EXCLI Journal 2016;15:403-405 – ISSN 1611-2156
Received: January 23, 2016, accepted: June 21, 2016, published: June 22, 2016

Letter to the editor:

DISTRIBUTIONS OF SUSCEPTIBILITY LOCI TO LATE ONSET ALZHEIMER'S DISEASE ON HUMAN CHROMOSOMES

Mostafa Saadat

Department of Biology, College of Sciences, Shiraz University, Shiraz 71467-13565, Iran,
Tel: +98-71-36137432; Fax: +98-71-32280926
E-mail: saadat@shirazu.ac.ir and msaadat41@yahoo.com

http://dx.doi.org/10.17179/excli2016-161

Dear Editor,

Alzheimer's disease is a major public health problem in the world. Alzheimer's disease is a progressive, complex and heterogeneous neurodegenerative disorder. There are two types of Alzheimer's disease: familial Alzheimer's disease (FAD, also known as early onset Alzheimer's disease) and sporadic type (also known as late onset Alzheimer's disease; LOAD). FAD is relatively rare, accounting for less than 5 % of the total Alzheimer's disease burden which is expressed as a Mendelian trait with dominant inheritance (Acosta-Baena et al., 2011). In contrast to FAD, the LOAD is etiologically heterogeneous and results from a combination of many genetic and environmental factors (Gatz et al., 2006). Family, twin and adoption studies have provided major evidence for the role of genetics in LOAD (Shih et al., 2004). Heritability of LOAD was estimated to be up to 79 % based on twin and family studies (Gatz et al., 2006).

Many single nucleotide polymorphisms have been identified and confirmed to be associated with susceptibility to LOAD (Bertram et al., 2007; Rosenthal and Kamboh, 2014). Several meta-analyses based on genetic polymorphisms have been widely performed to assess the association between particular gene variants and risk of LOAD (Bertram et al., 2007; Rosenthal and Kamboh, 2014). Some of these studies indicated that polymorphisms were not associated with the risk of LOAD (Bertram et al., 2007).

Based on several lines of evidence it has been suggested that genes are distributed non-randomly on human chromosomes (Hecht, 1988; Lima-de-Faria et al., 1991; Mouchiroud et al., 1991; Saccone et al., 1996; Musio et al., 2002; Rafiee et al., 2008). Recently, we reported that polymorphic loci associated with susceptibility to breast cancer (Saify and Saadat, 2012), schizophrenia (Saadat, 2013), Parkinson's disease and multiple sclerosis (Saadat, 2014) are non-randomly distributed on human chromosome segments. Taken together, we suggested that loci associated with the risk of LOAD may be distributed non-randomly on human chromosomes. Therefore the present study was carried out.

Meta-analysis studies have been published with information of polymorphisms and susceptibility to LOAD was identified using Alzheimer's Disease Research Forum (AlzGene database) (http://www.alzgene.org) electronic database (Bertram et al., 2007) and from the study of Rosenthal and Kamboh, 2014.

EXCLI Journal 2016;15:403-405 – ISSN 1611-2156
Received: January 23, 2016, accepted: June 21, 2016, published: June 22, 2016

There were 1395 studies concerning the associations between 695 genes (2973 polymorphisms) and risk of LOAD. Table 1 shows the genes which their single nucleotide genetic polymorphisms associated with LOAD susceptibility in at least one ethnic group. There are 54 loci associated with the risk of LOAD. The method of Tai et al. (1993) was used to evaluate the non-randomness distribution of susceptible loci on each chromosomal band(s). The relative width of each band was measured using the diagram of the International System for Chromosome Nomenclature (ISCN, 1981). A probability of $P < 0.05$ was considered statistically significant.

Statistical analysis revealed that the LOAD susceptible loci distributed non-randomly on human chromosomes. Human chromosome segments 19q13 ($P < 0.001$) and 6p21.1 ($P < 0.001$) were bearing significantly higher numbers of susceptible loci for LOAD. There are nine and three genes which associated with susceptibility to LOAD on 19q13 (*GAPDHS*, *PLD3*, *BCAM*, *PVRL2*, *TOMM40*, *APOE*, *APOC1*, *APOC4*, and *CD33*) and 6p21.1 (*TNF*, *HLA-DRB5*, and *TREM2*) chromosome segments, respectively.

