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## Genetic factors involved in the bioavailability of tomato carotenoids

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**Abbreviations:** ABCA1 (ATP binding cassette subfamily A member 1); ABCB1 [ATP-binding cassette, sub-family B (MDR/TAP), member 1]; APOB (apolipoprotein B); BCO1 ( $\beta$ -carotene oxygenase 1); BCO2 ( $\beta$ -carotene oxygenase 2); CD36 (CD36 molecule); ELOVL2 (ELOVL fatty acid elongase 2); ISX (intestine specific homeobox); LIPC (lipase C, hepatic type); MTTP (microsomal triglyceride transfer protein); *SCARB1* (gene)/SR-BI (protein) (scavenger receptor class B, member 1); SNP (single nucleotide polymorphism).

## ABSTRACT

**Purpose of review:** To provide an update on the genetic factors recently associated with the interindividual variability of tomato carotenoid bioavailability.

**Recent findings:** Several clinical studies have demonstrated that the main carotenoids found in tomatoes (lycopene, phytoene, phytofluene,  $\beta$ -carotene, lutein) all display relatively large interindividual variabilities of their bioavailability, with CVs >70%. The bioavailability of the parent molecules, and the blood/tissue appearance of their metabolites, is modulated by numerous proteins, involved in intestinal absorption and metabolism, blood lipoprotein transport or tissue uptake. Several single nucleotide polymorphisms have been associated with the interindividual variability of lycopene, lutein and  $\beta$ -carotene bioavailability, with six genes consistently shared between the three carotenoids, and in particular one SNP in *ELOVL fatty acid elongase 2*. The effects of the genetic variants taken separately are relatively low, *i.e.* each variant is usually associated with only a few percent of the bioavailability, but multivariate analysis suggest that the additive effect of several genetic variants can explain a significant fraction of tomato carotenoid bioavailability.

**Summary:** Additional studies are needed to improve our knowledge of the genetic determinants of tomato carotenoid bioavailability but progress in this field could one day allow nutritionists to provide more personalized dietary recommendations.

**Keywords:** Single nucleotide polymorphism, beta-carotene, lycopene, lutein, absorption.

## INTRODUCTION

Tomatoes, whether consumed raw or processed, are an important component of many human diets. For example, in the US population, they constitute the second most consumed vegetable, only topped by potatoes [1]. Their consumption has been associated with a decreased risk to develop several chronic diseases, such as cardiovascular diseases [2], certain types of cancers [3] or age-related macular degeneration [4]. Tomatoes contain many potential health promoting compounds, *e.g.* minerals, vitamins or phytochemicals such as polyphenols and carotenoids [5]. Among these components, carotenoids have received considerable interest and results from many *in vitro*, animal, clinical and association studies point at their significant contribution to the observed health benefits of tomato consumption (see [6] for review). Carotenoids have been assumed to exert their biological effects through their well characterized antioxidant properties [7] or pro-vitamin A activities for some (mainly  $\beta$ -carotene,  $\alpha$ -carotene and  $\beta$ -cryptoxanthin). However, it is now established that carotenoids, as parent molecules or via the many metabolites they can generate [8, 9], also exhibit biological activities independent of their antioxidant properties, *e.g.* as modulators of inflammation [10-13] or nuclear receptor ligands [14, 15]. Lycopene is the carotenoid found at the highest concentration in tomatoes, giving them their usual red colour, but other carotenoids are also found in significant amounts, *i.e.*  $\alpha$ -,  $\beta$ -,  $\delta$ -,  $\gamma$ -carotene, lutein, and the colourless carotenoids phytoene and phytofluene [5, 16]. It should be stressed that the tomato carotenoid profile, including their isomeric profile [17], is highly variable, depending on factors such as cultivar, environment, agronomic practices, stage of ripeness, or conditioning, which might in turn also modify the related health properties. Carotenoid concentration at their site of action in the human body depends on both their intake and their bioavailability. Carotenoid bioavailability is a complex phenotype, involving many steps and, as a consequence, it is highly variable. Indeed, many factors are involved, from characteristics of the diet, *e.g.* amount of fat, of fibres, food processing, to host

related features, *e.g.* sex, age, pathologies or genetic characteristics [18, 19]. The early observation of a relatively high interindividual variability in  $\beta$ -carotene bioavailability [20] together with the more recent identification of several proteins involved in the intestinal absorption of carotenoids [21] has led to hypothesize that genetic variations in these genes could partly explain this variability. This field of research has lately received an increased interest, due to the emergence of affordable genotyping technologies, and several SNPs have been shown to be associated with the variability of tomato carotenoid bioavailability, opening the possibility for more personalized dietary recommendation that would improve the health benefits of tomato consumption.

