REVIEW

Genetic Variation in Human Vitamin C Transporter Genes in Common Complex Diseases[1–3]

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ABSTRACT

Adequate plasma, cellular, and tissue vitamin C concentrations are required for maintaining optimal health through suppression of oxidative stress and optimizing functions of certain enzymes that require vitamin C as a cofactor. Polymorphisms in the vitamin C transporter genes, compromising genes encoding sodium-dependent ascorbate transport proteins, and also genes encoding facilitative transporters of dehydroascorbic acid, are associated with plasma and tissue cellular ascorbate status and hence cellular redox balance. This review summarizes our current knowledge of the links between variations in vitamin C transporter genes and common chronic diseases. We conclude that emerging genetic knowledge has a good likelihood of defining future personalized dietary recommendations and interventions; however, further validations through biological studies as well as controlled dietary trials are required to identify predictive and actionable genetic biomarkers. We further advocate the need to consider genetic variation of vitamin C transporters in future clinical and epidemiologic studies on common complex diseases. *Adv Nutr* 2016;7:287–98.

Keywords: antioxidants, genomics, inflammation, nutrigenomics, vitamin C

Introduction

Vitamin C is an essential nutrient and the most important plasma water-soluble antioxidant that plays critical roles in the biosynthesis of neurotransmitters and collagen, absorption of nonheme iron, detoxification of exogenous compounds and cytochrome P-450 activity, and regulation of hypoxia-inducible factor 1α (1, 2). In addition, it plays a major role as an antioxidant and free radical scavenger and protects against lipid peroxidation (3). Vitamin C has also been shown to function in sparing or reconstituting vitamin E for protection of lipid membranes (4, 5). Therefore, maintaining adequate plasma and tissue cellular vitamin C concentrations is crucial for normal metabolic function of the body and preventing many common complex diseases (6–14).

Epidemiologic studies show that individuals with reduced plasma vitamin C concentrations display an elevated risk of different chronic diseases (6). A review (15) of data from >90 epidemiologic studies that related the dietary intake of vitamin C to various types of cancer (breast, oral, gastric, esophageal, pancreatic, lung, cervical, and rectal) revealed a negative correlation in three-fourths of the studies. Besides, each 20-μM increase in plasma vitamin C concentration is associated with a 20% reduced risk of all-cause mortality (16) and a 9% relative decline in risk of heart failure (17).

A marginal vitamin C deficit (11 μM < plasma concentration < 24 μM) was estimated to affect up to 10% of adults in industrialized countries (13, 18, 19). Although vitamin C status is mainly determined by the dietary intake, it should be noted that a complex interplay of intrinsic metabolic factors, such as oxidative stress, inflammation, recycling, and transmembrane transport, contributes to the metabolic turnover and therefore vitamin C status (20). The metabolic turnover can be affected by genetic variations, and thus vitamin C status could be impaired even at dietary intake amounts that are currently regarded as adequate for the general population, if an individual carries a detrimental allele.

Transporters of the different forms of vitamin C directly regulate vitamin C intracellular bioavailability (**Figure 1**A). The elimination of selected ascorbic acid transporters in the mouse results in severely affected pharmacokinetics and reduced offspring viability (31) or even total offspring

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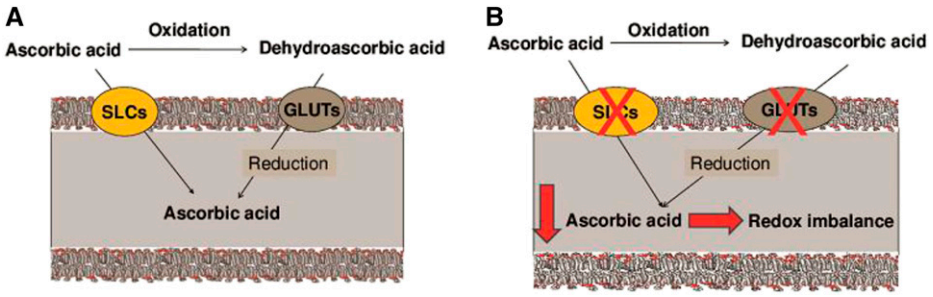

FIGURE 1 (A) General schematic for cellular uptake of vitamin C. The concentration of ascorbic acid in the intracellular environment is tightly controlled through regulation of the transporters. Ascorbic acid (ascorbate) is the functional form of vitamin C, which is transported into the cell through SLCs. SLCs comprise SLC23A1 and SLC23A2, which have specific cell expression and precise subcellular localization. The SLC23A1 protein is responsible for active transport of ascorbate from the epical luminal surface of the intestinal tract and kidney (21, 22). The SLC23A2 protein, expressed in most human tissues, except lung and skeletal muscle (22, 23), is thought to regulate intracellular concentrations of ascorbate for subsequent protection of the cell from oxidative stress as well as promote the maturation of type I collagen. DHA, the oxidized form of ascorbate, is transported into the cell by some members of the facilitative GLUT family, including GLUT1 (SLC2A1), GLUT2 (SLC2A2), and GLUT3 (SLC2A3) (24–27), which have specific cell expression and transport activity. Within cells, DHA is immediately recycled back to ascorbate, and this process sustains the intracellular ascorbate and therefore redox balance (28–30). (B) A proposed mechanism for an association between variations in vitamin C transporters and common complex diseases, as well as genetic variation in each ascorbic acid transporter (SLCs) or dehydroascorbic acid transporter (GLUTs), could modulate transport of ascorbate or DHA, thereby resulting in reduced intracellular vitamin C, redox imbalance, and thus increased risk of common complex diseases. DHA, dehydroascorbic acid; GLUT, glucose transporter; SLC, solute carrier family.

