Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 4 [1] December 2014: 160-162

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.533
Universal Impact Factor 0.9804

ORIGINAL ARTICLE

Study on Molecular Genetic on Alzheimer's Disease

Vahideh Keyvani[1], Hadi Yari[2],Abbasali Palizban[3*]
1Dept. of Medical Genetics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, I. R. Iran.
2Dept. of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, I. R. Iran.
3Dept. of Clinical Biochemistry, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, I. R. Iran.
E-mail: palizban@pharm.mui.ac.ir

ABSTRACT
The most important neurodegenerative disorder is Alzheimer's disease (AD) which leads to dementia in the elderly. There are different issues can cause AD such as age, gender, diet, amount of exercise, family history of the disease, etc. In more than 90 percent of cases AD develops after the age of 65 years the majority being sporadic. There is sufficient of evidence that AD has a genetic etiology but the molecular mechanism of it is unclear. However, three genes are recognized that when mutated cause autosomal dominant early onset AD (EOAD). These are (a) β-amyloid precursor protein (APP), (b) presenilin 1 (PS1) and (c) presenilin 2 (PS2). Moreover, over 100 genes have been related with late onset AD (LOAD). Though, only the E4 allele of the Apolipoprotein E gene (APOE) is accepted as most important genetic factor. However, the effective factors on AD need further research in different populations.
***Key Words**: Alzheimer's Disease, gene, neurodegeneration, presenilin*

Received 23.08.2014 **Revised 01.11.2014** **Accepted 03.12.2014**

INTRODUCTION

There is sufficient of evidence that genetic factors play an important role in the etiology of AD. Family history is one of the most consistent risk factors [1]. The repeatedly used criterion of a positive family history doesn't essentially indicate genetic susceptibility. There isn't difference between familial AD and sporadic AD [2]. But, rapid of familial AD is more than sporadic AD. The inheritance pattern of AD isn't clear yet but in a scarcity of pedigrees, the disease separates in a manner consistent with a fully penetrant autosomal dominant trait resulting from a single gene defect. Three genes are recognized that when mutated cause presenile AD: β-amyloid precursor protein gene, presenilin-1 gene and presenilin-2 gene. Mutations in these genes are by themselves sufficient to cause EOAD. No mutations in these genes have been known in LOAD. Possibility of PS1mutations in the EOAD families is more than the others.These three genes account for 30-50% of the families with autosomal AD, which represents about 1% of the whole AD population. Contrary to EOAD, in LOAD families the inheritance pattern is less clear. It is suggesting that a complex interaction of genetic and environmental factors cause the etiology of LOAD. Additional of genetic evidence demonstrations the possible role of ε4 allele of Apolipoprotein E gene (APOE) as a risk factor for late onset sporadic or familial LOAD. The existence of the ε4 allele is the most common genetic factor of susceptibility to AD. Though, the presence of only ε4 allele isn't enough to cause AD. Everybody having the ε4 allele won't develop the disease, and numerous who lack the allele will also develop AD.In this regard, histone modification and DNA methylation are the most investigated epigenetic mechanisms. These have been known as significant factors in controlling the expressed genome by gene transcription [1,2].

DNA methylation

Addition of a methyl group from S-adenosyl methionine to CpG islands via DNA methyltransferases is caused DNA methylation. Methylated CpG islands are near promoter regions of genes. In general, DNA methylation suppresses transcription and so it's associated with gene silencing. DNA methylation is dependent on two factors: (a) methylation potential and (b) one carbon metabolism. In the one carbon

metabolism Methylenetetrahydrofolate reductase is an important enzyme. This enzyme is coded by the gene MTHFR on chromosome 1 location p36.3 in humans [3].

Histone modifications

Histone modification is occurred at separate amino acid residues on their amino terminal fails. Some important examples of this modification are histone phosphorylation, methylation, acetylation, ubiquitylation. Histone acetylation is related to transcriptional activation but deacetylation is associated with transcriptional repression. Epigenetic modifications contribute to the phenotype's differences. DNA methylation was studied in monozygotic twins discordant for AD. In AD twin was detected reduced DNA methylation in contrast with non-AD twin [4]. Amyloid precursor protein has been exposed to be methylated, and hypomethylated with age and in AD patients, which enhanced making of Aβ. Age affected the hypomethylation and Aβ could be involved in the production of amyloid β peptide. DNA hypomethylation and neprilysinhypermethylation are affected by Amyloid β peptide. Consequently, this suppresses its expression in mRNA and protein level. Promoter region of PS1 Hypomethylation was improved presenilin expression, and increase amyloid β generation. At high levels in brain cells PS1 and BACE are expressed and these genes are unmethylated. Raise in histone acetylation can affect AD. Altered gene transcripton in AD has been related with alterations in histone acetylation profiles [5,6].