## **PROTEINS INVOLVED IN TOMATO CAROTENOID BIOAVAILABILITY**

Before discussing the genetic variations that have been associated with tomato carotenoid bioavailability, it is important to describe the successive steps involved, from their extraction from the food matrix during digestion to their distribution to their site of action, with an emphasis on the proteins implicated. Detailed descriptions can be found in several recent reviews [18, 19, 22] and we will here only focus on the more recent developments in this field. Carotenoids are lipids and their fate in the gastrointestinal tract during digestion, their absorption by enterocytes and their distribution in the circulation hence share common mechanisms with other lipid molecules, such as fat-soluble vitamins.

The first step involved in carotenoid bioavailability is their micellization, *i.e.* their transfer from the food matrix to mixed micelles. Digestive enzymes participate in this process by contributing to the degradation of the food matrix and indeed, pancreatic lipase, encoded by *PNLIP*, has been shown to facilitate the transfer of carotenoids from emulsified lipid droplets towards mixed micelles [23]. It should be emphasized that the efficiency of this process is relatively low, especially for lycopene where bioaccessibility values, *i.e.* percent of

incorporation in micelles, reported are typically  $\leq 2\%$  [24], and that consequently, a large fraction of ingested carotenoids are not absorbed in the small intestine. They hence reach the colon but data regarding interaction with the gut microbiota is missing [25] and the fate of metabolites that could be produced remains largely unknown.

The second step is the uptake of bioaccessible carotenoids by enterocytes. This process was long thought to occur by simple passive diffusion only but several proteins located at the apical membrane, at least temporarily, have been shown to participate in the facilitated diffusion of carotenoids [21]. Scavenger receptor class B member 1 (SR-BI), which is encoded by *SCARB1*, participates in the uptake of provitamin A carotenoids [26, 27], lutein [28], zeaxanthin [29], lycopene [30], phytoene and phytofluene (data submitted for publication). CD36 molecule (CD36) facilitates provitamin A carotenoid uptake [26] and could also facilitate lycopene uptake [31] while NPC1 like intracellular cholesterol transporter 1 could be involved in the uptake of lutein [32]. The precise mechanism(s) of carotenoid uptake in the enterocyte is still not known and it has recently been suggested that some of these proteins might actually interact indirectly by promoting the assembly and secretion of chylomicrons, thereby increasing their gradient between the intestinal lumen and the enterocyte [33, 34].

Following their apical uptake, carotenoids can be metabolised by two enzymes,  $\beta$ -carotene oxygenase 1 (BCO1) [35] and  $\beta$ -carotene oxygenase 2 (BCO2) [36], which differ in their substrates, products and cellular localization. BCO1 is a cytosolic enzyme which catalyses the oxidative central cleavage of provitamin A carotenoids, yielding at least one retinal molecules (2 for  $\beta$ -carotene), but also that of beta-apocarotenals and lycopene [37]. BCO2 is a mitochondrial inner membrane protein which cleaves carotenoids eccentrically and yields apo-carotenals. Overall, BCO1 is assumed to be the main cleaving enzyme for provitamin A carotenoids while BCO2 is assumed to favour that of non-provitamin A carotenoids [38]. Nevertheless, this does not apply to lycopene since its cleavage seems to depend on its

