# Macular xanthophylls, lipoprotein-related genes, and age-related macular degeneration[1–4]

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**ABSTRACT**

Plant-based macular xanthophylls (MXs; lutein and zeaxanthin) and the lutein metabolite meso-zeaxanthin are the major constituents of macular pigment, a compound concentrated in retinal areas that are responsible for fine-feature visual sensation. There is an unmet need to examine the genetics of factors influencing regulatory mechanisms and metabolic fates of these 3 MXs because they are linked to processes implicated in the pathogenesis of age-related macular degeneration (AMD). In this work we provide an overview of evidence supporting a molecular basis for AMD-MX associations as they may relate to DNA sequence variation in AMD- and lipoprotein-related genes. We recognize a number of emerging research opportunities, barriers, knowledge gaps, and tools offering promise for meaningful investigation and inference in the field. Overviews on AMD- and high-density lipoprotein (HDL)–related genes encoding receptors, transporters, and enzymes affecting or affected by MXs are followed with information on localization of products from these genes to retinal cell types manifesting AMD-related pathophysiology. Evidence on the relation of each gene or gene product with retinal MX response to nutrient intake is discussed. This information is followed by a review of results from mechanistic studies testing gene-disease relations. We then present findings on relations of AMD with DNA sequence variants in MX-associated genes. Our conclusion is that AMD-associated DNA variants that influence the actions and metabolic fates of HDL system constituents should be examined further for concomitant influence on MX absorption, retinal tissue responses to MX intake, and the capacity to modify MX-associated factors and processes implicated in AMD pathogenesis. *Am J Clin Nutr* 2014;100(suppl):336S–46S.

## INTRODUCTION

Age-related macular degeneration (AMD)[5] is a common (1) and complex (2) disease of public health significance (3), manifesting sight-threatening pathology in the neural and vascular retina (4). The composition of the macula is notable for high concentrations of constituent plant-based xanthophyll carotenoids (lutein and zeaxanthin), their high-affinity binding proteins (5, 6), and the lutein metabolite meso-zeaxanthin (7). Among >600 naturally occurring carotenoids, 30–50 common dietary carotenoids, and 10–15 carotenoids commonly detected in serum, only lutein, zeaxanthin, and meso-zeaxanthin have been detected in appreciable quantities within the macula (reviewed in reference 8). Biochemical and biophysical properties of these macular xanthophylls (MXs), their metabolites, and cofactors have been implicated in protective capacities for >3 decades (9–17), and a number of large-scale human studies have yielded evidence for associations of AMD with the intake and status of lutein and zeaxanthin (18–25). A chronology of watershed events and publications addressing intake status–structure function axes in the AMD-MX field are shown in **Figure 1**. Events are classified in the figure by the nature of their design; those designated with the "Intake-Status" label examined the retinal response to MX intake; those with "Intake-/RCT-AMD" and "Status-AMD" designations are for respective investigations of dietary, nutrient supplement, or blood/macular pigment MX exposures on advanced AMD endpoints.

Primates are unable to synthesize lutein and zeaxanthin de novo and have developed the capacity for efficient retinal MX uptake (35, 81), transport (5, 6), and retention (47, 82–85). Genetic, dietary, and environmental factors influence aspects of these 3 processes, as shown by family-based studies (86, 87), biochemical analysis, and in vivo imaging of the retina (reviewed in reference 17). In addition to genetic influences on MX concentrations and distribution in retinal areas affected by AMD, reports on twins (88, 89) and first-degree relatives (90–92) have supported a genetic-basis for AMD (93). In the sections that follow we provide an overview on the molecular genetics of

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[5] Abbreviations used: ABCA1, ATP-binding cassette, subfamily A member 1; AMD, age-related macular degeneration; apo E, apolipoprotein E; CD36, cluster determinant 36; CETP, cholesteryl ester transfer protein; COX-2, cyclooxygenase-2; LPL, lipoprotein lipase; LXR, liver X receptor; MPOD, macular pigment optical density; MX, macular xanthophyll; PPAR-$\gamma$, peroxisome proliferator-activated receptor $\gamma$; RAR, retinoid A receptor; RPE, retinal pigment epithelium; RXR, retinoid X receptor; SNP, single-nucleotide polymorphism; SR-BI, scavenger receptor class B type I; VEGF, vascular endothelial growth factor; WT, wild-type.

