rd exon (Kang et al. 2017)

[a]As per active collection of monogenic mutant stocks maintained at **C.M. Rick Tomato Genomic Resource Centre** at **Unversity of Callifornia, Davis, USA** (https://tgrc.ucdavis.edu/)

loss-of-function mutation attributed by one of the parents of the hybrid. Further analysis revealed a transversion (G > T) at the initial base of the 2nd intron, leading to the disruption of the 5′ splicing site. Naturally, the possible alternate splicing through this mutation results in the loss-of-function allele of the *SlMYB12* gene (Veerappan et al. 2016). Molecular characterization of two pink-fruited tomato mutants has revealed another null allele for the *SlMYB12* gene, where the genomic region between the 3rd intron and the end of the gene is deleted (Fernandez-Moreno et al. 2016). In the recent past, an attempt was made to explore more possible genetic variation(s) in the *SlMYB12* gene using 85 pink-fruited tomato lines (Jung et al. 2017). Out of the 85 lines, seven lines contained neither the upstream 603-bp deletion nor the previously reported single nucleotide polymorphisms (SNPs). Among these seven lines, six lines had two separate transitions (G > A) in the 3rd exon, leading to introduction of premature stop codon. Interestingly, one tomato line had deletion of ~ 45 kb genomic region containing the entire *SlMYB12* gene. Thus, three more loss-of-function allelic variants of the *SlMYB12* gene (2 SNPs at 3rd exon and 44.75 kb genomic deletion) can lead to the *colourless skin* phenotype in tomato (Jung et al. 2017). Pictorial representation of all these allelic variants of the *SlMYB12* gene is portrayed in supplementary Fig. Sf1.

Carotenoid biosynthesis and tomato fruit colour

Tomato fruit colour is predominantly governed by accumulation of carotenoids during fruit ripening. Carotenogenesis has been studied in great details in different plants including tomato (Porter and Lincoln 1950; Cunningham and Gantt 1998; Hirschberg 2001; Bramley 2002; Fraser and Bramley 2004; Giuliano 2014; Liu et al. 2015). The ability of the carotenoid biosynthetic enzymes to function in bacterial and cell-free systems has accelerated the identification of candidate genes (Lotan and Hirschberg 1995; Bartley et al. 1999; Isaacson et al. 2004; Chen et al. 2010; Yu et al. 2011). A simplified view of the carotenogenesis pathway in tomato fruits, along with the fruit colour-variants arising from mutations in the key genes of the pathway, is presented in Fig. 1.

Like other higher plants, carotenoids are synthesized in the chromoplasts of tomato, catalysed by enzymes coded by nuclear genes (Chappel et al. 1995; Davies 2009; Egea et al. 2010; Hirschberg 2001). The primary building blocks of carotenoids in tomato are isopentenyl diphosphate (IPP or IDP) and its isomer dimethylallyl diphosphate (DMADP), produced through the 2C-methyl-D-erythritol-4-phosphate (MEP) pathway in plastids (Lichtenthaler et al. 1997; Milborrow and Lee 1998; Lichtenthaler 1999; Eisenreich et al. 2001, 2004; Botella-Pavía et al. 2004; Enfissi et al. 2005). The conversion of IDP to DMADP and vice versa is carried out by IDP isomerase (IDI; Pankratov et al. 2016), which determines the relative amounts of IDP and DMADP, and ultimately regulates the carotenogenesis. The IDP and DMADP are converted to geranylgeranyl diphosphate (GGPP) by geranylgeranyl diphosphate synthase (GGPPS; Ament et al. 2006). Next, 2 GGPP molecules are condensed to form 15-*cis*-phytoene by phytoene synthase 1 (PSY1; Bird et al. 1991; Fray and Grierson 1993). The 15-*cis*-phytoene is then desaturated by phytoene desaturase (PDS; Mann et al. 1994) to tri-*cis*- ζ-carotene, which is subsequently converted to 9,9′-di-*cis*-ζ-carotene by ζ-carotene isomerase (ZISO; Chen et al. 2010). Then, 9,9′-di-*cis*-ζ-carotene is converted to tetra-*cis*-lycopene (prolycopene) with the help of ζ-carotene desaturase (ZDS; Bartley et al. 1999; Dong et al. 2007; McQuinn et al. 2020). Prolycopene is isomerized to lycopene by carotene isomerase (CrtISO; Isaacson et al. 2002). The synthesized lycopene can be cyclized in two distinct routes; the first route leads to the production of β-carotene with the help of lycopene β cyclase (CYC-B; Pecker et al. 1996; Ronen et al. 2000) and the second route produces δ-carotene and lutein by lycopene ε cyclase (LCY-E; Ronen et al. 1999). As both the *CYC-B* and *LCY-E* are down-regulated during fruit ripening, normal red ripe tomato fruits contain lycopene as the major carotenoid pigment with relatively less amounts of β-carotene and lutein. As the pathway is under stringent regulation, mutations in the biosynthetic genes lead to panoply of colour variations in ripe tomato fruits due to aberrant accumulation of pathway intermediates and end products.