isomerisation, which mostly takes place in the enterocyte [39]. Indeed, the all-*trans* isomer has been shown to be only cleaved by BCO1 [37, 40, 41], while the 5-*cis* and 13-*cis* isomers are only cleaved by BCO2 [42, 43]. These two enzymes are not solely expressed in enterocytes but it has been shown that more than  $\approx 70\%$   $\beta$ -carotene conversion occurs in the small intestine [44, 45]. Interestingly, both *BCO1* and *SCARB1* are under the regulation of an intestinal transcription factor named intestine specific homeobox (ISX): when cellular all-*trans* retinoic acid concentration increases, ISX is activated and in turns represses *BCO1* and *SCARB1* expression, which decreases carotenoid uptake and processing and ultimately retinoic acid production, thus constituting a negative feedback loop regulation of intracellular retinoic acid concentration [29]. Interestingly, a SNP in the ISX binding site in the *BCO1* promoter was found to be associated with decreased conversion rates of  $\beta$ -carotene by 50% and increased fasting blood concentrations of  $\beta$ -carotene [46]. Although this mechanism was first described for  $\beta$ -carotene [47], which yields two retinal molecules upon BCO1 cleavage, it has also been demonstrated for zeaxanthin [29], a xanthophyll, and probably applies to other carotenoids. The respective contribution of circulating retinol vs newly absorbed vitamin A or carotenoids to intracellular enterocyte retinoic acid concentration is not known. Furthermore, blood retinol concentration is homeostatically regulated and only poorly reflects total vitamin A status. Thus, whether this mechanism links vitamin A status to carotenoid bioavailability remains to be confirmed. Overall, these proteins play crucial roles in carotenoid absorption and thus genetic variations in their encoding genes are good candidates to explain the high interindividual variability in carotenoid bioavailability. Moreover, we hypothesize that these genetic variations could also influence the profile of carotenoid metabolites generated upon carotenoid intake and hence modify some of their health properties, but this remains to be demonstrated.

In order to reach the circulation, carotenoids, or their metabolites, must be secreted at the basolateral side of the enterocyte. No intracellular transport protein has been identified yet, so

the mechanism by which the parent molecules, which are highly apolar, as well as some of the more apolar metabolites, cross the enterocyte cytosol remains unknown. Native carotenoids are assumed to be mostly secreted with chylomicrons into the lymph, thus following the fate of other newly absorbed lipids. This process likely involves enzymes/apolipoproteins responsible for the assembly of chylomicrons, *e.g.* microsomal triglyceride transfer protein (MTP), apoA-IV, secretion associated Ras related GTPase 1B (SAR1B) and apoB48 (encoded by *APOB*) [48]. Nevertheless, secretion in intestinal HDL via the ATP binding cassette A1 (ABCA1) has also been hypothesized [49]. On the other hands, some of the more polar metabolites (with log P values less than 5) may be secreted to the portal vein and then reach the liver.

Carotenoids secreted in chylomicrons are taken up by the liver via the chylomicron-remnant receptors, *i.e.* the LDL-receptor (LDLR), the LDL-receptor related protein 1 (LRP1), and the heparan sulfate proteoglycans (HSPGs) [50]. The fate of carotenoid metabolites secreted in the portal vein has yet to be studied. Carotenoids that reach the liver via chylomicrons are stored in this organ, eliminated in the bile, or re-secreted into VLDL to be distributed to peripheral tissues. However, it cannot be excluded that a fraction of carotenoids are able to significantly transfer between lipoproteins or to transfer from lipoproteins to tissues during intravascular chylomicron metabolism [51]. Xanthophylls are less apolar than carotenes and are thus found closer to the outer layer of lipoproteins compared to carotenes, thereby facilitating their potential exchange between lipoproteins. In agreement, recent data have shown that xanthophylls are transported mostly in HDL while carotenes are found preferentially in LDL, which result from VLDL metabolism [52].

Regarding further carotenoid distribution, it is hypothesized that only tissues that express the LDL-receptor can take up carotenoids incorporated into LDL. Moreover, it has been shown that CD36, which is able to bind oxidized LDL, is involved in adipose tissue uptake of lycopene and lutein [31], and that SR-BI, which is found in many tissues, is involved in the uptake of



zeaxanthin into the retina. Indeed, it has recently been proposed that HDL-zeaxanthin uptake into the retina is facilitated by SR-BI while that of LDL-lutein is facilitated by the LDL receptor [52], thereby protecting the macula from light-induced damages [53, 54].