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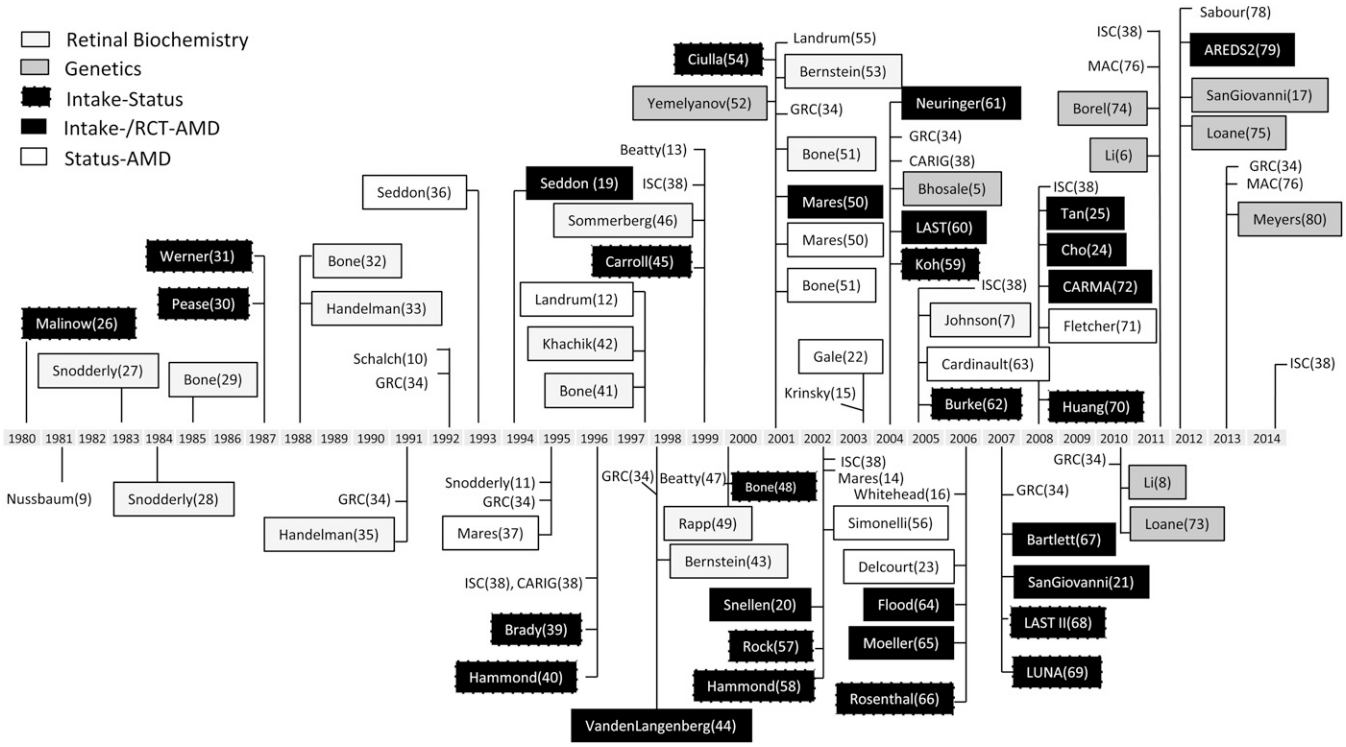



**FIGURE 1.** Timeline of selected events and publications devoted to investigation of intake status–structure function relations in the field of AMD-macular xanthophyll research. Numbers in parentheses correspond to references in this article. Publications and events not enclosed in boxes are for literature reviews and conferences, respectively. Events and publications are named and classified in shaded boxes by event type or study design. Labels for review articles and scientific meetings are not surrounded by boxes. Studies in the "Intake-Status" category were observational in nature and applied dietary intake measures to estimate nutrient exposure and in or ex vivo retinal xanthophyll status measures as endpoints. Studies in the "Intake-/RCT-AMD" category were observational or experimental in nature and applied dietary intake questionnaires or nutrient supplement interventions as exposures and clinical classifications of AMD as endpoints. Studies in the "Status-AMD" category were observational in nature and applied blood or in vivo retinal xanthophyll status measures as exposures and clinical classifications of AMD as endpoints. AMD, age-related macular degeneration; AREDS2, Age-Related Eye Disease Study 2; CARIG, Carotenoids Research Interactive Group Conference; CARMA, Carotenoids in Age-Related Maculopathy study; GRC, Gordon Research Conference; ISC, International Symposium on Carotenoids; LAST, Lutein Antioxidant Supplementation Trial; LUNA, LUtein Nutrition effects measured by Autofluorescence Study; MAC, Conference on Macular Carotenoids and AMD; RCT, randomized clinical trial.

AMD in relation to actions of MXs on factors and processes implicated in AMD pathogenesis.

## EXPANSION OF AN EMERGING CONCEPT

Large-scale genome-wide association studies (94, 95) have shown enrichment of AMD-related DNA sequence variants in genes encoding constituents of *1*) complement regulatory systems (95) and *2*) lipoprotein transport and metabolism systems (81, 95–98). Cholesterol (99, 100) and cholesterol metabolites (101) have been implicated in AMD pathogenesis due to their proinflammatory/immunoregulatory properties and presence in AMD-associated lesions. Sene et al (102) applied genetic and pharmacologic interventions influencing cholesterol efflux homeostasis to alter the severity of pathologic choroidal neovascularization (a hallmark of neovascular AMD) in mice; these authors acknowledged the complex nature of AMD-associated DNA variation in genes encoding proteins involved in cholesterol transport and metabolism, recognizing that allelic relations with advanced AMD do not always predict serum HDL or lipid status. When such observations are considered with the lack of evidence for protection of $\beta$-hydroxy-$\beta$-methylglutaryl coenzyme A reductase inhibitors (statins) against progression to advanced AMD (103, 104) and equivocal findings from large-scale observational studies on AMD endpoints examining dietary intake of cholesterol and saturated fat, it is clear that an expanded concept on the role of lipoprotein-related genes in AMD pathogenesis would offer valuable guidance for improving inquiry and inference in the field (17).

