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Cyp46 Polymorphisms in Alzheimer's Disease: A Review

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Abstract Increasing research findings argue for a link between brain cholesterol turnover and Alzheimer's disease (AD). High cerebral levels of this lipid increase Aß load. The elimination of cerebral cholesterol involves two mechanisms, dependent of apolipoprotein E and cholesterol 24-hydroxylase (CYP46). CYP46 is a gene associated with AD; the most studied single nucleotide polymorphism is the rs754203, which changes T→C. Some studies describe that this polymorphism is possibly associated with loss of function of CYP46; others describe that it is possibly associated with cerebral cholesterol accumulation or an increase of CYP46 activity leading to an accumulation of the 24S-hydroxycholesterol in cerebrospinal fluid. Publications about this subject around the world are controversial. Some studies associate the T allele with AD and others the C allele. The aim of this review is to describe and summarize the findings of the researches about the relationship between CYP46 and AD that have been published in the past 9 years.

Keywords Cyp46 · Alzheimer disease · 24S-hydroxycholesterol · Single nucleotide polymorphism

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting memory and cognition in elderly. Both genetic and environmental factors have been involved in the pathogenesis of AD. Apolipoprotein E (APOE) gene is accepted worldwide as a genetic factor for sporadic AD. However, the APOE gene only accounts for about 65% of all sporadic AD cases, indicating that other genes are involved in the etiology of sporadic AD (Richard and Amoyuel 2001).

Recent studies have shown evidence that cholesterol metabolism has an important role in the pathogenesis of AD. High serum cholesterol concentration increases the risk of AD (Notkola et al. 1998; Kivipelto et al. 2001).

Brain cholesterol is synthesized locally and is independent from nutritional intake (Jurevics and Morell 1995). Excess brain cholesterol derives either from increased synthesis or is due to neuronal cell death and needs to be eliminated from the brain (Goodrum 1991). Furthermore, it has been demonstrated that cholesterol affects the pathogenic mechanisms of the disease by modulating the amyloid precursor protein processing; high serum cholesterol is a factor that increases Aß biogenesis and Aß toxicity (Borroni et al. 2004).

Brain cholesterol is very stable compared to the cholesterol of the periphery, and it is mainly synthesized locally, as its transfer is restricted by the blood–brain barrier (Ma et al. 2006).

The turnover of cholesterol in the brain occurs via conversion of excess cholesterol into 24S-hydroxcholesterol, which is then secreted from the central nervous system into the plasma across the blood–brain barrier (Tedde et al. 2006).

24S-Hydroxycholesterol is the major cholesterol elimination product of the brain. More than 90% of plasma 24S-hydroxycholesterol originates from the brain; however, the exact transport mechanism for the elimination of 24S-

Table 1 A summarized analysis of the association between AD and CYP46

References	SNP	Allele/genotype	Polymorphism *Cyp46*/AD	*p* value	Sample size population
Desai et al. 2002; (whites)	rs754203	–	Absent	0.72	USA
Desai et al. 2002; (blacks)	rs754203	–	Absent	0.94	USA
Kölsch et al. 2002	rs754203	C	Absent	0.815	Germany
Papassotiropoulos et al. 2003[a]	rs754203	TT	Present	<0.001	Switzerland/Greece/Italy
Borroni et al. 2004	rs754203	C	Present	<0.0001	Italy
Chalmers et al. 2004	rs754203	–	Absent	0.650	UK
Combarros et al. 2004[a]	rs754203	CC	Present	–	Spain
Ingelsson et al. 2004	rs754203	–	Absent	0.11	USA
Johansson et al. 2004	rs754203	T	Absent	0.250/0.140/0.59	Sweden and Scotland
Kabbara et al. 2004	rs754203	C	Absent	>0.05	France
Wang et al. 2004	rs754203	T	Present	0.001	China
Golanska et al. 2005	rs754203	C	Present	0.024	Poland
Juhász et al. 2005	rs754203	–	Absent	0.421/0.466	Hungary
Fernández del Poso et al. 2005	rs754203	T	Present	–	Spain
Helisalmi et al. 2006[a]	rs754203	CC	Present	0.015	Finland
LI et al. 2006	rs754203	C	Present	0.047	China
Ma et al. 2006	rs754203	T	Absent	0.687	China
Ma et al. 2006	rs3742376	C	Present	0.047	China
Tedde et al. 2006	rs754203	–	Absent	0.342	Italy
Wang and Jia 2007	rs754203	–	Absent	0.558	China
Golanska et al. 2009	rs754203	C	Present	<0.05	Poland
Fu et al. 2009[b]	rs754203	T	Present	0.011	China*
Kölsch et al. 2009	rs7157609	G	Present	0.016	Germany
Kölsch et al. 2009	rs4900442	C	Present	0.019	Germany