Mutations in the genes of carotenoid biosynthetic pathway

Biosynthesis of carotenoids is of pivotal importance as carotenoids are indispensible for photosynthesis in green plant tissues. Naturally, major carotenoid biosynthetic genes are expressed constitutively in the green plant parts (Galpaz et al. 2006). Deleterious mutations in the key genes involved in carotenogenesis in green plant tissues are lethal and hence remain undetected. Interestingly, regulations of carotenogenesis in tomato fruits (and flowers) are distinct from those operating in green tissues (Thelander et al. 1986; Fraser et al. 1994; Galpaz et al. 2006). As the carotenoids in flowers and fruits are not inevitably essential for the physiology in these tissues, carotenogenesis mutants altering fruit pigmentation are not lethal and can be detected (Hirschberg 2001; Galpaz et al. 2006). Mutations in the fruit and chromoplast-specific isoforms of the carotenoid biosynthetic genes (like *IDI, PSY* and *CYC-B*) contribute towards variation in tomato fruit colour (Galpaz et al. 2006; Pankratov et al. 2016). Mutation in the *CrtISO* gene can also be detected as the gene action can be substituted by light in the green plant parts (Li et al. 2007). Furthermore, two additional distant homologs of *CrtISO*:

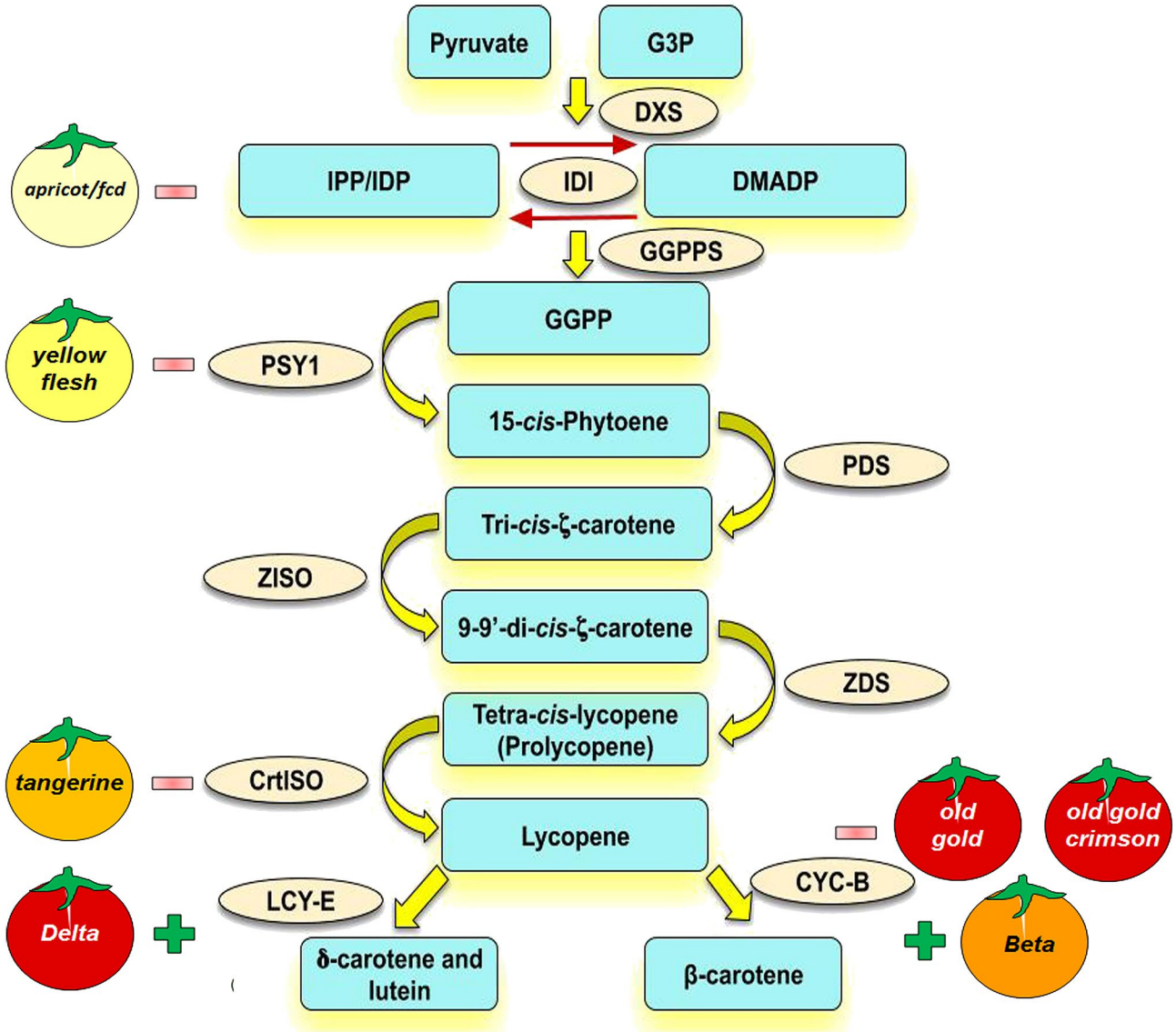

Fig. 1 Simplified view of the carotenoid biosynthesis pathway in tomato fruits and fruit colour-variants associated with mutant alleles of the biosynthetic genes. *G3P* = *Glyceraldehyde 3 phosphate; IPP/IDP* = *Isopentenyl diphosphate; DMADP* = *Dimethylallyl diphosphate; GGPP* = *Geranylgeranyl di-phosphate; DXS* = *1-deoxy-d-xylulose 5-phosphate synthase; IDI* = *IDP isomerase; GGPPS* = *Geranylgeranyl diphosphate synthase; PSY1* = *Phytoene synthase 1; PDS* = *Phytoene desaturase; ZISO* = *ζ-carotene isomerase; ZDS* = *ζ-carotene desaturase; CrtISO* = *Carotene isomerase; CYC-B* = *Lycopene β cyclase; LCY-E* = *Lycopene ε cyclase. Negative* and *positive* signs represent loss-of-function and gain-of-function mutations, respectively

CrtISO-L1 and *CrtISO-L2* genes play role in a metabolic side branch containing all-*trans*-ζ-carotene (Fantini et al. 2013). But natural loss-of-function mutations in the single genes (like *PDS* and *ZDS*) most likely remain undetectable due to the possible lethality associated with them. Nevertheless, role of lycopene biosynthetic genes, including *PDS* and *ZDS*, in regulating tomato fruit colour and carotenoid composition has been clearly demonstrated using virus induced gene silencing (VIGS) in tomato fruits (Fantini et al. 2013). Thus, gene duplication-mediated development of chromoplast (predominantly present in fruits and flowers; Sadali et al. 2019)-specific carotenogenesis in fruits (Galpaz et al. 2006) explains the availability of different fruit colour mutants in tomato.

Tomato fruit carotenogenesis mutants can be classified as (1) mutations that reduce the overall carotenoid content in tomato and (2) mutations that alter the carotenoid profile in tomato.

Mutations that reduce the overall carotenoid content in tomato

Mutations in the genes governing early steps of carotenogenesis (*IDI* and *PSY*, Fig. 1) greatly reduce the overall carotenoid content in tomato fruits. The loss-of-function mutations in these genes are pictorially presented in supplementary Fig. Sf2 and sequentially discussed below.

