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Nature and nurture- genes and environment- predict onset and progression of macular degeneration

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ABSTRACT

Age-related macular degeneration (AMD) is a common cause of irreversible visual loss and the disease burden is rising world-wide as the population ages. Both environmental and genetic factors contribute to the development of this disease. Among environmental factors, smoking, obesity and dietary factors including antioxidants and dietary fat intake influence onset and progression of AMD. There are also several lines of evidence that link cardiovascular, immune and inflammatory biomarkers to AMD. The genetic etiology of AMD has been and continues to be an intense and fruitful area of investigation. Genome-wide association studies have revealed numerous common variants associated with AMD and sequencing is increasing our knowledge of how rare genetic variants strongly impact disease. Evidence for interactions between environmental, therapeutic and genetic factors is emerging and elucidating the mechanisms of this interplay remains a major challenge in the field. Genotype–phenotype associations are evolving. The knowledge of non-genetic, modifiable risk factors along with information about heritability and genetic risk variants for this disease acquired over the past 25 years have greatly improved patient management and our ability to predict which patients will develop or progress to advanced forms of AMD. Personalized medicine and individualized prevention and treatment strategies may become a reality in the near future.

Contents

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1. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the United States (Friedman et al., 2004; Seddon and Sobrin, 2013). The etiology of AMD is multifactorial: both environmental and genetic factors contribute to the development of disease. Smoking is the most consistently identified modifiable risk factor (Seddon et al., 1996; Tomany et al., 2004). Overall and abdominal obesity and dietary factors including antioxidants and dietary fat intake also affect AMD incidence and progression. A lifestyle that includes a healthy diet, physical activity, weight control and smoking avoidance, can reduce the risk of AMD (Cho et al., 2001, 2004; Mares-Perlman et al., 1995a; Mares et al., 2011; Seddon et al., 1994a,b, 2001a, 2003a,b). There has also been great progress in identifying the genetic variants that impact risk of AMD (Chen et al., 2010; Dewan et al., 2006; Edwards et al., 2005; Fritsche et al., 2013; Hageman et al., 2005; Haines et al., 2005; Jakobsdottir et al., 2005; Klein R.J. et al., 2005; Maller et al., 2006, 2007; Neale et al., 2010; Raychaudhuri et al., 2011; Seddon et al., 2013c; Yang et al., 2006; Yu et al., 2011). The knowledge of genetic risk variants for the disease coupled with knowledge of non-genetic risk factors over the past two and a half decades have improved both the ability to manage and advise patients as well as the ability to predict which patients will develop advanced forms of the disease (Seddon et al., 2009a, 2011b, 2013a). Understanding the interplay between environmental, therapeutic and genetic factors will lead to new preventive and therapeutic strategies in the evolving field of personalized medicine.

1.1. Prevalence and impact of AMD

Population-based studies have provided information on the prevalence and incidence of AMD within the US. The Beaver Dam Eye Study (BDES) was a census of the population of Beaver Dam, Wisconsin (Klein R. et al., 1992). Incidence of early AMD increased from 3.9% in individuals aged 43–54 years to 22.8% in persons 75 years of age and older. Persons 75 years of age or older had a 5.4% incidence rate and a 7.1% prevalence rate of late AMD, defined as choroidal neovascularization (CNV) and/or geographic atrophy (GA). Similarly, the Visual Impairment Project in Australia found that the 5-year incidence of AMD was 6.3% in those age 80 years and older at baseline (Mukesh et al., 2004). The Blue Mountains Eye Study (BMES) in Australia found that end-stage AMD was present in 1.9% of the Caucasian population, rising from 0% among people younger than 55 years of age to 18.5% among those 85 years of age or older (Mitchell et al., 1995). Prevalence of early and late AMD in an Asian Malay population was similar to that reported in the BMES (Kawasaki et al., 2008). The recent National Health and Nutrition Examination Survey (NHANES), conducted from 2005 to 2008, sampled approximately 5500 persons (Klein R. et al., 2011). The total prevalence of any AMD in this civilian, noninstitutionalized US population aged 40 years or older was 6.5% (7.2 million people), and 809,000 persons were estimated to have the late stages of AMD (Klein R. et al., 2011). While some data suggest that the incidence of advanced AMD in the USA may be on the decline, due in part to changes in lifestyle habits of the American public over the last 40 years, (Klein R. et al., 2008) the prevalence of AMD is still expected to increase by 97% by the year 2050 (Klein B. 2009).

Ophthalmologists rarely observe visual loss caused by CNV among US ethnic minority groups. In the Baltimore Eye Survey, AMD accounted for 30% of bilateral blindness among whites and for 0% among African Americans (Sommer et al., 1991). Data from a population-based study of blacks in Barbados, West Indies, (Leske et al., 2004; Schachat et al., 1995) revealed that incidence of AMD and signs of AMD changes occurred commonly but at a lower frequency than in predominantly white populations in other studies. Hispanics also have a lower prevalence of advanced AMD than non-Hispanics. The Los Angeles Latino Eye Study indicates Latinos have a relatively high rate of early AMD but not late AMD (Varma et al., 2004). Overall, the literature to date suggests that early AMD is common among blacks and Hispanics, although less common than among non-Hispanic whites, whereas advanced AMD is much less common in these groups compared with non-Hispanic whites.

AMD adversely affects quality of life and activities of daily living, causing many affected individuals to lose their independence in their retirement years. Patients with vision loss resulting from AMD often report AMD as their worst medical problem and have a diminished quality of life (Alexander et al., 1988; Mangione et al., 1999). In one study of well-being, patients with AMD had lower quality of life scores than patients with chronic obstructive pulmonary disease and acquired immunodeficiency syndrome; the lower quality of life in patients with AMD was related to greater emotional distress, worse self-reported general health, and greater difficulty carrying out daily activities (Williams et al., 1998).

1.2. Proportion of disease attributable to nature vs nurture: twin studies

Twin studies have allowed dissection of the relative contribution of genetic and environmental factors in AMD. In the first large population-based twin study of AMD including over 12,000 WWII veterans in the National Academy of Sciences-National Research Council Twin Registry, the roles of environment and heredity were quantified by studying both monozygotic and dizygotic twins and