[a] Genotype association

[b] Association between CYP46 and mild cognitive impairment (MCI)

hydroxycholesterol from brain into blood is unknown (Björkhem et al. 1998). Compared to controls, serum 24S-hydroxycholesterol/cholesterol ratios had decreased and were lower during the progress of AD. High levels of neurotoxic 24S-hydroxycholesterol, especially during early stages of AD, might have lead to advanced neurodegeneration, and thus, 24S-hydroxycholesterol is suggested to be an additional risk factor (Kölsch et al. 2002).

In addition, it is believed that the cerebrospinal fluid (CSF) concentration of 24S-hydroxycholesterol is altered in

Table 2 A summarized description of the risk for AD related to CYP46 C/T polymorphism in case–control studies

References	OR (95%)	CI	*p* value
CYP46 T			
Papassotiropoulos et al. 2003;	2.16	1.41–3.32	<0.001
Wang et al. 2004;	2.98	1.64–5.44	<0.001
Fernández del Poso et al. 2005	2.262	1.337–4.202	–
CYP 46 C			
Kölsch et al. 2002	2.159	1.112–4.192	0.023
Combarros et al. 2004	2.91	1.36–6.25	0.004
Borroni et al. 2004	2.56	1.58–4.08	–
Li et al. 2006	2.01	1.05–3.87	0.036
Ma et al. 2006	0.66	0.42–1.02	0.047
Helisalmi et al. 2006	2.13	1.25–3.62	0.005

AD-related neurodegeneration, and thus, CSF 24S hydroxcholesterol may be a marker for monitoring the onset and progression of the disease (Papassotiropoulos et al. 2002).

The Cyp46 enzyme is a member of the cytocrome P-450 family proteins and converts cholesterol to 24S-hydroxycholesterol. Cyp46 is expressed exclusively in the brain, where it regulates the elimination of excess cholesterol by adding a hydroxyl group to cholesterol producing a product that is more soluble than cholesterol and able to be exported from the brain (Bjorkhem et al. 1998; Lund et al. 1999; Tedde et al. 2006).

Interestingly, polymorphisms in the CYP46 gene (which encodes for cholesterol 24S-hydroxylase) influence both Aß peptide load in the brain and the genetic risk for late-onset sporadic AD (LOAD) (Kolsch et al. 2003; Wolozin 2003). It is suggested that increases in the membrane distribution of cholesterol (in contrast to total cholesterol content) may provide an enriched environment for Aß production and release in the brain (Gibson et al. 2003; Kolsch et al. 2003). In addition, Aß peptide induction of membrane-associated oxidative stress may contribute to altered ceramide and cholesterol metabolism that in turn trigger AD-type neurodegeneration and brain disease (Cutler et al. 2004)

A single nucleotide polymorphism (T/C) (rs754203) in intron 2 of CYP46 gene has been identified and reported to be significantly associated with increased risk for LOAD. According to the report, the frequency of CYP46 T allele and TT genotype was significantly higher in AD patients from Switzerland, Greece, and Italy than in controls (Papassotiropoulos et al. 2003). In contrast, Borroni et al. (2004) reported that CYP46C allele might act as a risk factor for LOAD in Italian patients, meaning that the susceptibility polymorphism might differ in different ethnic groups (Wang et al. 2004).

Recently, Kölsch et al. (2009) identified two single nucleotide polymorphisms (SNPs) in CYP46A1 influenced AD risk and suggest that CYP46A1 gene variations might act as risk factors for AD via influence on brain cholesterol metabolism.

This was a key initiative, considering the importance of studies about this issue. The aim of this paper is to report the results of studies about AD genetics and the CYP46 gene that have been published in the last 9 years.

Case–Controls Studies

The first publication about the relationship between CYP46 and AD was published by Bogdanovic et al. (2001). Since this publication, a lot of research has been done to elucidate the importance of the CYP46 gene in the pathogenesis of AD.

The studies that analyzed the association of CYP46 in development of LOAD, between 2001 and 2009 years, are summarized in Table 1.

With respect to the alleles (T/C) in the region rs754203 that be considered risk factors for LOAD, it is observed that 60% from the studies revealed the allele C association (Table 2)

In view of the contradictory results previously reported about the connection between CYP46 polymorphisms and AD, it is possible that the reasons for these controversial results would be caused by ethnical variability in different populations, methodological differences, or both. To confirm a connection between CYP46 as well as genetic control of cholesterol homeostasis in general and the pathogenesis of AD, further research is needed, including analysis of other genes influencing CNS cholesterol and amyloid metabolism and/or neighboring CYP46.