The present study revealed that the human chromosome segments 19q13 and 6p21.1 were bearing significantly higher numbers of susceptible loci for developing late onset Alzheimer's disease. The present finding has two important aspects: First, genes did not randomly distrib-

Table 1: List of polymorphic genes associated with susceptibility to late onset Alzheimer's disease

Gene Symbol	Location	OMIM	Gene Symbol	Location	OMIM
MTHFR	1p36.22	607093	***CELF1***	11p11.2	601074
ECE1	1p36.12	600423	***MS4A6A***	11q12.2	606548
CHRNB2	1q21.3	118507	***GAB2***	11q14.1	606203
CR1	1q32.2	120620	***PICALM***	11q14.2	603025
IL1A	2q13	147760	***SORL1***	11q24.1	602005
IL1B	2q13	147720	***FERMT2***	14q22.1	607746
BIN1	2q14.3	601248	***SLC24A4/RIN3***	14q32.12	609840
INPP5D	2q37.1	601582	***ADAM10***	15q21.3	602192
CCR2	3p21.31	601267	***TNK1***	17p13.1	608076
TF	3q22.1	190000	***THRA***	17q21.1	190120
IL8	4q13.3	146930	***GRN***	17q21.31	138945
MEF2C	5q14.3	600662	***ACE***	17q23.3	106180
NEDD9	6p24.2	602265	***ABCA7***	19p13.3	605414
TNF	6p21.33	191160	***LDLR***	19p13.2	606945
HLA-DRB5	6p21.32	604776	***GAPDHS***	19q13.12	609169
TREM2	6p21.1	605086	***PLD3***	19q13.2	615698
CD2AP	6p12	604241	***BCAM***	19q13.32	612773
NME8	7p14.1	607421	***PVRL2***	19q13.32	600798
EPHA1	7q34	179610	***TOMM40***	19q13.32	608061
PTK2B	8p21.2	601212	***APOE***	19q13.32	107741
CLU	8p21.1	185430	***APOC1***	19q13.32	107710
IL33	9p24.1	608678	***APOC4***	19q13.32	600745
DAPK1	9q21.33	600831	***CD33***	19q13.41	159590
TFAM	10q21.1	600438	***PRNP***	20p13	176640
CH25H	10q23.31	604551	***CST3***	20p11.21	604312
CALHM1	10q24.33	612234	***APP***	21q21.3	104760
SORCS1	10q25.1	606283	***OTC***	Xp11.4	300461

ute on human chromosomes. Second, as mentioned previously for other multifactorial traits (Saify and Saadat, 2012; Saadat, 2013, 2014), a mass screening test might be designed using polymorphic loci located on these chromosome segments (particularly for the segment 19q13) for diagnosis of LOAD.

Previously it has been reported that polymorphic loci associated with risks of breast cancer (Saify and Saadat, 2012), schizophrenia (Saadat, 2013) and multiple sclerosis (Saadat, 2014) non-randomly located on human chromosome segments 19q13, 6p21, and 19q13, respectively. It could be concluded that polymorphic loci on a particular chromosome segment have significant associations with different diseases. It should be noted that at present it is impossible to explain the biological significance of the defined clustering of genes in the etiology of the LOAD or other multi-factorial disease.

Acknowledgments

This study was supported by Shiraz University.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

Acosta-Baena N, Sepulveda-Falla D, Lopera-Gómez CM, Jaramillo-Elorza MC, Moreno S, Aguirre-Acevedo DC, et al. Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. Lancet Neurol. 2011;10:213-20.

Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat Genet. 2007;39:17-23.

Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, et al. Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry. 2006;63:168-74.

Hecht F. Fragile sites, cancer chromosome breakpoints, and oncogenes all cluster in light G bands. Cancer Genet Cytogenet. 1988;31:17-24.

ISCN. An international system for human cytogenetic nomenclature-high resolution banding. Cytogenet Cell Genet. 1981;31:1-23.

Lima-de-Faria A, Mitelman F, Blomberg J, Pfeifer-Ohlsson S. Telomeric location of retroviral oncogenes in humans. Hereditas. 1991;114:207-11.

Mouchiroud D, D' Onofrio G, Aissani B, Macaya G, Gautier C, Bernardi G. The distribution of genes in the human genome. Gene. 1991;100:181-7.

Musio A, Mariani T, Vezzoni P, Frattini A. Heterogeneous gene distribution reflects human genome complexity as detected at the cytogenetic level. Cytogenet Cell Genet. 2002;134:168-71.

Rafiee L, Mohsenzadeh S, Saadat M. Nonrandom gene distribution on human chromosomes. EXCLI J. 2008;7:151-3.

Rosenthal SL, Kamboh MI. Late-onset Alzheimer's disease genes and the potentially implicated pathways. Curr Genet Med Rep. 2014;2:85–101.

Saadat M. Chromosomal distribution of schizophrenia susceptibility loci. J Mol Neurosci. 2013;51:401-2.

Saadat M. Distributions of susceptibility loci of Parkinson's disease and multiple sclerosis on human chromosomes. EXCLI J. 2014;13:724-7.

Saccone S, Caccio S, Kusuda J, Andreozzi L, Bernardi G. Identification of the gene richest bands in human chromosomes. Gene. 1996;174:85-94.

Saify K, Saadat M. Non-random distribution of breast cancer susceptibility loci on human chromosomes. Breast Cancer Res Treat. 2012;136:315-8.

Shih RA, Belmonte PL, Zandi PP. A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. Int Rev Psychiatry. 2004;16:260-83.

Tai JJ, Hou CD, Wang-Wuu S, Wang CH, Leu SY, Wuu KD. A method for testing the nonrandomness of chromosomal breakpoints. Cytogenet Cell Genet. 1993;63:147-50.