

## Risk Factors for AMD

AMD is a complex disease and is thought to have several different causes. A number of genetic and environmental risk factors have been associated with the development of AMD. Non-modifiable risk factors are age (increasing), race (white European), family history & genetics (first degree relative). Modifiable risk factors are smoking, diet, physical activity and hypertension.

### **Non-modifiable risk factors:**

- **Age:** The strongest non-modifiable risk factor for developing AMD is age. AMD prevalence increases exponentially with increasing age. A recent European study found that prevalence rates were 3.5% in people aged 55–59 yrs rising to 17.6% in those aged ≥85 yrs.<sup>1,2</sup>
- **White race:** Studies indicate ethnic variability in the prevalence of AMD, with higher rates observed in individuals of white European descent, compared with individuals of Asian, African, or Hispanic descent.<sup>3,4</sup>
- **Family history:** People with a family history of AMD are more likely to develop the condition themselves; this risk is increased 2 to 3-fold by having an affected first-degree relative. Studies in twins have reported concordance rates ranging from 46–71%, with higher rates observed in monozygotic (identical) vs. dizygotic (non-identical) twins. Overall, these familial studies suggest that genetic factors play a substantial role in the aetiology of AMD.<sup>5,6,7</sup>
- **Genetics:** Identification of genetic factors associated with the pathogenesis of AMD is an important area of ongoing research. Genetic testing does not yet generally play a role in the routine screening for AMD, or in the risk stratification of people diagnosed with the condition, however as introduction of genetic testing is rolled out across the world, it is anticipated that a much deeper understanding of the genetic factors associated with increased risk for development of AMD will be elucidated. Large genome-wide association studies have so far identified 34 genes associated with the risk of developing of AMD, however, only a small number of these genes in fact appear to have a major impact on AMD.

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<sup>1</sup> Colijn JM, Buitendijk GHS, Prokofyeva E, Alves D, Cachulo ML, Khawaja AP, *et al.* Prevalence of Age-Related Macular Degeneration in Europe: The Past and the Future. *Ophthalmology*. 2017.

<sup>2</sup> Rudnicka AR, Kapetanakis VV, Jarrar Z, Wathern AK, Wormald R, Fletcher AE, *et al.* Incidence of Late-Stage Age-Related Macular Degeneration in American Whites: Systematic Review and Meta-analysis. *American journal of ophthalmology*. 2015;160(1): 85-93 e83.

<sup>3</sup> Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, Wong TY. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *The Lancet Global health*. 2014;2(2): e106-116.

<sup>4</sup> Klein R, Klein BE, Knudtson MD, Wong TY, Cotch MF, Liu K, *et al.* Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the multi-ethnic study of atherosclerosis. *Ophthalmology*. 2006;113(3): 373-380.

<sup>5</sup> Cho E, Hung S, Willett WC, Spiegelman D, Rimm EB, Seddon JM, *et al.* Prospective study of dietary fat and the risk of age-related macular degeneration. *The American journal of clinical nutrition*. 2001;73(2): 209-218.

<sup>6</sup> Seddon JM, Cote J, Rosner B. Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake. *Archives of ophthalmology*. 2003;121(12): 1728-1737.

<sup>7</sup> Cooke Bailey JN, Hoffman JD, Sardell RJ, Scott WK, Pericak-Vance MA, Haines JL. The Application of Genetic Risk Scores in Age-Related Macular Degeneration: A Review. *Journal of clinical medicine*. 2016;5(3).

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A large risk effect has been reported for genetic variants that disrupt genes in the complement pathway, which is responsible for regulation of inflammation.<sup>8,9,10</sup> It should be noted that the presence of these genes does not mean that one will inevitably develop AMD, rather one is at higher risk of developing AMD.

### Modifiable risk factors:

- **Smoking:** The principal modifiable risk factor for AMD development and progression is smoking. Population-based studies have shown that smokers have a 2- to 4-fold increased risk for developing AMD, compared with non-smokers.<sup>11,12</sup>
- **Diet:** There is some evidence that a poor quality diet (either low in carotenoids or other antioxidants, or high in fat) may be associated with an increased risk of developing AMD.<sup>5,6,13,14</sup> Eating foods rich in antioxidants such as lutein, zeaxanthin, omega-3 fatty acids, beta carotene, vitamin C, vitamin E and zinc, may slow the progression or reduce the risk of AMD.
- **Physical activity:** A recent meta-analysis of nine studies reported that physical activity may reduce the risk of the onset and progression of AMD.<sup>15</sup>
- **Hypertension:** A number of studies have associated hypertension (high-blood pressure) as a risk factor for developing AMD.<sup>16,17</sup>

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<sup>8</sup> Fritsche LG, Igl W, Bailey JN, Grassmann F, Sengupta S, Bragg-Gresham JL, *et al.* A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nature genetics.* 2016;48(2): 134-143.

<sup>9</sup> Kumaramanickavel G. Age-Related Macular Degeneration: Genetics and Biology. *Asia-Pacific journal of ophthalmology.* 2016;5(4): 229-235.

<sup>10</sup> Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The Pathophysiology of Geographic Atrophy Secondary to Age-Related Macular Degeneration and the Complement Pathway as a Therapeutic Target. *Retina.* 2017;37(5): 819-835.

<sup>11</sup> Velilla S, Garcia-Medina JJ, Garcia-Layana A, Dolz-Marco R, Pons-Vazquez S, Pinazo-Duran MD, *et al.* Smoking and age-related macular degeneration: review and update. *Journal of ophthalmology.* 2013;2013: 895-147.

<sup>12</sup> Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, *et al.* Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology.* 2001;108(4): 697-704.

<sup>13</sup> Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, *et al.* Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. *Jama.* 1994;272(18): 1413-1420.

<sup>14</sup> Mares JA, Voland RP, Sondel SA, Millen AE, Larowe T, Moeller SM, *et al.* Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. *Archives of ophthalmology.* 2011;129(4): 470-480.

<sup>15</sup> McGuinness MB, Le J, Mitchell P, Gopinath B, Cerin E, Saksens NTM, *et al.* Physical Activity and Age-related Macular Degeneration: A Systematic Literature Review and Meta-analysis. *American journal of ophthalmology.* 2017;180: 29-38.

<sup>16</sup> Klein R, Klein BE, Tomany SC, Cruickshanks KJ. The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam eye study. *Ophthalmology.* 2003;110(4): 636-643.

<sup>17</sup> Van Leeuwen R, Ikram MK, Vingerling JR, Witteman JC, Hofman A, de Jong PT. Blood pressure, atherosclerosis, and the incidence of age-related maculopathy: the Rotterdam Study. *Investigative ophthalmology & visual science.* 2003;44(9): 3771-3777.