Hans Journal of Food and Nutrition Science 食品与营养科学, 2016, 5(2), 37-44
Published Online May 2016 in Hans. http://www.hanspub.org/journal/hjfns
http://dx.doi.org/10.12677/hjfns.2016.52006

Hans汉斯

The Advance of Research on the Role of Lipids on the Biological Utilization of Lutein

Xue Huang, Wei Ying, Xianrong Xu*

Department of Prevention, School of Medicine, Hangzhou Normal University, Hangzhou Zhejiang
Email: *xuxianrong1984@163.com

Received: Apr. 28th, 2016; accepted: May 17th, 2016; published: May 20th, 2016

Abstract

Lutein is a fat-soluble carotenoid present in various kinds of food, such as green leafy vegetables and eggs. The utilization of lutein in human body, including digestion, absorption, transport and metabolism, is associated with lipids. The digestion and absorption of lutein from food require the participation of fat. Both the amount and quality of dietary fat could influence the bioavailability of lutein. In circulation, lutein is transported in serum with lipoprotein. The percentage distribution of lutein varies among different lipoproteins, and serum cholesterol level could influence its transport efficiency. Furthermore, the lipid receptors, lipid-related hormone and gene play an important role on the tissue utilization of lutein. In this article, we reviewed the roles of lipids in the biological utilization of lutein in human body and trying to provide some beneficial information on the dietary supplement of luteinin population.

Keywords

Lutein, Dietary Fat, HDL, SR-BI, ApoE

叶黄素生物利用与脂类相关性研究进展

黄　雪，应　威，徐贤荣*

杭州师范大学医学院预防医学系，浙江　杭州
Email: *xuxianrong1984@163.com

*通讯作者。

文章引用: 黄雪, 应威, 徐贤荣. 叶黄素生物利用与脂类相关性研究进展[J]. 食品与营养科学, 2016, 5(2): 37-44.
http://dx.doi.org/10.12677/hjfns.2016.52006

收稿日期：2016年4月28日；录用日期：2016年5月17日；发布日期：2016年5月20日

摘　要

叶黄素是一种脂溶性类胡萝卜素，广泛存在于绿叶蔬菜、鸡蛋等食物中。其在人体中的整个生物利用过程，包括消化、吸收、运输、代谢等过程均与脂类有密切关系。膳食叶黄素的消化吸收需要多种脂类参与，膳食脂肪的质与量均影响其生物利用度。在循环中，叶黄素需要与载脂蛋白一起在血液中运输。其在不同载脂蛋白中的分配比例有很大的差异，血浆胆固醇种类和含量均可能影响其转运效率。此外，脂类相关受体，基因和激素在叶黄素的组织利用过程中发挥重要作用。本文通过综述脂类在叶黄素人体生物利用中的作用，拟为叶黄素应用于人群干预提供有益信息。

关键词

叶黄素，膳食脂肪，高密度脂蛋白，SR-BI，ApoE

1. 引言

叶黄素是一种脂溶性类胡萝卜素，在深色绿叶蔬菜、鸡蛋、玉米及花椰菜中含量丰富。尽管人群膳食中类胡萝卜素含量高达 30~50 种，但只有 10~15 种在血清中能够检测到，而在视网膜上仅存在叶黄素、玉米黄素和内消旋玉米黄素[1]。人体对叶黄素选择性摄取的确切机制及其特异性转运途径一直是营养学研究的重点。

多项流行病学研究表明，膳食叶黄素摄入量与老年黄斑变性(age-related macular degeneration, AMD) [2]、动脉粥样硬化(atherosclerosis, AS) [3]、阿尔茨海默病(alzheimer's disease, AD) [4]等慢性退行性疾病患病风险负相关，但临床干预研究却没有发现其对 AMD、AD 具有显著的防护效应。其可能原因为人群基因和敏感性的差异影响了研究的结果。研究发现脂类及其相关激素、基因在叶黄素的吸收、消化和利用中均扮演重要的角色[5]-[7]，对于叶黄素从食物中释放，血浆转运及视网膜摄取和利用十分重要，其变异可能会影响人体叶黄素补充的效果。本文将对脂质及其基因在叶黄素吸收、转运、利用中的作用进行综述，拟为叶黄素和脂类相关的研究提供有益信息。

