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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 (β -carotene oxygenase 1); BCO2 (β -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).

1 **ABSTRACT**

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

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

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

19

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

21

22

23

24 INTRODUCTION

25 Tomatoes, whether consumed raw or processed, are an important component of many
26 human diets. For example, in the US population, they constitute the second most consumed
27 vegetable, only topped by potatoes [1]. Their consumption has been associated with a decreased
28 risk to develop several chronic diseases, such as cardiovascular diseases [2], certain types of
29 cancers [3] or age-related macular degeneration [4]. Tomatoes contain many potential health
30 promoting compounds, *e.g.* minerals, vitamins or phytochemicals such as polyphenols and
31 carotenoids [5]. Among these components, carotenoids have received considerable interest and
32 results from many *in vitro*, animal, clinical and association studies point at their significant
33 contribution to the observed health benefits of tomato consumption (see [6] for review).
34 Carotenoids have been assumed to exert their biological effects through their well characterized
35 antioxidant properties [7] or pro-vitamin A activities for some (mainly β -carotene, α -carotene
36 and β -cryptoxanthin). However, it is now established that carotenoids, as parent molecules or
37 via the many metabolites they can generate [8, 9], also exhibit biological activities independent
38 of their antioxidant properties, *e.g.* as modulators of inflammation [10-13] or nuclear receptor
39 ligands [14, 15]. Lycopene is the carotenoid found at the highest concentration in tomatoes,
40 giving them their usual red colour, but other carotenoids are also found in significant amounts,
41 *i.e.* α -, β -, δ -, γ -carotene, lutein, and the colourless carotenoids phytoene and phytofluene [5,
42 16]. It should be stressed that the tomato carotenoid profile, including their isomeric profile
43 [17], is highly variable, depending on factors such as cultivar, environment, agronomic
44 practices, stage of ripeness, or conditioning, which might in turn also modify the related health
45 properties. Carotenoid concentration at their site of action in the human body depends on both
46 their intake and their bioavailability. Carotenoid bioavailability is a complex phenotype,
47 involving many steps and, as a consequence, it is highly variable. Indeed, many factors are
48 involved, from characteristics of the diet, *e.g.* amount of fat, of fibres, food processing, to host

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

58

59 **PROTEINS INVOLVED IN TOMATO CAROTENOID BIOAVAILABILITY**

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

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

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

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

90 Following their apical uptake, carotenoids can be metabolised by two enzymes, β -carotene
91 oxygenase 1 (BCO1) [35] and β -carotene oxygenase 2 (BCO2) [36], which differ in their
92 substrates, products and cellular localization. BCO1 is a cytosolic enzyme which catalyses the
93 oxidative central cleavage of provitamin A carotenoids, yielding at least one retinal molecules
94 (2 for β -carotene), but also that of beta-apocarotenals and lycopene [37]. BCO2 is a
95 mitochondrial inner membrane protein which cleaves carotenoids eccentrically and yields apo-
96 carotenals. Overall, BCO1 is assumed to be the main cleaving enzyme for provitamin A
97 carotenoids while BCO2 is assumed to favour that of non-provitamin A carotenoids [38].
98 Nevertheless, this does not apply to lycopene since its cleavage seems to depend on its

99 isomerisation, which mostly takes place in the enterocyte [39]. Indeed, the all-*trans* isomer has
100 been shown to be only cleaved by BCO1 [37, 40, 41], while the 5-*cis* and 13-*cis* isomers are
101 only cleaved by BCO2 [42, 43]. These two enzymes are not solely expressed in enterocytes but
102 it has been shown that more than $\approx 70\%$ β -carotene conversion occurs in the small intestine [44,
103 45]. Interestingly, both *BCO1* and *SCARB1* are under the regulation of an intestinal
104 transcription factor named intestine specific homeobox (ISX): when cellular all-*trans* retinoic
105 acid concentration increases, ISX is activated and in turns represses *BCO1* and *SCARB1*
106 expression, which decreases carotenoid uptake and processing and ultimately retinoic acid
107 production, thus constituting a negative feedback loop regulation of intracellular retinoic acid
108 concentration [29]. Interestingly, a SNP in the ISX binding site in the *BCO1* promoter was
109 found to be associated with decreased conversion rates of β -carotene by 50% and increased
110 fasting blood concentrations of β -carotene [46]. Although this mechanism was first described
111 for β -carotene [47], which yields two retinal molecules upon BCO1 cleavage, it has also been
112 demonstrated for zeaxanthin [29], a xanthophyll, and probably applies to other carotenoids. The
113 respective contribution of circulating retinol vs newly absorbed vitamin A or carotenoids to
114 intracellular enterocyte retinoic acid concentration is not known. Furthermore, blood retinol
115 concentration is homeostatically regulated and only poorly reflects total vitamin A status. Thus,
116 whether this mechanism links vitamin A status to carotenoid bioavailability remains to be
117 confirmed. Overall, these proteins play crucial roles in carotenoid absorption and thus genetic
118 variations in their encoding genes are good candidates to explain the high interindividual
119 variability in carotenoid bioavailability. Moreover, we hypothesize that these genetic variations
120 could also influence the profile of carotenoid metabolites generated upon carotenoid intake and
121 hence modify some of their health properties, but this remains to be demonstrated.