## **GENETIC VARIATIONS ASSOCIATED WITH TOMATO CAROTENOID BIOAVAILABILITY**

Many clinical trials have investigated the interindividual variability in the response to carotenoid intake. Although there were many differences in the study designs (food *vs* supplement, carotenoid dose ingested, measurement of carotenoid concentration in tissue *vs* blood, number and characteristics of subjects), they systematically reported a high interindividual variability in carotenoid bioavailability, including with tomato products as a source for carotenoids (see [18] for review).

Genetic variations between individuals have been suggested to explain, at least in part, this phenomenon [18, 19, 55, 56]. Consequently, several studies have aimed to identify genetic variants involved in the variability of the bioavailability of carotenoids (*see Table 1 and Figure 1* for summary of published studies). Several different approaches have been used to estimate carotenoid bioavailability [57], which might yield different results depending on the relative contribution of the proteins involved. We have thus proposed to use the postprandial chylomicron carotenoid concentration as an estimate of carotenoid bioavailability in order to allow for comparison between studies [57].

## **GENETIC VARIATIONS ASSOCIATED WITH LYCOPENE BIOAVAILABILITY**

There are only two studies dedicated to identify genetic variations associated with lycopene bioavailability, using either watermelon juices or tomato puree as a source of lycopene. The first one investigated the association between 2 non-synonymous SNPs in *BCO1* and the plasma

lycopene concentration in 23 healthy adults following the consumption of watermelon juices (representing 20 mg lycopene per day) for 3 weeks but no significant association was observed [58]. The second study sought to identify a combination of SNPs associated with tomato lycopene bioavailability, which was estimated by measuring the postprandial chylomicron lycopene response to a test-meal containing tomato puree (representing 9.7 mg all-*trans* lycopene) in 33 healthy male subjects [59]. This study showed that lycopene bioavailability was associated with a combination of 28 SNPs in or near 16 candidate genes. Seven of these genes [*ABCA1*, *lipoprotein lipase*, *insulin induced gene 2*, *solute carrier family 27 member 6*, *hepatic lipase (LIPC)*, *CD36*, and *APOB*] had been associated with the postprandial chylomicron triacylglycerol response in the same group of subjects [60]. Four of these genes were more specifically associated with the variability in lycopene bioavailability. *ABCB1* encodes for the P-glycoprotein, an ATP-dependent drug efflux pump for xenobiotics with broad substrate specificity, highly expressed in enterocytes. The association of P-glycoprotein with postprandial lycopene concentrations suggests that it could participate in the efflux of lycopene back to the intestinal lumen, as was recently shown for vitamin D [61]. *ELOVL2* encodes for ELOVL fatty acid elongase 2 which catalyzes the elongation of eicosapentaenoic acid to docosapentaenoic acid and docosapentaenoic acid to docosahexaenoic acid. Carotenoids are not known substrates for this enzyme but this association could be due to an interaction between omega 3 fatty acid metabolism and carotenoids since eicosapentaenoic acid has been shown to inhibit  $\beta$ -carotene absorption [62]. *MTTP* encodes for the microsomal triglyceride transfer protein, which is involved in the packaging of triacylglycerols within chylomicrons, which carry newly absorbed carotenoids in the circulation. *SOD2* encodes the superoxide dismutase 2 that is responsible for converting superoxide by-products to hydrogen peroxide and diatomic oxygen. It was hypothesized that, when this enzyme is not efficient, superoxide by-products are quenched by lycopene, leading to its degradation [63].