Mutations in the isopentenyl diphosphate (IDP) isomerase 1 (IDI1) gene

Carotenoids are biosynthesized and accumulated in the chromoplasts of tomato fruit. GGPP, the biosynthetic precursor for carotenoids, is produced from IDP and its isomer DMADP (Fig. 1) through the MEP pathway in plastids (Botella-Pavía et al. 2004; Enfissi et al. 2005). Though the plastidial MEP pathway produces both IDP and DMADP, IDP can be isomerized to DMADP and vice versa by the enzyme IDP isomerase (IDI, Fig. 1), where the equilibrium favours the forward reaction (conversion of IDP to DMADP). The ratio of IDP and DMADP determines the nature of isoprenoids to be synthesized; for example, the 1:1 ratio leads to monoterpene, the 2:1 ratio leads to sesquiterpenes and sterols, whereas the 3:1 ratio leads to diterpene, phytol, carotenoid and much higher ratio leads to long-chain polyprenols and polyterpenes biosynthesis (Gershenzon and Kreis 1999; Phillips et al. 2008). Interestingly, 6:1 ratio of IDP:DMADP has been obtained in vitro using the enzyme 1-hydroxy-2-methylbutenyl 4-diphosphate reductase, which catalyses the last step of the MEP pathway (Rohdich et al. 2003; Eisenreich et al. 2004). Naturally, IDI activity is very much important to modulate the IPP:DMADP ratio to trigger carotenogenesis in plastids (Phillips et al. 2008). Among the two *IDI* isoforms (*IDI1* and *IDI2*) in tomato, *IDI2* is cytoplasmic and *IDI1* contains chloroplast transit peptide (Pankratov et al. 2016). Though the cytoplasmic form (previously designated as *SlIPI1*, *Solanum lycopersicum* isopentenyl diphosphate isomerase) was reported to be involved in carotenogenesis using bacterial expression system (Sun et al. 2010), later the pivotal role of the chloroplastic *IDI1* (and not *IDI2*) in carotenogenesis in tomato fruits was established (Pankratov et al. 2016). This observation and gene nomenclature is in unison with the *IDI* genes previously identified and characterized in tobacco (Nakamura et al. 2001). The role of the *IDI1* gene in regulating carotenogenesis has been analysed using mutant tomato lines (designated as *fruit carotenoid deficient*, *fcd*) with reduced carotenoid content in ripe fruits (Pankratov et al. 2016). In the *fcd* mutant lines, three distinct point mutations, yielding loss-of-function alleles of *IDI1* gene, have been reported. In the first one (*fcd1-2* allele), a transition (G > A) in the 4th exon introduces a premature stop codon; in the second one (*fcd1-1* allele), deletion of three nucleotides (TGG) from the 5th exon removes a Trp residue (W206-); and in the third one (*fcd1-3 allele*), another transition (G > A) in the 5th exon causes missense mutation (G207R) (Pankratov et al. 2016). Furthermore, this study also identified another allele ($fcd1^{at}$) with a nonsense mutation (K234*) in the synonymous *apricot* tomato mutant (Jenkins and Mackinney 1955) with reduced fruit carotenoids. Accordingly, this nonsense mutation, originating from insertion of a T in the 6th exon (that produces truncated non-functional IDI1 protein) was found in other *apricot* mutant lines in the recent past (Shin et al. 2019). Thus, loss of IDI1 function causes extremely low total carotenoid content in pale yellow flower and yellow fruits of *fcd* and *apricot* tomato mutants. All these allelic variants of the *IDI1* gene are pictorially presented in supplementary Fig. Sf2.a.