AD genetic risk factors

Various factors can cause Alzheimer's disease. Among these factors genetic as well as environmental factors are included in AD pathology. Recently, some genes include in AD have been detected. There aren't any single genes responsible for an origin of AD. Mutations in amyloid precursor protein, presinilin 1 and presinilin 2 are responsible for AD. Polymorphisms and mutations contribute to sporadic AD [7].

Familiar type of Alzheimer's disease

Resently, Rosenberg and coworkers reported that 5-10% of whole patients devided in familiar type of AD. Mutations in 3 genes enhance creation of $A\beta_{42}$ peptide and have an important role in an autosomal dominant hereditary of AD. These are amyloid precursor proteingenes on chromosome 21q21, gene for presenilin 1 on chromosome 14q24.2 and gene for presenilin 2on chromosome 1q42.13. In familiar type of AD increased level of amyloid β peptide years before any clinical symptoms of Alzheimer`s disease are observed. Also, tau gene mutations are not related with AD [7].

Amyloid precursor protein

an example of single transmembrane protein is amyloid precursor protein. It has 23 residue hydrophobic stretch. These are located near its carboxyl terminal that serves to anchor app in the phospholipid bilayer of internal and external. For internal sites we can list golgi, endosome, and plasma-lemma membranes for external type. Missense mutations in APP gene are clustered around secretes cleavage sites. Increased of production of Aβ is a result of these mutations that be able to cumulate and make amyloid plaques. Amount of Aβ is raised in Down syndrome patients. The majority of these patients have neuritic plaques and tangles in their 40s. The APP gene maps to chromosome 21 and patients with Down syndrome have trisomy 21, and it cause of AD development [8].

Presenilins

The presenilin-1 and presenilin-2 are members of a novel gene family. The function of this gene isn't clear yet. 467 and 448 amino acids are the code of PS1 and PS2, respectively, with 8 transmembrane domains. Presenilins are the most important candidates for γ-secretase. The PS1 and PS2 mutations are associated to early onset AD. PS1 takes places in a normal processing of APP. Various PS1 mutations have been recognized in 390 families. PS1 mutations might be responsible for missing cleaving of APP and production of $A\beta_{42}$ the most aggressive variant for generation of amyloid plaques in the human brain. Besides, PS1 acts together with glycogen synthase kinase (GSK3b). Glycogen synthase kinase included in tau phosphorylation and it is one of the critical protein kinases. In some cases mutations of PS1 cause an unusual interaction of PS1 with GSK3b. Increase hyperphosphorylation of tau protein is duo to this interaction and this form of tau protein then does not play its physiological roles. Possibility of mutations in PS2 is smaller than in PS1 mutations [9].

Sporadic type of AD

In spite of frequent attempts, our information of the heredity of AD remains incomplete. There are disagreements about the participation of gene polymorphisms in AD sporadic form. Genes for apolipoprotein E (ApoE), alfa-2-macroglobulins, component of oxoglutarate dehydrogenase complex, glycogen synthase kinase (GSK3B) might be involved in familiar AD too. Secretases and β-amyloid peptide degrading enzymes have been recommended as candidate genes for AD. They have an essential role in a procedure of formation of senile plaques. The BACE1 promoter polymorphisms may contribute to sporadic AD. Neprilysin gene, and insulin degrading enzyme polymorphisms growth the possibility for AD. Gene of Angiotensin converting enzyme insertion/deletion polymorphism is considered as a biomarker for AD. Insertion/deletion and other ACE polymorphisms have an important effect on the

possibility of AD. It is found that in all organisms catalase is a common antioxidant enzyme. Catalase gene polymorphism does not confirm a defensive role in AD patients. Glutathione transferases (GSTs) may have a vital role as risk factors for AD. The reason is that GSTs detoxify products of oxidative damage. Polymorphisms of GSTs could be involved in AD [10-12]

