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Application of Nutrigenomics in Eye Health

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Running title : Nutrigenomics in eye health

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ABSTRACT :

This paper reviews recent findings on the implication of nutritional and genetic factors in age-related eye diseases: age-related macular degeneration (AMD, a degenerative disease of the retina) and cataract (opacification of the lens).

Because of direct exposure to light, the eye is particularly sensitive to oxidative stress. Antioxidants, such as vitamin E, C or zinc clearly have a protective effect in AMD and probably in cataract. In addition, two carotenoids, lutein and zeaxanthin may play a more specific role in the eye: they accumulate in the retina, where they form the macular pigment, and in the lens. Their role is probably to filter out phototoxic blue light and to quench singlet oxygen. Finally, docosahexaenoic acid (DHA, an ω-3 polyunsaturated fatty acid) is particularly important for the retina, where it exerts structural, functional and protective actions.

Besides, these diseases are strongly influenced by genetics, as demonstrated by familial and twin studies. The apolipoliprotein E4 allele is associated with a reduced risk of AMD, while an association of AMD with Complement Factor H polymorphism has recently been demonstrated.

Nutrigenomics, by studying the interactions between genetic variability and nutritional factors represent a new challenge in order to account for interindividual variations in disease susceptibility. Such potential interactions are presented.

There is growing evidence for major implication of nutrition and genetics in the aetiology of age-related eye diseases (age-related macular degeneration (AMD), cataract and glaucoma), which are the major causes of blindness worldwide [1]. However, the interest in nutritional risk factors for these diseases and the identification of the associated genes is still recent. As such, the interactions between nutritional and genetic factors have not yet been studied. Some hypotheses can be drawn from the known interactions between nutrition and specific biological mechanisms.

AMD is a degeneration of the central retina, known as the macula. It is associated with extracellular deposits forming yellow spots on the retina, named drusen. These deposits are probably related to decreased degradation and elimination of cellular components during the process of renewal of the photoreceptors. Late-stage AMD is characterized by the development of choroidal neovascularization (exsudative AMD) or by the disappearance of photoreceptors and underlying retinal pigment epithelium (atrophic AMD). Cataract is an opacification of the lens, which focuses the light on the retina. Glaucoma is a neuropathy of the optic nerve, leading to gradual loss of peripheric visual field and leading finally to total blindness. The prevalence of these diseases increases sharply with age. They are multifactorial, with both genetic and environmental factors. Some risk factors have been clearly identified, such as apolipoprotein E, Complement Factor H polymorphisms and smoking for AMD ; light exposure, smoking, diabetes and oral corticosteroid use for cataract; and intraocular pressure (IOP) for glaucoma.

Oxidative stress plays an important role in eye ageing . The retina is particularly susceptible to oxidative stress because, on the one hand, of its high content of easily peroxidizable long-

chain polyunsaturated fatty acids (PUFA), in particular docosahexaenoic acid (DHA, an ω-3 PUFA) [2]. Its susceptibility is also due, on the other hand, to the high level of in-site ROS production, due in particular to light exposure and high metabolic activity [2]. Opacification of the lens is due to oxidation of the structural proteins of the lens, inducing their aggregation [3].

Three types of nutritional factors offer or may offer protection against eye ageing: antioxidants, such as vitamin C and E or zinc; lutein and zeaxanthin, two carotenoids which accumulate specifically in the retina and lens; ω-3 PUFA, and in particular DHA, which have important structural and protective functions in the retina. Initial epidemiological observations, showing that high vitamin E plasma levels may protect against AMD [4], have been confirmed by a large randomised clinical trial performed in the United States. In this study, performed on nearly 5,000 subjects, supplementation for 6 years with high doses of antioxidants (vitamin E, C and beta-carotene) and zinc significantly reduced by 34 % the risk of developing advanced AMD in subjects with early AMD [5]. In parallel, numerous studies have evidenced a 20% to 50 % reduction of the risk for nuclear cataract (one of the subtypes of cataract, based on the localization of the opacities) in subjects with high dietary intakes or high plasma concentrations of vitamin C and vitamin E [6]. However, in several large randomized clinical trials, the risk for cataract was not reduced with antioxidant supplementation [7-9]. Only the REACT study showed an effect of supplementation with vitamin C, E and beta-carotene on cortical cataract [10]

A more recent research domain regards the role of two carotenoids, lutein and zeaxanthin, for the protection of the retina and the lens. These carotenoids accumulate in the macula, where they are known as the macular pigment [11], and they are also the only carotenoids found in the lens [12]. Besides their anti-oxidant properties, they probably act as a filter against the

phototoxic effects of blue light [11]. Two clinical studies have shown that eyes at risk of AMD have lower density of the macular pigment [13,14]. Epidemiological studies also suggest that a high intake or high plasma levels of lutein and zeaxanthin could protect against AMD and cataract [15-22]. Although all these studies have yielded results in the direction of a protective effect, they were not always significant due to small sample sizes. A small randomized study showed improvement of near visual acuity with lutein supplementation, in subjects with atrophic AMD [23].