## 200 GENETIC VARIATIONS ASSOCIATED WITH LUTEIN BIOAVAILABILITY

201       There are only two studies dedicated to identify genetic variations associated with lutein  
202 bioavailability. Neither used tomatoes or tomato products as a source of lutein since other food  
203 sources, *e.g.* spinach, provide higher amounts thereof. In the first one, Yonova-Doing *et al.*  
204 measured macular pigment optical density, which is a marker of lutein and zeaxanthin  
205 concentration in the macula, in 310 Caucasian female twins aged 20-50 before and after  
206 receiving 54 mg lutein and 7.2 mg zeaxanthin daily for 6 months [64]. They found four SNPs  
207 to be significantly associated with the change in macular pigment optical density following  
208 supplementation, which can be considered as a marker of xanthophyll bioavailability. A SNP  
209 in *ABCA1*, possibly due to the role of this membrane protein in lipid influx in the retinal pigment  
210 epithelium [65] and/or to enterocyte basolateral secretion of HDL-lutein [49], a SNP in  
211 *SCARB1*, a SNP in *fatty acid desaturase 1* and a SNP in *retinal pigment epithelium 65*. Fatty  
212 acid desaturase 1 is involved in the conversion of  $\alpha$ -linolenic acid to eicosapentaenoic acid,  
213 which again suggests an association between omega 3 fatty acid metabolism and carotenoid  
214 bioavailability. *Retinal pigment epithelium 65* encodes a protein highly expressed in the retinal  
215 pigment epithelium, working as a retinol isomerase of the visual cycle, which is involved in  
216 visual pigment regeneration and was recently shown to be responsible for the macular  
217 production of *meso*-zeaxanthin from lutein [66]. In the second study, the variability in the  
218 postprandial chylomicron lutein response to a test-meal supplemented with 15 mg free lutein  
219 was associated with a combination of 29 SNPs in 15 genes in a group of 39 healthy adult men  
220 [67]. Seven of these genes (*ABCA1*, *APOA1*, *APOB*, *cordon-bleu WH2 repeat protein like 1*,  
221 *hepatic lipase*, *insulin induced gene 2*, *insulin receptor substrate 1*, *lipoprotein lipase*, and  
222 *melanocortin 4 receptor*) were previously associated with the interindividual variability in the  
223 postprandial chylomicron triglyceride response in the same group of subjects (39). Four genes

were more specifically associated with lutein bioavailability: *ATP-binding cassette, subfamily G, member 2*, *ELOVL2*, *ISX* and *MTTP*. Interestingly, SNPs in the last 3 genes were also associated with lycopene variability. *ATP-binding cassette, subfamily G, member 2* encodes for a breast cancer resistance protein (BCRP), which is a multidrug transporter [68], and this association suggests it could also be involved in lutein transport.

## **GENETIC VARIATIONS ASSOCIATED WITH BETA-CAROTENE BIOAVAILABILITY**

There have been four studies, based on three different trials, investigating the effects of genetic variants on  $\beta$ -carotene bioavailability, although only one used tomato puree as a source, while the others used either a supplement or watermelon juices. Two common nonsynonymous SNPs in *BCOI* have been associated with the postprandial triglyceride-rich lipoprotein  $\beta$ -carotene and retinyl palmitate concentrations following consumption of a meal supplemented with 120 mg  $\beta$ -carotene [69] and also with blood  $\beta$ -carotene concentration following consumption for 3 weeks of a watermelon juice, providing a more nutritional dose of  $\beta$ -carotene (2.5 mg per day) [58]. In a re-analysis of the first trial, 3 SNPs upstream from *BCOI* were associated with  $\beta$ -carotene conversion capacity [70]. In the most recent study, the variability in the postprandial chylomicron  $\beta$ -carotene response to a test-meal containing 100 g tomato puree, providing 0.4 mg  $\beta$ -carotene, was associated with a combination of 25 SNPs in 12 genes [71]. Four genes (*ABCA1*, *APOB*, *hepatic lipase*, *transcription factor 7-like 2*) were previously associated with the interindividual variability in the postprandial chylomicron triglyceride response in the same group of subjects [60], while 8 were more specifically associated with the  $\beta$ -carotene response. Interestingly, a SNP in *ISX* and a SNP in *BCOI* were identified, thereby confirming the key role played by *ISX* in  $\beta$ -carotene bioavailability [46]. The second association of interest was found in *ELVOL2*. Moreover, it should be stressed that the same

SNP in *ELOVL2* that was associated with the variability of lycopene and lutein bioavailability was associated with  $\beta$ -carotene bioavailability.

Overall, six genes (*ABCA1*, *APOB*, *ELOVL2*, *ISX*, *LIPC* and *polycystin 1 like 2*) have been consistently shown to have SNPs associated with the variability in the bioavailability of  $\beta$ -carotene, lutein and lycopene, and in particular the same SNP in *ELOVL2* across all three carotenoids. Furthermore, these results were obtained in the same group of subjects [59, 67, 71].