2. 叶黄素消化、吸收与脂类

食物中的叶黄素，通常与蛋白质结合，储存在食物基质中，在消化过程中难以释放。在烹饪过程中，加入一定量的油脂，能够有效促进叶黄素的溶出和释放。在动物实验中发现，膳食脂肪含量从 0%增加到 6%过程中，血清膳食叶黄素代谢产物不断增高，提示在 6%的浓度范围内，叶黄素生物利用率随脂肪的含量增加而增加[8]。存在黄曲霉毒素污染的情况下，油脂对叶黄素生物利用率的促进效应将受到影响，当脂肪含量较低时表现尤为明显。就脂肪种类而言，不同脂肪酸对叶黄素生物利用率的促进效应大小依次为油酸 > 亚麻酸 > 豆蔻酸 > 硬脂酸。日常生活使用的油脂中，橄榄油、花生油、葵花籽油均能促进叶黄素的吸收，其中橄榄油效率最高，其可能原因为橄榄油富含油酸[5]。系统研究显示，膳食脂肪的量及其来源均能影响叶黄素的吸收[6]。人群研究则显示，叶黄素的吸收与甘油三酯含量丰富的脂蛋白密切相关[7]。

脂类与叶黄素在肠道内的扩散密切相关。肠道内的脂类经胆汁乳化和胰液消化后，会形成微胶粒，其成分包括胆酸、胆固醇、溶血卵磷脂和单酰基甘油。微胶粒的形成是叶黄素在肠道内扩散的关键。尽

管叶黄素极性并非最强，但其主要结构依然是由疏水共轭烯烃组成，在人体温度条件下呈固态而非液态，在亲水的肠道中扩散非常困难。因此，叶黄素需要溶解于脂类中，形成微胶粒在肠道内扩散[9]。升高温度、降低 ph 值以及去除可溶性的蛋白和变性膜蛋白将有利于叶黄素等类胡萝卜素掺入油脂中[10]。叶黄素的扩散和溶解效率显著影响其生物活性，对于其在上皮细胞中的吸收非常关键。

肠道微胶粒中脂类的量及成分同样影响肠道上皮细胞对叶黄素的吸收。研究发现，存在溶血卵磷脂的情况下将会增加 Caco-2 细胞对类胡萝卜素的摄取，而卵磷脂将会抑制其吸收[11]。动物实验也发现，叶黄素的吸收与卵磷脂的种类与含量有关。一次给予卵磷脂会抑制叶黄的吸收，而多次给予卵磷脂则促进其在肠道内的吸收。溶血卵磷脂则能够促进其吸收，增加叶黄素在肝脏中的含量[12]，表明卵磷脂需在肠道内水解为溶血卵磷脂后方能发挥作用[13]。采用磷脂与叶黄素混合，制成乳化制剂后，将大大增加叶黄素吸收率和生物活性，与普通制剂相比，可增加约 4.6 倍[14]。富含脂类的鳄梨或鳄梨油能够促进叶黄素的吸收，使洋葱中的叶黄素吸收量增加 5.1 倍[15]。蛋黄是叶黄素的良好来源，每天摄入 1.5 个蛋黄可增加人体叶黄素水平而不会升高血脂[16]，鸡蛋与其他蔬菜一起摄入，能够增加其他食物来源叶黄素的吸收率[17]，提示卵磷脂在叶黄素吸收中的重要作用。

脂类也是影响叶黄素转运进入肠上皮细胞的重要影响因素。类胡萝卜素从微胶粒转运到肠道细胞主要以简单扩散的方式进行，沿着浓度梯度通过细胞膜。体外实验发现，当类胡萝卜素溶解到微胶粒中后，与人肠上皮 Caco-2 细胞相互孵育，类胡萝卜素的疏水性与类胡萝卜素被肠道摄取之间呈现正相关。这些研究结果表明，类胡萝卜素可能通过简单扩散机制进入肠上皮细胞，因为疏水性物质比极性物质通过细胞膜的能力更强[11]。然而，相比较而言，除了以简单扩散方式运输以外，叶黄素可能通过特定的脂类转运通道进行，如与清道夫受体 1 (scavenger receptor class B type 1, SR-BI)结合。体外研究表明，应用化学手段和抗体阻断 SR-BI 通道后，其叶黄素吸收率分别下降 57%和 30%，提示该途径在叶黄素转运过程中的重要作用[18]。采用降脂药物能够显著降低 β-胡萝卜素的吸收率，而对叶黄素的吸收影响并不明显[19]，进一步表明叶黄素存在特异的转运通道。

