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# Genetic determinants of lycopene concentration in subcutaneous adipose tissue: insights into interindividual variability in adult males

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**Background and objectives:** Lycopene (LYC) is a carotenoid obtained primarily from tomatoes and tomato-based products. LYC displays potent antioxidant properties and its intake and circulating concentrations have been associated with a reduced risk of prostate and breast cancers as well as cardiovascular diseases. Following absorption, it is mainly stored in adipose tissue, which accounts for approximately two-thirds of total body stores, where it may influence processes such as oxidative stress and inflammation. However, the factors determining LYC concentration in adipose tissue remain poorly understood. This study aimed to characterize the interindividual variability of adipose tissue LYC concentration and identify single nucleotide polymorphisms (SNPs) associated with it. **Methods:** Forty-three healthy adult males (mean age:  $32.0 \pm 2.0$  year; mean BMI:  $23.0 \pm 0.3$  kg m<sup>-2</sup>) underwent whole-genome genotyping. Periumbilical adipose tissue samples were collected on six occasions (in the fasting state and 8 h after consumption of three different standardized meals), and plasma and adipose tissue LYC concentrations were quantified by HPLC. Forty-three candidate genes potentially involved in LYC metabolism were selected, and the association of 3786 SNPs from these genes with adipose tissue LYC concentration was assessed using partial least squares regression. **Results:** Adipose tissue LYC concentration showed marked interindividual variability (CV = 55%). Adipose tissue and fasting plasma LYC concentrations were significantly, but moderately, correlated (Pearson's  $r = 0.37$ ; 95% CI: 0.07–0.61). An internally validated PLS regression model consisting of 17 SNPs in 11 genes—*ABCA1*, *APOB*, *CD36*, *ELOVL5*, *GRAMD1C*, *INSIG2*, *IRS1*, *ISX*, *PPARG*, *SOD2*, and *TCF7L2*—explained 55% of the variability in adipose tissue LYC concentration (adjusted  $R^2$ ). **Conclusions:** Adipose tissue LYC concentration displays high interindividual variability, which can be explained in part by genetic variants in genes involved in carotenoid and lipid metabolism.

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## 1. Introduction

Lycopene (LYC) is an acyclic, non-oxygenated carotenoid found in tomatoes, watermelon, and several other red fruits, where it is responsible for their characteristic red color. Humans cannot synthesize LYC and obtain it entirely through dietary sources. The average dietary intake is estimated at approximately  $5 \text{ mg d}^{-1}$ ,<sup>1</sup> with tomatoes and tomato-based products being the primary contributors.<sup>2</sup> LYC accumulates significantly in the human body and is typically among the carotenoids found at the highest concentrations in blood.<sup>1</sup> While LYC and

its metabolites demonstrate strong antioxidant activity *in vitro*,<sup>3</sup> they also display a range of other biological effects that could be beneficial for human health.<sup>4</sup> Consistent with this, both dietary intake and circulating concentrations of LYC have been associated with a reduced risk of several diseases, including prostate cancer<sup>5,6</sup> and cardiovascular disease.<sup>7–9</sup>

The main storage site of LYC in the human body is adipose tissue, which has been estimated to account for approximately 61 and 72% of the total LYC pool in males and females, respectively.<sup>10</sup> An *in vitro* study investigating the subcellular distribution of LYC in adipocytes (3T3-L1 cells) reported the following localization: lipid droplets (32–51%), plasma membrane (32–37%), and nuclear membrane (19–29%).<sup>11</sup> Although the majority of dietary LYC occurs in the all-*trans* conformation,<sup>12</sup> *cis* isomers predominate in circulation and adipose tissue,<sup>13</sup> likely due to a combination of enhanced bioavailability, thermodynamic stability, and endogenous isomerization during digestion, absorption and tissue distribution.<sup>12</sup>

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In addition, LYC can undergo enzymatic cleavage by  $\beta$ -carotene oxygenase 2 (BCO2), generating apo-lycopenoids with distinct biological activities.<sup>14</sup> Apo-lycopenoids have been found in human blood following chronic consumption of tomato juice,<sup>15,16</sup> although at much lower concentrations than *cis* or *trans* isomers of LYC. To date, their presence, abundance, and physiological relevance in human adipose tissue remain poorly characterized.<sup>17</sup> In a study by Chung *et al.*, carotenoid concentrations were measured in subcutaneous adipose tissue from three anatomical locations (abdomen, buttock, and thigh) in 25 healthy adults (12 males, 13 females; mean age =  $31.9 \pm 2$  years; BMI =  $24.5 \pm 0.5$  kg m<sup>-2</sup>).<sup>13</sup> Although LYC was not the predominant carotenoid in the participants' diet or serum, it was consistently the most abundant carotenoid in adipose tissue, with the sum of its *trans* and *cis* isomers representing 56.1%, 55.8%, and 58.6% of total carotenoids in the abdominal, buttock, and thigh depots, respectively. However, other authors have reported a lower contribution of LYC to total adipose carotenoid concentrations.<sup>18</sup> In this tissue, LYC may exert several biological roles. In addition to its well-established and potent antioxidant properties,<sup>19</sup> it has been suggested that it also has anti-inflammatory effects.<sup>9</sup> This is particularly relevant, as adipose tissue is a key organ in the initiation of metabolic inflammation, which is implicated in the development of various cardiometabolic diseases.<sup>9</sup>

Despite its physiological relevance, the factors influencing LYC concentration in adipose tissue remain poorly understood.<sup>1</sup> LYC in adipose tissue is derived from circulating lipoproteins: in the fasting state, it is primarily associated with LDL (76%), HDL (17%), and VLDL (7%),<sup>10</sup> while in the post-prandial state, it also circulates in chylomicrons. Nonetheless, correlations between circulating and adipose tissue LYC concentrations are generally weak to moderate. For example, Chung *et al.* reported Pearson's correlation coefficients of 0.38, 0.33, and 0.27 between serum and abdominal, buttock, and thigh adipose tissue LYC concentrations, respectively.<sup>13</sup> Furthermore, our group has shown in rats that carotenoid uptake by adipose tissue is not correlated with the physico-chemical properties of the carotenoids,<sup>20</sup> suggesting that mechanisms beyond passive diffusion are involved. Supporting this hypothesis, both *in vitro* and *ex vivo* studies from our laboratory have demonstrated that CD36 molecule (CD36), an integral membrane protein expressed in many cell types, plays a role in LYC uptake by adipocytes.<sup>21</sup> Given the possibility that additional proteins may be involved in LYC transport and metabolism in adipose tissue, we hypothesized that genetic variations in genes encoding these proteins could partly explain interindividual differences in adipose tissue LYC concentrations.

Therefore, the objectives of this study were: (1) to characterize interindividual variability in LYC concentration within subcutaneous white adipose tissue in a sample of 43 healthy adult males, and (2) to identify single nucleotide polymorphisms (SNPs) associated with adipose tissue LYC concentrations using a candidate gene approach.