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

124 the mechanism by which the parent molecules, which are highly apolar, as well as some of the
125 more apolar metabolites, cross the enterocyte cytosol remains unknown. Native carotenoids are
126 assumed to be mostly secreted with chylomicrons into the lymph, thus following the fate of
127 other newly absorbed lipids. This process likely involves enzymes/apolipoproteins responsible
128 for the assembly of chylomicrons, *e.g.* microsomal triglyceride transfer protein (MTP), apoA-
129 IV, secretion associated Ras related GTPase 1B (SAR1B) and apoB48 (encoded by *APOB*)
130 [48]. Nevertheless, secretion in intestinal HDL via the ATP binding cassette A1 (ABCA1) has
131 also been hypothesized [49]. On the other hands, some of the more polar metabolites (with log
132 P values less than 5) may be secreted to the portal vein and then reach the liver.

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

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

149 zeaxanthin into the retina. Indeed, it has recently been proposed that HDL-zeaxanthin uptake
150 into the retina is facilitated by SR-BI while that of LDL-lutein is facilitated by the LDL receptor
151 [52], thereby protecting the macula from light-induced damages [53, 54].

152

153 **GENETIC VARIATIONS ASSOCIATED WITH TOMATO CAROTENOID** 154 **BIOAVAILABILITY**

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

161 Genetic variations between individuals have been suggested to explain, at least in part, this
162 phenomenon [18, 19, 55, 56]. Consequently, several studies have aimed to identify genetic
163 variants involved in the variability of the bioavailability of carotenoids (*see Table 1 and Figure*
164 **1** for summary of published studies). Several different approaches have been used to estimate
165 carotenoid bioavailability [57], which might yield different results depending on the relative
166 contribution of the proteins involved. We have thus proposed to use the postprandial
167 chylomicron carotenoid concentration as an estimate of carotenoid bioavailability in order to
168 allow for comparison between studies [57].

169

170 **GENETIC VARIATIONS ASSOCIATED WITH LYCOPENE BIOAVAILABILITY**

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

174 lycopene concentration in 23 healthy adults following the consumption of watermelon juices
175 (representing 20 mg lycopene per day) for 3 weeks but no significant association was observed
176 [58]. The second study sought to identify a combination of SNPs associated with tomato
177 lycopene bioavailability, which was estimated by measuring the postprandial chylomicron
178 lycopene response to a test-meal containing tomato puree (representing 9.7 mg all-*trans*
179 lycopene) in 33 healthy male subjects [59]. This study showed that lycopene bioavailability
180 was associated with a combination of 28 SNPs in or near 16 candidate genes. Seven of these
181 genes [*ABCA1*, *lipoprotein lipase*, *insulin induced gene 2*, *solute carrier family 27 member 6*,
182 *hepatic lipase (LIPC)*, *CD36*, and *APOB*] had been associated with the postprandial
183 chylomicron triacylglycerol response in the same group of subjects [60]. Four of these genes
184 were more specifically associated with the variability in lycopene bioavailability. *ABCB1*
185 encodes for the P-glycoprotein, an ATP-dependent drug efflux pump for xenobiotics with broad
186 substrate specificity, highly expressed in enterocytes. The association of P-glycoprotein with
187 postprandial lycopene concentrations suggests that it could participate in the efflux of lycopene
188 back to the intestinal lumen, as was recently shown for vitamin D [61]. *ELOVL2* encodes for
189 ELOVL fatty acid elongase 2 which catalyzes the elongation of eicosapentaenoic acid to
190 docosapentaenoic acid and docosapentaenoic acid to docosahexaenoic acid. Carotenoids are not
191 known substrates for this enzyme but this association could be due to an interaction between
192 omega 3 fatty acid metabolism and carotenoids since eicosapentaenoic acid has been shown to
193 inhibit β -carotene absorption [62]. *MTTP* encodes for the microsomal triglyceride transfer
194 protein, which is involved in the packaging of triacylglycerols within chylomicrons, which
195 carry newly absorbed carotenoids in the circulation. *SOD2* encodes the superoxide dismutase 2
196 that is responsible for converting superoxide by-products to hydrogen peroxide and diatomic
197 oxygen. It was hypothesized that, when this enzyme is not efficient, superoxide by-products are
198 quenched by lycopene, leading to its degradation [63].