3. 血浆载脂蛋白与叶黄素转运

叶黄素为脂溶性类胡萝卜素，在血液循环中需经在载脂蛋白中运输。低密度脂蛋白胆固醇(LDL-C)和高密度脂蛋白胆固醇(HDL-C)为两种与叶黄素转运密切相关的载脂蛋白，叶黄素在两者中分配比例不均，HDL-C：LDL-C 两者之比约为 3:1。人群研究发现，膳食类胡萝卜素中 52%叶黄素和 44%的玉米黄素由 HDL-C 转运，22%由 LDL-C 转运；而 β 胡萝卜素、番茄红素则 50%~70%经 LDL-C 转运，20%~25%由 HDL-C 转运[20]。在动物实验中发现，在体内缺乏 HDL-C 的情况下，血浆和视网膜叶黄素水平仅分别为对照的 9%和 6%。采用高叶黄素含量膳食补充后，尽管血浆叶黄素浓度大大增加，但视网膜叶黄素水平仅为对照的 6% [21]。这项研究结果表明，叶黄素从血浆项视网膜转运过程中主要依靠 HDL-C 进行。采用降脂药物辛伐他丁等降脂药物干预人群后，可引起血浆总胆固醇，LDL-C，oxLDL-C 和 C-反应蛋白水平的下降，同时伴随着血浆叶黄素水平下降。但调整血脂后，血浆叶黄素反而呈上升状态，提示辛伐他丁等降脂药物并不会影响人体叶黄素的利用效率[22]。采用植物甾烷醇干预轻度高血脂的人群后，血清血浆总的胆固醇和 LDL-C 浓度显著下降，而并不影响血浆叶黄素水平。这些研究表明，血浆叶黄素主要通过高密度脂蛋白胆固醇进行运输，常规的降血脂方法并不会影响叶黄素在人体中的吸收与利用。

此外，研究显示，叶黄素在运输过程中对血浆胆固醇的氧化修饰和机体炎症状态均存在影响。摄入阿月混子(开心果)、蛋黄等富含叶黄素的食物能够改善高血脂患者体内氧化应激状态，减少氧化型低密度脂蛋白胆固醇(oxLDL)水平[23]，增加 LDL-C 粒子的尺寸[24]。血清叶黄素可抑制 LDL-C 共轭双烯烃的形成，减少其氧化修饰。由于氧化型低密度脂蛋白是动脉粥样硬化的始动因子，LDL-C 粒子的大小是其

致动脉粥样硬化能力的重要特性，叶黄素在运输过程中，可通过以上的作用，发挥防护人体动脉粥样硬化的效用。

4. 叶黄素视网膜利用与脂类

叶黄素在人体内发挥多种生物学功能，其中最为重要的为其能够在视网膜上选择性浓集，参与构成黄斑色素(Macular Pigment, MP)。多项大型的人群研究显示，叶黄素的摄入量及人体水平与老年黄斑变性(AMD)的发病风险相关。老年黄斑变性是一种不可逆的致盲性眼病，在我国 50 岁以上人群中发病率高达 5%，严重危害老年人生活质量。大规模的 GWS 研究表明，AMD 患者中与脂类代谢和转运相关的基因位点存在变异[25]，提示脂类代谢相关基因可能会影响视网膜对叶黄素的摄取和利用。同时，研究发现视网膜黄斑色素密度(Macular pigment optical density，MPOD)具有遗传性[26] [27]，基因决定了人群 MPOD70%的变异度和 30%口服补充叶黄素引起的 MPOD 变化[28]。这些研究结果均表明，与脂类代谢相关的基因的变异，可能会影响叶黄素在体内的吸收，从而影响 AMD 的预防与治疗效果。

研究发现与 HDL-C 相关的基因在 AMD 的发病中发挥重要功能，主要的基因包括清道夫受体 B 家族 I 型(SCARB1)，决定簇 36(CD36)，载脂蛋白 E(APOE)相关的基因。

清道夫受体 B 类 I 亚型(SR-BI)，一种细胞表面 CD36 超家族的糖蛋白，对 HDL 具有很强的结合作用。在 AREDS 研究中发现 SR-BI 基因位点(rs10744182)与 MPOD 中的黄斑色素水平改变相关[29]。另外一项研究表明，SR-BI 基因位点(rs5888)变异将导致 SR-BI 表达减少[30]，同时增加人群中 AMD 的发病风险(OR = 2.9, 95% CI:1.6-5.3) [31]。同时，在 CAREDS 研究中发现，SR-BI 基因 AMD 发病风险相关，并且与血清及视网膜中叶黄素浓度相关[32]。在健康人群中的研究结果表明，人体服用叶黄素后血清叶黄素浓度的增加幅度与基因密切相关，包括 SR-BI 基因[33]。动物及体外实验研究结果也表明，SR-BI 与玉米黄素吸收密切相关，SR-BI 敲除小鼠视网膜出现脂质沉积、视感受器外界及内核层结构紊乱，同时出现 Bruch 膜的增厚[34]。此外，SR-BI-/-小鼠的脉络膜中胶原纤维的异常分布加剧，脉络膜下局部炎症水平增加(与巨噬细胞进入相关)。尽管 SR-BI$^{-/-}$小鼠并不表现出脉络膜下新生血管形成，但视网膜外核层中血管内皮细胞生长因子(VEGF)出现表达增加[34]。这些特征与人体重 AMD 的病理特征十分类似，提示 SR-BI 基因在黄斑色素的转运及 AMD 的发病中具有重要作用。