Mutations in the phytoene synthase 1 (PSY1) gene

The yellow flesh mutant of tomato has been explored since the rediscovery of Mendelism in tomato (Price and Drinkard 1909). Mutations at the *r* locus give pale yellow flower corolla, yellow fleshed fruits and intense yellow pigmentation in the fruit skin (Fray and Grierson 1993). Another spontaneous mutation r^y, allelic to the *r* locus, gives similar fruit colour with normal flower corolla colouration. Later, the involvement of mutant alleles of the phytoene synthase (*PSY*, Fig. 1) gene in determining *yellow flesh* phenotype was proven. The tomato genome contains 3 *PSY* genes (*PSY 1*, *PSY 2* and *PSY 3*) out of which only *PSY 1* is active during ripening of fruits (Bartley and Scolnik 1993; Fraser et al. 1999; Giorio et al. 2008; Li et al. 2008; Welsch et al. 2008). The *yellow flesh* mutant alleles, *r* and r^y are the non-functional versions of the tomato *PSY1* gene, as proved through sequencing, complementation and co-suppression (Fray and Grierson 1993). The *r* allele arises due to insertion of *Rider* transposon in the *PSY1* gene, whereas the r^y allele has a short deletion leading to *trans*-splicing (Jiang et al. 2012). Apart from the *r* and r^y alleles, the non-functional allele r^{3756} has a transition (G > A) in the 2nd exon causing a nonsense mutation (W151*) to abolish the PSY1 activity (Kachanovsky et al. 2012). Another yellow flesh tomato line contains a different allele with a transition (A > G) in the 4th intron (Yuan et al. 2008). Later a chimeric transcript of the *PSY1* gene (designated as *PSY1/Unknown*), where the 3′ end of the chimeric transcript corresponds to an unknown gene coded by the complementary strand of the gene encoding Acyl-CoA synthase was found (Kang et al. 2014). The intron–exon arrangement of the unknown gene is different from *Acyl-CoA synthase*, indicating its novelty. A very similar *trans*-splicing of the *PSY1* gene resulted in yellow flesh colour in a cherry tomato line (Chen et al. 2019). Possible loss-of-function alleles of the *PSY1* gene in

tomato have been identified also through Targeting Induced Local Lesions IN Genomes (TILLING; Gady et al. 2012). Two mutant lines, with significantly reduced phytoene and lycopene content were analysed, where one line contained a transition (C > T) in the 3rd exon causing missense mutation (P192L) affecting PSY1 activity. The other mutant line contained a transition (G > A) in the 3rd exon causing nonsense mutation (W180*), generating a knock out allele of the *PSY-1* gene (Gady et al. 2012). Another non-functional allele of the gene with a large insertion in the 1st exon was identified in a green-fruited tomato line (Kang et al. 2017). In the recent past, two more causal mutations in the *PSY1* gene resulted in *yellow flesh* colour of tomato. One yellow-fruited tomato line had a deletion of 691 bp in the upstream promoter region, whereas the other line had a transversion (T > A) in the 6th exon (Shin et al. 2019). The transversion in the 6th exon introduces a premature stop codon resulting in a truncated (lacking last 30 amino acid residues) PSY1 protein. Allelic variants of the *PSY1* gene are pictorially presented in supplementary Fig. Sf2.b.

Mutations that alter the carotenoid profile in tomato

Mutations in the genes governing later steps of carotenogenesis (*CrtISO*, *CYC-B* and *LCY-E*, Fig. 1) greatly influence the carotenoid composition in tomato fruits. The loss-of-function and/or gain-of-function mutations in these genes that modify carotenoid composition in tomato fruits are pictorially presented in supplementary Fig. Sf3 and sequentially discussed below.

