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Genetic determinants of vitamin E status.

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1 Vitamin E: chemistry, dietary sources, intake and recommended dietary allowances

Vitamin E (VE) is the generic term for molecules that possess qualitatively the biological activity of α -tocopherol. Four tocopherols (α , β , γ , and δ) and four tocotrienols (α , β , γ , and δ) occur naturally, with α - and γ -tocopherol the main vitamers present in Western diets. Natural tocopherols are found in foods as unesterified *RRR* stereoisomers. However, synthetic VE, which is widely used as an antioxidant food additive and in dietary supplements, is usually a racemic mixture of eight stereoisomers and is esterified, usually as all*rac*- α -tocopheryl acetate or succinate, to protect the phenol group against oxidation. Foods naturally rich in VE include some vegetable oils and nuts, but it is also found in other food matrices, e.g., wheat germ and lettuce.

9 The average VE intake of Americans is still below the U.S. recommended dietary allowances 10 (15 mg/day for people \geq 14 years of age) and about three-fourths of Americans (19–30 years of age) consume 11 less than 10 mg/day. In Europe, 8% of men and 15% of women fail to meet 67% of the European recommended 12 dietary allowances for VE (12 mg/day). A recent study of global α -tocopherol status has shown that only 21% 13 of participants exhibited serum α -tocopherol concentrations >30 µmol/L, which is the proposed threshold for 14 adequate VE status (1).

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16 Role of vitamin E in humans

Based on its chemistry and on in vitro experiments, VE is considered to be the primary fat-soluble dietary antioxidant consumed by humans: it acts as a chain-breaking antioxidant, especially against peroxyl radicals, and is thus essential in maintaining the integrity of the long-chain polyunsaturated fatty acids found in cell membranes. Nevertheless, other studies have shown that VE has biological activities independent of its antioxidant properties. Indeed, it can modify gene expression, inhibit cell proliferation, modulate platelet aggregation and monocyte adhesion, and is involved in the regulation of bone mass.

Based on the assumption that free radicals are involved in the etiology of several diseases, e.g., cardiovascular diseases and cancers, the potential benefit of high VE intake from foods or dietary supplements has been extensively studied. In summary, although VE intake or VE status have been consistently found to be inversely associated with the incidence of several diseases, most randomized controlled trials have failed to demonstrate an effect of VE supplementation on the incidence of these diseases. To explain the apparent discrepancy between the results obtained in population studies and randomized controlled trials, it has been suggested that genetic variations in genes involved in VE absorption and metabolism may have interfered with the protective effects of VE supplementation (2). It is therefore crucial to identify such genetic influences and to estimate their biological effect in order to take into account this source of interindividual variability in future randomized controlled trials.

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Proteins and corresponding genes involved in vitamin E status

35 The most widely used and validated marker of VE status is obtained by measuring plasma or 36 serum α -tocopherol concentration after an overnight fast. In order to identify genetic variations that can 37 modulate VE status, two complementary approaches have been used most commonly. Genome-wide association studies (GWAS) display the advantage that they do not make any assumption on the genetic 38 39 variations that may affect the studied disease or phenotype, thus allowing researchers to identify unexpected associations. Yet, excessive statistical stringency used in this approach might lead to false negative conclusions, 40 i.e., to reject genetic variants that are marginally associated with the phenotype. Another drawback of GWAS is 41 42 their cost. Since a very large number of genetic variants is investigated, the sample size required to limit false 43 positive associations is high (typically > 10,000 subjects). This is not necessarily an issue if the phenotype of 44 interest is cheap to measure (e.g. with single-point measurements such as plasma/serum VE concentration) but 45 this can become a limiting factor for more complex phenotypes (e.g. VE absorption assessed with several 46 measurement points). Additionally, the studied population needs to be well characterized to account for confounding variable that could decrease the relative effect of genetic variation on the phenotype/disease of 47 48 interest (e.g., usual VE intake in GWAS of VE status). The second approach used to identify genetic variations 49 that can modulate VE status is candidate gene association studies. By selecting only genes or genetic variations 50 that are assumed to be involved with the phenotype of interest, it allows researchers to use a much smaller study 51 population, improving their capacity to characterize the population and lowering the cost of the study. However, many genes and SNPs that potentially have effects on the bioavailability of fat-soluble vitamins and 52