此外，研究发现 CD36 基因也可能是与视网膜上黄斑色素集聚密切相关的脂类代谢调控基因。CD36 是一种糖蛋白，参与 HDL-C 入胞和氧化型 LDL-C 的转运过程，并可能对脂肪酸转运具有调控作用。尽管研究发现，CD36 与叶黄素的视网膜转运关联并不显著，但基因敲除动物中，脉络膜年龄相关性退化显著加剧，脉络膜血管层的无血管区域可出现 100%~300%的增厚，提示其参与 AMD 过程。体外研究发现，CD36 参与叶黄素的摄取，阻断该受体显著减少脂肪组织对叶黄素的摄取能力[35]。在蚕中开展的研究发现，CD36 家族中的特定亚型对于叶黄素结构具有特异性的识别作用[36]。Borel 等在一个队列研究中发现，CD36 基因的一个位点(rs1761667)与黄斑色素密度相关[37]。Kondo 等发现，在 19 个与新生血管型 AMD 相关的 CD36 基因位点中，携带入 rs3173798 和 rs3211883 基因位点的人群与其他人群相比，疾病风险下降 50% [38]。

载脂蛋白 E (apolipoprotein E, apoE)是脂类代谢过程中的一种重要脂蛋白，对于 HDL-C、乳糜微粒及极低密度脂蛋白(VLDL)的正常分解代谢至关重要。apoE 为构成 LDL-C 和 HDL-C 的必要组分，可与叶黄素相结合，携带其在血液中运输。APOE 基因的 DNA 多态性对 AMD 的发生发展十分重要，因为 apoE 是视网膜玻璃疣的组分之一。在敲除 APOE 基因的 C57BL/6 小鼠中，给予标准饲料喂养后，与野生型小鼠相比，神经视网膜中叶黄素浓度下降 50%，但玉米黄素浓度无变化。人群研究也发现，APOE 基因多态性与 MPOD 浓度密切相关。Loane 等发现，携带 APOEε4 等位基因的个体与不携带的个体相比，MPOD

值显著增高[39]。Adams 等通过病例对照研究发现，APOEε2 等位基因增加 AMD 发病风险，并与吸烟状态相关，在当前吸烟者中 APOEε4 等位基因为早期 AMD 的保护性因素[40]。一项包含了 15 项研究的 Meta 分析结果表明，在调整了年龄、性别、吸烟状态后发现，APOEε4 等位基因为 AMD 保护性因素，而 APOEε2 等位基因则为 AMD 的危险因素[41]，但在中国汉族人群中却没有发现 APOE 基因 rs2075650 位点与进展型 AMD 的相关性[42]。另外一项多中心、大型的研究发现，在 APOErs4420638 位点中，A 等位基因是进展型 AMD 的危险因素[25]。

上述研究结果表明，人体脂蛋白及其受体的表达情况和多态性将会影响视网膜对叶黄素的摄取与利用，从而影响 AMD 等疾病的发生和发展。深入研究脂质相关基因在人体叶黄素利用和代谢过程中的作用对于制定叶黄素个性化的人群干预方案，预防疾病发生发展具有重要意义。

5. 研究结论和展望

综上所述，脂类在叶黄素的消化、吸收、转运及利用和代谢过程中发挥重要作用。人类脂类相关基因的变异将会影响叶黄素整个生物利用过程及其对疾病的预防和治疗效果。因此，进一步明确脂类及其相关受体和基因在叶黄素利用过程中得到作用，将有助于制定个性化的叶黄素补充方案，优化叶黄素剂型，改善人群干预效果。

基金项目

浙江省新苗人才计划项目(2015R423062)；浙江省自然基金青年基金项目(LQ15H260002)；国家自然基金面上项目(81273063)。

参考文献 (References)

[1] Bernstein, P.S., Li, B., Vachali, P.P., Gorusupudi, A., Shyam, R., Henriksen, B.S. and Nolan, J.M. (2016) Lutein, Zeaxanthin, and Meso-Zeaxanthin: The Basic and Clinical Science Underlying Carotenoid-Based Nutritional Interventions against Ocular Disease. *Progress in Retinal and Eye Research*, **50**, 34-66. http://dx.doi.org/10.1016/j.preteyeres.2015.10.003

[2] Scripsema, N.K., Hu, D.N. and Rosen, R.B. (2015) Lutein, Zeaxanthin, and Meso-Zeaxanthin in the Clinical Management of Eye Disease. *Journal of Ophthalmology*, **2015**, 865179.