## 2. Methods

### 2.1. Participants

Forty-three healthy, non-overweight, non-obese, and non-smoking adult males participated in this study. To maximize the ability to detect genetic determinants of adipose tissue LYC concentration, the study was restricted to healthy males in order to limit biological variability unrelated to genetics, including sex-related differences in adiposity, lipid metabolism, and hormonal regulation. Exclusion criteria included a history of chronic disease, hyperlipidemia, or hyperglycemia, as well as the use of any medication or dietary supplement that could affect lipid metabolism (*e.g.*, tetrahydrolipstatin, ezetimibe, cholestyramine, fibrates, statins) within one month prior to or during the study. Due to the relatively large volume of blood drawn, an additional inclusion criterion was a blood hemoglobin concentration  $>130$  g L<sup>-1</sup>. Baseline characteristics of the participants are presented in Table 1. The study was approved by the regional ethics committee for human experimentation (No. 2008-A01354-51, Comité de Protection des Personnes Sud Méditerranée I, France). All procedures were conducted in accordance with the Declaration of Helsinki (1975), as revised in 1983. Written informed consent was obtained from each participant.

### 2.2. Study design

This study constitutes a secondary analysis of data from a randomized cross-over clinical trial dedicated to the identification of genetic variants associated with the bioavailability of lipid micronutrients, such as  $\alpha$ -tocopherol, LYC,  $\beta$ -carotene, lutein and phytofluene.<sup>22–27</sup> Since no study investigating the association between genetic variations and adipose tissue LYC concentration has been published, it was not possible to carry out a power calculation. Therefore, this study should be considered exploratory.

Participants were provided with three different test meals, which they consumed in a randomized order, with a washout period of at least three weeks between each meal. All meals had the same basic composition: 70 g of semolina cooked in 200 mL of water, 40 g of white bread, 60 g of hard-boiled egg whites, 50 g of peanut oil, and 330 mL of mineral water. The

**Table 1** Baseline characteristics of the study participants ( $n = 43$ )

Characteristic	Mean (SEM)
Age, years	31.9 (1.9)
BMI, kg m <sup>-2</sup>	23.0 (0.3)
Plasma total cholesterol <sup>a</sup> , g L <sup>-1</sup>	1.6 (0.1)
Plasma LDL-cholesterol <sup>a</sup> , g L <sup>-1</sup>	1.1 (0.1)
Plasma HDL-cholesterol <sup>a</sup> , g L <sup>-1</sup>	0.5 (0.01)
Plasma triglycerides <sup>a</sup> , g L <sup>-1</sup>	0.8 (0.1)
Plasma glucose <sup>a</sup> , mmol L <sup>-1</sup>	4.7 (0.1)
Plasma hemoglobin <sup>a</sup> , g dL <sup>-1</sup>	15.0 (0.1)
Plasma lycopene <sup>a,b</sup> , nmol L <sup>-1</sup>	103.6 (12.1)

<sup>a</sup> Quantified in fasting plasma samples. <sup>b</sup> Mean of 3 samples collected at least 3 weeks apart.



only difference between the meals was their micronutrient content: the control meal contained no added micronutrients; the vitamin E meal included a capsule containing RRR- $\alpha$ -tocopheryl acetate equivalent to 67 mg (100 IU) of  $\alpha$ -tocopherol (Holland & Barrett, Nuneaton, Warwickshire, England); and the tomato puree meal included 100 g of tomato puree, providing 9.7 mg of all-*trans* LYC as measured by high-performance liquid chromatography (HPLC). Participants were instructed to avoid carotenoid-rich foods (e.g., tomatoes, carrots) for 48 h before each test meal, with a list of such foods provided. On the evening before each test, participants were asked to eat dinner between 7:00 and 8:00 p. m. without alcohol and to refrain from consuming any food or drink other than water until arriving at the Center for Clinical Investigation (La Conception Hospital, Marseille, France) the next morning. At the center, participants consumed one of the three test meals, and blood samples were collected at regular intervals for up to 8 h post-consumption to assess the bio-availability of the meal's micronutrients.<sup>22–25,27</sup> Participants were instructed to eat the meal at a consistent pace, consuming half within the first 10 min and the remainder within the next 10 min. No other food was permitted during the following 8 h, although participants were allowed to drink any remaining water provided with the meal.

### 2.3. Adipose tissue biopsy

Adipose tissue sampling has been described in detail elsewhere.<sup>28</sup> Briefly, subcutaneous adipose tissue samples from the periumbilical region were collected by a trained physician at two time points: in the fasting state and 8 h after the intake of the three test meals.

### 2.4. Fasting and postprandial biochemical measurements

Baseline fasting plasma concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, glucose, and hemoglobin were measured as previously described.<sup>4</sup>

Postprandial plasma chylomicron LYC concentrations (from 1 to 8 h) following consumption of the tomato puree meal were measured as previously described.<sup>23</sup>

### 2.5. Measurement of adipose tissue LYC concentration

Approximately 50 mg (wet weight) of subcutaneous periumbilical adipose tissue was homogenized in 300  $\mu$ L of phosphate-buffered saline (PBS) with two 3 mm stainless steel balls using an MM301 ball mill (Retsch, Eragny-sur-Oise, France). A 50  $\mu$ L aliquot was collected for protein quantification using the BiCinchoninic Acid Assay kit (Pierce, Montluçon, France), diluted 1 : 5 in PBS. Lipids, including LYC, were extracted from the remaining 250  $\mu$ L using 2 mL of trichloromethane/methanol (1/1, v/v) and 0.9 mL PBS. All extractions were performed at room temperature under yellow light to prevent light-induced degradation. The extract was dried and incubated at 37 °C for 1.5 h with 100  $\mu$ L of 12% ethanolic pyrogallol solution (as an antioxidant) and 1 mL of 5.5% ethanolic potassium hydroxide solution to saponify and quantify total LYC. After cooling, 100  $\mu$ L of ethanolic apo-8'-carotenal (DSM-Firmenich AG,

Kaiseraugst, Switzerland) was added as the internal standard. The mixture was then extracted twice with 3 mL of hexane. The extract was evaporated to dryness under nitrogen and re-dissolved in 100  $\mu$ L of methanol/dichloromethane (65/35, v/v) for HPLC analysis.

A volume of 90  $\mu$ L was used for HPLC analysis. The separation was performed using a 10.0  $\times$  4.0 mm Modulo-Cart QS guard column with a 2  $\mu$ m particle size (Interchim, Montluçon, France), followed by a 250  $\times$  4.6 mm YMC C30 analytical column with a 5  $\mu$ m particle size (Interchim), maintained at a constant temperature of 35 °C. The mobile phase consisted of HPLC-grade methanol (component A), methyl *tert*-butyl ether (component B), and water (component C) (Carlo Erba-SDS). A linear gradient was applied, starting with 96% A, 2% B, and 2% C at time 0, transitioning to 18% A, 80% B, and 2% C by 27 min, at a flow rate of 1 mL min<sup>-1</sup>. The HPLC system consisted of a pump (Waters 2690) associated with a photodiode-array detector (Waters 2996) (Waters). Detection of LYC occurred *via* UV spectra and retention time coincident with an authentic standard (Sigma-Aldrich, Saint Quentin Fallavier, France), with quantification at 472 nm, considering the sum of all its geometric isomers (*cis* and *trans* forms). Peak integration and quantification were carried out using Chromeleon CDS software (version 6.80, Dionex), using an external calibration curve normalized to the internal standard.

### 2.6. DNA isolation and genotyping

Twenty-five  $\mu$ g of DNA was extracted from saliva samples using the Oragene extraction kit (DNA Genotek, Ottawa, Ontario, Canada). DNA preparation and genotyping methods were performed as previously described.<sup>29</sup> The whole genome was genotyped using HumanOmniExpress BeadChips (Illumina, California, USA), which allow for the analysis of  $\approx 7.33 \times 10^5$  SNPs/DNA sample.