Although it appears that for some of the associations reported between the variability in carotenoid bioavailability and SNPs, tomatoes or tomato products were not used as a source of carotenoids, we believe these results can be extrapolated to tomatoes or tomato products because the main source of variability in these clinical trials originates from genetic variations. Nonetheless, if the effect of the food matrix on carotenoid bioavailability were to be high, it could potentially not allow the comparison with tomatoes or tomato products.

## CONCLUSION

Several genetic variants have now been involved in the variability of the bioavailability of the major carotenoids found in tomatoes and they could explain to some extent the variability observed in the health effects associated with tomato and tomato product consumption. Yet, some carotenoids found in significant amount in tomato and tomato products, such as phytoene and phytofluene, have been completely left out of studies so far although they might also be associated with the health properties of tomatoes and tomato products. We now need clinical studies with more participants (including more ethnic groups) to confirm these promising results. More SNPs/genes should be investigated and other genetic variations (*e.g.* copy number variants) or epigenetic modifications should also be considered. To date, there is no data on the

274 effects of genetic variations on the production and bioavailability of carotenoid metabolites,  
275 which could be responsible for some of the health effects conferred by tomatoes. Although a  
276 lot of work remains to be done, this field of research is promising, and the results generated will  
277 contribute to provide personalized dietary recommendations in order to improve the benefit of  
278 tomato consumption.

## **KEY POINTS**

- Tomato carotenoid bioavailability is highly variable and some of this variability is due to genetic differences between individuals.
- Many proteins are involved in the bioavailability of carotenoids and their metabolites.
- Several single nucleotide polymorphisms in the genes encoding these proteins have been associated with the observed interindividual variability in tomato carotenoid bioavailability.
- More studies are needed to predict individual responses to tomato carotenoids and provide personalized dietary recommendations.

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## **CONFLICTS OF INTEREST**

None.

## **AUTHOR CONTRIBUTIONS**

C. Desmarchelier, J.F. Landrier and P. Borel contributed equally to the writing of this review.



**Figure 1. Summary of the genes involved in the variability of tomato carotenoid bioavailability.**

Genes displayed are those for which SNPs have been associated with the variability of the bioavailability of lycopene,  $\beta$ -carotene or lutein. Genes in bold letters are those for which SNPs have been associated with the variability of the bioavailability of these three carotenoids.

**Table 1.** Summary of SNPs associated with tomato carotenoid bioavailability.

SNP	Global MAF <sup>1</sup>	Nearest Gene	Carotenoid	Reference
rs1331924*	0.245	<i>ABCA1</i>	Lycopene	[59]
rs2791952*	0.140	<i>ABCA1</i>	Lycopene	[59]
rs3887137*	0.123	<i>ABCA1</i>	Lycopene	[59]
rs4149299*	0.082	<i>ABCA1</i>	Lycopene	[59]
rs4149316*	0.122	<i>ABCA1</i>	Lycopene	[59]
rs10248420	0.347	<i>ABCB1</i>	Lycopene	[59]
rs10280101	0.145	<i>ABCB1</i>	Lycopene	[59]
rs1871744	0.499	<i>ABCG2</i>	Lycopene	[59]
rs1042031*	0.153	<i>APOB</i>	Lycopene	[59]
rs4112274*	0.224	<i>CD36</i>	Lycopene	[59]
rs3798709	0.252	<i>ELOVL2</i>	Lycopene	[59]
rs911196	0.252	<i>ELOVL2</i>	Lycopene	[59]
rs9468304	0.302	<i>ELOVL2</i>	Lycopene	[59]
rs17006621*	0.172	<i>INSIG2</i>	Lycopene	[59]
rs2056983	0.117	<i>ISX</i>	Lycopene	[59]
rs12914035*	0.096	<i>LIPC</i>	Lycopene	[59]
rs8035357*	0.150	<i>LIPC</i>	Lycopene	[59]
rs17482753*	0.088	<i>LPL</i>	Lycopene	[59]
rs7005359*	0.298	<i>LPL</i>	Lycopene	[59]
rs7841189*	0.148	<i>LPL</i>	Lycopene	[59]
rs1032355	0.251	<i>MTTP</i>	Lycopene	[59]
rs17029173	0.135	<i>MTTP</i>	Lycopene	[59]
rs745075	0.095	<i>MTTP</i>	Lycopene	[59]
rs17725246	0.254	<i>NPC1L1</i>	Lycopene	[59]
rs935933	0.139	<i>PKD1L2</i>	Lycopene	[59]
rs11197742	0.087	<i>PNLIP</i>	Lycopene	[59]
rs10053477*	0.209	<i>SLC27A6</i>	Lycopene	[59]
rs9365046	0.169	<i>SOD2</i>	Lycopene	[59]