phytochemicals are left out of the analyses. Moreover, it requires a thorough knowledge of the studied phenotype to appropriately select promising candidate genes. The last part of this paragraph is therefore dedicated to list some of the proteins that are known, assumed, or reasonably hypothesized, to modulate, directly or indirectly, the fasting plasma/serum concentration of VE, i.e. VE status. Genes encoding for these proteins are therefore candidate genes for association studies.

The metabolism of vitamin E in the human digestive tract has been reviewed recently (3). It might begin in the stomach where VE esters might be partially hydrolyzed by gastric lipase. In the duodenum, VE esters are hydrolyzed, at least partly, by carboxyl ester hydrolase. Moreover, digestive enzymes, i.e., proteases, amylases, and lipases, have been suggested to be involved in the release of VE from food matrices.

62 After its incorporation into mixed micelles, VE is taken up by enterocytes. Significant advances on this 63 key step of VE absorption have been made in the last ten years. Indeed, although it was thought that VE uptake 64 takes place only by passive diffusion, studies in cell cultures and in transgenic mice have established that 65 several proteins are involved in this process (4): three apical membrane proteins, SR-BI, NPC1L1 and CD36, have been involved in VE uptake. Genetic variations in genes that encode for these proteins are thus candidates 66 67 for the modulation of VE absorption and consequently of VE status. After uptake across the apical side of the 58 enterocyte, VE has to reach the basolateral side to be secreted in the body. Surprisingly, there is no data yet on protein(s) involved in its intracellular transport. Candidates could be sec14p-like proteins (encoded by TAP1, 2, 59 70 and 3 in humans) and Niemann-Pick type C1/C2 (NPC1/2) proteins, which have been shown to transport VE in 71 other cells. However, it is not yet known whether these proteins are expressed in enterocytes (4).

Most newly absorbed VE is secreted by enterocytes with chylomicrons (3, 4) but recently, one membrane protein, ABCA1, has been shown to modulate VE efflux at the basolateral side of the enterocyte and another basolateral membrane protein, ATP-binding cassette sub-family G member 1 (ABCG1), has also been suggested to participate in this efflux (5). (3, 4)The incorporation of VE into these lipoproteins depends on several proteins, including microsomal transfer protein (MTP), which is likely involved in its incorporation in nascent chylomicrons, and ABCA1, which is involved in its secretion in nascent HDL. Chylomicrons and intestinal HDL then carry VE to the liver, which is a key organ for the metabolism of VE, and to other tissues. Apolipoproteins that are constituents of these lipoproteins, e.g. apoB48 and apoAI, as well as proteins that are involved in the blood metabolism of these lipoproteins, e.g. lipoprotein lipase, CETP, PLTP, apoB receptor, are also candidate genes for the modulation of VE status.

Following the hydrolysis of chylomicron triglycerides by lipoprotein lipase, some VE can be taken up 82 83 by extrahepatic tissues through a SR-BI dependent mechanism. Chylomicron remnants are then taken up by the 84 liver via endocytic receptors such as the LDL receptor and heparan sulfate proteoglycans (of which syndecan 1 85 is the primary one). The fate of VE that is incorporated into intestinal HDL, or transferred to hepatic HDL 86 during its circulation in the blood since VE can exchange in between lipoproteins, is not known but it is 87 assumed that most HDL-VE is transported to the liver where it is taken up via SR-BI. After its uptake by the 88 liver, VE can be stored, secreted into bile, re-secreted into circulation with VLDL or catabolised. VE 89 catabolism starts with an ω -hydroxylation of the side-chain, which is catalyzed by CYP4F2 or CYP3A4, followed by β -oxidation but the first step is limiting. One enzyme has been shown to metabolize VE in human: 90 91 the ω -hydroxylase cytochrome P450-4F2 (CYP4F2). These enzymes are therefore good candidates to modulate 92 tissue VE concentration and in turn blood VE status. A key protein involved in these pathways is the α -93 tocopherol transfer protein (α -TTP). Indeed, it binds VE, preferentially the RRR- α -tocopherol isomer, with a high specificity and allows its incorporation into very-low-density lipoprotein (VLDL). Loss-of-function 94 variants of the gene that encodes this protein can strongly impair the transfer of tocopherol into VLDL, 95 resulting in a disease called "ataxia with isolated VE deficiency". It is therefore likely that genetic variations in 96 97 this gene can significantly affect VE status.