### 2.7. Candidate SNP selection

Following a literature review, genes encoding proteins previously shown to influence LYC concentration in adipose tissue—either directly, by participating in adipocyte uptake and lipid droplet distribution, or indirectly, by affecting circulating LYC concentration—were selected. This process resulted in the identification of 43 candidate genes (SI Table S1), corresponding to 3786 SNPs represented on the DNA chips. SNPs with a genotype call rate below 95% or showing a significant deviation from Hardy-Weinberg equilibrium ( $p < 0.05$ ; chi-squared test) were excluded, leaving 3183 SNPs for further analysis. Next, SNPs in high linkage disequilibrium (LD), defined as  $R^2 > 0.80$  based on the LD TAG SNP Selection tool from the SNPinfo Web Server (HapMap, European [CEU] population; <https://snpinf.niehs.nih.gov>), were also excluded, resulting in 2196 remaining SNPs. These SNPs were tested under both additive and dominant genetic models. SNPs with fewer than five observations in any genotypic group under either model were excluded, yielding 572 SNPs for the additive



model and 1783 for the dominant model. The SNP selection process is summarized in SI Fig. S1.

## 2.8. SNP function prediction

PolyPhen-2, integrated within the Ensembl Variant Effect Predictor (available at <https://www.ensembl.org/Tools/VEP>), was used to assess the impact of exonic variants as described previously. The PolyPhen-2 score ranges from 0 to 1, with higher scores indicating that the variant is more likely to affect protein structure or function. The potential functional effects of other genetic variants, such as intronic and intergenic variants, were predicted using RegulomeDB (available at: <https://regulomedb.org/>). The RegulomeDB score ranges from 0 to 1, where a score of 1 indicates the variant is more likely to be regulatory.<sup>30</sup>

## 2.9. Gene expression data

Gene expression data were retrieved from the Human Protein Atlas (version 24.1, <https://www.proteinatlas.org>; accessed 15 October 2025).<sup>31</sup>

## 2.10. Statistics

Data were expressed as means  $\pm$  SEM. Adipose tissue LYC concentrations measured in the fasting state and 8 h after consumption of the three test meals were analyzed with linear mixed models, using a full factorial design with meal (control, vitamin E and tomato puree) and time (in the fasting state and 8 h postprandial) as fixed within-subject variables, and participant as the random variable. Five different covariance structures were tested, *i.e.*, autoregressive order one, diagonal, scaled identity, unstructured covariance, and compound symmetry, using Akaike's Information Criterion (AIC). Residual scatterplots were examined to determine departure from homoscedasticity, while QQ plots were used to determine departure from normality. Since neither meal nor time had a significant effect on adipose tissue LYC concentrations, these concentrations within each participant were treated as technical replicates. The presence of outliers among the technical replicates was assessed using 2-tailed Grubbs' tests (available at <https://www.graphpad.com/quickcalcs/Grubbs1.cfm>). Subsequently, the arithmetic mean of adipose tissue LYC concentrations was calculated for each participant and is hereafter referred to simply as adipose tissue LYC concentration. Note that, since some participants did not consume all three meals, the mean was calculated from two to six individual adipose tissue LYC measurements. The bilinear relationships between this concentrations and anthropometric measurements and plasma concentration of other lipids were measured using Pearson's *r*. CV of plasma and adipose tissue LYC concentrations were compared according to Forkman.<sup>32</sup> For all tests, the bilateral alpha risk was  $\alpha = 0.05$ . Statistical analyses were performed using SPSS 28 (SPSS Inc., Chicago, IL, USA).

Partial least squares (PLS) regression was used to identify combinations of SNPs best explaining the variance in adipose tissue LYC concentration. A two-step approach was applied, combining dimension reduction by univariate filtering fol-

lowed by PLS regression, as previously described for SNP data.<sup>27,28,33–37</sup> The univariate filtering step was based on selecting SNPs showing a Wald test asymptotic *p*-value  $<0.05$  in either the additive or the dominant genetic model, as obtained from PLINK (v1.07, <https://pnu.mgh.harvard.edu/purcell/plink/>). A PLS regression model was then built. The *X* variables included all selected SNPs, anthropometric measurements, and fasting plasma lipid concentrations showing a non-zero correlation (Pearson's *r*) (*e.g.*, LYC, cholesterol, *etc.*). The *Y* variable was adipose tissue LYC concentration. All variables were mean-centered and scaled to unit variance (UV scaling). *X* variables were ranked according to their variable importance in the projection (VIP) values, which estimate the contribution of each variable to explaining the *Y* variable in the PLS model. Several PLS regression models were then built using increasing VIP threshold values, as described in detail elsewhere.<sup>38</sup> The model that maximized the explained variance (adjusted  $R^2$ ) and was statistically significant according to cross-validation ANOVA<sup>39</sup> was selected.

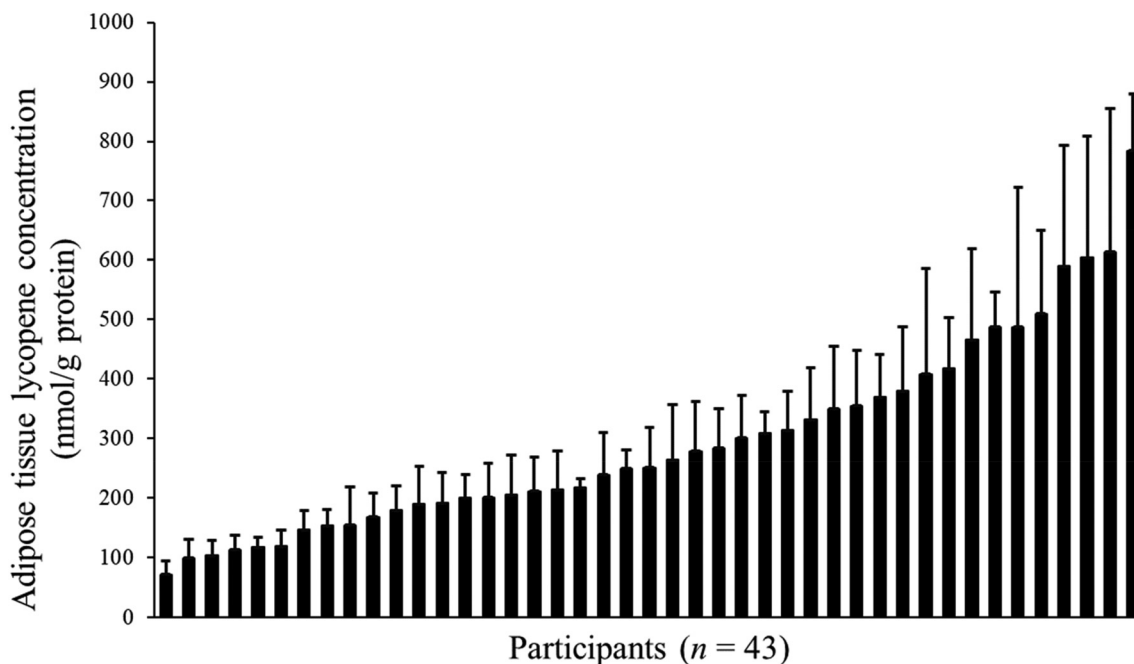
This model was further internally validated using leave-*k*-out cross-validation,<sup>40</sup> regression coefficient stability testing,<sup>29</sup> and response permutation testing, as detailed in the SI. For response permutation testing, the explained variance and the explained variance after cross-validation of the original model were compared with the explained variance and the explained variance after cross-validation of 100 models based on data where the order of the *Y* matrix for the participants (adipose tissue LYC concentration) was randomly permuted, while the *X* matrix (SNPs and covariates) was kept intact. The SIMCA® Multivariate Data Analytics Solution software (Version 17.0.0.24543, Umetrics, Umeå, Sweden) was used for all PLS regression analyses and internal validation tests.