rs1929841	0.252	<i>ABCA1</i>	Lutein	[64]
rs174534	0.295	<i>FADS1</i>	Lutein	[64]
rs4926339	0.225	<i>RPE65</i>	Lutein	[64]
rs11057841	0.179	<i>SCARB1</i>	Lutein	[64]
rs4149316*	0.117	<i>ABCA1</i>	Lutein	[67]
rs390253*	0.257	<i>ABCA1</i>	Lutein	[67]
rs9919066*	0.063	<i>ABCA1</i>	Lutein	[67]
rs2020926*	0.105	<i>ABCA1</i>	Lutein	[67]
rs17731631	0.125	<i>ABCG2</i>	Lutein	[67]
rs6532059	0.047	<i>ABCG2</i>	Lutein	[67]
rs2070665*	0.180	<i>APOA1</i>	Lutein	[67]
rs2854725*	0.092	<i>APOB</i>	Lutein	[67]
rs3769877*	0.189	<i>COBLL1</i>	Lutein	[67]
rs9468304	0.309	<i>ELOVL2</i>	Lutein	[67]
rs3798709	0.250	<i>ELOVL2</i>	Lutein	[67]
rs17006621*	0.203	<i>INSIG2</i>	Lutein	[67]
rs2178704*	0.199	<i>IRS1</i>	Lutein	[67]
rs1316328*	0.142	<i>IRS1</i>	Lutein	[67]
rs137252	0.090	<i>ISX</i>	Lutein	[67]
rs137269	0.132	<i>ISX</i>	Lutein	[67]
rs5749706	0.199	<i>ISX</i>	Lutein	[67]
rs137238	0.122	<i>ISX</i>	Lutein	[67]
rs5755368	0.234	<i>ISX</i>	Lutein	[67]
rs12591216*	0.096	<i>LIPC</i>	Lutein	[67]
rs12593880*	0.075	<i>LIPC</i>	Lutein	[67]
rs1441778*	0.189	<i>LPL</i>	Lutein	[67]
rs7821631*	0.204	<i>LPL</i>	Lutein	[67]
rs10096561*	0.146	<i>LPL</i>	Lutein	[67]
rs256*	0.140	<i>LPL</i>	Lutein	[67]
rs11873337*	0.128	<i>MC4R</i>	Lutein	[67]

