Macular xanthophylls, lipoprotein-related genes, and age-related macular degeneration¹–⁴

Euna Koo, Martha Neuringer, and John Paul SanGiovanni

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.  

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 constitutive 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-zeaxanthine 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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⁵Abbreviations 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-γ, peroxisome proliferator-activated receptor γ; RAR, retinoid A receptor; 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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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/AMD, MX status/AMD, and 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.

### Table 1

<table>
<thead>
<tr>
<th>Symbol</th>
<th>HDL function</th>
<th>Retinal MX status</th>
<th>AMD association</th>
<th>Model system (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCARB1</td>
<td>LPB</td>
<td>rs10744182 (80)</td>
<td>rs5888 (97)</td>
<td>ARPE (118), mouse (122)</td>
</tr>
<tr>
<td>CD36</td>
<td>LPI</td>
<td>rs1761667 (74)</td>
<td>rs3173789/rs3211883 (130)</td>
<td>ARPE (118), mouse (126–128)</td>
</tr>
<tr>
<td>ABCA1</td>
<td>LPSBC</td>
<td>rs1929841 (80)</td>
<td>rs1883025 (81, 95)</td>
<td>hRPE (134), WHAM chick (106)</td>
</tr>
<tr>
<td>APOE</td>
<td>LPM</td>
<td>rs429358/rs7412 (73)</td>
<td>rs429358/rs7412 (113, 137)</td>
<td>Mouse (140)</td>
</tr>
<tr>
<td>LPL</td>
<td>LPM</td>
<td>—</td>
<td>rs12678919 (95)</td>
<td>Human (153)</td>
</tr>
<tr>
<td>CETP</td>
<td>LPT</td>
<td>rs1864163 (94)</td>
<td>rs920915 (94)</td>
<td>Human (146)</td>
</tr>
<tr>
<td>LIPC</td>
<td>LPU</td>
<td>rs60078 (80)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

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](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; LFB, 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.
induction of vascular endothelial growth factor (VEGF; a molecule involved in retinal angiogenesis) expression in the outer nuclear layer of the SR-BI

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; \( P = 0.010 \)) co-inherited (\( D' = 0.98, r^2 = 0.82 \)) 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 (rs1761607) 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 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).

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 α 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 γ (PPAR-γ) agonist pioglitazone and liver X receptor (LXR) agonist T0901317 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-γ, which forms a bioactive heterodimer with the retinoid X receptor (RXR). RXR heterodimerizes with the retinoid A receptors (RARs). RXR heterodimerizes with PPAR-γ and LXR; this process activates ABCA1, leading to A2E hydrolysis. Lutein is a ligand to the RXRs and may thus influence the activation of the RAR-RXR-PPAR-γ-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 β-cryptoxanthin (a mono-hydroxy xanthophyll with similar binding structure and functional groups to MXs) was effective in activating ABCA1. Duncan et al (134) reported that exposure of human RPE cells 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<sup>e<sub>e</sub></sup><sup>_−/−<sub>−</sub></sup> 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<sup>e<sub>e</sub></sup><sup>_−/−<sub>−</sub></sup> 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 APOE<sub>2</sub> risk variant has been reported. Compared with WT mice, the APOE<sub>2</sub> 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 APOE<sub>e<sub>e</sub></sub><sub>4</sub> 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 associations 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 APOE<sub>e<sub>e</sub></sub><sub>4</sub> alleles and risk of the APOE<sub>e<sub>e</sub></sub><sub>2</sub> 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 SCARBI, 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

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

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

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