Findings on MX-lipoprotein relations may be a linchpin for inference on AMD-lipoprotein relations because MX uptake and transport is a facilitated process (105) involving many proteins that also act in cholesterol transport (77). The majority of circulating MXs are carried on HDL particles (106–108); as such, activity and distribution of lipoprotein constituents may influence the availability and accretion of MXs to the retina (77, 108, 109). The consequence of this condition can be considered in the context of central premises guiding AMD-MX research. These are as follows: *1*) MX concentration is amplified 1000- to 10,000-fold from the circulation to the healthy retina (15, 110) via active transport mechanisms involving specific binding proteins (5, 6), *2*) MXs are resident in retinal regions affected in AMD (46, 49), *3*) MXs show a capacity to act on processes implicated in AMD pathogenesis (reviewed in references 11, 15, and 17), and *4*) MX intake→MX status, MX status→AMD, MX intake→AMD relations have been observed in model systems and large-scale human studies (Figure 1 and Tables S1 and S2 under "Supplemental data" in the online issue). Variation in macular pigment optical density (MPOD; an in vivo measure of retinal MX status) has a hereditary component (86, 87, 111, 112). Meyers et al (80)

noted the polygenic nature of MPOD variation and commented on the significance of extant works attributing genetic contributions to ~70% of MPOD status (86) and ~30% of variation in MPOD change, as associated with oral supplementation of MXs (112).

## AMD-ASSOCIATED HDL-RELATED GENES AND PROTEINS AFFECTING MXs

AMD-associated polymorphisms in loci of genes encoding cholesteryl ester transfer protein (CETP); lipoprotein lipase (LPL); ATP-binding cassette, subfamily A member 1 (ABCA1); and hepatic lipase also yield variation in blood HDL-cholesterol concentrations (reviewed in reference 95). The observation that AMD-associated sequence variants exist in at least 3 other genes that encode proteins involved in HDL-resident systems [scavenger receptor class B type I (*SCARB1*), cluster determinant 36 (*CD36*), and apolipoprotein E (*APOE*)] supports an AMD-HDL nexus. In this work we discuss the confluence of evidence on a number of AMD-associated genes implicated in HDL transport and metabolism (94, 95, 113), retinal response to MX intake (73, 74, 80, 114), and alterations in the activity of MX-related molecular targets, regulatory mechanisms, and metabolic fate affecting retinal physiology (17). Our conclusion is that AMD-associated DNA variants that influence the actions and metabolic fates of HDL system constituents should be examined for concomitant influence on MX absorption, retinal tissue responses to MX intake, and the capacity to modify MX-related factors and processes implicated in AMD pathogenesis.

The subsections that follow begin with overviews on the state-of-science for AMD-associated and HDL-related genes encoding receptors, transporters, and enzymes affecting or affected by MXs, their metabolites, and cofactors. The overviews are followed with information on localization of the respective HDL-related proteins to retinal cell types manifesting AMD-related pathophysiology. Evidence on the relation of each gene or gene product with retinal MX response to intake is then presented. This information is followed by a review of findings from mechanistic studies designed to investigate retinal disease-gene relations. We then present findings on the relation of AMD and retinal MX status with DNA sequence variations in these HDL-related genes (**Table 1**). In the final section, we comment on the promise of this emerging evidence base for informing applied clinical research projects.