lethality (32). Therefore, variations in genes of the human vitamin C transporter pathways may affect disease development and outcomes (Figure 1B). This review summarizes existing knowledge on the variations in vitamin C transporter genes and disease associations. Two vitamin C transmembrane pathways are distinct by their substrates, where solute carriers (SLC) SLC23A1 and SLC23A2 mediate ascorbic acid transport, whereas dehydroascorbic acid is shuttled by the 4 members of the facilitative glucose transporter family GLUT1 (*SLC2A1*), GLUT2 (*SLC2A2*), GLUT3 (*SLC2A3*), and GLUT4 (*SLC2A4*), which will all be reviewed.

Current Status of Knowledge

Sodium-dependent vitamin C transporters

The active transport of ascorbate across the cell membrane is generated by 2 sodium-dependent ascorbate transporters that were first cloned in 1999 (33). The 2 transporters, SLC23A1 and SLC23A2, mediate sodium and energy-dependent ascorbate transport against a concentration gradients into cells, resulting in intracellular concentrations that can be 50-fold higher than the extracellular fluids (33, 34). SLC23A1 and SLC23A2 cotransport Na^+ and ascorbate with a 2:1 stoichiometry, using the electrochemical Na^+ gradient (35, 36).

The SLC23A1 and SLC23A2 are responsible for the maintenance of vitamin C concentrations in nearly all cells (except erythrocytes), tissues, and extracellular fluids (20). The genetic patterns of both *SLC23A1* and *SLC23A2* share common intron/exon borders and have related coding sequence, but the genes differ 10-fold in size (16 kb compared with 160 kb, respectively) and in linkage disequilibrium (37). The encoded proteins of the 2 transporters are comparable in amino acid sequence and structure, but they have different tissue distributions (33, 37).

SLC23A1 expression is confined to epithelia, such as intestinal, renal, and hepatic tissues (33, 38), and it has the major role in whole-body ascorbate homeostasis, through its function as a sole apical ascorbic acid transporter in the proximal renal epithelial cell (31). SLC23A1 has low affinity [Michaelis constant (K_m)[4] of 65–252 μM] (21) and high capacity [the maximum rate achieved by the system, at saturating substrate concentrations (V_{max}) of ~15 pmol · min^{-1} · $cell^{-1}$] (39), establishing the ability of this transporter to maintain the whole-body homeostasis (21, 22).

The *SLC23A1* locus on human chromosome 5q31.2 contains 16 exons (37, 40), spanning about 17.3 kb. A total of 1440 variations are listed in the Single Nucleotide Polymorphism Database of which 294 locate to the coding region (187 missense, 91 synonymous, 11 frameshift, 4 insertions). Many of the variations in *SLC23A1* have not been verified in different populations, such as the HapMap cohorts (41), and most variations are neither reported in the literature nor functionally characterized. Genetic linkage throughout the locus is high, with some evidence of linkage blocks in the 5′ and 3′ of the gene (37). Variations in *SLC23A1* seem to affect the vitamin C status, but current evidence remains inconclusive (42).

SLC23A2 is distributed in cells of most tissues (33) and contributes to delivering vitamin C into cells for some metal ion-dependent enzymatic reactions as well as protecting cells from oxidative stress (33, 43, 44). SLC23A2 has low capacity (~1 pmol · min^{-1} · $cell^{-1}$) (21, 39) and high affinity (K_m values of 8–69 μM) (21, 35, 45) for ascorbate transport, mediating uptake of ascorbate by cells of peripheral organs from the extracellular fluid (22, 23). A difference in membrane epithelial cells distribution of SLC23A1 and

[4] Abbreviations used: CVD, cardiovascular disease; DHA, dehydroascorbic acid; GLUT, glucose transporter; K_m, Michaelis constant; NAFLD, nonalcoholic fatty liver disease; SLC, solute carrier family; SNP, single-nucleotide polymorphism; V_{max}, the maximum rate achieved by the system, at saturating substrate concentrations.

SLC23A2 suggests nonredundant functions for these 2 transporters (46, 47).