Mutations in the carotene isomerase (CrtISO) gene

Prolycopene (7,9,7′,9′tetra-*cis* lycopene) is enzymatically converted by carotene isomerase (CrtISO) to all-*trans*-lycopene (Fig. 1), which is predominantly accumulated in red tomatoes. The *CrtISO* gene has been analysed in *tangerine* mutants with orange flesh (due to accumulation of prolycopene in place of all-*trans*-lycopene; Isaacson et al. 2002). Initially, two alleles of the *CrtISO* gene were identified in the *tangerine* mutants. The *tangerine*^{3183} (t^{3183}) mutant allele contains a 348-bp deletion in the upstream promoter region, which drastically reduces transcription of the gene. On the other hand, the *tangerine*^{mic} (t^{mic}) mutant allele contains a 282-bp deletion (24 bp of the first exon and 258 bp of the first intron of the gene), which eliminates a splicing site and results in a truncated non-functional enzyme (Isaacson et al. 2002). Later, a mutant line was found to contain a single nucleotide (T) insertion in the 2nd exon of the gene, leading to the introduction of a premature stop codon (Kachanovsky et al. 2012). In a similar manner, this study identified some other alleles in induced mutant lines, like, t^{4838} (where G > A transition in the 3rd exon causes L241K missense mutation), t^{3406} (where G > A transition in the 11th exon causes G520R missense mutation), and t^{9776} (where G > A transition in the 11th exon causes G546E missense mutation). Apart from these, other mutations in the *CrtISO* gene have been identified in orange-fruited tomato lines in the recent past (Yoo et al. 2017). Among these, insertion of an A in the 8th exon of the gene leads to nonsense mutation. The other allele contained a transition (C > T) in the 7th exon of the gene. Interestingly, epistatic interaction of *CrtISO* mutant (*tangerine)* on *PSY-1* mutant (yellow flesh) has been reported, where the transcription of *PSY-1* is partially restored (involving *cis*-carotenoid metabolites) for sufficient production of phytoene and downstream carotenoids in *tangerine* background (Kachanovsky et al. 2012). This indicated towards the complex regulation of carotenogenesis in tomato fruits through interaction(s) between different mutant alleles. Allelic variants of the *CrtISO* gene are pictorially depicted in supplementary Fig. Sf3.a.

Mutations in the lycopene β cyclase (CYC-B) gene

In the carotenoid biosynthetic pathway, cyclization of lycopene is a central branch point, from which the pathway either moves towards the production of β-carotene, zeaxanthin, violaxanthin and neoxanthin (precursors of the ABA and strigolactone biosynthesis) or towards the production of δ-carotene and lutein (Fig. 1). The β-carotene production from lycopene is catalysed by the enzyme lycopene β cyclase (Pecker et al. 1996). Two distinct genes encoding lycopene β cyclase have been reported in tomato; the *SlLCY-B1 (SlCRTL-B)* gene is active in green tissues and flowers, whereas the *SlLCY-B2 (SlCYC-B)* gene is chromoplast-specific (Ronen et al. 2000). Interestingly, an almost identical gene from tomato exhibits neoxanthin synthase activity but not lycopene β cyclase activity upon prokaryotic and eukaryotic heterologous expression (Bouvier et al. 2000). Later, this controversy has been addressed in different communications (Hirschberg 2001; Botella-Pavía and Rodríguez-Concepción 2006; Neuman et al. 2014) and the possibility of lycopene β cyclase in tomato to be bi-functional (cyclase as well as neoxanthin synthase activities) has been proposed. But, presence of neoxanthin in *CYC-B* loss-of-function mutants indicates the presence of a distinct gene encoding neoxanthin synthase (Hirschberg 2001). Although a gene is involved in neoxanthin biosynthesis in tomato (Neuman et al. 2014), the distinct neoxanthin synthase gene in tomato is yet to be identified (Karniel et al. 2020). As the up-regulation of the *SlCYC-B* gene increases β-carotene content in the fruits of tomato mutant *Beta* with orange coloured fruits, putative role of 5′ upstream sequence variations in transcriptional up-regulation of the gene was suggested (Ronen et al. 2000). In the recent past, the 5′ upstream region of the *SlCYC-B* gene from red, yellow and orange fruited tomato lines have been

analysed to identify 4 SNPs (at positions − 837, − 506, − 401 and − 77), out of which the transversion (G > T) at − 77 position is crucial (Hwang et al. 2016).

Apart from the gain-of-function *Beta* mutant, tomato lines have been found with loss-of-function mutations in the *SlCYC-B* gene. Frame-shift mutations in this gene (leading to the production of non-functional protein) results in *old-gold* (*og*) and *old-gold crimson* (og^c) mutants, where the lack of lycopene β cyclase activity causes a complete absence of β-carotene and a significant increase in lycopene content in the ripe tomato fruits (Ronen et al. 2000). Sequence variations in the *CYC-B* gene present in different tomato genotypes have also been analysed through EcoTILLING (Mohan et al. 2016). A loss-of-function allele of the *CYC-B* gene with 2 SNPs was documented. The first one, the transversion (A > C), causes missense mutation (K106T), whereas the 2nd one, the transition (G > A), introduces a premature stop codon (W190*). Moreover, the authors also documented a transcriptionally more active promoter (in comparison to the '*Beta type*' promoter) in 2 *og* mutant lines, where a 256-bp insertion occurs at − 281 position. Thus, the *SlCYC-B* gene sets a classic example, where both gain-of-function (*Beta*) and loss-of-function (*og* and og^c) alleles have been found. Allelic variants of the *CYC-B* gene are pictorially depicted in supplementary Fig. Sf3.b.

