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Genetic determinants of vitamin E status.

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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.

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

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 peroxy 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

27 demonstrate an effect of VE supplementation on the incidence of these diseases. To explain the apparent
28 discrepancy between the results obtained in population studies and randomized controlled trials, it has been
29 suggested that genetic variations in genes involved in VE absorption and metabolism may have interfered with
30 the protective effects of VE supplementation (2). It is therefore crucial to identify such genetic influences and to
31 estimate their biological effect in order to take into account this source of interindividual variability in future
32 randomized controlled trials.

34 **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
38 association studies (GWAS) display the advantage that they do not make any assumption on the genetic
39 variations that may affect the studied disease or phenotype, thus allowing researchers to identify unexpected
40 associations. Yet, excessive statistical stringency used in this approach might lead to false negative conclusions,
41 i.e., to reject genetic variants that are marginally associated with the phenotype. Another drawback of GWAS is
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
47 confounding variable that could decrease the relative effect of genetic variation on the phenotype/disease of
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.
52 However, many genes and SNPs that potentially have effects on the bioavailability of fat-soluble vitamins and

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

58 The metabolism of vitamin E in the human digestive tract has been reviewed recently (3). It might begin
59 in the stomach where VE esters might be partially hydrolyzed by gastric lipase. In the duodenum, VE esters are
60 hydrolyzed, at least partly, by carboxyl ester hydrolase. Moreover, digestive enzymes, i.e., proteases, amylases,
61 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,
66 have been involved in VE uptake. Genetic variations in genes that encode for these proteins are thus candidates
67 for the modulation of VE absorption and consequently of VE status. After uptake across the apical side of the
68 enterocyte, VE has to reach the basolateral side to be secreted in the body. Surprisingly, there is no data yet on
69 protein(s) involved in its intracellular transport. Candidates could be sec14p-like proteins (encoded by *TAP1*, 2,
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).

72 Most newly absorbed VE is secreted by enterocytes with chylomicrons (3, 4) but recently, one
73 membrane protein, ABCA1, has been shown to modulate VE efflux at the basolateral side of the enterocyte and
74 another basolateral membrane protein, ATP-binding cassette sub-family G member 1 (ABCG1), has also been
75 suggested to participate in this efflux (5). (3, 4)The incorporation of VE into these lipoproteins depends on
76 several proteins, including microsomal transfer protein (MTP), which is likely involved in its incorporation in
77 nascent chylomicrons, and ABCA1, which is involved in its secretion in nascent HDL. Chylomicrons and
78 intestinal HDL then carry VE to the liver, which is a key organ for the metabolism of VE, and to other tissues.

79 Apolipoproteins that are constituents of these lipoproteins, e.g. apoB48 and apoAI, as well as proteins that are
80 involved in the blood metabolism of these lipoproteins, e.g. lipoprotein lipase, CETP, PLTP, apoB receptor, are
81 also candidate genes for the modulation of VE status.

82 Following the hydrolysis of chylomicron triglycerides by lipoprotein lipase, some VE can be taken up
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,
90 followed by β -oxidation but the first step is limiting. One enzyme has been shown to metabolize VE in human:
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
94 high specificity and allows its incorporation into very-low-density lipoprotein (VLDL). Loss-of-function
95 variants of the gene that encodes this protein can strongly impair the transfer of tocopherol into VLDL,
96 resulting in a disease called "ataxia with isolated VE deficiency". It is therefore likely that genetic variations in
97 this gene can significantly affect VE status.

98 After its secretion into VLDL by the liver, VE is distributed to other lipoprotein classes either by their
99 natural conversion to LDL, or by PLTP-mediated transfer to HDL. The fate of VE in lipoproteins is not well
00 known. It is assumed that a fraction is degraded by oxidation when VE reacts with free radicals and when it is
01 not regenerated by other antioxidants, e.g. vitamin C or polyphenols. The remaining fraction is either taken up
02 by the liver or other tissues when lipoproteins are taken up by these organ/tissues. VE is then either degraded by
03 oxidation when it reacts with reactive oxygen species or is metabolized to be eliminated.

04 The last candidate proteins/genes that could modulate blood VE concentration are those involved in the
05 production/neutralisation of reactive oxygen species. Indeed, the blood/tissue concentration of these species can
06 modulate the blood/tissue concentration of VE. This explain why variants of the haptoglobin gene (HP) have
07 been associated with VE status.

09 **Genetic variations associated with vitamin E absorption**

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

26 **Genetic variations associated with fasting blood vitamin E concentrations**

27 As previously mentioned, fasting serum/plasma VE concentration is used as a marker for VE status.
28 Thus, several studies have assessed associations between genetic variations and fasting serum/plasma VE
29 concentration. Three GWAS have shown that a SNP near *ZNF259*, *BUD13* and *APOA1/C3/A4/A5*, a SNP in

30 *CYP4F2*, and a SNP in *SCARB1* are associated with VE status (8-10). *SCARB1* encodes for SR-BI, which is a
31 membrane receptor for HDL and has been involved in VE uptake by several tissues. Concerning *CYP4F2*, it
32 encodes for cytochrome P450 4F2, which is an enzyme metabolizing VE in humans. The association with the
33 SNP near *ZNF259*, *BUD13* and the cluster *APOA1/C3/A4/A5* is likely due to a variation in *APOA5* as suggested
34 by Ferrucci et al. (10), since *ZNF259* and *BUD13* encode for proteins that have no known role on VE
35 metabolism.

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

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

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,
46 GWAS allow us to identify only SNPs that have a relatively high effect on this status and candidate gene
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.

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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18

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

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