## HDL-RELATED GENES AND MX UPTAKE IN RETINA

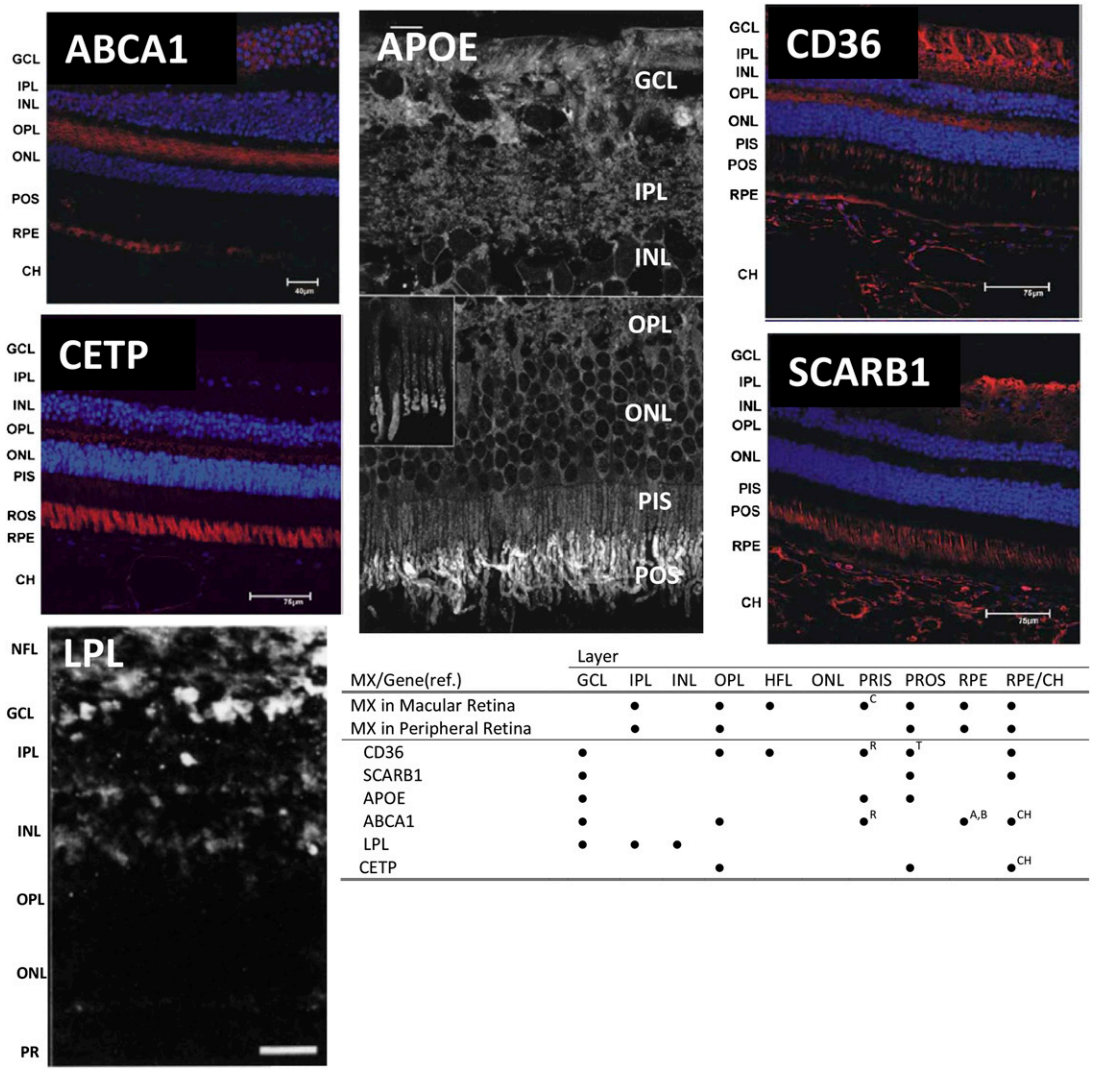
### *SCARB1*

The scavenger receptor class B type I (SR-BI), a cell surface glycoprotein of CD36 superfamily with high affinity to HDL and localized to the apical surface of the enterocyte, has been implicated in nonspecific binding and absorption of MXs at the intestinal brush border (115). SR-BI is encoded by *SCARB1* (12q24.31), a gene expressed in primary human retinal pigment epithelium (RPE) cells (116). SR-BI mRNA has been detected in human neural retina using reverse transcriptase–polymerase chain reaction (117). Immunohistochemical localization of the protein in monkey retina showed the strongest signal in retinal ganglion cells, outer segments of photoreceptor rods and cones, and the choriocapillaris (the vascular interface to the RPE and neural retina) (**Figure 2**). Equivocal evidence exists for strong expression of the protein in primate RPE. A specific SR-BI antibody-blocking technique and small interfering RNA on a differentiated human RPE–derived cell line (ARPE-19) showed that zeaxanthin uptake can be driven by an SR-BI–dependent process (118). The authors of the ARPE-19 study (118) discuss a gene-MX-disease link, pointing to a mutation in ninaD, an insect gene with high sequence identity to *SCARB1* that is associated with reduced carotenoid uptake, reduced zeaxanthin deposition, and blindness in *Drosophila* (119–121). The retinal ultrastructure of SR-BI$^{-/-}$ and wild-type (WT) mice manifested differences after a feeding regimen enriched in components carried on HDL (122). Relative to the WT mice, SR-BI$^{-/-}$ animals showed increased lipid inclusions and disorganization of photoreceptor outer segments and areas within the outer nuclear layer. Also, Bruch's membrane, a permeable 5-layer structure of basement membranes, collagen, and elastin existing between the choroid and RPE, was thickened in the SR-BI$^{-/-}$ mice and showed sparse sub-RPE deposits. The relevance to AMD is that altered flow of essential compounds across Bruch's membrane has been implicated in the progression to advanced forms of the disease. In addition to these changes, the choroid of the SR-BI$^{-/-}$ mice manifested abnormal distribution of collagen fibers and a vacuolization associated with local inflammation in the subretinal space (linked to the infiltration of macrophages); SR-BI$^{-/-}$ mice did not exhibit abnormal choroidal neovascularization. However,

**TABLE 1**
Genes and selected sequence variants associated with retinal status of MXs and AMD[1]

| | | Sequence variant (ref) | | |
|---|---|---|---|---|
| Symbol | HDL function | Retinal MX status | AMD association | Model system (ref) |
| *SCARB1* | LPB | rs10744182 (80) | rs5888 (97) | ARPE (118), mouse (122) |
| *CD36* | LPI | rs1761667 (74) | rs3173789/rs3211883 (130) | ARPE (118), mouse (126–128) |
| *ABCA1* | LPSBC | rs1929841 (80) | rs1883025 (81, 95) | hRPE (134), *WHAM* chick (106) |
| *APOE* | LPM | rs429358/rs7412 (73) | rs429358/rs7412 (113, 137) | Mouse (140) |
| *LPL* | LPM | — | rs12678919 (95) | Human (153) |
| *CETP* | LPT | — | rs1864163 (94) | Human (146) |
| *LIPC* | LPU | rs6078 (80) | rs920915 (94) | — |

[1] Associations were determined with logistic regression, examining the likelihood of having advanced AMD, relative to the distribution of specific nucleotide bases for each of the sequence variants listed. The list of sequence variants is not comprehensive (*see* References for complete list). Full names and additional details on genes can be found at http://www.ncbi.nlm.nih.gov/gene. An additional AMD-associated single-nucleotide polymorphism exists in *APOE* rs4420638 (94). AMD, age-related macular degeneration; ARPE, differentiated human retinal pigment epithelial–derived cell line; hRPE, human retinal pigment epithelial cells; LPB, lipoprotein binding; LPI, lipoprotein internalization; LPM, lipoprotein metabolism; LPSBC, lipoprotein secretion by (efflux from) cells; LPT, transfer of lipoproteins; LPU, lipoprotein uptake at the cell surface; MX, macular xanthophyll; ref, reference number.