The *SLC23A2* locus on human chromosome 20p13 contains 17 exons (37), spanning about 160 kb and is roughly 10 times bigger than *SLC23A1*. A total of 8165 variations are listed in dbSNP, of which 262 locate to the coding region (138 missense, 120 synonymous, 4 frameshift). Many of the variations in *SLC23A2* have not been verified in different populations, such as the HapMap cohorts (41), and most of these variations are neither reported in the literature nor functionally characterized. Genetic linkage throughout the locus is moderate (37), but linkage blocks are not defined (37). Variations in *SLC23A2* are yet to be reported to affect the vitamin C status.

When the patterns of single-nucleotide polymorphisms (SNPs) in *SLC23A1* and *SLC23A2* were compared, a substantial number of the SNPs in *SLC23A1* were population specific in either Caucasians or African Americans, including 4 nonsynonymous SNPs; however, nearly all SNPs in *SLC23A2* are shared between the 2 populations, African Americans and Caucasians (48). It was deduced that the *SLC23A1* gene does tolerate variations better than *SLC23A2*, indicating a higher physiologic importance for the latter.

Polymorphisms in sodium-dependent vitamin C transporters and pathologic relevance

The risk association of several SNPs in *SLC23A1* and *SLC23A2* genes with a variety of common chronic diseases, including various cancers (49–55), inflammatory bowel disease (56), preterm delivery (57), coronary heart disease (58), and optic neuropathy (59, 60), has been evaluated (**Table 1**).

Cancer. Vitamin C plasma and tissue concentrations have been postulated to affect relative cancer risk. The antioxidant effect of vitamin C may prevent cancers by inducing apoptosis and suppressing tumor cell growth (61–63) while counterbalancing DNA damage through scavenging of reactive oxygen species (64). Vitamin C also protects mucosal tissues from oxidative damage (65, 66) and plays an antitumorigenic role via sustaining proper collagen formation and matrix stabilization (67). As such, the risk association of vitamin C transporter genes with various intestinal cancers has been the key interest for several studies. In a study (50) with 656 patients with colorectal adenoma and 665 healthy controls, participants were genotyped for 4 SNPs in the *SLC23A1* gene and 11 different SNPs in the *SLC23A2* gene. No association between common SNPs in *SLC23A1* and colorectal cancer was revealed. For *SLC23A2*, there was no association with SNPs, but the haplotype G-C (rs4987219 and rs1110277) was associated with a reduction in the risk of colorectal adenoma (50). In a study on gastric cancer (53), an association between 13 genetic variants of the *SLC23A1* and *SLC23A2* genes with the disease was examined. Among the 13 SNPs examined, gastric cancer was inversely associated with one SNP (rs12479919) in the *SLC23A2* gene, whereas no association with variants in the *SLC23A1* gene was determined. Compared with rs12479919-G/G genotypes, homozygotes for the minor allele A/A had a lower risk of gastric cancer (53). In the aforementioned study, a haplotype in the *SLC23A2* gene, containing the common allele of the rs6139591, rs2681116, and rs14147458 SNPs, was inversely associated with gastric cancer (53). Likewise, in another study with 365 patients with gastric cancer and 1284 controls (54), the genotype rs6116569-C/T and the 2 haplotypes, CGTC (rs6052937, rs3787456, rs6116569, rs17339746) and ATC (rs6139587, rs6053005, rs2326576), in the *SLC23A2* gene were associated with gastric cancer risk, whereas no association was found with variants in *SLC23A1*.

Variants in vitamin C transporter genes have also been associated with other type of cancers. In a population-based study with 832 patients with bladder cancer and 1191 healthy controls (55), variant rs12479919-C/T in *SLC23A2* has been identified as a high-risk genotype for a gene-gene effect on bladder cancer. Indeed, the interaction of *SLC23A2* (rs12479919) and *SCARB1*- rs4765621 (the gene scavenger receptor class B) showed the strongest effect on the higher risk of bladder cancer (55). In another study with 1292 patients and 1375 healthy controls (49), several SNPs in *SLC23A1* and *SLC23A2* have been associated with an increased risk of non-Hodgkin lymphoma. In this study, individuals with the *SLC23A1* genotypes rs6596473-C/C and rs11950646-G/G showed an 80% elevated risk of lymphoma. Moreover, several SNPs in *SLC23A2* (Table 1) as well as 2 haplotypes (AA: rs1776948, rs6139587 and AAC: rs1715385, rs6133175, rs1715364) in the gene were associated with increased risk of the disease (49). Authors conclude that both vitamin C uptake and storage are involved in the pathogenesis of lymphoma (49).

Variation in the *SLC23A2* gene also affected the initiation or sustention of head and neck cancer in patients with human papillomavirus type 16 infection (51). In a study with 319 patients with head and neck cancer and 495 frequency-matched controls (51), the risk of the cancer associated with human papillomavirus type 16 was decreased among rs4987219-C/C homozygotes in the *SLC23A2* gene compared with those with a wild-type allele. The authors suggest that the SNP modifies the risk of head and neck cancer associated with human papillomavirus type 16 infection through the role of ascorbate in the maintenance of the epidermal barrier, maturation of type I procollagen, intracellular antioxidant, or its immunostimulatory effect (51).