[3] Dwyer, J.H., Navab, M., Dwyer, K.M., Hassan, K., Sun, P., Shircore, A., Hama-Levy, S., Hough, G., Wang, X., Drake, T., Merz, C.N. and Fogelman, A.M. (2001) Oxygenated Carotenoid Lutein and Progression of Early Atherosclerosis: The Los Angeles Atherosclerosis Study. *Circulation*, **103**, 2922-2927. http://dx.doi.org/10.1161/01.CIR.103.24.2922

[4] Min, J.Y. and Min, K.B. (2014) Serum Lycopene, Lutein and Zeaxanthin, and the Risk of Alzheimer's Disease Mortality in Older Adults. *Dementia and Geriatric Cognitive Disorders*, **37**, 246-256. http://dx.doi.org/10.1159/000356486

[5] Lakshminarayana, R., Raju, M., Krishnakantha, T.P. and Baskaran, V. (2007) Lutein and Zeaxanthin in Leafy Greens and Their Bioavailability: Olive Oil Influences the Absorption of Dietary Lutein and Its Accumulation in Adult Rats. *Journal of Agricultural and Food Chemistry*, **55**, 6395-400. http://dx.doi.org/10.1021/jf070482z

[6] Goltz, S.R., Campbell, W.W., Chitchumroonchokchai, C., Failla, M.L. and Ferruzzi, M.G. (2012) Meal Triacylglycerol Profile Modulates Postprandial Absorption of Carotenoids in Humans. *Molecular Nutrition & Food Research*, **56**, 866-877. http://dx.doi.org/10.1002/mnfr.201100687

[7] O'Neill, M.E. and Thurnham, D.I. (1998) Intestinal Absorption of Beta-Carotene, Lycopene and Lutein in Men and Women Following a Standard Meal: Response Curves in the Triacylglycerol-Rich Lipoprotein Fraction. *British Journal of Nutrition*, **79**, 149-159. http://dx.doi.org/10.1079/BJN19980026

[8] Schaeffer, J.L. and Hamilton, P.B. (1990) Effect of Dietary Lipid on Lutein Metabolism during Aflatoxicosis in Young Broiler Chickens. *Poultry Science*, **69**, 53-59. http://dx.doi.org/10.3382/ps.0690053

[9] Rich, G.T., Faulks, R.M., Wickham, M.S. and Fillery-Travis, A. (2003) Solubilization of Carotenoids from Carrot Juice and Spinach in Lipid Phases: II. Modeling the Duodenal Environment. *Lipids*, **38**, 947-956. http://dx.doi.org/10.1007/s11745-003-1148-z

[10] Rich, G.T., Bailey, A.L., Faulks, R.M., Parker, M.L., Wickham, M.S. and Fillery-Travis, A. (2003) Solubilization of

Carotenoids from Carrot Juice and Spinach in Lipid Phases: I. Modeling the Gastric Lumen. *Lipids*, **38**, 933-945. http://dx.doi.org/10.1007/s11745-003-1147-0

[11] Sugawara, T., Kushiro, M., Zhang, H., Nara, E., Ono, H. and Nagao, A. (2001) Lysophosphatidylcholine Enhances Carotenoid Uptake from Mixed Micelles by Caco-2 Human Intestinal Cells. *Journal of Nutrition*, **131**, 2921-2927.

[12] Baskaran, V., Sugawara, T. and Nagao, A. (2003) Phospholipids Affect the Intestinal Absorption of Carotenoids in Mice. *Lipids*, **38**, 705-711. http://dx.doi.org/10.1007/s11745-003-1118-5

[13] Lakshminarayana, R., Raju, M., Krishnakantha, T.P. and Baskaran, V. (2006) Enhanced Lutein Bioavailability by Lyso-Phosphatidylcholine in Rats. *Molecular and Cellular Biochemistry*, **281**, 103-110. http://dx.doi.org/10.1007/s11010-006-1337-3

[14] Shanmugam, S., Park, J.H., Kim, K.S., Piao, Z.Z., Yong, C.S., Choi, H.G. and Woo, J.S. (2011) Enhanced Bioavailability and Retinal Accumulation of Lutein from Self-Emulsifying Phospholipid Suspension (SEPS). *International Journal of Pharmaceutics*, **412**, 99-105. http://dx.doi.org/10.1016/j.ijpharm.2011.04.015

[15] Unlu, N.Z., Bohn, T., Clinton, S.K. and Schwartz, S.J. (2005) Carotenoid Absorption from Salad and Salsa by Humans Is Enhanced by the Addition of Avocado or Avocado Oil. *Journal of Nutrition*, **135**, 431-436.