After its secretion into VLDL by the liver, VE is distributed to other lipoprotein classes either by their natural conversion to LDL, or by PLTP-mediated transfer to HDL. The fate of VE in lipoproteins is not well known. It is assumed that a fraction is degraded by oxidation when VE reacts with free radicals and when it is not regenerated by other antioxidants, e.g. vitamin C or polyphenols. The remaining fraction is either taken up by the liver or other tissues when lipoproteins are taken up by these organ/tissues. VE is then either degraded by oxidation when it reacts with reactive oxygen species or is metabolized to be eliminated. The last candidate proteins/genes that could modulate blood VE concentration are those involved in the production/neutralisation of reactive oxygen species. Indeed, the blood/tissue concentration of these species can modulate the blood/tissue concentration of VE. This explain why variants of the haptoglobin gene (HP) have been associated with VE status.

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O9 Genetic variations associated with vitamin E absorption

Since VE is not synthesized in humans, all VE present in the human body comes from food and dietary 10 supplements. VE bioavailability has been shown to be variable, with absorption in the range 10-79%, and in a 11 recent clinical trial where a VE-rich meal was given to a group of healthy subjects, the coefficient of variation 12 13 of the VE response to the meal was 81% (6). It is thus reasonable to hypothesize that genetic variations in genes involved in VE absorption could in turn affect VE status. In the above-mentioned trial, 82% of the variability 14 was explained by a combination of 28 SNPs in or near 11 candidate genes. Seven of these genes were involved 15 in the postprandial chylomicron triacylglycerol response (7). This is not surprising since most newly absorbed 16 VE is carried from the intestine to the liver via chylomicrons. Four of these genes were specifically associated 17 with the VE response: solute carrier family 10 (sodium/bile acid cotransporter), member 2 (SLC10A2), 18 19 pancreatic lipase (PNLIP), sterol regulatory element binding transcription factor 2 (SREBF2), and ATP-binding cassette, sub-family G (WHITE), member 1 (ABCG1). The associations observed in this study, which need to 20 21 be confirmed in another population, show that several SNPs in genes involved in different pathways can impact 22 VE bioavailability. Although the effect of each SNP was, as expected, relatively low, their additive effect 23 significantly contributed to explain the variability in this phenotype. Furthermore, they can indirectly affect VE 24 status as well because it was shown in this study that VE bioavailability was correlated with VE status.

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26 Genetic variations associated with fasting blood vitamin E concentrations

As previously mentioned, fasting serum/plasma VE concentration is used as a marker for VE status. Thus, several studies have assessed associations between genetic variations and fasting serum/plasma VE concentration. Three GWAS have shown that a SNP near *ZNF259*, *BUD13* and *APOA1/C3/A4/A5*, a SNP in *CYP4F2*, and a SNP in *SCARB1* are associated with VE status (8-10). *SCARB1* encodes for SR-BI, which is a membrane receptor for HDL and has been involved in VE uptake by several tissues. Concerning *CYP4F2*, it encodes for cytochrome P450 4F2, which is an enzyme metabolizing VE in humans. The association with the SNP near *ZNF259*, *BUD13* and the cluster *APOA1/C3/A4/A5* is likely due to a variation in *APOA5* as suggested by Ferrucci et al. (10), since *ZNF259* and *BUD13* encode for proteins that have no known role on VE metabolism.

Candidate gene associations studies have confirmed the involvement of the genes that have been identified in the GWAS studies (11-15) and also suggested that of *CD36* (16), *CETP* (13) and *APOE* (14).