Vitamin C transporter genes not only have been associated with an increased risk of different types of cancer but also have been suggested as predictive biomarkers for therapies. In a study with 49 patients with esophageal squamous cell carcinoma (52), rs4987219 and rs1110277 in the *SLC23A2* gene showed correlation with severe toxicities (acute stomatitis and leucopenia) (Table 1) after treatment with a definitive 5-fluorouracil/cisplatin-based chemoradiotherapy (52).

Inflammatory bowel disease. In addition to associations with various intestinal cancers, a variation in ascorbate

TABLE 1 Phenotype-genotype associations of SNPs in the human sodium-dependent ascorbate transporter genes with chronic diseases[1]

Gene	SNP	Allele, major/minor	Location	Disease	Population	Sample size, case/control, *n*	Findings	Study (reference)
SLC23A1	rs11950646	A/G	chr5: 139378785	Follicular lymphoma	United States	1292/1375	↑ Risk GG genotype	Skibola et al., 2008 (49)
				Small lymphocytic lymphoma/chronic lymphocytic leukemia	Germany	494/494	↑ Risk GG genotype	Skibola et al., 2008 (49)
	rs6596473	G/C	chr5: 139374887	Follicular lymphoma	United States	1292/1375	↑ Risk CC genotype	Skibola et al., 2008 (49)
				Chronic lymphocytic leukemia, diffuse large B-cell lymphoma	Germany	494/494	↑ Chronic lymphocytic leukemia risk; ↓ diffuse large B-cell lymphoma risk CC genotype	Skibola et al., 2008 (49)
				Lower concentration of ocular ascorbate	India	60/—	↑ Risk C-carrier	Senthilkumari et al., 2014 (60)
	rs10063949	A/G	chr5: 139383837	Inflammatory bowel disease	Canada	311/142	↑ Crohn disease risk G-carrier	Amir Shaghaghi et al., 2014 (56)
SLC23A2	rs6133175	A/G	chr20: 4911113	Non-Hodgkin lymphoma, diffuse large B-cell lymphoma, small lymphocytic lymphoma	United States	1292/1375	↑ Risk GG genotype	Skibola et al., 2008 (49)
	rs1715364	T/C	chr20: 4918250	Small lymphocytic lymphoma, diffuse large B-cell lymphoma	United States	1292/1375	↑ Risk CC genotype	Skibola et al., 2008 (49)
				Small lymphocytic lymphoma, diffuse large B-cell lymphoma	Germany	494/494	↑ Risk CC genotype	Skibola et al., 2008 (49)
	rs1715385	G/A	chr20: 4907024	Non-Hodgkin lymphoma, diffuse large B-cell lymphoma	United States	1292/1375	↑ Risk AA genotype	Skibola et al., 2008 (49)
	rs1776948	G/A	chr20: 4950467	Non-Hodgkin lymphoma, follicular lymphoma, small lymphocytic lymphoma	United States	1292/1375	↑ Risk AA genotype	Skibola et al., 2008 (49)
				Non-Hodgkin lymphoma, follicular lymphoma	Germany	494/494	↑ Risk AA genotype	Skibola et al., 2008 (49)
	rs6139587	T/A	chr20: 4961828	Non-Hodgkin lymphoma, small lymphocytic lymphoma	United States	1292/1375	↑ Risk AA genotype	Skibola et al., 2008 (49)
	rs4987219	G/C	chr20: 4884300	Colorectal adenoma	United States	656/665	↓ Risk C-carrier	Erichsen et al., 2008 (50)
				Human papillomavirus, head and neck squamous cell carcinomas association	United States	319/495	↑ Risk G-carrier	Chen et al., 2009 (51)
				Esophageal squamous cell carcinoma	Japan	49/—	↑ Risk leukopenia C-carrier	Minegaki et al., 2014 (52)
	rs1110277	T/C C/T	chr20: 4874036	Colorectal adenoma	United States	656/665	↓ Risk C-carrier	Erichsen et al., 2008 (50)
				Esophageal squamous cell carcinoma	Japan	49/—	↑ Risk stomatitis T-carrier	Minegaki et al., 2014 (52)
	rs12479919	C/T	chr20: 5000094	Gastric cancer	Poland	279/414	↓ Risk TT genotype	Wright et al., 2009 (53)
				Bladder cancer	United States	832/1191	↑ Risk CT genotype	Andrew et al., 2009 (55)
				Lower concentration of ocular ascorbate	India	60/—	↑ Risk TT genotype	Senthilkumari et al., 2014 (60)

(Continued)

TABLE 1 (*Continued*)