[16] van der Made, S.M., Kelly, E.R., Berendschot, T.T., Kijlstra, A., Lutjohann, D. and Plat, J. (2014) Consuming a Buttermilk Drink Containing Lutein-Enriched Egg Yolk Daily for 1 Year Increased Plasma Lutein but Did Not Affect Serum Lipid or Lipoprotein Concentrations in Adults with Early Signs of Age-Related Macular Degeneration. *The Journal of Nutrition*, **144**, 1370-1377. http://dx.doi.org/10.3945/jn.114.195503

[17] Kim, J.E., Gordon, S.L., Ferruzzi, M.G. and Campbell, W.W. (2015) Effects of Egg Consumption on Carotenoid Absorption from Co-Consumed, Raw Vegetables. *The American Journal of Clinical Nutrition*, **102**, 75-83. http://dx.doi.org/10.3945/ajcn.115.111062

[18] Reboul, E., Abou, L., Mikail, C., Ghiringhelli, O., Andre, M., Portugal, H., Jourdheuil-Rahmani, D., Amiot, M.J., Lairon, D. and Borel, P. (2005) Lutein Transport by Caco-2 TC-7 Cells Occurs Partly by a Facilitated Process Involving the Scavenger Receptor Class B Type I (SR-BI). *Biochemical Journal*, **387**, 455-461. http://dx.doi.org/10.1042/BJ20040554

[19] O'Sullivan, L., Aisling, S.A. and O'Brien, N.M. (2009) Investigation of Beta-Carotene and Lutein Transport in Caco-2 Cells: Carotenoid-Carotenoid Interactions and Transport Inhibition by Ezetimibe. *International Journal for Vitamin and Nutrition Research*, **79**, 337-347. http://dx.doi.org/10.1024/0300-9831.79.56.337

[20] Wang, W., Connor, S.L., Johnson, E.J., Klein, M.L., Hughes, S. and Connor, W.E. (2007) Effect of Dietary Lutein and Zeaxanthin on Plasma Carotenoids and Their Transport in Lipoproteins in Age-Related Macular Degeneration. *The American Journal of Clinical Nutrition*, **85**, 762-769.

[21] Connor, W.E., Duell, P.B., Kean, R. and Wang, Y. (2007) The Prime Role of HDL to Transport Lutein into the Retina: Evidence from HDL-Deficient WHAM Chicks Having a Mutant ABCA1 Transporter. *Investigative Ophthalmology & Visual Science*, **48**, 4226-4231. http://dx.doi.org/10.1167/iovs.06-1275

[22] Ryden, M., Leanderson, P., Kastbom, K.O. and Jonasson, L. (2012) Effects of Simvastatin on Carotenoid Status in Plasma. *Nutrition, Metabolism and Cardiovascular Diseases*, **22**, 66-71. http://dx.doi.org/10.1016/j.numecd.2010.04.009

[23] Kay, C.D., Gebauer, S.K., West, S.G. and Kris-Etherton, P.M. (2010) Pistachios Increase Serum Antioxidants and Lower Serum Oxidized-LDL in Hypercholesterolemic Adults. *The Journal of Nutrition*, **140**, 1093-1098. http://dx.doi.org/10.3945/jn.109.117366

[24] Mutungi, G., Waters, D., Ratliff, J., Puglisi, M., Clark, R.M., Volek, J.S. and Fernandez, M.L. (2010) Eggs Distinctly Modulate Plasma Carotenoid and Lipoprotein Subclasses in Adult Men Following a Carbohydrate-Restricted Diet. *The Journal of Nutritional Biochemistry*, **21**, 261-267. http://dx.doi.org/10.1016/j.jnutbio.2008.12.011

[25] Fritsche, L.G., Chen, W., Schu, M., Yaspan, B.L., Yu, Y., Thorleifsson, G., Zack, D.J., Arakawa, S., Cipriani, V., Ripke, S., Igo Jr., R.P., Buitendijk, G.H., Sim, X., Weeks, D.E., Guymer, R.H., Merriam, J.E., Francis, P.J., Hannum, G., Agarwal, A., Armbrecht, A.M., Audo, I., Aung, T., Barile, G.R., Benchaboune, M., Bird, A.C., Bishop, P.N., Branham, K.E., Brooks, M., Brucker, A.J., Cade, W.H., Cain, M.S., Campochiaro, P.A., Chan, C.C., Cheng, C.Y., Chew, E.Y., Chin, K.A., Chowers, I., Clayton, D.G., Cojocaru, R., Conley, Y.P., Cornes, B.K., Daly, M.J., Dhillon, B., Edwards, A.O., Evangelou, E., Fagerness, J., Ferreyra, H.A., Friedman, J.S., Geirsdottir, A., George, R.J., Gieger, C., Gupta, N., Hagstrom, S.A., Harding, S.P., Haritoglou, C., Heckenlively, J.R., Holz, F.G., Hughes, G., Ioannidis, J.P., Ishibashi, T., Joseph, P., Jun, G., Kamatani, Y., Katsanis, N., C.N.K., Khan, J.C., Kim, I.K., Kiyohara, Y., Klein, B.E., Klein, R., Kovach, J.L., Kozak, I., Lee, C.J., Lee, K.E., Lichtner, P., Lotery, A.J., Meitinger, T., Mitchell, P., Mohand-Said, S., Moore, A.T., Morgan, D.J., Morrison, M.A., Myers, C.E., Naj, A.C., Nakamura, Y., Okada, Y., Orlin, A., Ortube, M.C., Othman, M.I., Pappas, C., Park, K.H., Pauer, G.J., Peachey, N.S., Poch, O., Priya, R.R., Reynolds, R., Richardson, A.J., Ripp, R., Rudolph, G., Ryu, E., *et al.* (2013) Seven New Loci Associated with Age-Related Macular Degeneration. *Nature Genetics*, **45**, 433-439. http://dx.doi.org/10.1038/ng.2578