Altogether, these associations studies show that genetic variants in *CYP4F2*, *SCARB1* and likely in one of several genes of the *APOA1/C3/A4/A5* cluster can modulate VE status. The associations with *CD36*, *CETP* and *APOE* remain to be confirmed in other studies.

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42 Future research on genetic variants that can modulate vitamin E status

43 Although associations between SNPs in several genes and VE bioavailability or fasting blood VE 44 concentration have been observed, a lot of work remains to be done to identify all the genetic variations 45 involved in VE status and to provide a list of the main genetic variations that govern VE status (17). Indeed, GWAS allow us to identify only SNPs that have a relatively high effect on this status and candidate gene 46 47 studies miss genes not thought to affect this status. Recent results have also shown that it is absolutely 48 necessary to study the additive effects of genetic variants. Indeed, although each variant has generally a very 49 low effect, the additive effect of several variants can have a very significant impact. It should also be reminded 50 that SNPs are not the only genetic variations that occur in humans: there are also copy number variants, 51 insertion/deletion variants as well as epigenetic modifications. A genetic score that would aim to predict VE 52 status should therefore take into account all genomic variations that can have a significant impact on VE status. 53 Furthermore, association studies have to be performed in different populations to be sure that the associations 54 are not specific to particular ethnic groups.

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In summary, it is now clear that VE status is modulated in part by variants in several genes. Although a lot of work remains to be done to obtain a combination of genetic variations (SNPs but also other kinds of genetic variations) that will allow us to confidently predict the VE status of an individual by knowing his compound genotype, the potential usefulness of this area of research is exciting with regard to personalized nutrition and for future clinical trials dedicated to assess biological effects of VE. Nevertheless, genetics only represents one variable in the equation, albeit stable over the lifespan, since other factors, such as VE dietary intake, dietary habits, oxidative stress (through e.g. smoking), can affect VE status.

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64 **References**

65		
66	1.	Peter S, Friedel A, Roos FF, Wyss A, Eggersdorfer M, Hoffmann K, Weber P. A Systematic Review of
67		Global Alpha-Tocopherol Status as Assessed by Nutritional Intake Levels and Blood Serum
68		Concentrations. Int J Vitam Nutr Res 2016:1-21.

- Zingg JM, Azzi A, Meydani M. Genetic polymorphisms as determinants for disease-preventive effects of vitamin E. Nutr Rev 2008;66:406-14.
- Borel P, Preveraud D, Desmarchelier C. Bioavailability of vitamin E in humans: an update. Nutr Rev 2013;71:319-31.
- 4. Reboul E, Borel P. Proteins involved in uptake, intracellular transport and basolateral secretion of fatsoluble vitamins and carotenoids by mammalian enterocytes. Prog Lipid Res 2011;50:388-402.
- Olivier M, Bott GR, Frisdal E, Nowick M, Plengpanich W, Desmarchelier C, Roi S, Quinn CM,
 Gelissen I, Jessup W, et al. ABCG1 is involved in vitamin E efflux. Biochim Biophys Acta
 2014;1841:1741-51.
- Borel P, Desmarchelier C, Nowicki M, Bott R, Tourniaire F. Can genetic variability in alpha-tocopherol bioavailability explain the heterogeneous response to alpha-tocopherol supplements? Antioxid Redox Signal 2015;22:669-78.
- 7. Desmarchelier C, Martin JC, Planells R, Gastaldi M, Nowicki M, Goncalves A, Valero R, Lairon D,
 Borel P. The postprandial chylomicron triacylglycerol response to dietary fat in healthy male adults is
 significantly explained by a combination of single nucleotide polymorphisms in genes involved in
 triacylglycerol metabolism. J Clin Endocrinol Metab 2014;99:E484-8.
- Major JM, Yu K, Chung CC, Weinstein SJ, Yeager M, Wheeler W, Snyder K, Wright ME, Virtamo J, Chanock S, et al. Genome-wide association study identifies three common variants associated with serologic response to vitamin E supplementation in men. J Nutr 2012;142:866-71.
- Major JM, Yu K, Wheeler W, Zhang H, Cornelis MC, Wright ME, Yeager M, Snyder K, Weinstein SJ,
 Mondul A, et al. Genome-wide association study identifies common variants associated with circulating
 vitamin E levels. Hum Mol Genet 2011;20:3876-83.
- Ferrucci L, Perry JR, Matteini A, Perola M, Tanaka T, Silander K, Rice N, Melzer D, Murray A, Cluett
 C, et al. Common Variation in the beta-Carotene 15,15'-Monooxygenase 1 Gene Affects Circulating
 Levels of Carotenoids: A Genome-Wide Association Study. Am J Hum Genet 2009;84:123-33.
- I1. Zanon-Moreno V, Asensio-Marquez EM, Ciancotti-Oliver L, Garcia-Medina JJ, Sanz P, Ortega-Azorin
 C, Pinazo-Duran MD, Ordovas JM, Corella D. Effects of polymorphisms in vitamin E-, vitamin C-, and