Gene	SNP	Allele, major/minor	Location	Disease	Population	Sample size, case/control, *n*	Findings	Study (reference)
	rs6116569	C/T	chr20: 4884071	Gastric cancer	Europe	365/1284	↑ Risk T-carrier	Duell et al., 2013 (54)
	rs2681116	G/A	chr20: 4970685	Preterm delivery	United States	271/572	↑ Risk GA genotypes	Erichsen et al., 2006 (57)
	rs6139591	C/T	chr20: 4970713	Preterm delivery	United States	271/572	↑ Risk T-carrier	Erichsen et al., 2006 (57)
				Acute coronary syndrome	Denmark	936/1580	↑ Risk TT genotype	Dalgard et al., 2013 (58)
	rs1776964	C/T	chr20: 4880308	Preterm delivery	United States	271/572	↓ Risk TT genotype	Erichsen et al., 2006 (57)
				Acute coronary syndrome	Denmark	936/1580	↑ Risk TT genotype	Dalgard et al., 2013 (58)
	rs1279383	A/G	chr20: 5002446	Primary open glaucoma	Mediterranean	150/150	↑ Risk GG genotype	Zanon-Moreno et al., 2011 (59)

[1] chr, chromosome; SLC, solute carrier family; SNP, single-nucleotide polymorphism.

transporters is associated with inflammatory bowel disease, where oxidative damage plays a key role in the initiation and progression of the disease (68). In a study with 311 people with inflammatory bowel disease and 142 controls (56), the SNP rs10063949-G allele in the *SLC23A1* gene was associated with an increased risk of Crohn disease. Specifically, rs10063949-A/G heterozygotes had a 2.5-fold elevated risk of Crohn disease, whereas rs10063949-G/G homozygotes had a 4.7-fold elevated risk compared with wild-type homozygotes (56).

Pregnancy complications. Vitamin C deficiency (measured by dietary intake or ascorbic acid concentrations in serum, leukocytes, or cord blood) has been found in several epidemiologic investigations (14, 71–75) to be associated with premature rupture of membranes and preterm delivery (<37 wk of gestation), a leading cause of neonatal mortality and morbidity (57). In view of the necessity of vitamin C for preservation of collagen and potency of membrane tensile (57, 69), genetic variants in *SLC23A1* and *SLC23A2* have also been associated with the risk of preterm delivery. Associations have been found between haplotypes in the *SLC23A1* gene and spontaneous preterm delivery (57). Moreover, a carrier of 1 or 2 minor alleles of variant rs6139591-T of the *SLC23A2* gene showed a 1.7-fold and a 2.7-fold higher risk of spontaneous preterm birth, respectively (57). Likewise, heterozygous individuals for rs2681116-G/A in *SLC23A2* showed a 1.9-fold increased risk of preterm birth, but analysis of the homozygous-carrying minor alleles (rs2681116-A/A) showed no effects. The authors speculate that the failure to detect a significant association between rs2681116-A/A homozygous individuals and the risk of preterm delivery was related to small numbers of the study population (57).

Coronary heart disease. Variations in *SLC23A2* have also been associated with acute coronary syndrome (58), where vitamin C is suggested to have cardioprotective influences due to its antioxidative effects and its beneficial effects on endothelial function and the collagen content of the atherosclerotic plaques (58, 74). A 5.4-fold elevated risk of acute coronary syndrome was observed (58) in women with the rs6139591-T/T genotype who had a low intake of dietary vitamin C. Moreover, women with the rs1776964-T/T genotype with a high intake of vitamin C had a 3.4-fold increased risk of acute coronary syndrome compared with C/C-homozygotes with low intake. Accordingly, the authors conclude that the effects of genotype may not be completely compensated by high dietary intake of vitamin C (58).

Optic neuropathy. Lack of vitamin C antioxidant capacity is also associated with glaucomatous optic neuropathy, where oxidative stress is related to neuronal death (75, 76). Indeed, statistically significant lower concentrations of vitamin C have been observed in plasma (59), normal tension (77), and the secondary aqueous humor (78) of glaucomatous patients. In a study among 150 patients with open-angle

glaucoma and 150 controls (59), genotype rs1279386-G/G in *SLC23A2* was associated with a higher risk of the disease (1.7-fold) as well as lower plasma vitamin C concentration (mean ± SD values of 9.0 ± 1.4 μg/mL compared with 10.5 ± 1.6 μg/mL in patients and 10.9 ± 1.6 μg/mL compared with 12.1 ± 1.8 μg/mL in controls). In this study, no association was found between polymorphisms in the *SLC23A1* gene with open-angle glaucoma (59). In another study (60), polymorphisms in the *SLC23A1* and *SLC23A2* genes were found to influence ascorbate concentration in the aqueous humor and lens nucleus of 60 patients undergoing small-incision cataract surgery. SNPs rs6596473 in the *SLC23A1* gene and rs12479919 in the *SLC23A2* gene showed an association with decreased ocular ascorbate concentration in carriers of the variant allele compared with the common homozygotes. For rs6596473, the per variant allele-C difference in aqueous humor ascorbate was −217 μmol/L, whereas for rs12479919, the per variant allele-T difference in lens nucleus ascorbate was 0.085 μmol/G (60) compared with homozygotes' common allele (G/G and C/C, respectively).