Mutation in the lycopene ε cyclase (LCY-E) gene

The second route from the central branch point of lycopene cyclization leads to the production of δ-carotene and lutein (Fig. 1), catalysed by the enzyme lycopene ε cyclase (LCY-E or CRTL-E), which shares ~ 36% identity with tomato lycopene β cyclase, CRTL-B (Ronen et al. 1999). Though the expression of *LCY-E* is decreased during fruit ripening, the expression of the same is drastically increased by ~ 30 fold in the dominant *Delta* mutant. This increased expression is the reason behind increased δ-carotene (and lutein) content in the fruits of the *Delta* mutant. Interestingly, the deduced amino acid sequence of *LCY-E* gene is almost identical in the *Delta* mutant and wild-type tomato lines and both are equally functional in heterologous expression system (*Escherichia coli*). Naturally, the sequence variation in the upstream promoter region should explain the transcriptional up-regulation of *LCY-E* in the *Delta* mutant (Ronen et al. 1999). Accordingly, the promoter region of the *LCY-E* gene in an orange-fruited tomato accession contained 1014-bp insertion at − 326 position (Yoo et al. 2017; Fig. Sf3.c).

The ripening-associated chlorophyll degradation mutants and tomato fruit colour

During the ripening process, carotenogenesis is significantly increased coupled with rapid degradation of chlorophyll (during chloroplast to chromoplast transition), which gives the ripe tomato fruits their characteristic colour. However, in some cases, up-regulated carotenogenesis is accompanied by retention of chlorophyll, which modifies the ripe fruit colour of tomatoes. Due to retention of chlorophyll, mutant tomatoes of this class are termed as *green flesh (gf;* Cheung et al. 1993), where the mutation is attributed to the *STAYGREEN* (*SGR*) gene (Barry et al. 2008). Comparison of the deduced amino acid sequences from the wild type and mutant has revealed a transversion (A > T) in the 3rd exon causing missense mutation (R143S) in the loss-of-function *gf* allele (Barry et al. 2008; Barry and Pandey 2009). Similarly, other loss-of-function alleles have been identified in different *gf* mutant tomatoes, where the alleles have been designated as gf^2, gf^3, gf^4 and gf^5 (Barry and Pandey 2009). In case of the gf^2 and gf^3 null alleles, insertion and deletion mutations in the 3rd and 2nd exon, respectively, lead to frame-shift mutation and introduction of premature stop codons to truncate the STAYGREEN protein. The gf^4 null allele results from a nonsense transition mutation (C > T) in the 2nd exon, whereas the deletion of 1163 bp from the gene (including part of the 2nd intron, the entire 3rd exon, the entire 3rd intron and part of the 4th exon) results in the gf^5 null allele (Barry and Pandey 2009). Another loss-of-function allele contained a transition (T > C) at the last base of the 3rd exon of the gene that leads to splice-variant generation with a truncated non-functional STAYGREEN protein (Kang et al. 2017). Pictorial representation of all these allelic variants of the *SGR* gene is portrayed in Fig. Sf4. Interestingly, carotenoid biosynthesis during tomato fruit ripening involves the direct interaction of SlSGR1 with SlPSY1 (Luo et al. 2013). The authors have demonstrated the inhibitory effect of SlSGR1 on SlPSY1 using bacterial expression system and transgenic suppression of *SlSGR1* in tomato. Apart from regulating fruit carotenogenesis, SlSGR1 regulates fruit ripening in tomato by influencing ethylene signal transduction (Luo et al. 2013).

Other mutations

Mutations in the genes, not directly involved in skin colour development, carotenogenesis and ripening-associated chlorophyll degradation, also modify tomato ripe fruit colour. For example, the tomato fruit colour is regulated by the genes influencing carotenogenesis (Liu et al. 2003). Using the green-fruited wild introgression lines in the cultivated tomato background, the chromosome segments that modify the fruit colour intensity in tomato have been found, where additional candidate genes include *farnesyl diphosphate synthase* (*FPS*), *geranylgeranyl diphosphate reductase* (*GGPR*), *plastid lipid-associated protein* (*PAP*) and *DEETIOLATED-1* (*DET1*). Furthermore, 11 quantitative trait loci (QTL) lacking carotenogenesis genes were

identified, justifying quantitative variation in tomato fruit colour beyond the regulation of candidate carotenoid genes (Liu et al. 2003). The study also indicated the wild relatives of tomato as an important source for mutant alleles that can influence fruit colour in both qualitative and quantitative manner.

During tomato fruit ripening, carotenogenesis occurs in the plastids; naturally, genes that regulate plastid number, size and thylakoid stacking can markedly influence the same. The *high pigment* (*hp*) mutants of tomato with significantly increased carotenoid content in ripe fruits have enhanced chromoplast number and size. The *high pigment 1* (*hp1*) mutant, having mutation in the tomato UV-damaged DNA-binding protein 1 (*DDB1*) homolog, contains significantly more number of plastids in fruits (Liu et al. 2004). The *high pigment 2* (*hp2*) mutant contains more and larger plastids, where mutations occur in the *DEETIOLATED1* (*DET1*) gene, a negative regulator of light signal transduction (Mustilli et al. 1999; Levin et al. 2003; Kolotilin et al. 2007). The plastid compartment is enlarged in *high pigment 3* (*hp3*) mutants arising from mutation in the gene encoding zeaxanthin epoxidase (Zep), which converts zeaxanthin to violaxanthin (Galpaz et al. 2008). Furthermore, the intensity and distribution pattern of plastid on tomato fruits is governed by the *U* locus, encoding GOLDEN 2-LIKE 2 (SlGLK2) MYB transcription factor (Powell et al. 2012). The lines carrying this functional gene show *green shoulder* phenotype resulting from the latitudinal gradient of *SlGLK2* expression (Nguyen et al. 2014). However, the *uniform ripening* (*u*) mutant lacks this gene activity due to insertion of A in the 1st exon of the gene, which introduces a premature stop codon and translates to a non-functional protein (Powell et al. 2012). The *uniform ripening* tomato fruits appear pale and contain less carotenoid pigments.