## 3. Results

### 3.1. Adipose tissue LYC concentration

Neither sampling time ( $p = 0.435$ )—*i.e.*, in the fasting state or 8 h after the test meal—nor the type of test meal ( $p = 0.433$ )—*i.e.*, control, vitamin E, or tomato puree—nor their interaction ( $p = 0.188$ ) had a significant effect on adipose tissue LYC concentration (as also verified by exploratory paired *t*-tests following each meal; see SI Table S2B). Since neither meal nor time had a significant effect, all six measurements of adipose tissue LYC concentration were treated as technical replicates for downstream analyses. This approach allowed for a more precise estimate of each participant's adipose tissue LYC concentration. The mean adipose tissue LYC concentration across the three test meals and two time points for each of the 43 participants (maximum of six values per participant) is presented in Fig. 1. Adipose tissue LYC concentration exhibited high interindividual variability, with a CV of 55%, while fasting plasma LYC concentrations showed even higher variability, with a CV of 75%. No significant difference was found between the relative variability of adipose tissue and plasma LYC concentrations ( $F$ -statistic = 0.61;  $p = 0.12$ ).





**Fig. 1** Adipose tissue lycopene concentration of the participants. Adipose tissue lycopene concentration (nmol per g protein) for each participant was calculated as the arithmetic mean of measurements taken from samples collected in the fasting state and 8 h after consumption of three test meals, administered at intervals of at least three weeks. Each value represents the mean ( $n = 2-6$ )  $\pm$  SEM. A total of 43 participants were ranked in ascending order based on their adipose tissue lycopene concentration. Each bar along the x-axis corresponds to the mean value for an individual participant.

**Table 2** Pearson's correlation coefficients between adipose tissue lycopene concentration and selected anthropometric measurements and blood lipid concentrations

	Pearson's $r$	95% CI	$p$ -Value
Age, years	-0.11	-0.40, 0.19	0.47
BMI, $\text{kg m}^{-2}$	-0.15	-0.43, 0.16	0.33
Fasting plasma concentration			
Lycopene, $\text{nmol L}^{-1}$	0.37	0.07, 0.61	0.01 <sup>b</sup>
Cholesterol, $\text{g L}^{-1}$	0.31	0.01, 0.56	0.04 <sup>b</sup>
LDL-cholesterol, $\text{g L}^{-1}$	0.15	-0.19, 0.45	0.38
HDL-cholesterol, $\text{g L}^{-1}$	0.39	0.07, 0.63	0.02 <sup>b</sup>
Triglycerides, $\text{g L}^{-1}$	0.17	-0.14, 0.45	0.27
Postprandial chylomicron lycopene concentration <sup>a</sup>	-0.14	-0.46, 0.22	0.45

<sup>a</sup> For each participant, the baseline-adjusted area under the curve of the postprandial plasma chylomicron lycopene concentration over 8 h following the consumption of the tomato puree test meal,<sup>2</sup> an acknowledged marker of carotenoid bioavailability, was calculated. <sup>b</sup> Parameters were considered significant at 0.05 level.

Adipose tissue LYC concentration was significantly correlated with fasting plasma LYC concentration ( $r = 0.37$ ). In addition, it was also significantly correlated with fasting plasma total cholesterol ( $r = 0.31$ ) and HDL-cholesterol concentration ( $r = 0.39$ ) (Table 2).

### 3.2. SNPs associated with adipose tissue LYC concentration

SNPs significantly associated with adipose tissue LYC concentration, based on univariate analysis, are presented in Table 3. Under the additive model, 15 SNPs within 10 genes showed significant associations, while 82 SNPs within 22 genes were significantly associated under the dominant model, with no

overlap. Unstandardized regression coefficients ( $B$  coefficients), which represent the average change in adipose tissue LYC concentration per additional copy of the minor allele (additive model), or in the presence *versus* absence of the minor allele (dominant model), are provided in Table 3. Although most of the significantly associated SNPs were located in intronic regions, a substantial proportion received high RegulomeDB scores, indicating strong evidence of regulatory potential. Such scores are typically observed for variants lying within gene regulatory elements, such as transcription factor binding sites or enhancers, and may therefore point to loci with possible effects on gene expression.