Finally, DHA is a major component of the photoreceptors, where it exerts structural (membrane fluidity, interaction with rhodopsin) and protective functions [24]. The protective functions include the systemic anti-inflammatory, anti-angiogenic and anti-apoptotic functions, but also specific actions such as increase in lysosomial acid lipase, leading to increased lipid degradation in the retinal pigment epithelium [24]. Few epidemiological studies are available concerning the associations of AMD with fat. In two cross-sectional studies [25,26], weekly fish consumption, which is the main source of DHA, was associated with a 50 to 60 % reduction in risk for AMD, after multivariate adjustment. In the Eye Disease Case Control Study, a high dietary intake of ω6 PUFA was significantly associated with a 2 fold increased risk for exsudative AMD, after multivariate adjustment. Consumption of ω3 PUFA was significantly associated with a 31 % reduction in risk for AMD after age and gender adjustment, but not after multivariate adjustment. Results were similar for fish intake [27]. In a pooled analysis of the Nurses' Health and Health Professionals' cohort studies, subjects consuming fish had a reduced risk of developing AMD, after multivariate adjustment [28]. High DHA intakes were also associated with a reduced risk of AMD, whereas, surprisingly, high intakes in alpha-linolenic acid were associated with an increased risk. Finally, in a study on 261 patients, initially presenting early AMD, total fat intake, and more specifically, intakes of vegetable fat, MUFA and PUFA (mainly due to ω6

PUFA) were positively associated with the risk of developing late AMD [29]. Fish intake was associated with a decreased risk of late AMD only in those with a low dietary intake of linoleic acid. Globally, these results suggest that excessive intake of ω-6 PUFA, and low intake of ω-3 PUFA may be associated with increased risk for AMD. Recent studies suggest that ω-3 and ω-6 PUFA may also be implicated in other eye conditions, such as glaucoma [30] or dry eye syndrome [31].

Beside the nutritional dimension of AMD and cataract, these diseases are strongly influenced by genetics, as demonstrated by familial and twin studies [32-37]. The apolipoliprotein E4 allele is associated with a 50% reduced risk of AMD [38-43]. Recently, three independent teams simultaneously demonstrated a significant association between the Y402H polymorphism of the complement factor H (CFH) gene and AMD in North American subjects [44-46], immediately followed by three other corroborating papers in North American populations [47-49], one study from France [50] and one from Iceland [51]. Y402H is a common variant, with about 30 % of the general populations bearing the minor (C) allele (at least in Caucasians). In these studies, subjects heterozygotes for C have a 2.5 to 4 fold increased risk for AMD, while subjects homozygotes for C have a 3.5 to 7.5- fold increased risk for AMD [50]. Complement Factor H is a key regulator of the complement system of innate immunity [52]. Histologic observations are consistent with inappropriate activation of the complement system in AMD [53].

Finally, several linkage studies show an association of AMD with chromosome 10p26 [54]. With respect to cataract, a recent linkage study identified a major locus on chromosome 6p12-q12 for cortical cataract [55]

Interactions between genetic variability and nutritional factors represent a new challenge in order to account for interindividual variations in disease susceptibility. While some properties of nutritional factors rely on direct effects (such as antioxidant properties, or structural functions of DHA), many nutritional factors also have cellular effects and interact with genes. Nutrigenomics in eye health therefore potentially include all genes implicated in the metabolism or activities of nutritional factors associated with eye diseases, and all nutrients implicated in the activities of genes associated with eye diseases, thereby opening a vast research domain. Since the genes identified to date are from the lipid metabolism (apolipoprotein E) and innate immunity (Complement Factor H), interactions with lipids and antioxidants are particularly expected. Recently, in an animal model, combination of the apoE4 allele with high-fat diet induced modifications of the retina that mimic the pathology associated with human AMD [56]. It is also well known that PUFA and zinc interact with genes of inflammation and immunity [57,58]. Whether the risk for AMD may be modified by interactions of PUFA and zinc with the CFH gene remains to be determined. Zinc has recently been implicated in the binding of CFH with its target complement factor (C3b) [59]. In the field of carotenoids, Pi isoform of the glutathione S-transferase (GSTP1) has recently been identified as a membrane-bound binding protein for zeaxanthin in the macula [60]. The same authors have shown that GSTP1 and zeaxanthin act in synergy for the prevention of membrane lipid peroxidation [61]. Interestingly, GSTP1 polymorphism was associated with the risk of cortical cataract in an Estonian population [62]. These data globally suggest that interaction of the GSTP1 gene with dietary zeaxanthin may be implicated in AMD and cataract.

In conclusion, age-related eye diseases, which are the major causes of blindness worldwide, are strongly influenced by nutrition and genetics. Nutrigenomics, by studying the interactions of nutritional and genetic factors, opens a new research avenue. Understanding the interaction

of nutrients with genes may help target susceptible individuals for nutritional prevention of eye diseases.

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