The ripe fruit colour of tomato can become purple through accumulation of the flavonoid anthocyanin. Generally, anthocyanin accumulation fails to occur in the tomato fruits, though the presence of this flavonoid is detected in the fruits of related wild undomesticated types, like *S. chilense*, *S. hirsutum*, *S. cheesmanii* and *S. lycopersicoides* (Rick 1964; Georgiev 1972; Rick et al. 1994). The *Aft* (*Anthocyanin fruit*) dominant gene derived from *S. chilense* accumulates anthocyanin in the epidermis and pericarp tissues of ripe tomato fruits (Jones et al. 2003). Very recently, an R2R3 Myb transcription factor (positive regulator of anthocyanin biosynthetic pathway) gene *SlAN2-like* has been proven as the candidate gene for *Aft* (Colanero et al. 2020; Sun et al. 2020; Yan et al. 2020). Interestingly, the effect of *Aft* is dramatically increased in tomato lines harbouring another recessive gene *atv* (*atroviolacium*) derived from *S. cheesmanii* (Rick et al. 1968; Mes et al. 2008; Gonzali et al. 2009; Povero et al. 2011). Through fine mapping, *atv* was found to originate from a mutation in an R3 type Myb transcription factor (negative regulator of anthocyanin biosynthetic pathway) gene *SlMybATV* (Cao et al. 2017; Colanero et al. 2018). Another dominant gene *Aubergine* (*Abg*), derived from *S. lycopersicoides,* increases anthocyanin content in tomato fruits, when coupled with *atv* (Rick et al. 1994; Mes et al. 2008). Interestingly, some tomato *green flesh (gf)* mutant lines have 'purple' in their names (like Purple Calabash, Purple Prince, Purple Russian), but they are not anthocyanin-rich 'purple' mutants. The purple colour comes from retention of chlorophyll and higher content of lycopene in the ripe fruits (Barry and Pandey 2009).

The natural mutations in the genes involved in ripening process also effectively regulate tomato ripe fruit colour. These genes include *Ripening-inhibitor* (*Rin*; Vrebalov et al. 2002), *Colourless non-ripening* (*Cnr*; Manning et al. 2006), *Never-ripe* (*Nr*; Wilkinson et al. 1995) *Green-ripe* (*Gr*; Barry and Giovannoni 2006), *non-ripening* (*nor*; Tigchelaar et al. 1973; Karlova et al. 2014) and *alcobaca* (*alc*; Kopeliovitch et al. 1981). Furthermore, the carotenogenesis is regulated by environmental factors and hormonal networks through several genes and transcription factors (reviewed in Liu et al. 2015; Enfissi et al. 2017; Stanley and Yuan, 2019), a detailed description of which is beyond the scope of this article.

Conclusion and future prospect

Genetic regulation behind tomato fruit colour variation has remained a rewarding area of both basic and applied research in plant science. Though several factors determine the fruit colour in tomato, regulation of skin colour, pigment variation through carotenogenesis and ripening-associated chlorophyll degradation in fruits are the three major determinants. Identification and analyses of important mutant alleles of the key genes governing these three characters have paved the way for detailed genetic characterization of the associated traits. Interestingly, several fruit colour variation is possible through combining different naturally available and/or induced mutant alleles belonging to these three categories only, as shown in Fig. 2. Moreover, different epistatic interactions for some other allelic combinations (Kachanovsky et al. 2012; Luo et al. 2013) add further variations in tomato fruit colour. Thus, the allelic combinations are not only supposed to create unique colour-variants of tomato for practical utility, but also to generate unique lines for deciphering the genetics behind fruit colour variation, in detail. For example, successful breeding of an orange-brown tomato line using *CYC-B* and *SGR* mutant alleles has been reported in the recent past (Manoharan et al. 2017). The flavonoid accumulating mutant allele *Aft* was stacked with the *high pigment* ($hp2^{dg}$) mutant allele to obtain a 'purple tomato' line (Hazra et al. 2018). It will be really interesting to