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References

Bjorkhem, I., Lütjohann, D., Diczfalusy, U., Stahle, L., Ahlborg, G., & Wahren, J. (1998). Cholesterol homeostasis in human brain: turnover of 24S-hydroperoxycholesterol and evidence for a cerebral origin of most of this oxysterol in the circulation. *Journal of Lipid Research, 39*, 1594–1600.

Björkhem, I., Lütjohann, D., Diczfalusy, U., Ståhle, L., Ahlborg, G., & Wahren, J. (1998). Cholesterol homeostasis in human brain: turnover of 24S-hydroxycholesterol and evidence for a cerebral origin of most of this oxysterol in the circulation. *Journal of Lipid Research, 39*, 1594–1600.

Bogdanovic, N., Bretillon, L., & Lund, E. G. (2001). On the turnover of brain cholesterol in patients with Alzheimer's disease. Abnormal induction of the cholesterol-catabolic enzyme CYP46 in glial cells. *Neuroscience Letters, 314*, 45–48.

Borroni, B., Archetti, S., Agosti, C., et al. (2004). Intronic CYP46 polymorphism along with ApoE genotype in sporadic Alzheimer Disease: from risk factors to disease modulators. *Neurobiology of Aging, 25*, 747–751.

Chalmers, K. A., Culpan, D., Kehoe, P. G., Wilcock, G. K., Hughes, A., & Love, S. (2004). APOE promoter, ACEI and CYP46 polymorphisms and b-amyloid in Alzheimer's disease. *NeuroReport, 15*, 95–98.

Combarros, O., Infante, J., Llorca, J., & Berciano, J. (2004). Genetic association of CYP46 and risk for Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 18*, 257–260.

Cutler, R. G., Kelly, J., Storie, K., Pedersen, W. A., Tammara, A., Hatanpaa, K., et al. (2004). Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 2070–2075.

Desai, P., DeKosky, S. T., & Kamboh, M. I. (2002). Genetic variation in the cholesterol 24-hydroxylase (CYP46) gene and the risk of Alzheimer's disease. *Neuroscience Letters, 328*, 9–12.

Fernández del Poso, V., Álvarez, M. A., Martínez, M. F., et al. (2005). Polymorphism in the cholesterol 24S-hidroxylase gene (CYP46A1)

associated with the APOEe3 allele increases the risk of Alzheimer's disease and of mild cognitive impairment progressing to Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 21*, 81–87.

Fu, B. Y., Ma, S. L., Tang, N. L., et. al. (2009). Cholesterol 24-hydroxylase (CYP46A1) polymorphisms are associated with faster cognitive deterioration in Chinese older persons: a two-year follow up study. *International Journal of Geriatric Psychiatry, 24*, 921–926.

Gibson Wood, W., Eckert, G. P., Igbavboa, U., & Muller, W. E. (2003). Amyloid beta-protein interactions with membranes and cholesterol: Causes or casualties of Alzheimer's disease. *Biochimica et Biophysica Acta, 1610*, 281–290.

Golanska, E., Hulas-Bigoszewska, K., Wojcik, I., et al. (2005). CYP46: A risk factor for Alzheimer's disease or a coincidence? *Neuroscience Letters, 383*, 105–108.

Golanska, E., Hulas-Bigoszewska, K., Sieruta, M., et. al. (2009) Earlier onset of Alzheimer's disease: Risk polymorphisms within PRNP, PRND, CYP46, and APOE Genes. *Journal of Alzheimer's Disease, 17*(2), 359–368.

Goodrum, J. F. (1991). Cholesterol from degenerating nerve myelin becomes associated with lipoproteins containing apolipoprotein E. *Journal of Neurochemistry, 56*, 2082–2086.

Helisalmi, S., Vepsäläinen, S., Koivisto, A. M., et al. (2006). Association of CYP46 intron 2 polymorphism in Finnish Alzheimer's disease samples and a global scale summary. *Journal of Neurology, Neurosurgery and Psychiatry, 77*, 421–422.

Ingelsson, M., Jesneck, J., Irizarry, M. C., Hyman, B. T., & Rebeck, G. W. (2004). Lack of association of the cholesterol 24-hydroxylase (CYP46) intron 2 polymorphism with Alzheimer's disease. *Neuroscience Letters, 367*, 228–231.