[26] Tariq, A., Mahroo, O.A., Williams, K.M., Liew, S.H., Beatty, S., Gilbert, C.E., Van Kuijk, F. J. and Hammond, C.J. (2014) The Heritability of the Ring-Like Distribution of Macular Pigment Assessed in a Twin Study. *Investigative Ophthalmology & Visual Science*, **55**, 2214-2219. http://dx.doi.org/10.1167/iovs.13-13829

[27] Liew, S.H., Gilbert, C.E., Spector, T.D., Mellerio, J., Marshall, J., van Kuijk, F.J., Beatty, S., Fitzke, F. and Hammond, C.J. (2005) Heritability of Macular Pigment: A Twin Study. *Investigative Ophthalmology & Visual Science*, **46**, 4430-4436. http://dx.doi.org/10.1167/iovs.05-0519

[28] Hammond, C.J., Liew, S.H., Van Kuijk, F.J., Beatty, S., Nolan, J.M., Spector, T.D. and Gilbert, C.E. (2012) The Heritability of Macular Response to Supplemental Lutein and Zeaxanthin: A Classic Twin Study. *Investigative Ophthalmology & Visual Science*, **53**, 4963-4968. http://dx.doi.org/10.1167/iovs.12-9618

[29] Meyers, K.J., Johnson, E.J., Bernstein, P.S., Iyengar, S.K., Engelman, C.D., Karki, C.K., Liu, Z., Igo Jr., R.P., Truitt, B., Klein, M.L., Snodderly, D.M., Blodi, B.A., Gehrs, K.M., Sarto, G.E., Wallace, R.B., Robinson, J., LeBlanc, E.S., Hageman, G., Tinker, L. and Mares, J.A. (2013) Genetic Determinants of Macular Pigments in Women of the Carotenoids in Age-Related Eye Disease Study. *Investigative Ophthalmology & Visual Science*, **54**, 2333-2345. http://dx.doi.org/10.1167/iovs.12-10867

[30] Constantineau, J., Greason, E., West, M., Filbin, M., Kieft, J.S., Carletti, M.Z., Christenson, L.K. and Rodriguez, A. (2010) A Synonymous Variant in Scavenger Receptor, Class B, Type I Gene Is Associated with Lower SR-BI Protein Expression and Function. *Atherosclerosis*, **210**, 177-182. http://dx.doi.org/10.1016/j.atherosclerosis.2009.11.029

[31] Zerbib, J., Seddon, J.M., Richard, F., Reynolds, R., Leveziel, N., Benlian, P., Borel, P., Feingold, J., Munnich, A., Soubrane, G., Kaplan, J., Rozet, J.M. and Souied, E.H. (2009) rs5888 Variant of *SCARB*1 Gene Is a Possible Susceptibility Factor for Age-Related Macular Degeneration. *PLoS ONE*, **4**, e7341. http://dx.doi.org/10.1371/journal.pone.0007341

[32] Meyers, K.J., Mares, J.A., Igo Jr., R.P., Truitt, B., Liu, Z., Millen, A.E., Klein, M., Johnson, E.J., Engelman, C.D., Karki, C.K., Blodi, B., Gehrs, K., Tinker, L., Wallace, R., Robinson, J., LeBlanc, E.S., Sarto, G., Bernstein, P.S., SanGiovanni, J.P. and Iyengar, S.K. (2014) Genetic Evidence for Role of Carotenoids in Age-Related Macular Degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS). *Investigative Ophthalmology & Visual Science*, **55**, 587-599. http://dx.doi.org/10.1167/iovs.13-13216

[33] Borel, P., Desmarchelier, C., Nowicki, M., Bott, R., Morange, S. and Lesavre, N. (2014) Interindividual Variability of Lutein Bioavailability in Healthy Men: Characterization, Genetic Variants Involved, and Relation with Fasting Plasma Lutein Concentration. *The American Journal of Clinical Nutrition*, **100**, 168-175. http://dx.doi.org/10.3945/ajcn.114.085720

