

Alzheimer's disease and age-related macular degeneration have different genetic models for complement gene variation

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Abstract

Alzheimer's disease (AD) and age-related macular degeneration (AMD) are both neurodegenerative disorders which share common pathological and biochemical features of the complement pathway. The aim of this study was to investigate whether there is an association between well replicated AMD genetic risk factors and AD. A large cohort of AD ($n = 3898$) patients and controls were genotyped for single nucleotide polymorphisms (SNPs) in the complement factor H (CFH), the Age-related maculopathy susceptibility protein 2 (ARMS2) the complement component 2 (C2), the complement factor B (CFB), and the complement component 3 (C3) genes. While significant but modest associations were identified between the complement factor H, the age-related maculopathy susceptibility protein 2, and the complement component 3 single nucleotide polymorphisms and AD, these were different in direction or genetic model to that observed in AMD. In addition the multilocus genetic model that predicts around a half of the sibling risk for AMD does not predict risk for AD. Our study provides further support to the hypothesis that while activation of the alternative complement pathway is central to AMD pathogenesis, it is less involved in AD.

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1. Introduction

Alzheimer's disease (AD) and age-related macular degeneration (AMD) are both common degenerative diseases of older people associated with activation of the complement system. Both diseases are also characterized by the accumulation of extracellular aggregated proteins, amyloid plaques and tangles in the case of AD, and drusen in AMD. In AMD the extracellular drusen, deposited between the basal surface of the retinal pigment epithelium (RPE) and Bruch's membrane contains inflammatory mediators, acute-phase reactants, and activated components of the complement system similar to those found in AD plaques (Anderson et al., 2002; Hageman et al., 2001; Johnson et al., 2000, 2001). Additionally, the principal component of amyloid plaques in AD, the amyloid beta ($A\beta$) peptide, is found with activation-specific fragments of complement component 3 (C3) in vesicular components within drusen in AMD patients (Johnson et al., 2002).

Complement is a critical part of the innate immune system and interacts with the antibody responses of the adaptive immune system. At the heart of the complement pathway is a proteolytic cascade leading to the activation of C3. Activation of C3 leads to opsonization of targets by C3b/iC3b for phagocytosis, release of anaphylatoxins that promote inflammation and formation of the membrane attack complex (MAC) which can lyse the target membrane. This cascade can be activated through 3 pathways; classical, lectin, and alternative.

Current evidence through immunohistochemical, genetic, and biochemical studies suggests that AMD pathogenesis involves mainly the alternative complement pathway, which is under constant low level activation by spontaneous hydrolysis of an internal thioester bond in C3 (reviewed in Charbel Issa et al., 2011). In AD, however, the picture is less clear. Although all complement factors are produced in brain, and their activation is increased in affected brain areas (reviewed in Veerhuis et al., 2011), it has been widely known since the early 80s, through immunohistochemical (Eikelenboom and Stam, 1982; Eikelenboom et al., 1989; McGeer et al., 1989; Rogers et al., 1992) and transgenic knockout mice studies (Fonseca et al., 2004), that it is the classical pathway, through C1q target binding and further activation of a cascade of proteases (C1r, C1s, C4, C2, and C3), and not the alternative pathway, that is activated. For example, it has been shown that tangles and plaques of AD are clearly marked with the classical component complement fragments C4d and C3d (Eikelenboom et al., 1989; McGeer et al., 1989). Nevertheless, although predominantly classical pathway activation products were found to colocalize with most cerebral $A\beta$ deposits in AD

brain, a number of studies provide support for the activation of the alternative pathway in AD. As it has been reported that $A\beta$ peptides can activate both the classical and alternative complement pathways (Bradt et al., 1998) and alternative pathway components, such as complement component B and activation products Bb and Ba, have been found to be increased in the brains of AD patients compared with controls (Strohmeier et al., 2000). Additionally, complement factor H (CFH), an inhibitor of the alternative complement pathway, has been found to be elevated in the amyloid plaques of AD brains compared with controls (Strohmeier et al., 2002) and a human proteome study found plasma CFH to be specifically elevated in late onset AD (Hye et al., 2006). Finally, activation of the alternative pathway has been also observed in mouse model studies (Fonseca et al., 2011), and although there was no deposition of classical pathway components in C1q^{-/-} AD mouse models, cleaved C3 products and properdin were prominently present on the fibrillar amyloid plaques (Fonseca et al., 2011; Zhou et al., 2008). All these suggest that although the main pathway to be activated in AD is the classical pathway, there is evidence for the involvement of the alternative pathway as well.

A number of studies have investigated comorbidity between AD and AMD and reported significant associations between late AMD and cognitive impairment or AD (Klaver et al., 1999; Pham et al., 2006). In the Rotterdam study, late stage AMD was associated with increased incident AD at 2-year follow-up, though the risk was attenuated by adjustment for smoking or atherosclerosis (Klaver et al., 1999). Lower cognitive function scores but not AD was associated with symptoms of early AMD in the Cardiovascular Health Study (Baker et al., 2009).

In view of the striking pathological and etiological similarities between AMD and AD we decided to look for common genetic risk factors between the 2 disorders. The most common genetic variation affecting risk for AMD is within genes of the alternative pathway such as the CFH Y420H (rs1061170) and the intronic rs1410996 polymorphisms, the age-related maculopathy susceptibility protein 2 (ARMS2) single nucleotide polymorphisms (SNPs) A69S (rs10490924), 4 variants in the complement component 2 and factor B (C2-CFB) locus (the L9H: rs4151667 and R32Q: rs641053 polymorphisms in the complement factor B [CFB] gene and the E318D: rs9332739 and intron 10: rs547154 polymorphisms in the complement component 2 [C2] gene) and the C3 gene (R102: rs2230199 SNP). The CFH, ARMS2, and C3 SNP risk alleles have been shown to act individually in an additive manner increasing the risk for AMD between 2- and 9-fold and absence of the C2-CFB

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