| MX/Gene(ref.) | Layer GCL | IPL | INL | OPL | HFL | ONL | PRIS | PROS | RPE | RPE/CH |
|---|---|---|---|---|---|---|---|---|---|---|
| MX in Macular Retina | | ● | | ● | ● | | ●[C] | ● | ● | ● |
| MX in Peripheral Retina | | ● | | ● | | | | ● | ● | ● |
| CD36 | ● | | | ● | ● | | ●[R] | ●[T] | | ● |
| SCARB1 | ● | | | | | | | ● | | ● |
| APOE | ● | | | | | | ● | ● | | |
| ABCA1 | ● | | | ● | | | ●[R] | | ●[A,B] | ●[CH] |
| LPL | ● | ● | ● | | | | | | | |
| CETP | | | | ● | | | | ● | | ●[CH] |

**FIGURE 2.** Retinal localization of proteins involved in uptake, transport, and cleavage of MXs. Immunohistochemical localization studies in primate retina were reported by Tserentsoodol et al (117) for *ABCA1*, *CD36*, *CETP*, and *SCARB1*; by Anderson et al (152) for *APOE*; and by Casaroli-Marano et al (147) for *LPL*. For micrographs of *ABCA1*, *CD36*, *CETP*, and *SCARB1*, areas in red indicate regions of the respective MX-related protein localization. For *APOE* and *LPL*, lucent areas indicate protein localization. Reproduced with permission from references 117, 147, and 152. CH, retinal choroid layer; GCL, ganglion cell layer; HFL, Henle Fiber layer; INL, inner nuclear layer; IPL, inner plexiform layer (interneurons); MX, macular xanthophyll; NFL, nerve fiber layer; ONL, outer nuclear layer; OPL, outer plexiform layer; PR, photoreceptors; PRIS or PIS, photoreceptor inner segments; PROS, photoreceptor outer segments; PROS or POS, photoreceptor outer segments; ref., reference; RPE, retinal pigmented epithelium.

induction of vascular endothelial growth factor (VEGF; a molecule involved in retinal angiogenesis) expression in the outer nuclear layer of the SR-BI$^{-/-}$ mice was observed.

A locus in *SCARB1* (rs10744182) has been associated with alterations in MPOD within the Carotenoids in Age-related Eye Disease Study, a project involving 1585 women participating in the Women's Health Initiative Observational Study (80). An exonic sequence variant in *SCARB1* (rs5888) linked to lower SR-BI expression (123) has been associated with advanced AMD in a large-scale genotyping project in French- and US-based cohorts (97). We have reported relations of AMD with a common intronic variant (rs989892; $P = 0.010$) coinherited ($D' = 0.98$, $r^2 = 0.82$) with rs5888 and another single-nucleotide polymorphism (SNP; rs838878; $P = 0.007$) in complete linkage disequilibrium with an SNP (rs838884) proximal to the 3′ untranslated region of *SCARB1* (124).

## CD36

CD36 is a major glycoprotein that acts as a primary anti-angiogenic receptor of thrombospondin-1. CD36 binds long-chain fatty acids, collagen, anionic phospholipids, and oxidized LDL in macrophages. CD36 is involved in internalization of HDL and transport of oxidized LDL particles and may act in the transport of and/or as a regulator of fatty acid transport. In the retina, CD36 acts in phagocytosis of photoreceptor outer segments. CD36 is encoded by the *CD36* gene (7q11.2); the protein is localized in the primate retina within RPE, tips of rod outer segments, rod inner segments, the choriocapillaris, the outer plexiform layer, and in the ganglion cell layer (117) (Figure 2). In a study on human retina, the expression of *CD36* varied by >8-fold in the neural retina and by >20-fold in RPE between donors (125). During et al (118) did not detect MX transport actions of CD36 in their work on differentiated human RPE cells: a CD36-specific

antibody did not prevent accumulation of zeaxanthin in ARPE-19 cells after the addition of MX to the medium.

*CD36*$^{-/-}$ mice manifest a progressive age-related choroidal involution typically involving a 100–300% increase in the avascular area within the choriocapillaris (126). Progressive choroidal degeneration accompanies reduced cyclooxygenase-2 (*PTGS2*) and *VEGF* (126) expression. CD36 activating antibody stimulates *PTGS2* expression in RPE cell cultures, whereas CD36 deficiency was associated with inhibition of COX-2 and subsequent lack of VEGF response to outer segment or antibody stimulation in vitro (126). Picard et al (127) used *CD36*$^{-/-}$ and *CD36*$^{+/+}$ mice to show an age-related CD36-dependent process of deposition and clearance of subretinal deposits that bears similarity to those typically seen in AMD; in this study, *CD36*$^{-/-}$ animals developed basal laminar deposits. In a mouse model showing similar pathology (*ApoE*$^{-/-}$) to the *CD36*$^{-/-}$ model, the administration of a CD36 agonist inhibited the formation of pathologic subretinal deposits. CD36 may be linked to AMD-like retinal pathology in spontaneous hypertensive rats as well. These animals develop retinal and choroidal degeneration independent of hypertension (128). *CD36* mutations exist in some spontaneous hypertensive rat strains (129).