Methylene tetrahydro folate reductase

In DNA synthesis and homocysteineremethylation, 5, 10-Methylene tetra hydrofolatereductase has a fundamental roll. Improved plasma homocysteine level is a risk factor for the development of AD. Kang and van der Put groups were detected two genetic polymorphisms in the MTHFR. Theses are gene C677T and A1298T. MTHFR polymorphism causes diminished enzymatic action of MTHFR and enhanced of the plasma total homocysteine level. Mutation in MTHFR is slightly linked with the start of senile dementia. The MTHFR is a component of one carbon metabolism. Therefore it can interact with methionine, vitamins B_6, B_{12}, and B_9 in relations with AD [13].

Apolipoprotein E

Apolipoprotein E is the most important genetic risk factor for AD. This is because of its ε4 allele. For a normal metabolism of lipoproteins, cholesterol and triacylgylcerolsapoE is necessary. The APOE gene is located on the proximal arm of chromosome 19, at 19q13.2a in gene family cluster with APOC-I, APOC-I' and APOC-II. It consists of 4 exons and 3 introns and is approximately 3.7 kb in length. ApoE has three forms: (1)ApoE ε2 variant, (2) ApoE ε3 variant, and (3) ApoE ε4 variant. ApoE ε4 variant increased the risk of AD more than the other types [14].

CONCLUSION

AD as a part of neurological diseases is so serious medical problem. Over 100 million people suffer from these diseases. Molecular and genetic investigates denote a high potential for more investigation on the field of AD. The role of mentioned gene polymorphisms and many others gene polymorphisms is still dialectical. In this work we survey the most important molecular and genetic factors of AD.

REFERENCES

1. Ott A., Slooter A.J.C., Hofinan A., Lancet. 351 (1998) 1840-1843.
2. Duara R., Lopez Alberola R.F., Barker W.W., Neurology. 3 (1993) 1377-1384.
3. Goyette P., Sumner J.S., Milos R., Duncan A.M., Rosenblatt D.S., Matthews R.G., Rozen R., Nature Genetic 7 (1994) 195-200.
4. Felsenfeld G., Groudine M., Nature 421 (2003) 448-453.
5. Berger S.L., Nature 447 (2007) 407-412.
6. Rosenberg R.N., Neurology 54 (2000) 2045-2054.
7. Schellenberg G.D., Bird T.D., Wijsman E.M., Orr H.T., Anderson L., Nemens E., White
8. J.A., Bonnycastle L., Weber, J.L., Alonso M.E., Science, 258 (1992) 668-671.
9. Doan A, Thinakaran G, Borchelt DR, Slunt HH, RatovirskylPodlisny M, Selkoe DJ, Seeger
10. M, Gandy SE, Price DL, Sisodia SS., Neuron. 17 (1996) 1023-1030.
11. Poirier, J., J. Psychiatry Neuroscience, 21 (1996) 128-134.
12. Blacker D., Wilcox M.A., Laird N.M., Rodes L., Horvath S.M., Go R.C., Perry R., Watson
13. B. Jr., Bassett S.S., McInnis M.G., Albert M.S., Hyman B.T.,Tanzi R.E. Nature 19 (1998) 3357-3360.
14. Vepsinen S., Helisalmi S., Mannermaa A., Pirttil T., Soininen H., Hiltunen M., Journal of Neurology, Neurosurgery, 80 (2009) 1268-1270.
15. Seshadri S., Beiser A., Selhub J., Jacques P.F., Rosenberg I.H., D'Agostino R.B., Wilson
16. P.W., Wolf P.A., The New England Journal of Medicine 346 (2002) 476-483.
17. Lusis AJ, Heinzmann C, Sparkes RS, Scott J, Knott TJ, Geller R, Sparkes MC, Mohandas T. Proceedings of National Academy of SciencesUSA. 83 (1986) 3929-3933.

ITATION OF THIS ARTICLE

Vahideh K, Hadi Y,Abbasali P . Study on Molecular Genetic on Alzheimer's Disease. Bull. Env. Pharmacol. Life Sci., Vol 4[1] December 2014: 160-162