**Table 3** SNPs significantly associated with adipose tissue lycopene concentration following univariate analyses

SNP	Gene	Alleles	Alternate allele frequency <sup>a</sup> (European population)	Gene region	Unstandardized regression coefficient <sup>b</sup>	p-Value <sup>c</sup>	Variant effect prediction score <sup>d</sup>
<b>Additive model</b>							
rs2205810	<i>ISX</i>	A > G	G = 0.70	Intergenic	106.7	0.002	0.13
rs4277044	<i>TCF7L2</i>	G > A	A = 0.35	Intron	106.7	0.002	0.13
rs1501460	<i>ABCA1</i>	T > C	C = 0.44	Intergenic	-109.0	0.004	0.59
rs9920375	<i>LIPC</i>	T > C	C = 0.56	Intergenic	78.7	0.016	0.61
rs12953429	<i>MC4R</i>	A > G	G = 0.51	Intergenic	86.6	0.019	0.18
rs1422450	<i>SLC27A6</i>	T > C	C = 0.60	Intergenic	87.1	0.025	0.15
rs13398058	<i>IRS1</i>	G > A	A = 0.61	Intergenic	77.1	0.025	0.13
rs1033772	<i>TCF7L2</i>	G > A	A = 0.35	Intergenic	82.9	0.028	0.61
rs4743764	<i>ABCA1</i>	T > C	C = 0.42	Intron	67.5	0.034	0.61
rs4276037	<i>INSIG2</i>	G > A	A = 0.73	Intergenic	69.2	0.036	0.33
rs2017523	<i>ISX</i>	G > A	A = 0.33	Intergenic	78.1	0.036	0.41
rs17770539	<i>INSIG2</i>	T > C	C = 0.41	Intergenic	-65.4	0.037	0.30
rs4684104	<i>PPARG</i>	A > G	G = 0.57	Intergenic	71.0	0.044	0.61
rs3823037	<i>SOD2</i>	T > C	C = 0.40	Intergenic	66.7	0.049	0.22
rs9967057	<i>MC4R</i>	G > A	A = 0.61	Intergenic	-74.6	0.049	0.13
<b>Dominant model<sup>e</sup></b>							
rs12629751	<i>PPARG</i>	C > T	T = 0.10	Intron	124.9	6.68 × 10 <sup>-4</sup>	0.18
rs5755436	<i>ISX</i>	C > T	T = 0.10	Intergenic	96.1	9.30 × 10 <sup>-4</sup>	0.13
rs2817114	<i>ELOVL5</i>	T > G	G = 0.11	Intergenic	85.3	0.002	0.61
rs5749894	<i>ISX</i>	T > C	C = 0.90	Intergenic	93.1	0.002	0.00
rs4682144	<i>GRAMD1C</i>	A > G	G = 0.32	Intron	74.0	0.002	0.13
rs7575840	<i>APOB</i>	G > T	T = 0.32	Intergenic	-71.8	0.003	0.24
rs10186364	<i>INSIG2</i>	A > G	G = 0.84	Intergenic	77.1	0.004	0.61
rs7754295	<i>SOD2</i>	C > T	T = 0.06	Intergenic	92.9	0.004	0.61
rs5749872	<i>ISX</i>	G > A	A = 0.83	Intergenic	78.0	0.005	0.13
rs7558381	<i>IRS1</i>	T > C	C = 0.64	Intergenic	70.1	0.005	0.13
rs11196218	<i>TCF7L2</i>	G > A	A = 0.28	Intron	-67.5	0.005	0.59
rs2056983	<i>ISX</i>	G > T	T = 0.06	Intergenic	86.4	0.005	0.61
rs6959775	<i>CD36</i>	A > G	G = 0.56	Intergenic	73.1	0.005	0.13
rs9607112	<i>ISX</i>	G > A	A = 0.06	Intergenic	81.9	0.006	0.13
rs5750060	<i>ISX</i>	T > C	C = 0.17	Intergenic	73.2	0.006	0.61
rs8023369	<i>LIPC</i>	T > G	G = 0.38	Intergenic	-68.8	0.007	0.61
rs7185427	<i>BCO1</i>	C > T	T = 0.82	Intergenic	74.8	0.007	0.57
rs11152240	<i>MC4R</i>	T > C	C = 0.09	Intergenic	93.2	0.007	1.00
rs16866988	<i>IRS1</i>	G > A	A = 0.04	Intergenic	100.8	0.007	0.18
rs7858499	<i>ABCA1</i>	T > C	C = 0.20	Intergenic	65.4	0.008	0.61
rs10039077	<i>SLC27A6</i>	G > A	A = 0.12	Intergenic	81.8	0.009	0.13
rs134225	<i>ISX</i>	T > G	G = 0.96	Intergenic	99.1	0.009	0.59
rs1561166	<i>ABCA1</i>	T > C	C = 0.09	Intergenic	98.8	0.009	0.13
rs737821	<i>ISX</i>	C > T	T = 0.73	Intergenic	-63.2	0.009	0.61
rs9456400	<i>SOD2</i>	A > G	G = 0.14	Intergenic	90.7	0.009	0.18
rs12711901	<i>INSIG2</i>	C > T	T = 0.89	Intergenic	77.1	0.010	0.61
rs11057841	<i>SCARB1</i>	C > T	T = 0.16	Intron	62.0	0.011	0.13
rs1316328	<i>IRS1</i>	A > G	G = 0.12	Intergenic	88.8	0.011	0.61
rs2937359	<i>ABCA1</i>	T > C	C = 0.56	Intergenic	65.5	0.011	0.61
rs1152001	<i>PPARG</i>	G > A	A = 0.79	Intron	-62.6	0.012	0.61
rs135159	<i>ISX</i>	T > C	C = 0.22	Intergenic	61.5	0.013	0.13
rs7022410	<i>ABCA1</i>	A > G	G = 0.04	Intergenic	81.9	0.013	0.13
rs2740486	<i>ABCA1</i>	T > G	G = 0.47	Intron	69.3	0.013	0.51
rs2120825	<i>PPARG</i>	T > G	G = 0.10	Intron	-68.6	0.014	0.61
rs4694627	<i>CXCL8</i>	C > T	T = 0.39	Intergenic	61.2	0.014	0.59
rs7082458	<i>TCF7L2</i>	A > G	G = 0.16	Intron	63.8	0.014	0.59
rs4820135	<i>ISX</i>	C > T	T = 0.21	Intergenic	-65.9	0.015	0.26
rs4849726	<i>INSIG2</i>	G > A	A = 0.25	Intergenic	59.0	0.017	0.18
rs7573503	<i>INSIG2</i>	T > C	C = 0.05	Intergenic	90.6	0.017	0.13
rs5749854	<i>ISX</i>	A > G	G = 0.15	Intergenic	68.3	0.018	0.24
rs496356	<i>TCF7L2</i>	T > C	C = 0.90	Intergenic	59.2	0.019	0.98
rs4564774	<i>INSIG2</i>	T > C	C = 0.07	Intergenic	82.5	0.019	0.15
rs6989064	<i>LPL</i>	C > T	T = 0.56	Intergenic	64.3	0.022	0.61
rs2413241	<i>ISX</i>	T > C	C = 0.74	Intergenic	56.1	0.023	0.13
rs9382183	<i>ELOVL5</i>	A > G	G = 0.89	Intergenic	63.4	0.024	0.59
rs12497191	<i>PPARG</i>	A > G	G = 0.14	Intron	74.8	0.024	0.22
rs12711897	<i>INSIG2</i>	G > A	A = 0.92	Intergenic	74.7	0.024	0.61
rs5755445	<i>ISX</i>	T > C	C = 0.24	Intergenic	56.6	0.025	0.61



Table 3 (Contd.)

SNP	Gene	Alleles	Alternate allele frequency <sup>a</sup> (European population)	Gene region	Unstandardized regression coefficient <sup>b</sup>	p-Value <sup>c</sup>	Variant effect prediction score <sup>d</sup>
rs1873233	ISX	T > C	C = 0.20	Intergenic	60.4	0.027	0.13
rs9365050	SOD2	G > A	A = 0.73	Intergenic	55.9	0.027	0.13
rs9652472	LIPC	G > A	A = 0.95	Intron	78.0	0.027	0.57
rs709150	PPARG	C > G	G = 0.39	Intron	60.2	0.027	0.61
rs4917644	TCF7L2	C > T	T = 0.16	Intron	-54.7	0.028	0.61
rs608318	MGLL	G > T	T = 0.86	Intron	-58.2	0.029	0.61
rs567384	MGLL	C > T	T = 0.88	Intron	65.4	0.030	0.04
rs130575	ISX	A > G	G = 0.14	Intergenic	58.9	0.031	0.18
rs2816376	ELOVL5	T > C	C = 0.28	Intergenic	52.8	0.032	0.61
rs3211881	CD36	A > G	G = 0.07	Intron	58.8	0.032	0.84
rs5994853	ISX	A > G	G = 0.20	Intergenic	-52.5	0.033	0.13
rs2414555	LIPC	A > G	G = 0.26	Intergenic	-52.8	0.033	0.93
rs7598775	APOB	G > A	A = 0.09	Intergenic	59.8	0.034	0.55
rs7652615	MGLL	G > T	T = 0.84	Intron	-56.4	0.035	0.52
rs435066	RPE65	T > C	C = 0.17	Intergenic	-54.3	0.035	0.32
rs6737960	IRS1	A > C	C = 0.18	Intergenic	-55.2	0.035	0.55
rs9919066	ABCA1	C > T	T = 0.09	Intergenic	-60.8	0.036	0.00
rs579902	TCF7L2	A > G	G = 0.25	Intergenic	-52.4	0.037	0.59
rs1247683	CXCL8	C > T	T = 0.97	Intergenic	79.8	0.037	0.61
rs6744750	APOB	T > C	C = 0.23	Intergenic	51.8	0.037	0.59
rs16866708	IRS1	A > G	G = 0.14	Intergenic	-55.5	0.038	0.45
rs2842994	SOD2	G > A	A = 0.16	Intergenic	52.5	0.039	0.61
rs739066	ISX	C > T	T = 0.78	Intergenic	50.3	0.042	0.61
rs2915775	PNLIP	T > C	C = 0.83	Intron	57.4	0.042	0.89
rs3124016	ABCA1	A > G	G = 0.74	Intergenic	50.8	0.042	0.11
rs2396261	IRS1	C > T	T = 0.76	Intergenic	-54.9	0.042	0.18
rs12587408	RDH12	C > A	A = 0.16	Intergenic	-57.2	0.043	0.50
rs4149290	ABCA1	T > C	C = 0.11	Intron	-64.0	0.043	0.59
rs17186765	BCO1	C > T	T = 0.12	Intergenic	-59.0	0.043	0.18
rs10933143	IRS1	G > A	A = 0.26	Intergenic	49.6	0.045	0.61
rs6567169	MC4R	T > C	C = 0.62	Intergenic	49.3	0.048	0.18
rs1361325	SOD2	C > T	T = 0.22	Intergenic	51.7	0.049	0.22
rs980069	TCF7L2	G > A	A = 0.27	Intergenic	-48.5	0.049	0.57
rs1339326	SOD2	A > C	C = 0.87	Intergenic	65.5	0.050	0.13