Borel et al (74) examined 5 sequence variants in *CD36* for the association of MPOD response to a 6-mo regimen of daily supplementation with a formula containing 10 mg lutein esters in a 30-person French cohort. A *CD36* locus (rs1761667) was associated with variation in macular status of MXs; persons homozygous for the major allele (G) had significantly higher MPOD than those carrying the minor allele (A). This SNP was tested by Meyers et al (80) and did not yield MPOD variations in their US-based cohort of women. Kondo et al (130) examined the allelic frequency of 19 SNPs resident in *CD36* for association with neovascular AMD in a Japanese cohort of 109 people with neovascular AMD and 182 unrelated controls. There was a 50% lower likelihood of having neovascular AMD among carriers of the minor allele for 2 intronic sequence variants in the gene (rs3173798 and rs3211883).

The central messages on *SCARB1* and *CD36* (HDL-related genes both expressed in retina and implicated in retinal uptake of intake-based MXs within model systems) are as follows: *1*) animal models applying gene deletions of either *SCARB1* or *CD36* manifest AMD-like pathology, *2*) DNA variation (in this case, SNPs) in *SCARB1* and *CD36* is associated with variation in MPOD in a number of human studies, and *3*) *SCARB1*-AMD relations have been reported in multiple cohorts.

## HDL-RELATED GENES AND MX TRANSPORT AND METABOLISM IN THE RETINA

### ABCA1

The ATP-binding cassette, subfamily A member 1 (ABCA1) protein, encoded by the *ABCA1* gene (9q31.1), is a member of the superfamily of ATP-binding cassette transporters. The protein acts as a major lipoprotein transporter and works with apolipoprotein A-I (*APOA1*) in the process of cholesterol and phospholipid metabolism as an efflux pump from tissue to nascent HDL. ABCA1 controls the intracellular transport and secretion of APOE and APOA1 (117). A mutation mapped to *ABCA1* exists in persons with Tangier disease [Online Mendelian Inheritance in Man (OMIM) 205400], an autosomal recessive disorder characterized by extremely reduced concentrations of plasma HDL, leading to tissue accumulation of cholesterol esters. Immunolocalization of ABCA1 in primate retina indicates that the highest concentrations of the protein are found in the macular ganglion cell layer, the MX-rich outer plexiform layer, and RPE (117). Within the polarized RPE cell, both basal (side of choroidal apposition) and apical (side of photoreceptor apposition) aspects showed specific ABCA1 staining (Figure 2).

Connor et al (106) applied an avian model expressing a sex-linked recessive mutation in *ABCA1* [the Wisconsin hypo $\alpha$ mutant (*WHAM*) chick] to show the critical role of HDL-mediated MX transport to the retina. The *WHAM* chick exhibits similar concentrations of VLDL and LDL to WT Leghorn chicks but shows a 90% reduction in HDL cholesterol. Hepatic accumulation of MXs in the *WHAM* chick was not appreciably different from that in the WT birds; however, differences were seen in plasma, heart, adipose, and retina. Repletion of all tissues except for retina was attained with a 1-mo lutein-rich feeding regimen. With the lutein-rich diet, the absolute concentration of retinal MXs remained 15-fold lower than those in the WT chicks. The *WHAM* mutation acts by inhibiting APOA1-mediated efflux of hydrophobic molecules from peripheral tissue to HDL. APOA1 is rapidly degraded when low in lipid content.

Lakkaraju et al (131) used immortalized human and bovine primary RPE cell cultures to show that activation of *ABCA1* by the peroxisome proliferator–activated receptor $\gamma$ (PPAR-$\gamma$) agonist pioglitazone and liver X receptor (LXR) agonist TO901317 is effective in hydrolyzing A2E, a quaternary amine and retinoid by-product of the visual cycle responsible for pathologic accumulation of free and esterified cholesterol in RPE cells. Blue-light exposure in RPE cells induces A2E to generate singlet oxygen that has the capacity to damage DNA and lead to apoptotic cell death (132); lutein, which is present in inner retinal layers, acts as a filter for blue light. The implications of these findings for AMD-MX research may not be readily apparent. Pioglitazone acts on PPAR-$\gamma$, which forms a bioactive heterodimer with the retinoid X receptor (RXR). RXR heterodimerizes with the retinoid A receptors (RARs). RXR heterodimerizes with PPAR-$\gamma$ and LXR; this process activates ABCA1, leading to A2E hydrolysis. Lutein is a ligand to the RARs and may thus influence the activation of the RAR-RXR-PPAR-$\gamma$-LXR complex (133). This putative relation ties the *ABCA1*-MX relation to a process implicated in AMD pathogenesis and raises the possibility that lutein (or a lutein metabolite) may activate *ABCA1* to influence A2E catabolism. Work by Matsumoto et al (133) indicates that $\beta$-cryptoxanthin (a mono-hydroxy xanthophyll with similar bonding structure and functional groups to MXs) was effective in activating *ABCA1*. Duncan et al (134) reported that exposure of human RPE cell cultures to glyburide, a nonspecific *ABCA1* inhibitor (also inhibiting *SCARB1*), prevents HDL-stimulated basal transport of photoreceptor-derived lipids implicated in AMD pathogenesis. These findings are intriguing, considering the MX-binding capacity of SCARB1, the role of *ABCA1* in MX transport, and the putative activation of ABCA1 by MXs via RARA and RARG.