All the studies mentioned above confirmed numerous minor frequency genotypes and haplotypes of the *SLC23A1* and *SLC23A2* genes, associated with various chronic diseases. Most findings were reported on an individual basis in cohorts of limited sizes. Therefore, it is warranted to validate these findings in larger cohorts to use it as actionable biomarker of the respective common complex diseases.

Facilitated diffusion vitamin C transporters

Dehydroascorbic acid (DHA) is one dietary source of vitamin C, beside ascorbate, that can be absorbed across the brush-border membrane. Upon entry into the enterocyte, DHA is reduced either enzymatically or chemically back to ascorbate and thus maintains a concentration gradient, favoring DHA uptake (23, 27). Local DHA absorption may be especially important during intestinal inflammatory conditions, where the immune cells' oxidative burst increases extracellular oxidation of ascorbate to DHA (23, 79). The produced DHA is transported into enterocytes or other bystander cells, followed by immediate reduction to ascorbate, and thus boosts intracellular concentrations of the free radical scavenger (28–30). With regard to whole-body homeostasis, this might also prevent patients with chronic intestinal inflammation from becoming scorbutic (23, 27). Likewise, in any inflammatory condition throughout the body, where ascorbate gets oxidized to DHA in extracellular fluid, the produced DHA is taken up by specific facilitative diffusion transporters for various cells/tissues to elevate intracellular ascorbate (80–86).

SLC2A1 (GLUT1), SLC2A2 (GLUT 2), SLC2A3 (GLUT3), SLC2A4 (GLUT4), and SLC2A8 (GLUT8) are the 5 facilitated DHA transporters identified (24–27). They are members of the *SLC2A* solute carriers' gene family, encoding for the glucose transporter (GLUT) proteins of facilitated sugar transporters. It is postulated that vitamin C accumulation in cells occurs in part through transport of DHA by the carriers of the SLC2A family. It should be noted that DHA diffusion to some specific cell types is competitively inhibited by excessive glucose in plasma (24, 26). However, this inhibition might not be relevant in tubular cells of the kidney and on the luminal surface of absorptive intestinal epithelia (26, 45, 87, 88). Moreover, DHA diffusion into cells might be impeded during high-glucose status through the lack of location of SLC2A transporters to the plasmalemma membrane.

The DHA-GLUT transporters show tissue- and cell-specific expression as well as various affinities and efficiencies in DHA transport (24, 26, 89, 90). SLC2A1 is expressed in an extensive variety of cells throughout the body, with a particularly high expression in endothelial and epithelial-like barriers of the brain, peripheral nerve, eye, placenta, and lactating mammary gland (24, 91, 92), and exhibits a DHA transport activity defined by a K_m of 1.1 mM and a V_{max} of 108 pmol · min^{-1} · $oocyte^{-1}$ (24). SLC2A2 is mainly expressed in the brain, spleen, kidney, pancreas, liver, and basolateral membranes of intestinal epithelial cells (90, 91, 93) and transports DHA with a K_m of 2.33 mM and a V_{max} of 25.9 pmol · min^{-1} · $oocyte^{-1}$ (27). SLC2A3 is expressed particularly in the brain, neurons, and intestinal epithelial cells (24, 91) and has DHA transport activity defined by a K_m of 1.7 mM and a V_{max} of 241 pmol · min^{-1} · $oocyte^{-1}$ (24). SLC2A4 is mainly found in adipose tissues as well as skeletal and cardiac muscle cells (26, 91) with a DHA transport activity showing a K_m of 0.98 mM and a V_{max} of 66 pmol · min^{-1} · $oocyte^{-1}$ (26). GLUT8 is expressed in the testis, blastocyst, brain, muscle, and adipose tissues with a DHA transport activity defined by a K_m of 3.23 mM and a V_{max} of 10.1 pmol · min^{-1} · $oocyte^{-1}$ (27).

Polymorphisms in facilitative diffusion vitamin C transporters and pathologic relevance

Genetic variation in the DHA-GLUT transporter genes is associated with various common complex diseases, which could be attributed to not only disturbed monosaccharide transport but also disturbed transport of alternative substrates, such as DHA. The link between diabetes-related traits and impaired glucose metabolism is not the main focus of this section of the review. Our focus is to review the association studies with respect to DHA-GLUT variation and common complex disease, other than directly to diabetes-related traits (e.g., fasting blood glucose). The number of these studies is relatively limited (**Table 2**).