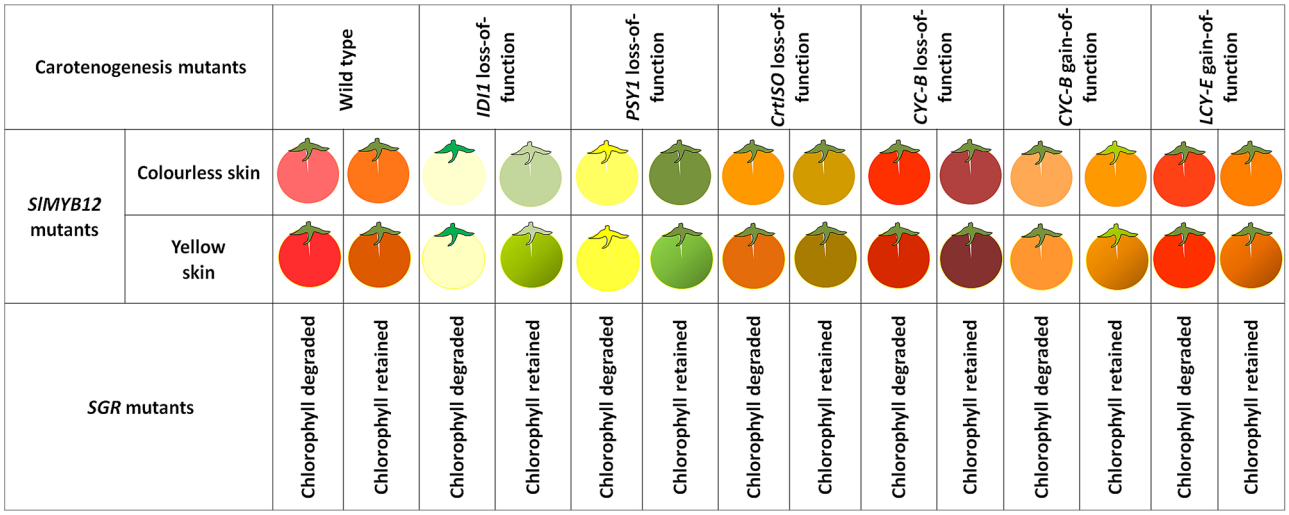

Fig. 2 The possible colour variations in ripe tomato fruits through stacking of skin pigmentation, carotenoid biosynthesis and ripening-associated chlorophyll degradation mutant alleles in different combinations

investigate the capacity of the combination of the *hp* mutants (with modified plastids to have increased carotenogenesis) and lycopene enhancer mutants (like *og* and *og*^{c}) to enhance lycopene content in tomato through conventional breeding, as encouraging results in this direction has already been obtained (Stommel 2007). Similarly, keeping the low bioavailability of lycopene from fresh tomatoes in mind (Burri et al. 2009; Cooperstone et al. 2015), breeding for enhanced prolycopene content using the *CrtISO* mutant allele should be rewarding. Recently, different fruit colour mutant alleles, individually or in combinations, have been introgressed in a cultivar to create a beautiful repertoire of tomato fruit colour-variants (Dono et al. 2020a,b). Another classical example of achieving novel fruit colour and pigment composition is the development of zeaxanthin-rich tomato 'Xantomato' by pyramiding different mutant alleles (Karniel et al. 2020). These achievements would definitely motivate the tomato breeders to attempt for similar programmes in their locally adapted cultivars. Moreover, precise genome editing using CRISPR-Cas9 technology along with TILLING, EcoTILLING and next-generation sequencing (NGS) techniques has broadened the way for creation and identification of novel mutant alleles that can be explored for fruit colour and nutritional improvement in tomato.

Unfortunately, a few spontaneous and induced fruit colour mutants show deleterious pleiotropic effect on plant growth, fruit set and other economic characters. For example, the *high pigment* and *dark green* mutants exhibit undesirable traits like brittle stems and shortened seedling hypocotyls (Jarret et al. 1984). Hence, accurate identification of causal mutation(s) is not only required for deciphering the molecular mechanism underlying the trait-development but also is a prerequisite for utilization of the mutants in breeding programme. Other challenges associated with the breeding programmes targeting pigment improvement in tomato include the precise quantification of different pigments (which is often labour and cost intensive) and the effect of environmental factors on these characters (reviewed in Cebolla-Cornejo et al. 2013). The DNA-based molecular markers are indispensible tools in this regard that can lead to environment-independent marker-assisted selection and introgression of the mutant allele(s) to develop improved cultivar(s). The detailed characterization of the important mutant alleles, as presented here, should help in developing diagnostic molecular markers using the available whole genome sequence information in tomato.

Acknowledgement The authors thank BAU Sabour and BCKV Nadia for providing facilities. PH thanks Department of Science and Technology, Govt. of India for providing financial assistance through sanctioning the research project entitled: 'Enhancement of nutritional quality of tomato by increasing lycopene and anthocyanin contents through mutant genes'. AM thanks Indian Council of Agricultural Research (ICAR) for providing fellowship during his postgraduate studies at BAU. The authors acknowledge all the scientists whose published (or unpublished)works could not be cited in this article due to space constrains. This article bears the BAU COMMUNICATION NO. 819/2020.

Author contribution TC conceptualized and prepared the manuscript. PH critically supplemented themanuscript. SA, DM, AM and SR assisted in preparing the manuscript. All authors read the final version of the manuscript, provided necessary suggestions and approved it for publication.

Compliance with ethical standards

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

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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