<sup>a</sup> Alternate allele frequencies were retrieved from dbSNP (<https://www.ncbi.nlm.nih.gov/snp/>) using the Allele Frequency Aggregator (ALFA) dataset (pooled allele frequency data from dbSNP and the dbGaP) in the European population (10.04.2025). All SNPs were either intronic or intergenic. <sup>b</sup> Unstandardized regression coefficients represent the mean change in adipose tissue lycopene concentration (nmol per g protein) for each additional copy of the minor allele under the additive model and in the presence of the minor allele under the dominant model. <sup>c</sup> SNPs are ranked by increasing p-values. <sup>d</sup> Variant Effect Prediction Score was estimated using RegulomeDB for intron or intergenic SNPs (accessed on 10.04.2025). <sup>e</sup> For SNPs under the dominant model, participants homozygous for the lesser frequent allele were grouped with heterozygous participants and were compared with participants homozygous for the more frequent allele. Abbreviations: gene names can be found in SI Table S1.

### 3.3. Combination of SNPs associated with adipose tissue LYC concentration

PLS regression was then used to identify the combination of SNPs—selected through univariate filtering across both genetic models—and covariates that best explained the interindividual variability in adipose tissue LYC concentration. As shown in SI Table S3, the initial model, which included all 100 selected variables (97 SNPs, fasting plasma LYC, HDL-C, and total cholesterol concentrations), explained a large proportion of the variance in this phenotype ( $R^2 = 0.85$ ). However, this estimate was positively biased, as indicated by the high adjusted  $R^2$  value (1.11), likely due to overfitting caused by the high number of predictors included. In PLS regression, such values can occur prior to cross-validation and should not be interpreted as predictive performance. Model predictability was therefore assessed using cross-validated metrics, which are reported in the SI Table S3. By applying various thresholds to the VIP scores, the optimal model retained 17 SNPs (not in LD) located in or near 11 genes, and

explained 55% of the variance in adipose tissue LYC concentration (adjusted  $R^2$ ) while non-genetic covariates showed VIP values below the inclusion threshold (Table 4). This model was first validated by cross-validation ANOVA ( $p = 1.98 \times 10^{-10}$ ) (SI Table S3). Its robustness and stability were further confirmed using three additional methods: leave- $k$ -out cross-validation, regression coefficient stability testing, and random permutation testing (SI Table S4, Fig. S2 and S3).

### 3.4. Genetic score to explain adipose tissue LYC concentration

Knowing a participant's genotype at the 17 SNPs in the selected model, it was possible to estimate his adipose tissue LYC concentration using the following equation:

$$\text{Adipose tissue LYC concentration} = 299.1 + \sum_{i=1}^{17} (r_i) \times \text{number of minor allele SNP}_i \quad (1)$$



**Table 4** Combination of 17 SNPs associated with adipose tissue lycopene concentration

Gene <sup>a</sup>	SNP	VIP value <sup>b</sup>	Regression coefficient <sup>c</sup>
<i>PPARG</i>	rs12629751	1.37	54.98
<i>ISX</i>	rs5755436	1.34	42.31
<i>ELOVL5</i>	rs2817114	1.27	37.54
<i>ISX</i>	rs5749894	1.24	40.99
<i>GRAMD1C</i>	rs4682144	1.24	-32.58
<i>ISX</i>	rs205810	1.23	23.49
<i>TCF7L2</i>	rs4277044	1.23	23.48
<i>APOB</i>	rs7575840	1.23	-31.63
<i>INSIG2</i>	rs10186364	1.18	33.96
<i>ABCA1</i>	rs1501460	1.18	-23.99
<i>SOD2</i>	rs7754295	1.17	40.91
<i>ISX</i>	rs5749872	1.16	34.36
<i>IRS1</i>	rs7558381	1.16	-30.84
<i>TCF7L2</i>	rs11196218	1.15	-29.71
<i>ISX</i>	rs2056983	1.15	38.03
<i>CD36</i>	rs6959775	1.15	-32.17
<i>ISX</i>	rs9607112	1.14	36.04

<sup>a</sup> Gene names can be found in SI Table S1. <sup>b</sup> Variables were ranked according to their variable importance in the projection (VIP) value, which estimates the contribution of each SNP in the projection used in the PLS regression model. <sup>c</sup> Regression coefficients are for untransformed variables and represent the mean change in adipose tissue lycopene concentration (nmol per g protein) for each additional copy of the minor allele under the additive model and in the presence of the minor allele under the dominant model.

with  $r_i$  the unstandardized regression coefficient of the  $i^{\text{th}}$  SNP in the PLS regression model (provided in Table 4). When SNPs were entered under the dominant model, participants homozygous for the lesser frequent allele were grouped with heterozygous participants and the number of minor alleles for both these groups was considered to be 1.