199

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 α -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

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

229

230 **GENETIC VARIATIONS ASSOCIATED WITH BETA-CAROTENE** 231 **BIOAVAILABILITY**

232 There have been four studies, based on three different trials, investigating the effects of
233 genetic variants on β -carotene bioavailability, although only one used tomato puree as a source,
234 while the others used either a supplement or watermelon juices. Two common nonsynonymous
235 SNPs in *BCO1* have been associated with the postprandial triglyceride-rich lipoprotein β -
236 carotene and retinyl palmitate concentrations following consumption of a meal supplemented
237 with 120 mg β -carotene [69] and also with blood β -carotene concentration following
238 consumption for 3 weeks of a watermelon juice, providing a more nutritional dose of β -carotene
239 (2.5 mg per day) [58]. In a re-analysis of the first trial, 3 SNPs upstream from *BCO1* were
240 associated with β -carotene conversion capacity [70]. In the most recent study, the variability in
241 the postprandial chylomicron β -carotene response to a test-meal containing 100 g tomato puree,
242 providing 0.4 mg β -carotene, was associated with a combination of 25 SNPs in 12 genes [71].
243 Four genes (*ABCA1, APOB, hepatic lipase, transcription factor 7-like 2*) were previously
244 associated with the interindividual variability in the postprandial chylomicron triglyceride
245 response in the same group of subjects [60], while 8 were more specifically associated with the
246 β -carotene response. Interestingly, a SNP in *ISX* and a SNP in *BCO1* were identified, thereby
247 confirming the key role played by *ISX* in β -carotene bioavailability [46]. The second
248 association of interest was found in *ELVOL2*. Moreover, it should be stressed that the same

249 SNP in *ELOVL2* that was associated with the variability of lycopene and lutein bioavailability
250 was associated with β -carotene bioavailability.

251

252 Overall, six genes (*ABCA1*, *APOB*, *ELOVL2*, *ISX*, *LIPC* and *polycystin 1 like 2*) have been
253 consistently shown to have SNPs associated with the variability in the bioavailability of β -
254 carotene, lutein and lycopene, and in particular the same SNP in *ELOVL2* across all three
255 carotenoids. Furthermore, these results were obtained in the same group of subjects [59, 67,
256 71].

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

263

264 **CONCLUSION**

265 Several genetic variants have now been involved in the variability of the bioavailability of
266 the major carotenoids found in tomatoes and they could explain to some extent the variability
267 observed in the health effects associated with tomato and tomato product consumption. Yet,
268 some carotenoids found in significant amount in tomato and tomato products, such as phytoene
269 and phytofluene, have been completely left out of studies so far although they might also be
270 associated with the health properties of tomatoes and tomato products. We now need clinical
271 studies with more participants (including more ethnic groups) to confirm these promising
272 results. More SNPs/genes should be investigated and other genetic variations (*e.g.* copy number
273 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, β -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 ¹	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]
rs9111196	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>NPCIL1</i>	Lycopene	[59]
rs935933	0.139	<i>PKDIL2</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>	β -carotene	[69], [58]
rs7501331	0.152	<i>BCO1</i>	β -carotene	[69], [58]
rs6420424	0.434	<i>BCO1</i>	β -carotene	[70]
rs11645428	0.156	<i>BCO1</i>	β -carotene	[70]
rs6564851	0.476	<i>BCO1</i>	β -carotene	[70]
rs2791952*	0.148	<i>ABCA1</i>	β -carotene	[71]
rs10991408*	0.127	<i>ABCA1</i>	β -carotene	[71]
rs3887137*	0.123	<i>ABCA1</i>	β -carotene	[71]
rs2278357	0.214	<i>ABCG5</i>	β -carotene	[71]
rs1042031*	0.153	<i>APOB</i>	β -carotene	[71]
rs4643493*	0.103	<i>APOB</i>	β -carotene	[71]
rs35364714*	0.127	<i>APOB</i>	β -carotene	[71]
rs7196470	0.244	<i>BCO1</i>	β -carotene	[71]
rs1247620	0.129	<i>CXCL8</i>	β -carotene	[71]
rs6834586	0.177	<i>CXCL8</i>	β -carotene	[71]
rs1358594	0.254	<i>CXCL8</i>	β -carotene	[71]
rs9468304	0.309	<i>ELOVL2</i>	β -carotene	[71]
rs3798709	0.252	<i>ELOVL2</i>	β -carotene	[71]
rs911196	0.251	<i>ELOVL2</i>	β -carotene	[71]
rs5755368	0.234	<i>ISX</i>	β -carotene	[71]
rs16994824	0.196	<i>ISX</i>	β -carotene	[71]
rs202313	0.142	<i>ISX</i>	β -carotene	[71]
rs1869138*	0.117	<i>LIPC</i>	β -carotene	[71]
rs11857380*	0.154	<i>LIPC</i>	β -carotene	[71]
rs12185072*	0.192	<i>LIPC</i>	β -carotene	[71]
rs8043708	0.227	<i>PKD1L2</i>	β -carotene	[71]
rs4926340	0.083	<i>RPE65</i>	β -carotene	[71]

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

Abbreviations: ¹MAF: 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 β -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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