- glutathione peroxidase-related genes on serum biomarkers and associations with glaucoma. Mol Vis 2013;19:231-42.
- Athinarayanan S, Wei R, Zhang M, Bai S, Traber MG, Yates K, Cummings OW, Molleston J, Liu W,
 Chalasani N. Genetic polymorphism of cytochrome P450 4F2, vitamin E level and histological response
 in adults and children with nonalcoholic fatty liver disease who participated in PIVENS and TONIC
 clinical trials. PLoS ONE 2014;9:e95366.
- Borel P, Moussa M, Reboul E, Lyan B, Defoort C, Vincent-Baudry S, Maillot M, Gastaldi M, Darmon M, Portugal H, et al. Human fasting plasma concentrations of vitamin E and carotenoids, and their association with genetic variants in apo C-III, cholesteryl ester transfer protein, hepatic lipase, intestinal fatty acid binding protein and microsomal triacylglycerol transfer protein. Br J Nutr 2009;101:680-7.
- Borel P, Moussa M, Reboul E, Lyan B, Defoort C, Vincent-Baudry S, Maillot M, Gastaldi M, Darmon M, Portugal H, et al. Human plasma levels of vitamin E and carotenoids are associated with genetic polymorphisms in genes involved in lipid metabolism. J Nutr 2007;137:2653-9.
- 15. Girona J, Guardiola M, Cabre A, Manzanares JM, Heras M, Ribalta J, Masana L. The apolipoprotein A5 gene -1131T-->C polymorphism affects vitamin E plasma concentrations in type 2 diabetic patients.
 Clin Chem Lab Med 2008;46:453-7.
- 16. Lecompte S, Szabo de Edelenyi F, Goumidi L, Maiani G, Moschonis G, Widhalm K, Molnar D, Kafatos
 A, Spinneker A, Breidenassel C, et al. Polymorphisms in the CD36/FAT gene are associated with
 plasma vitamin E concentrations in humans. Am J Clin Nutr 2011;93:644-51.
- Borel P, Desmarchelier C. Bioavailability of Fat-Soluble Vitamins and Phytochemicals in Humans:
 Effects of Genetic Variation. Annu Rev Nutr 2018;38:69-96.
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19 Figure. Summary of the proteins involved in the variability of vitamin E status.

Proteins displayed are those encoded by the main candidate genes involved in VE status or by genes for which genetic variations have been associated with the variability of VE status. A question mark next to a name indicates that the proposed function of the gene is still awaiting confirmation.

Table. Summary of the SNPs that have been associated with either fasting blood vitamin E concentration