## 4. Discussion

The main goal of this study was to identify SNPs, as well as demographic and biochemical variables, associated with LYC concentration in white adipose tissue, which constitutes the main body pool of LYC. To this aim, we carried out a secondary analysis of a randomized cross-over clinical trial where we collected abdominal

adipose tissue from 43 healthy adult males in the fasting state and 8 h after the intake of three test meals. Of the three meals, only the tomato puree meal provided a significant amount of LYC, *i.e.* 9.7 mg (18.1  $\mu\text{mol}$ ) of all-*trans*-LYC, which is relatively close to the estimated adipose tissue LYC pool size in healthy adult males (17.2  $\mu\text{mol}$  (ref. 10)). However, we did not expect to observe a significant increase in adipose tissue LYC concentration over 8 h, because this tissue acts as a slow-turnover reservoir for LYC.<sup>41</sup> Model predictions indicate that a 10 mg LYC dose administered in tomato juice would correspond to an absorbed mass of approximately 3.4 mg ( $\sim 6.3 \mu\text{mol}$ ).<sup>41</sup> This is likely an overestimate in our case, since LYC was delivered in tomato puree rather than juice. Given the slow kinetics of LYC uptake by adipose tissue,<sup>41</sup> the expected increase in adipose LYC over an 8-h interval would represent only a few percent of baseline. Such a change would fall within the analytical and sampling variability typically observed for adipose biopsies and would therefore be unlikely to be detectable or biologically relevant. In line with this expectation, the difference in adipose tissue LYC concentrations before and after the tomato puree meal was not significant ( $p = 0.15$ ). Likewise, neither sampling time nor meal type had a detectable effect on adipose tissue LYC concentration (see Results), which justified pooling all six measurements as technical replicates to obtain a more accurate estimate of adipose tissue LYC concentration. This approach contrasts with previous studies that relied on single measurements.<sup>13,18,42-44</sup>

In this group of healthy adult males, adipose tissue LYC concentration exhibited a CV of 55%, which is relatively high given the homogeneous characteristics of this healthy male cohort. This implies that variability may be even greater in the general population. Still, this estimate falls within the range reported in previous studies (Table 5). Adipose tissue LYC concentration was only modestly correlated with fasting plasma LYC concentration ( $r = 0.37$ ), in agreement with earlier reports.<sup>13,18,43</sup> In addition, positive associations with plasma total cholesterol ( $r = 0.31$ ) and HDL-cholesterol concentrations ( $r = 0.39$ ) are consistent with the role of lipoproteins in LYC transport and tissue delivery. Altogether, these findings suggest that interindividual differences in adipose tissue LYC concentration reflect both systemic factors related to lipoprotein metabolism and tissue-specific mechanisms of cellular uptake and storage.

**Table 5** Interindividual variability of adipose tissue LYC concentration in selected observational studies

Population characteristics	Mean	SD	%CV <sup>a</sup>	Ref.
213 healthy participants; gluteal adipose tissue				43
91 males; age: $52.5 \pm 1.0$ year; BMI: $25.7 \pm 0.3 \text{ kg m}^{-2}$	0.3 $\mu\text{g g}^{-1}$ fatty acid	0.2	67	
122 females; age: $61.3 \pm 0.6$ years; BMI: $25.8 \pm 0.4 \text{ kg m}^{-2}$	0.4 $\mu\text{g g}^{-1}$ fatty acid	0.3	75	
458 healthy participants; gluteal adipose tissue				18
347 males; age: $56 \pm 0.6$ years; BMI: $25.5 \pm 0.2 \text{ kg m}^{-2}$	0.17 $\mu\text{g g}^{-1}$ tissue <sup>b</sup>	0.19	112	
111 females; age: $59 \pm 0.9$ years; BMI: $26.2 \pm 0.4 \text{ kg m}^{-2}$	0.28 $\mu\text{g g}^{-1}$ tissue <sup>c</sup>	0.21	75	
25 healthy adults; abdominal adipose tissue <sup>b</sup>	3.3 $\mu\text{mol mg}^{-1}$ tissue <sup>c</sup>	2.2	67	13
13 males; age: $32.2 \pm 2.7$ years; BMI: $23.9 \pm 0.5 \text{ kg m}^{-2}$				
12 females; age: $31.6 \pm 2.9$ years; BMI: $24.5 \pm 2.0 \text{ kg m}^{-2}$				

<sup>a</sup> The value of %CV was calculated, when SD or SEM was reported. <sup>b</sup> Femoral and gluteal adipose tissue LYC concentration were also measured.

<sup>c</sup> The value provided included participants of both sexes.



Since these processes involve proteins, and therefore genes, we sought to identify single nucleotide polymorphisms (SNPs) associated with adipose tissue LYC concentration using a candidate gene approach. With a two-step strategy, *i.e.*, univariate filtering followed by PLS regression, we identified a combination of 17 SNPs located in or near 11 genes associated with this trait. Notably, non-genetic covariates such as plasma LYC and cholesterol concentrations were not retained in the final PLS model, suggesting that the selected SNPs accounted for part of the variability shared with these circulating measures. Among them, the SNP showing the strongest effect in the final PLS model (Table 5), based on its VIP value, was rs12629751 in *PPARG*. This gene encodes peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), a nuclear receptor that acts as a lipid-sensing transcription factor. It is highly expressed in adipose tissue, where it regulates adiposity by coordinating adipocyte differentiation and lipid metabolism.<sup>45</sup> PPAR $\gamma$  influences these processes through the regulation of multiple genes and pathways,<sup>46</sup> including *scavenger receptor class B type 1* (*SCARB1*)<sup>47</sup> and *CD36*.<sup>48</sup> Scavenger receptor class B type 1 (SR-B1), which is encoded by *SCARB1*, and *CD36* both encode membrane proteins involved in lipid transport, including lipophilic micronutrients,<sup>49</sup> and are expressed in several tissues such as adipocytes, hepatocytes, and enterocytes. In enterocytes, SR-B1 mediates the apical uptake of LYC,<sup>50</sup> while *CD36* has been shown to participate in LYC uptake by adipocytes (3T3-L1 cells), and reduced carotenoid uptake in adipose tissue explants from *CD36*<sup>-/-</sup> mice further supports its role in this process.<sup>21</sup> Therefore, PPAR $\gamma$  could affect LYC accumulation in adipocytes both indirectly, through its broader regulation of lipid metabolism, and directly, by modulating *CD36* and *SCARB1* expression and potentially facilitating LYC uptake into these cells. Notably, a SNP in *CD36*, rs6959775, was also retained in the final PLS regression model. Interestingly, this SNP in *PPARG* was also the strongest genetic determinant of adipose tissue retinol concentration in the same group of participants.<sup>37</sup> Moreover, other *PPARG* variants, not in LD with rs12629751, were associated with adipose tissue concentrations of  $\alpha$ -tocopherol,<sup>28</sup> lutein, and zeaxanthin<sup>36</sup> in this cohort. Altogether, these findings highlight the pivotal role of *PPARG* in the regulation of lipophilic micronutrient concentrations in adipose tissue.

We also identified six SNPs in *ISX* (rs5755436, rs5749894, rs205810, rs5749872, rs2056983, rs9607112) associated with adipose tissue LYC concentration. *ISX* encodes intestine-specific homeobox, a transcription factor restricted to the intestine that represses two key genes involved in intestinal carotenoid metabolism and transport: *BCO1* and *SCARB1*.<sup>51</sup> *BCO1* is one of two enzymes capable of cleaving LYC, the other being *BCO2*. Although *BCO2* has recently been established as the main enzyme responsible for LYC cleavage,<sup>14</sup> several SNPs in *BCO1* have previously been associated with fasting plasma/serum LYC concentration<sup>52</sup> and LYC bioavailability.<sup>53,54</sup> Taken together, these observations suggest that genetic variations in *ISX* could modulate LYC bioavailability and, consequently, its deposition in tissues such as adipose tissue. Supporting this

hypothesis, we also identified rs2056983 in *ISX* as being associated with LYC bioavailability—estimated by the 0–8 h area under the curve of postprandial chylomicron LYC concentration—following the consumption of the tomato puree meal in the same cohort.<sup>23</sup>

Adipose tissue LYC concentration was also associated with rs2817114 in *ELOVL5*, which encodes an enzyme that catalyzes the elongation of eicosapentaenoic acid (EPA) to docosapentaenoic acid and subsequently to docosahexaenoic acid (DHA). Although carotenoids are not substrates of enzymes in the omega-3 biosynthetic pathway, several interactions between omega-3s and carotenoids have been reported. We previously showed that SNPs in *ELOVL2* and *ELOVL5* are associated with the bioavailability of LYC,  $\beta$ -carotene, lutein, and phytofluene.<sup>22–24,27</sup> *In vitro* studies using Caco-2 cells have demonstrated that EPA inhibits  $\beta$ -carotene absorption, at least partly through activation of the PPAR $\alpha$  receptor,<sup>55</sup> and that both EPA and DHA reduce the expression of SR-B1.<sup>55,56</sup> Notably, rs2817114 was also associated with adipose tissue concentrations of lutein and zeaxanthin in the same cohort.<sup>36</sup> This association may reflect indirect effects of *ELOVL5* variants on LYC bioavailability, as well as downstream effects on SR-B1 expression mediated by long-chain omega-3 fatty acids.