Meyers et al (80) reported variations in MPOD related to allelic variants in the *ABCA1* SNP rs1929841; persons carrying the *CC* genotype showed a 20% lower value for MPOD than persons with *AA* or *AC* genotypes. Sequence variants in *ABCA1* have been associated with AMD in numerous large-scale genotyping projects (81, 95, 98, 124, 135, 136).

### Apolipoprotein E

Apolipoprotein E (apo E) is an apolipoprotein acting in lipid metabolism as a ligand to lipoprotein receptors and in response to injury within the central nervous system (137, 138). apo E is necessary for the normal catabolism of HDL, triglyceride-rich components of chylomicrons, and VLDL (73). SNPs in the *APOE* gene (19q13.2) are associated with increased plasma concentrations of cholesterol and triglycerides. DNA sequence variants in *APOE* have been a focus of work on AMD, because apo E is a component of drusen (retinal lipid deposits first evident in early AMD). In the retina, *APOE* is expressed primarily in astrocytes and Müller cells; it has been localized to Bruch's membrane, the RPE, and the photoreceptor outer segment layer (reviewed in reference 117) (Figure 2). MXs are transported in serum on apo E in HDL and LDL (73, 139).

Six-month-old $ApoE^{-/-}$ C57BL/6 mice fed standard laboratory feed pellets (9605/8; Harlan Teklad TRM) showed a 50% lower concentration of lutein in the neural retina, relative to WT animals of the same inbred strain fed the same diet. Zeaxanthin concentrations were unchanged (140). Retinal ultrastructure in the $ApoE^{-/-}$ mice was characterized by AMD-associated lesions, including severe basal laminar deposits/vacuolization and thickening of Bruch's membrane. Choroid-RPE homogenates of these animals showed 42% higher VEGF concentrations than those in WT mice, as analyzed by Western blots. Abnormal lipid accumulation in the RPE and Bruch's membrane in a transgenic mouse expressing the human *APOEε2* risk variant has been reported. Compared with WT mice, the *APOEε2* transgenic animals exhibited an overexpression of *VEGF* and basic fibroblast growth factor (*bFGF*). Dysregulation of *VEGF* and *bFGF* are central events in diseases characterized by pathologic retinal angiogenesis.

DNA variants in *APOE* are associated with MPOD concentrations. Loane et al (73) reported that persons carrying at least one *APOEε4* allele have higher MPOD values across the macula than did noncarriers. Meyers et al (80) did not observe MPOD variation with haplotypes of the SNPs (rs7142, rs429358) examined by Loane et al. The *APOE*-AMD relations reported by Souied et al (113) and Klaver et al (137) in 1998 were among the first gene-AMD associations published. Findings have been replicated numerous times (138, 141–145). An age-, sex-, and smoking-adjusted pooled analysis of 15 studies ($n$ = 21,160) confirmed the protective association of the *APOEε4* alleles and risk of the *APOEε2* alleles on late AMD (96). Our findings on rs405509 are similar to those of the pooled analysis. A large multicenter study incorporating data from >77,000 people identified advanced AMD associations with the presence of the A allele in rs4420638 (94).

### CETP

CETP is a secreted soluble protein that acts with ABCA1 in the transfer of cholesteryl esters between lipoproteins during reverse cholesterol transport; it is encoded by the *CETP* gene (16q21) and expressed in retina mainly within the photoreceptor outer segments and the outer plexiform layer (117). A study examining exchange of carotenoids between human VLDL and HDL (146) showed that CETP inhibitors significantly increased the proportion of lutein in HDL. To our knowledge. there are no studies using in vivo model systems to examine the role of CETP on health and disease of the retina or the actions of MXs.

Meyers et al (80) examined the influence of 3 intronic *CETP* SNPs (rs173539, rs3764261, and rs708272) on retinal MX status. In no case were these variants associated with MPOD. AMD-associated DNA sequence variants in *CETP* (rs173539, rs3764261, rs1864163) have been reported in numerous studies (94, 95, 135).

### LPL

LPL is a water-soluble enzyme that hydrolyzes triglycerides in lipoproteins and enables cellular uptake of chylomicron remnants, cholesterol-dense lipoproteins, and free fatty acids. The enzyme is encoded by the *LPL* gene (8p22) and requires the apolipoprotein C2 (encoded by the *APOC2* gene) as a cofactor in these processes. In the primate, the LPL protein is localized within the inner retinal layers (nerve fiber, ganglion cell, inner plexiform, and inner nuclear layers) and the choroid (147) (Figure 2). Within the choroid, it is most likely to be attached to the luminal epithelium. Carriers of an exonic sequence variant X447 (rs328) in *LPL* show a 20% reduction in serum MXs, relative to carriers of the S447S alleles (148). The authors of this work suggest that this stop polymorphism alters shedding of MXs from their surface positions on chylomicrons during lipolysis. To our knowledge, there are no reported relations of LPL sequence variants with MPOD, although one (rs328) was tested in this capacity by Meyers et al (80). A sequence variant in *LPL* known to influence HDL cholesterol (rs12678919) has been reported in association with advanced (95), but not early (136), AMD. We have reported on another variant (rs10099160) also associated with advanced AMD (124).