rs17029213	0.051	<i>MTTP</i>	Lutein	[67]
rs12596941	0.203	<i>PKD1L2</i>	Lutein	[67]
rs1924546	0.119	<i>RPE65</i>	Lutein	[67]
rs12934922	0.227	<i>BCO1</i>	$\beta$ -carotene	[69], [58]
rs7501331	0.152	<i>BCO1</i>	$\beta$ -carotene	[69], [58]
rs6420424	0.434	<i>BCO1</i>	$\beta$ -carotene	[70]
rs11645428	0.156	<i>BCO1</i>	$\beta$ -carotene	[70]
rs6564851	0.476	<i>BCO1</i>	$\beta$ -carotene	[70]
rs2791952*	0.148	<i>ABCA1</i>	$\beta$ -carotene	[71]
rs10991408*	0.127	<i>ABCA1</i>	$\beta$ -carotene	[71]
rs3887137*	0.123	<i>ABCA1</i>	$\beta$ -carotene	[71]
rs2278357	0.214	<i>ABCG5</i>	$\beta$ -carotene	[71]
rs1042031*	0.153	<i>APOB</i>	$\beta$ -carotene	[71]
rs4643493*	0.103	<i>APOB</i>	$\beta$ -carotene	[71]
rs35364714*	0.127	<i>APOB</i>	$\beta$ -carotene	[71]
rs7196470	0.244	<i>BCO1</i>	$\beta$ -carotene	[71]
rs1247620	0.129	<i>CXCL8</i>	$\beta$ -carotene	[71]
rs6834586	0.177	<i>CXCL8</i>	$\beta$ -carotene	[71]
rs1358594	0.254	<i>CXCL8</i>	$\beta$ -carotene	[71]
rs9468304	0.309	<i>ELOVL2</i>	$\beta$ -carotene	[71]
rs3798709	0.252	<i>ELOVL2</i>	$\beta$ -carotene	[71]
rs911196	0.251	<i>ELOVL2</i>	$\beta$ -carotene	[71]
rs5755368	0.234	<i>ISX</i>	$\beta$ -carotene	[71]
rs16994824	0.196	<i>ISX</i>	$\beta$ -carotene	[71]
rs202313	0.142	<i>ISX</i>	$\beta$ -carotene	[71]
rs1869138*	0.117	<i>LIPC</i>	$\beta$ -carotene	[71]
rs11857380*	0.154	<i>LIPC</i>	$\beta$ -carotene	[71]
rs12185072*	0.192	<i>LIPC</i>	$\beta$ -carotene	[71]
rs8043708	0.227	<i>PKD1L2</i>	$\beta$ -carotene	[71]
rs4926340	0.083	<i>RPE65</i>	$\beta$ -carotene	[71]

rs12139131	0.102	<i>RPE65</i>	$\beta$ -carotene	[71]
rs2501175	0.298	<i>SOD2</i>	$\beta$ -carotene	[71]
rs946199*	0.173	<i>TCF7L2</i>	$\beta$ -carotene	[71]

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Abbreviations:                   <sup>1</sup>MAF:                   minor                   allele                   frequency

(<https://www.ncbi.nlm.nih.gov/projects/SNP/>); The gene official symbols are those found in PubMed (available online: <https://www.ncbi.nlm.nih.gov/gene/>) and approved by the Hugo Gene Nomenclature Committee (available online: <http://www.genenames.org/>). \*These SNPs were associated with the variability of carotenoid bioavailability, but this was likely due to their association with the variability of the chylomicron triacylglycerol response [60].

## REFERENCES AND RECOMMENDED READING

Papers of particular interest published during the review period (2015-2018) have been highlighted as:

\* of special interest:

[2] This meta-analysis shows that tomato and lycopene supplementation are associated with improvement of cardiovascular disease risk factors.

[3] This meta-analysis shows that consumption of tomato foods and cooked tomatoes and sauces, but not that of raw tomatoes, is associated with a decrease in prostate cancer risk in a dose-dependent fashion.

[4] In this prospective follow-up studies, > 100,000 subjects were followed for ≈25 years.

[14] This study shows lycopene has partial provitaminA in mice.

[17] This is a nice demonstration of the effect of lycopene isomeric form on its bioavailability.

[33] This study shows SR-BI could have an indirect effect on fat-soluble vitamin and carotenoid uptake in the enterocyte by promoting chylomicron synthesis.

[38] This study shows that intestinal BCO2 is not significantly involved in postprandial conversion of newly absorbed  $\beta$ -carotene.

[40] This study refines the knowledge on the substrate specificity of BCO2.

[54] A nice demonstration of the protective effects of photoreceptors by carotenoids.

[62] This article highlights the interaction between omega-3 metabolism and carotenoid bioavailability.

[66] A nice demonstration of the origin of *meso*-zeaxanthin in the eye.

\*\* of outstanding interest:

[29] An important study nicely demonstrating the regulation of SR-B1 and BCO1 activity by intracellular retinoic acid levels, with effects on both carotene and xanthophyll uptake and metabolism.

[52] This study proposes a new mechanisms to explain the differential accumulation of lutein and zeaxanthin in retinal pigment epithelial cells based on differences in blood lipoprotein transport.

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## Figure