Diabetes complications. A variety of studies have found associations between variations in DHA-GLUT genes and diabetes-related traits (99, 100, 102), as well as diabetes complications such as albuminuria (94), retinopathy (95, 107), and nephropathy (108), in which etiology might involve modulations to DHA transport. With regard to vitamin C metabolism, excess glucose during conditions of uncontrolled diabetes may competitively block uptake of DHA through facilitative GLUTs and thus impair the transport of DHA by cells and affect the intracellular redox

TABLE 2 Phenotype-genotype association of SNPs in the human dehydroascorbic acid transporter genes with chronic diseases[1]

Gene	SNP	Allele, major/minor	Location	Disease	Population	Sample size, case/control, *n*	Findings	Study (reference)
SLC2A1	rs841847	C/T	chr1: 42937037	Diabetic albuminuria and macroalbuminuria	n_1 = African American, n_2 = European American	n_1 = 2156/—, n_2 = 8122/ 9453	↑ Risk TT genotype (n_2)	Hsu et al., 2010 (94)
	rs841846	A/G	chr1: 42938000	Severe diabetic retinopathy	African American	473	↑ Risk (not specified)	Roy et al., 2009 (95)
	rs3754218	G/T	chr1: 42933897	Renal cell carcinoma	England	92/99	↑ Risk GT genotype	Page et al., 2005 (96)
	rs3820589	A/T	chr1: 42960373	Renal cell carcinoma	England	92/99	↑ Risk T-carrier	Page et al., 2005 (96)
	rs4658	C/G	chr1: 42926579	Nonalcoholic fatty liver disease	Spain	520/521	↑ Risk GG genotype	Vazquez-Chantada et al., 2013 (97)
	rs841856	G/T	chr1: 42934442	Nonalcoholic fatty liver disease	Spain	520/521	↑ Risk TT genotype	Vazquez-Chantada et al., 2013 (97)
	rs2229682	G/A	chr1: 42929964	Spina bifida meningomyelocele	Hispanic and Caucasian, American	507/184	↑ Risk A-carrier	Davidson et al., 2008 (98)
SLC2A2	rs5393	C/A	chr3: 171027131	Impaired glucose tolerance	Finland	259/248	↑ Risk AA genotype	Laukkanen et al., 2005 (99)
	rs5394	C/T	chr3: 171027104	Impaired glucose tolerance	Finland	259/248	↑ Risk of type 2 diabetes T-carrier	Laukkanen et al., 2005 (99)
	rs5404	G/A	chr3, 171007166	Impaired glucose tolerance	Finland	259/248	↑ Risk of type 2 diabetes A-carrier	Laukkanen et al., 2005 (99)
	rs5400	A/G	chr3: 171014511	Impaired glucose tolerance	Finland	259/248	↑ Risk A-carrier	Laukkanen et al., 2005 (99)
				Type 2 diabetes	Finland	1170/983	↑ risk GG genotype	Willer et al., 2007 (100)
				Prostate cancer	United States	6642	↓ Risk G-carrier	Meyer et al., 2010 (101)
	rs11920090	T/A	chr3 170999732	Healthy individuals	Europe	76,558/—	↑ Risk higher fasting glucode concentration and type 2 diabetes A-carrier	Dupuis et al., 2010 (102)
				History of CVD	Denmark	6049/— (interstudy)	↑ Risk A-carrier	Borglykke et al., 2012 (103)
				History of CVD	Denmark	9572/— (pooled analyses)	↑ Risk A-carrier	Borglykke et al., 2012 (103)
				History of CVD	Denmark	3523/— (Monica study)	↑ Risk A-carrier	Borglykke et al., 2012 (103)
	rs5398	T/C	chr3: 17099804	Negative mood delusions	n_1 = German, n_2 = European American	n_1 = 927/2168, n_2 = 1247/1434	↑ Risk C-carrier	Meier et al., 2012 (104)
	rs1499821	A/G	chr3: 172207423	Negative mood delusions	n_1 = German, n_2 = European American	n_1 = 927/2168, n_2 = 1247/1434	↑ Risk G-carrier	Meier et al., 2012 (104)
	rs11924032	A/G	chr3: 172217793	Negative mood delusions	n_1 = German,, n_2 = European American	n_1 = 927/2168, n_2 = 1247/1434	↑ Risk G-carrier	Meier et al., 2012 (104)
	rs9875793	A/G	chr3: 170686573	Negative mood delusions, bipolar disorder	n_1 = German n_2 = European American	n_1 = 927/2168, n_2 = 1247/1434	↑ Risk G-carrier	Meier et al., 2012 (104)

(Continued)

TABLE 2 (*Continued*)

Gene	SNP	Allele, major/minor	Location	Disease	Population	Sample size, case/control, *n*	Findings	Study (reference)
	rs8192675	G/A	chr3: 171007094	Negative mood delusions	n_1 = German, n_2 = European American	n_1 = 927/2168, n_2 = 1247/1434	↑ Risk A-carrier	Meier et al., 2012 (104)
				Hypertension	n_1 = African American, n_2 = European American	n_1 = 167, n_2 = 237	↓ High-density lipoprotein A-carrier (n_2)	Le et al., 2013 (105)
SLC2A4	rs5417	C/A	chr17, 7281743	Obstructive sleep apnea syndrome	China	412/156	↑ Risk A-carrier	Yin et al., 2014 (106)
SLC2A5	rs5438	G/A	chr1: 9069561	Hypertension	n_1 = African American, n_2 = European American	n_1 = 167, n_2 = 237	↑ Serum uric acid GA genotype (n_2)	Le et al., 2013 (105)

[1] chr, chromosome; CVD, cardiovascular disease; SLC, solute carrier family; SNP, single-nucleotide polymorphism.

imbalance (23). As such, considering diabetes as a well-established risk factor for cardiovascular disease (CVD) in a study with 2383 incidence cases of CVD (fatal and nonfatal) (103), the contribution of 46 type 2 diabetes-related SNPs to CVD incidence was examined. Of the 46 genetic variants examined, the variant rs11920090 in *SLC2A2* was associated with incident CVD, independent of baseline diabetes status (103).