The state of evidence on HDL-related genes both expressed in retina and implicated in retinal transport of intake-based MXs within model systems indicates the following: *1*) animal models of *ABCA1* and *APOE* gene deletions yield substantial reductions in retinal lutein, and in the case of *APOE*, manifest aspects of AMD-like lesions; *2*) human MPOD has varied with DNA variants in *ABCA1* and *APOE* in some studies; and *3*) *ABCA1*-, *APOE*-, and *CETP*-AMD relations have been replicated in large cohorts. We also reported on a HDL-related gene (LPL) expressed in retina and implicated in MX release from its carrier protein. While LPL-AMD relationships have been reported for advanced forms of the disease, there is no current support for influence on human macular status of MXs.

## CONCLUSIONS AND FUTURE DIRECTIONS

MX concentrations in the retina are, in some cases, dependent on and modifiable by MX intake. In this report, we recognize converging fields of evidence that implicate the influence of genes encoding constituents of HDL metabolism and transport systems with both with retinal MX status (106, 108) and AMD risk (95). At least 4 of the 6 AMD-associated HDL-related genes we discussed are known to carry DNA polymorphisms linked to variation in MPOD, a measure of retinal MX concentration in the retinal area sustaining AMD pathology. Animal models characterized by gene knockouts in *SCARB1*, *ABCA1*, and *APOE* yielded both alterations in retinal MX amounts and AMD-like pathology. Extensive testing of sequence variants in the 6 reviewed genes for effects on MPOD has not been applied in diverse cohorts and it is necessary to replicate findings while accounting for predictors and correlates (*see* **Table 2**) of MPOD status. Future studies should be

**TABLE 2**
Factors associated with advanced AMD and macular pigment optical density[1]

| Factor | AMD relation | Direction of MX-MPOD relation |
|---|---|---|
| Older age | Harm | ↓ (86, 154–157); ↔ (54, 62, 80, 158, 159) |
| Female | Harm | ↓ (40, 157); ↔ (54, 62, 156, 160, 161) |
| White race | Harm | ↓ (161) |
| Obesity/high BMI | Harm | ↓ (58, 60, 62, 80, 155, 162) |
| History of smoking | Harm | ↓ (157, 163); ↔(54, 161) |
| Circulating MX concentrations | *See* Table S1 under "Supplemental data" in the online supplement | ↑ (40, 48, 54, 62, 80, 155, 164–166); ↓ (167) |
| MX dietary intake | *See* Table S2 under "Supplemental data" in the online supplement | ↑ AMD-free (54, 62, 80, 82, 162, 168, 169); ↔ (82)<br>↑ Elderly (170) |
| MX supplement use | Suggestive benefit | ↑ AMD-free (83, 171–175)<br>↑ Elderly (59, 60, 69, 156, 162, 168, 176, 177); ↔ (69) |

[1] AMD, age-related macular degeneration; MPOD, macular pigment optical density; MX, diet-based macular xanthophylls (lutein + zeaxanthin); ↑, increase; ↔, no change; ↓, decrease.

designed with the provisions from a number of expert reviews that offer insightful commentary on strengths and limitations of in vivo imaging modalities for AMD-MX research (110, 149).

Neovascular AMD has been associated consistently with lower reported intakes of lutein + zeaxanthin (Supplemental Table S2 under "Supplemental data" in the online issue). We believe that this is the endpoint on which gene-MPOD studies are most likely to yield informative results. A recent work combining data from >77,000 people has shown neovascular AMD-*ABCA1* and -*CETP* relations (94). The AMD-associated SNPs in these genes (and SNPs coinherited with these) should be examined for influence on MPOD response to MX intake. Many proteins encoded by AMD-associated HDL-related genes act together; as such, it is essential to evaluate gene-gene relations for both MPOD and AMD endpoints. Epistasis (gene-gene interactions) for AMD- and MPOD-related SNPs should be examined within and between genes. The first AMD-*APOE* relations reported (113, 137) were based on allele combinations from 2 independent SNPs; this may be the case with other gene-based effect modifiers of AMD risk.

Diet influences the expression of *CD36* (150); to our knowledge, the other genes discussed above have not been tested for this capacity, and such information would aid in inference on retinal response to MX intake. The interindividual variation in *CD36* expression within the RPE is formidable, with an up to a 20-fold difference between donor eyes analyzed by Zheng et al (125).

Cholesterol efflux is important for preventing cytotoxic oxysterol production in the retina (101). Actions of ABCA1 appear to influence this process, and there is a link here with pathologic choroidal neovascularization (102). Oxidative degradation products of MXs exist in the retina (42), and we suspect that ABCA1 may also work in efflux of these compounds. The issue may be germane for AMD prevention because some oxidative degradation products of lutein have been shown to damage DNA of an immortalized RPE cell line in a dose- and time-dependent manner (151). An important opportunity now exists to examine the influence of ABCA1 on the clearance of oxidized xanthophylls from retinal cells.

In summary, a more-thorough investigation of AMD- and HDL-associated loci for their putative actions in the intake status–structure function axis in AMD-MX relations is reasonable given the following: *1*) the joint actions of lipoprotein-related genes in cholesterol and MX transport and metabolism and *2*) the biological plausibility of cholesterol and MXs and their metabolites for influencing processes implicated in AMD pathogenesis.

The authors' responsibilities were as follows—JPS and MN: conceived and designed the study; EK, MN, and JPS: wrote the manuscript and contributed meaningful commentary on all concepts addressed; and JPS: had primary responsibility for final content. All of the authors read and approved the final manuscript. None of the authors declared a conflict of interest.

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