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Negative results

Association study of the *CFH* Y402H polymorphism with Alzheimer's disease

Isabelle Le Fur [a], Geoffroy Laumet [a], Florence Richard [a], Nathalie Fievet [a], Claudine Berr [b], Olivier Rouaud [c], Cécile Delcourt [d], Philippe Amouyel [a], Jean-Charles Lambert [a,*]

[a] *INSERM U744, Institut Pasteur de Lille, Université de Lille 2, France*
[b] *INSERM U888, University of Montpellier-1, Montpellier, France*
[c] *Service de Neurologie, Centre Hospitalier Universitaire, Hôpital Général, Dijon, France*
[d] *INSERM U593, Université Victor Segalen, Bordeaux, France*

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Abstract

Several reports indicated that Alzheimer's disease (AD) and age-related macular degeneration (AMD) may share similar genetic and pathological features. We postulated that the functional Y402H polymorphism within the *CFH* gene and unambiguously recognised as a major genetic determinant of AMD, may also be a risk factor of AD. We analysed the association of this polymorphism with the AD risk in both prospective and cross-sectional studies. We were not able to detect such an association whatever the studied population, suggesting that the *CFH* gene is not a genetic determinant of AD.

Keywords: CFH; Alzheimer; Polymorphism; Prospective study; Cross-sectional study

The risk of Alzheimer's disease (AD) and age-related macular degeneration (AMD) both increase dramatically with advanced age and result from the interaction between environmental and genetic factors. Since an increased risk of incident AD may occur in subjects with advanced AMD (Klaver et al., 1999), it has been suggested that these two pathologies might share common risk factors. This hypothesis was reinforced by several observations: (i) both disorders are partly characterized by accumulation of abnormal extracellular deposits containing Aβ peptides (Johnson et al., 2002); (ii) Aβ immunization may be a pertinent therapeutic approach for AMD as already proposed for AD (Ding et al., 2008); (iii) the ε4 allele of the apolipoprotein E (APOE) gene, the only recognised genetic risk factor of AD, may be associated with a decreased risk of AMD (Thakkinstian et al., 2006a); (iv) the complement factor H (CFH), the main genetic risk factor of AMD, has been detected in Aβ plaques in the brain of AD patients (Strohmeyer et al., 2000) and has been found specifically increased in plasma of AD cases (Hye et al., 2006).

With this background, we postulated that the *CFH* gene might be a risk factor for AD. Since the Y402H (rs1061170) polymorphism was previously reported as highly associated with the risk of AMD (Thakkinstian et al., 2006b), we investigated the association of this polymorphism with the incidence of dementia and more specifically AD in the three-city prospective study (3C Study) and in a large cross-sectional AD case–control study (see supplemental materials for description). The Y402H and *ApoE* ε2/ε3/ε4 genotyping was performed using TaqMan Genotyping Assays (Applied Biosystems) as described by the suppliers. In the case–control study, the Y402H genotyping was determined by genomic DNA amplification (5′-TCATTGTTATGGTCCTTAGG-3′

* Corresponding author at: Unité INSERM 744, Institut Pasteur de Lille BP 245, 1 rue du professeur Calmette, 59019 Lille Cedex, France. Tel.: +33 3 20 87 73 91.
E-mail address: jean-charles.lambert@pasteur-lille.fr (J.-C. Lambert).

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and reverse primer 3′-CAATGTACATACCTCTTACC-5′) following by Nla III digestion. The analyses were performed using the SAS software (Release 8.02; SAS Statistical Institute, Cary, NC) and are more precisely described in the supplementary material.

In the 3C Study, no association of the Y402H polymorphism with the risk of incident dementia ($n = 211$) or AD ($n = 139$) was observed (see supplementary data, Table 3). However, we calculated that the incident demented or AD cases populations from the 3C Study were not fully adapted to detect a potential restricted association of the Y402H polymorphism with the risk of developing dementia or AD (respectively 76% and 57% assuming an α level of 0.05 and an OR of 1.5). In order to take into account this limitation, we also analysed the association of this polymorphism with the risk of developing AD in a large cross-sectional case–control study (642 controls and 562 AD cases). Again, we were not able to detect an association of this polymorphism with AD risk (see supplemental material, Table 4) whereas this population was adapted to detect even a restricted association (93% assuming an α level of 0.05 and an OR of 1.5). Finally, no significant statistical interaction between the Y402H polymorphism and age, gender or APOE status was detected whatever the studied population.

In conclusion, since it was suggested that AD and AMD may share some clinical, genetic and pathological features, we postulated that the functional Y402H polymorphism, previously described as a major genetic determinant of AMD, may be also a genetic risk factor of AD. Using both prospective and cross-sectional studies, we report here that this polymorphism is not associated with the risk of developing AD, suggesting that the *CFH* gene is not a genetic determinant of this disease.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2008.03.003.

References

Ding, J.D., Lin, J., Mace, B.E., Hermann, R., Sullivan, P., Bowes-Rickman, C., 2008. Targeting age-related macular degeneration with Alzheimer's disease based immunotherapies: anti-amyloid-beta antibody attenuates pathologies in an age-related macular degeneration mouse model. Vis. Res. 48, 339–345.

Hye, A., Lynham, S., Thambisetty, M., Causevic, M., Campbell, J., Byers, H.L., Hooper, C., Rijsdijk, F., Tabrizi, S.J., Banner, S., Shaw, C.E., Foy, C., Poppe, M., Archer, N., Hamilton, G., Powell, J., Brown, R.G., Sham, P., Ward, M., Lovestone, S., 2006. Proteome-based plasma biomarkers for Alzheimer's disease. Brain 129, 3042–3050.

Johnson, L.V., Leitner, W.P., Rivest, A.J., Staples, M.K., Radeke, M.J., Anderson, D.H., 2002. The Alzheimer's A beta-peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration. PNAS 99, 11830–11835.

Klaver, C.C., Ott, A., Hofman, A., Assink, J.J., Breteler, M.M., de Jong, P.T., 1999. Is age-related maculopathy associated with Alzheimer's Disease? The Rotterdam study. Am. J. Epidemiol. 150, 963–968.

Strohmeyer, R., Shen, Y., Rogers, J., 2000. Detection of complement alternative pathway mRNA and proteins in the Alzheimer's disease brain. Brain Res. Mol. Brain Res. 81, 7–18.

Thakkinstian, A., Bowe, S., McEvoy, M., Smith, W., Attia, J., 2006a. Association between apolipoprotein E polymorphisms and age-related macular degeneration: a HuGE review and meta-analysis. Am. J. Epidemiol. 164, 813–822.

Thakkinstian, A., Han, P., McEvoy, M., Smith, W., Hoh, J., Magnusson, K., Zhang, K., Attia, J., 2006b. Systematic review and meta-analysis of the association between complement factor H Y402H polymorphisms and age-related macular degeneration. Hum. Mol. Genet. 15, 2784–2790.