Juhász, A., Rimanóczy, A., Boda, K., et al. (2005). CYP46 T/C polymorphism is not associated with Alzheimer's dementia in a population from Hungary. *Neurochemical Research, 30*, 943–948.

Johansson, A., Katzov, H., Zetterberg, H., et al. (2004). Variants of CYP46A1 may interact with age and APOE to influence CSF Ab42 levels in Alzheimer's disease. *Human Genetics, 114*, 581–587.

Jurevics, H., & Morell, P. (1995). Cholesterol for synthesis of myelin is made locally, not imported into the brain. *Journal of Neurochemistry, 64*, 895–901.

Kabbara, A., Payet, N., Cottel, D., Frigard, B., Amoyouel, P., & Lambert, J. C. (2004). Exclusion of CYP46 and APOM as candidate genes for Alzheimer's disease in a French population. *Neuroscience Letters, 363*, 139–143.

Kivipelto, M., Helkala, E. L., Laakso, M. P., Hãnninen, T., Hallikainen, M., Alhainen, K., et al. (2001). Midlife vascular risk factors and Alzheimer's disease in later life: Longitudinal, population based study. *BMJ, 322*, 1447–1482.

Kölsch, H., Lütjohann, D., Ludwing, M., et al. (2002). Polymorphism in the cholesterol 24S-hydroxylase gene is associated with Alzheimer's disease. *Molecular Psychiatry, 7*, 899–902.

Kölsch, H., Lutjohann, D., von Bergmann, K., & Heun, R. (2003). The role of 24S-hydroxycholesterol in Alzheimer's disease. *Journal of Nutrition, Health & Aging, 7*, 37–41.

Kölsch, H., Lütjohann, D., & Jessen, F. (2009). CYP46A1 variants influence Alzheimer's disease risk and brain cholesterol metabolism. *European Psychiatry, 24*, 183–190.

Li, Y., Chu, L. W., Chen, Y. Q., et al. (2006). Intron 2 (T/C) CYP46 polymorphism is associated with Alzheimer's disease in Chinese patients. *Dementia and Geriatric Cognitive Disorders, 22*, 399–404.

Lund, E. G., Guileyardo, J. M., & Russell, D. W. (1999). cDNA cloning of cholesterol 24-hydroxylase, a mediator of cholesterol homeostasis in the brain. *Proceedings of the National Academy, 96*, 7238–7243.

Ma, S. L., Tang, N. L. S., Lam, L. C. W., & Chiu, H. F. K. (2006). Polymorphisms of the cholesterol 24-hydroxylase (CYP46A1) gene and the risk of Alzheimer's disease in a Chinese population. *International Psychogeriatrics, 18*, 37–45.

Notkola, I. L., Sultkava, R., Pekkanan, J., Erkinjuntti, T., Ehnholm, C., Kivinen, P., et al. (1998). Serum Total cholesterol, apolipoprotein E episilon 4 allele, and Alzheimer's disease. *Neuroepidemiology, 17*, 14–20.

Papassotiropoulos, A., Lütjohann, D., Bagli, M., et al. (2002). 24S-hydroxycholesterol in cerebrospinal fluid is elevated in early stages of dementia. *Journal of Psychiatric Research, 36*, 27–32.

Papassotiropoulos, A., Streffer, J. R., Tsolaki, M., et al. (2003). Increased brain b-Amyloid load, phosphorylated tau, and risk for Alzheimer disease associated with an intronic CYP46 polymorphism. *Archives of Neurology, 60*, 29–35.

Richard, F., & Amoyuel, P. (2001). Genetic susceptibility factors for Alzheimer's disease. *European Journal of Pharmacology, 412*, 1–12.

Tedde, A., Rotondi, M., Cellini, E., et al. (2006). Lack association between the CYP46 gene polymorphism and Italian late-onset sporadic Alzheimer's disease. *Neurobiology of Aging, 27*, 773. e1–773.e3.

Wang, F., & Jia, J. (2007). Polymorphism of cholesterol metabolism genes CYP46 and ABCA1 and the risk of sporadic Alzheimer's disease in Chinese. *Brain Research, 1147*, 34–38.

Wang, B., Zhang, C., & Zheng, W. (2004). Association between a T/C polymorphism in intron 2 of cholesterol 24S-hydroxylase gene and Alzheimer's disease in Chinese. *Neuroscience Letters, 369*, 104–107.

Wolozin, B. (2003). Cyp46 (24S-cholesterol hydroxylase)—A genetic risk factor for Alzheimer disease. *Archives of Neurology, 60*, 16–18.