[34] Provost, A.C., Vede, L., Bigot, K., Keller, N., Tailleux, A., Jais, J.P., Savoldelli, M., Ameqrane, I., Lacassagne, E., Legeais, J.M., Staels, B., Menasche, M., Mallat, Z., Behar-Cohen, F. and Abitbol, M. (2009) Morphologic and Electroretinographic Phenotype of SR-BI Knockout Mice after a Long-Term Atherogenic Diet. *Investigative Ophthalmology & Visual Science*, **50**, 3931-3942. http://dx.doi.org/10.1167/iovs.08-2527

[35] Moussa, M., Gouranton, E., Gleize, B., Yazidi, C.E., Niot, I., Besnard, P., Borel, P. and Landrier, J.F. (2011) CD36 Is Involved in Lycopene and Lutein Uptake by Adipocytes and Adipose Tissue Cultures. *Molecular Nutrition & Food Research*, **55**, 578-584. http://dx.doi.org/10.1002/mnfr.201000399

[36] Tsuchida, K. and Sakudoh, T. (2015) Recent Progress in Molecular Genetic Studies on the Carotenoid Transport System Using Cocoon-Color Mutants of the Silkworm. *Archives of Biochemistry and Biophysics*, **572**, 151-157. http://dx.doi.org/10.1016/j.abb.2014.12.029

[37] Borel, P., de Edelenyi, F.S., Vincent-Baudry, S., Malezet-Desmoulin, C., Margotat, A., Lyan, B., Gorrand, J.M., Meunier, N., Drouault-Holowacz, S. and Bieuvelet, S. (2011) Genetic Variants in BCMO1 and CD36 Are Associated with Plasma Lutein Concentrations and Macular Pigment Optical Density in Humans. *Annals of Medicine*, **43**, 47-59. http://dx.doi.org/10.3109/07853890.2010.531757

[38] Kondo, N., Honda, S., Kuno, S. and Negi, A. (2009) Positive Association of Common Variants in CD36 with Neovascular Age-Related Macular Degeneration. *Aging* (*Albany NY*), **1**, 266-274. http://dx.doi.org/10.18632/aging.100006

[39] Loane, E., McKay, G.J., Nolan, J.M. and Beatty, S. (2010) Apolipoprotein E Genotype Is Associated with Macular Pigment Optical Density. *Investigative Ophthalmology & Visual Science*, **51**, 2636-2643. http://dx.doi.org/10.1167/iovs.09-4397

[40] Adams, M.K., Simpson, J.A., Richardson, A.J., English, D.R., Aung, K.Z., Makeyeva, G.A., Guymer, R.H., Giles, G.G., Hopper, J., Robman, L.D. and Baird, P.N. (2012) Apolipoprotein E Gene Associations in Age-Related Macular Degeneration: The Melbourne Collaborative Cohort Study. *American Journal of Epidemiology*, **175**, 511-518. http://dx.doi.org/10.1093/aje/kwr329

[41] McKay, G.J., Patterson, C.C., Chakravarthy, U., Dasari, S., Klaver, C.C., Vingerling, J.R., Ho, L., de Jong, P.T., Fletcher, A.E., Young, I.S., Seland, J.H., Rahu, M., Soubrane, G., Tomazzoli, L., Topouzis, F., Vioque, J., Hingorani, A.D., Sofat, R., Dean, M., Sawitzke, J., Seddon, J.M., Peter, I., Webster, A.R., Moore, A.T., Yates, J.R., Cipriani, V.,

Fritsche, L.G., Weber, B.H., Keilhauer, C.N., Lotery, A.J., Ennis, S., Klein, M.L., Francis, P.J., Stambolian, D., Orlin, A., Gorin, M.B., Weeks, D.E., Kuo, C.L., Swaroop, A., Othman, M., Kanda, A., Chen, W., Abecasis, G.R., Wright, A.F., Hayward, C., Baird, P.N., Guymer, R.H., Attia, J., Thakkinstian, A. and Silvestri, G. (2011) Evidence of Association of APOE with Age-Related Macular Degeneration: A Pooled Analysis of 15 Studies. *Human Mutation*, **32**, 1407-1416. http://dx.doi.org/10.1002/humu.21577

[42] Kan, M., Weng, X., Wang, T., Liu, F., Ye, J., Zhang, H., Xu, M., Zhou, D., He, L. and Liu, Y. (2015) No Evidence of Association between Variant rs2075650 in Lipid Metabolism-Related Locus APOE/TOMM40 and Advanced Age-Related Macular Degeneration in Han Chinese Population. *Experimental Biology and Medicine* (*Maywood*), **240**, 230-234. http://dx.doi.org/10.1177/1535370214553770