A SNP in *GRAMD1C*, rs4682144, was also associated with adipose tissue LYC concentration. *GRAMD1C* encodes Aster-C, a member of the Aster protein family recently implicated in the non-vesicular transfer of cholesterol between the plasma membrane, endoplasmic reticulum, and mitochondria.<sup>57</sup> Given the chemical similarities between cholesterol and carotenoids, Aster proteins have been hypothesized to mediate carotenoid intracellular transport, a role confirmed in 2022 for Aster-B (encoded by *GRAMD1B*).<sup>58</sup> More recently, studies in mice demonstrated that Aster-C, which is highly expressed in enterocytes, influences zeaxanthin bioavailability.<sup>59</sup> Our findings therefore add to growing evidence linking Aster proteins to carotenoid metabolism. Although the mechanism underlying the association of rs4682144 with adipose tissue LYC concentration remains unclear, *GRAMD1C* (ASTER-C) is more highly expressed in small intestine and liver than in adipose tissue according to the Human Protein Atlas. It is therefore plausible that this variant—or another in LD—modulates *GRAMD1C* expression or activity in these tissues, thereby influencing LYC bioavailability and ultimately its deposition in adipose tissue.

Another SNP of interest associated with adipose tissue LYC concentration was rs7754295 in *SOD2*. *SOD2* encodes superoxide dismutase 2, a mitochondrial enzyme that converts superoxide radicals into hydrogen peroxide, thereby protecting cells against oxidative stress. Observational studies have consistently reported inverse correlations between oxidative stress biomarkers and circulating carotenoid concentrations, including LYC.<sup>60</sup> Although several intervention trials have reported reductions in oxidative stress biomarkers following carotenoid supplementation or consumption of carotenoid-rich foods (including tomatoes and tomato products) in participants with chronic diseases, results from similar trials conducted in



healthy individuals remain inconclusive.<sup>60</sup> Therefore, the causal direction of this relationship remains uncertain. Since LYC exhibits strong antioxidant activity *in vitro*,<sup>3</sup> a plausible explanation for the observed association is that reduced SOD2 activity could increase oxidative stress, resulting in greater utilization of antioxidants such as LYC and consequently lower tissue concentrations. Notably, this variant has also been suggested to act as an expression quantitative trait locus (eQTL), potentially influencing SOD2 expression.<sup>61</sup>

This study has several limitations. First, we did not assess dietary LYC intake, as no dietary survey was conducted. Because humans cannot synthesize carotenoids, all adipose tissue LYC originates from the diet, and it is reasonable to assume that intake influences adipose tissue concentrations. However, correlations between dietary intake and adipose tissue LYC are generally modest. El-Soheby *et al.* reported Spearman's  $\rho = 0.26$  in males and 0.14 in females,<sup>18</sup> while Chung *et al.* found  $r$  values of 0.41 (abdomen), 0.24 (buttocks), and 0.06 (thigh).<sup>13</sup> Our regression model included fasting circulating LYC concentrations, which can serve as a proxy for dietary LYC intake. Nevertheless, incorporating dietary LYC intake might have further enhanced the model's explanatory power. Second, our HPLC method did not allow full chromatographic resolution of LYC isomers, so we quantified LYC as the sum of all isomers. While dietary LYC is predominantly in the all-*trans* form, *cis*-isomers are more abundant in blood and tissues,<sup>10</sup> including adipose tissue,<sup>13</sup> due to higher bioavailability, greater thermodynamic stability at elevated temperatures, and endogenous isomerization.<sup>10</sup> Given that *cis*-isomers may exhibit stronger antioxidant activity than all-*trans* LYC<sup>62</sup> while sharing some of its biological functions,<sup>63</sup> future studies should investigate their determinants in adipose tissue. Third, we acknowledge that different fat depots, especially visceral fat, may exhibit distinct concentrations of LYC or genetic associations with LYC concentration. Future studies could explore these differences to provide further insights into the functional roles of LYC in different adipose depots. Fourth, our sample included only 43 Caucasian adult males. Given the relatively small sample size, the associations identified in this exploratory study require confirmation in larger, independent cohorts. In addition, these findings cannot currently be generalized to other populations, including females and individuals from different ethnic backgrounds. Females have been reported to display higher adipose tissue LYC concentrations than males,<sup>13,18,43</sup> raising the possibility of sex-related differences in LYC metabolism, potentially linked to differential expression of related proteins. Finally, our candidate gene approach may have missed important genes not previously implicated in adipose tissue LYC concentration. In addition, several SNPs in the selected genes were not included in the PLS regression because they were absent from the BeadChips or excluded during quality control (see Methods). Taken together, these limitations indicate that the present work should be considered exploratory and that the reported genetic associations should be interpreted as hypothesis-generating pending replication in larger and more diverse populations.

To conclude, this work represents the first step toward identifying genetic determinants of LYC concentration in human adipose tissue, its major storage site. The results suggest that some individuals may have a reduced capacity to accumulate LYC, which could influence their ability to benefit from its proposed health effects, including antioxidant protection and potential roles in cardiometabolic and cancer prevention. As with other fat-soluble micronutrients,<sup>28,36,37</sup> genetic variation may therefore contribute to interindividual differences in tissue status and related disease risk. Future studies should aim to replicate these findings in larger and more diverse populations, to clarify the mechanisms involved, and ultimately to determine whether genetic information could be used to identify individuals who might benefit from tailored dietary advice or LYC supplementation.

## Author contributions

The authors' responsibilities were as follows: M. P. Z.: data curation, formal analysis, investigation, methodology, software, validation, visualization, cowriting – original draft. P. B.: conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, visualization, writing – review & editing. C. D.: conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, writing – original draft. All authors have read and approved the final manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Abbreviations

HPLC	High-performance liquid chromatography
LD	Linkage disequilibrium
LYC	Lycopene
PBS	Phosphate-buffered saline
PLS	Partial least squares
SNP	Single nucleotide polymorphism
VIP	Variable importance in the projection

## Data availability

Although data sharing was not included in the original ethics approval, de-identified individual-level data or aggregated datasets may be made available upon reasonable request, subject to approval by the relevant ethics committee and in accordance with applicable data protection regulations.

Supplementary information (SI) is available. See DOI: <https://doi.org/10.1039/d5fo05171a>.



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