or vitamin E bioavailability

SNP	Global MAF ¹	Nearest gene	Trait	Reference	Study type
rs12272004	0.085	APOA5	Fasting blood α-tocopherol concentration	Ferrucci et al. 2009	GWAS
rs964184	0.222	BUD13/ZNF259/APOA5	Fasting blood α -tocopherol concentration following α -tocopherol supplementation	Major <i>et al</i> . 2011	GWAS
rs2108622	0.237	CYP4F2	Fasting blood α -tocopherol concentration following α -tocopherol supplementation	Major <i>et al</i> . 2011	GWAS
rs11057830	0.139	SCARB1	Fasting blood α -tocopherol concentration following α -tocopherol supplementation	Major <i>et al.</i> 2011	GWAS
rs7834588	0.433	NKAIN3	Fasting blood α -tocopherol concentration following α -tocopherol supplementation	Major <i>et al.</i> 2012	GWAS
rs10401969	0.118	SUGP1	Fasting blood α -tocopherol concentration	Wood <i>et al.</i> 2013	GWAS
rs58542926	0.067	TM6SF2	Fasting blood α -tocopherol concentration	Wood <i>et al.</i> 2013	GWAS
Rs675	0.099	APOA4	Fasting blood α - and γ -tocopherol concentration	Borel <i>et al.</i> 2007	CGAS
E2, E3, E4		APOE	Fasting blood α -tocopherol concentration	Borel <i>et al.</i> 2007	CGAS
rs4238001	0.064	SCARB1	Fasting blood γ-tocopherol concentration	Borel <i>et al.</i> 2007	CGAS
rs5888	0.323	SCARB1	Fasting blood α -tocopherol concentration	Borel <i>et al.</i> 2007	CGAS
rs662799	0.163	APOA5	Fasting blood α -tocopherol concentration in diabetic patients	Girona et al. 2008	CGAS
rs5128	0.234	APOC3	Fasting blood α -tocopherol concentration	Borel <i>et al.</i> 2009	CGAS
rs708272	0.378	СЕТР	Fasting blood α -tocopherol concentration	Borel <i>et al.</i> 2009	CGAS
rs1800588	0.387	LIPC	Fasting blood y-tocopherol concentration	Borel <i>et al.</i> 2009	CGAS
rs1527479	0.349	CD36	Fasting blood α-tocopherol concentration	Lecompte et al. 2011	CGAS
rs6994076	0.349	ТТРА	Fasting blood α -tocopherol concentration	Zanon-Moreno <i>et al.</i> 2013	CGAS
rs2108622	0.237	CYP4F2	Fasting blood α -tocopherol concentration following α -tocopherol supplementation	Athinarayanan <i>et al.</i> 2014	CGAS
rs3093105	0.157	CYP4F2	Fasting blood α -tocopherol concentration following α -tocopherol supplementation	Athinarayanan <i>et al.</i> 2014	CGAS
rs468320	0.234	ABCG1	α-tocopherol bioavailability	Borel, Desmarchelier <i>et al.</i> 2014	CGAS
rs2915775	0.257	PNLIP	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs3010494	0.294	PNLIP	α-tocopherol bioavailability	Borel, Desmarchelier <i>et al.</i> 2014	CGAS
rs1571513	0.240	SLC10A2	α-tocopherol bioavailability	Borel, Desmarchelier <i>et al.</i> 2014	CGAS

rs9558203	0.198	SLC10A2	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs16961116	0.162	SLC10A2	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs12874168	0.210	SLC10A2	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs2065550	0.160	SLC10A2	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs2839715	0.168	SREBF2	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs4822062	0.153	SREBF2	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs4149314*	0.069	ABCA1	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs11789603*	0.117	ABCA1	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs2274873*	0.082	ABCA1	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs4149297*	0.084	ABCA1	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs4643493*	0.082	APOB	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs1042031*	0.128	APOB	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs1713222*	0.155	APOB	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs10464587*	0.297	BET1	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs1316328 [*]	0.134	IRS1	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs4238329*	0.148	LIPC	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs8041525*	0.086	LIPC	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs7164909*	0.153	LIPC	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs8035357*	0.150	LIPC	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs12591216 [*]	0.084	LIPC	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs12593880*	0.068	LIPC	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs4921920 [*]	0.101	NAT2	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs7296124*	0.107	ZNF664	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS
rs1048497*	0.061	ZNF664	α-tocopherol bioavailability	Borel, Desmarchelier et al. 2014	CGAS

¹ Abbreviations: CGAS, candidate gene association study; MAF, minor allele frequency.

^{*} These SNPs were associated with the variability of α -tocopherol bioavailability but this association was likely due to their involvement in the postprandial metabolism of chylomicron triacylglycerol.

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