Cancer. Variants in DHA-GLUT genes have been proposed to have diverse effects on the relative risk of renal and prostate cancers; however, the overall studies are limited (96, 101), with no observed association in one study (109). In a study with 92 patients with renal cell carcinoma and 99 healthy controls (96), carriers of the minor allele rs3820589-T as well as heterozygotes for rs3754218-G/T in *SLC2A1* showed higher incidences of renal cancer. On the other hand, in a study with 6642 patients with prostate cancer (101) (participants in the Atherosclerosis Risk in Communities Study), SNP rs5400-G in *SLC2A2* was associated with a 24% lower cancer risk in Caucasians but not in African Americans. The authors suggest that, despite uncertainty about the mechanism involved in the observed association, *SLC2A2* may be involved in prostate cancer progression, with several reports linking several large-scale duplications on chromosome 3q, the region containing *SLC2A2*, with prostate cancer.

Psychological disorders. Variants in the *SLC2A2* gene were associated with bipolar disorder, which is a severe psychiatric condition with fundamental and distinctive alteration in emotion regulation and perception (104). In a study with 2174 patients with bipolar disorder and 3601 healthy controls (104), the minor alleles for several variants in *SLC2A2* (rs5398-C, rs1499821-G, rs8192675-A, rs11924032-G, rs9875793-G) were associated with higher susceptibility to the disease or its complications. The functions of ascorbate in the central nervous system and the brain have been extensively reviewed (110). Neurons have high amounts of oxidative metabolism, 10-fold higher rates than supporting glia, which make them particularly vulnerable to ascorbate deficiency (111, 112). The neuronal sensitivity to a low supply of ascorbate is most apparent in neurodegenerative disease conditions in which there is excess oxidant stress and a high oxidation rate of ascorbate to DHA (110). Radiotracer experiments have confirmed that DHA enters the brain and is converted to ascorbate (113). Therefore, in neurodegenerative diseases such as bipolar disorder, DHA-GLUT transporters, including SLC2A2, which is highly expressed in the brain, may play a key role to uptake of DHA, thus increasing cerebral ascorbate concentrations to counter the oxidative stress resulting from the disease.

Liver disease. Genetic variants in *SLC2A1* are observed to actively contribute to nonalcoholic fatty liver disease (NAFLD), independent of diabetes or obesity (97). In a

study of 520 patients with NAFLD and 521 healthy controls as well as 4414 individuals with type 2 diabetes and 4567 matched controls (97), genotypes rs4658-G/G and rs841856-T/T of *SLC2A1* showed an association with an increased risk of NAFLD but not of diabetes. In this study, gene expression analysis demonstrated a considerable downregulation of *SLC2A1* in the livers of patients with NAFLD. Moreover, in vitro silencing of *SLC2A1* resulted in increased oxidative stress and a higher lipid accumulation (97). SLC2A1 is involved in the DHA transport into mitochondria, resulting in mitochondrial vitamin C recycling and elevating protection against reactive oxygen species (97, 114). The mitochondrion has a key role in progression of NAFLD through impairing fatty liver homeostasis as well as inducing overproduction of reactive oxygen species and thus lipid peroxidation (95, 115). Variation in *SLC2A1* results in mitochondrial redox imbalance and hence could increase reactive oxygen species and regulate the proinflammatory environment at early stages of the disease (97).

Future Directions

Previously, observational studies have demonstrated that low vitamin C status increases the risk of many common chronic diseases. Today, genetic association studies on transporters of both vitamin C transport pathways support and expand on these observational findings. This review stresses the importance of considering and investigating genetic variations affecting overall status but also local tissue and cell concentrations of vitamin C to sustain health and prevent common complex diseases. As research progresses, it will be determined if human genetic variation on vitamin C transporters affects local or systemic pharmacokinetics. If pharmacokinetics is affected, recommendations will need to be adjusted for individuals or population subgroups of certain genotypes. This is apparent through the differential distributions of functional SNPs between African American and Caucasian individuals. Studies on variation in the genes coding different forms of vitamin C transporters are progressing, and the evidence could be incorporated into future dietary guidelines. However, the emerging evidence, as previously proposed by others (6, 42, 116), needs further replications, biological proof, and dietary intervention studies in targeted individuals carrying the specific variants to stand as valid diagnostic biomarkers. Moreover, the emerging fields of epigenetics and microbial analyses will contribute to the understanding of systematic interactions, and future studies will have to find a way to integrate genetics, epigenetics, and metagenomics data.

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