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Letter to the editor:

DISTRIBUTIONS OF SUSCEPTIBILITY LOCI OF PARKINSON'S DISEASE AND MULTIPLE SCLEROSIS ON HUMAN CHROMOSOMES

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Dear Editor,

It has been suggested that genes are distributed non-randomly on human chromosomes (Hecht, 1988; Lima-de-Faria and Mitelman, 1988; Lima-de-Faria et al., 1991; Mouchiroud et al., 1991; Saccone et al., 1992; 1996; Musio et al., 2002; Rafiee et al., 2008). Recently we reported that polymorphic loci associated with susceptibility to either breast cancer (Saify and Saadat, 2012) or schizophrenia (Saadat, 2013) are non-randomly distributed on some human chromosome segments.

It is well established that Parkinson's disease (PD) is a complex multifactorial neurodegenerative disease that was considered the result of environmental and genetic factors (Siderowf, 2001; Warner and Schapira, 2003; Allam et al., 2005; Trinh and Farrer, 2013). Based on familial aggregation studies and the study of twins, it has been established that genetic elements have significant roles in the development of multiple sclerosis (MS) (Ascherio, 2013; Cree, 2014).

Several meta-analyses based on genetic polymorphisms have been widely performed to assess the association between particular gene variants and PD or MS risk. Some of these studies were indicating that the study polymorphisms were not associated with the risks of PD or MS. However, in other studies significant associations with risks of PD or MS, at least in a specific ethnic group were reported (Lill et al., 2012a; b). Taken together, we suggested that loci associated with the risk of PD or MS may be distributed non-randomly on human chromosomes. Therefore the present study was carried out.

Meta-analysis studies published up to February 2014 with information of genetic polymorphisms and PD risk were identified using Parkinson's Disease Research Forum (PDGene database http://www.pdgene.org) electronic database (Lill et al., 2012a). Information of genetic polymorphisms and MS risk was identified using MSGene database (http://www.msgene.org) electronic database (Lill et al., 2012b).

To evaluate the non-randomness distribution of susceptible loci on each chromosomal band(s) the method of Tai et al. (1993) was used. 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.

There were 881 studies concerning the associations between 915 genes (3446 polymorphisms) and risk of PD. Table 1 shows the genes with their genetic polymorphisms associated with susceptibility to PD in at least one ethnic group. There are 20 loci associated with risk of PD. Statistical analysis revealed that the PD susceptible loci distributed non-randomly on human chromosomes. Human chromosome segments 1q31-1q32 ($P<0.001$) and 17q21-q23

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(P<0.001) were bearing significantly higher numbers of susceptible loci for PD. There are four genes which associated with susceptibility to PD on 1q31-q32 (*SLC45A3*, *NUCKS1*, *SLC41A1*, and *PM20D1/ PARK16*). There are three genes which associated with susceptibility to PD on 17q21-q23 (*PLEKHM1*, *MAPT*, and *MED13*).

There were 789 studies concerning the associations between 809 genes (2907 polymorphisms) and susceptibility to MS. Table 2 shows the genes with their genetic polymorphisms associated with risk of MS in at least one ethnic group. There are 44 loci associated with MS risk. Statistical analysis revealed that the MS susceptible loci distributed non-randomly on human chromosomes. Human chromosome segments 1p22, 5p13, 17q12-21.2, 19p13, and 19q13 (P<0.001) were bearing significantly higher numbers of susceptible loci for MS. There are four genes which associated with MS risk on 5p13 (*IL7R*, *PTGER4*, *C7*, and *HEATR7B2*). There are three genes which associated with susceptibility to MS on each chromosomal segments of 1p22 (*EVI5*, *RPL5*, and *FAM69A*), 17q12-21.2 (*CCL8*, *CCL1*, and *STAT*), 19p13 (*VAV1*, *TYK2*, and *IFI30*) and 19q13 (*TGFB1*, *APOE*, and *LILRA3*).

Already the non-random distributions of polymorphic loci associated with both breast cancer (Saify and Saadat, 2012) and schizophrenia (Saadat, 2013), were reported. A mass screening test might be designed using genes located on above mentioned chromosome segments for diagnosis of PD and MS. It is suggested that using simultaneously polymorphisms of the genes located on the above mentioned chromosome segment can increase the sensitivity and specificity of the mass screening test for detecting high risk individuals for developing Parkinson's disease and multiple sclerosis.

Table 1: List of genes that associated with Parkinson's disease risk

Gene Symbol	Location	OMIM
CCDC21	1p36.1	-
GBA	1q21	606463
SLC45A3	1q32.1	605097
NUCKS1	1q32.1	611912
SLC41A1	1q31-q32	610801
PM20D1/PARK16	1q32	613164
STK39	2q24.3	607648
ACMSD (NR4A2)	2q22-q23	601828
MCCC1	3q25-q27	609010
GAK	4p16	602052
DGKQ	4p16.3	601207
BST1	4p15.32	600387
SNCA	4q21	163890
MMRN1	4q22.1	601456
HLA-DRB5	6p21.3	604776
LRRK2	12q12	609007
PLEKHM1	17q21.3	611466
MAPT	17q21.1	157140
MED13	17q22-q23	603808
MAOB	Xp11.23	309860

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Table 2: List of genes that associated with multiple sclerosis risk

Gene symbol	Location	OMIM
MMEL1	1p36.3	-
EVI5	1p22	602942
RPL5	1p22.1	603634
FAM69A	1p22.1	614542
CD58	1p13	153420
FCRL3	1q21.2-q22	606510
RGS1	1q31	600323
KIF21B	1q31-q32	608322
SLC4A5	2p13	606757
CXCR4	2q21	162643
CBLB	3q13.11	604491
TMEM39A	3q21.1	-
IL12A	3q25.33	161560
CXCL10	4q21	147310
IL7R	5p13	146661
PTGER4	5p13.1	601586
C7	5p13	217070
HEATR7B2	5p13.2	-
HLA-DRB1	6p21.3	142857
OLIG3	6q23.3	609323
IL7	8q21.12	146660
IL2RA	10p15.1	147730
CHUK	10q24	600664
INPP5A	10q26.3	600106
CD6	11q12.2	186720
TNFRSF1A	12p13.31	191190
KLRB1	12p13.31	602890
CYP27B1	12q13.1-q13.3	609506
SH2B3	12q24.12	605093
MPHOSPH9	12q24.31	605501
RGMA	15q26.1	607362
CLEC16A	16p13.13	611303
IL21R	16p12.1	605383
CCL8	17q12	602283
CCL1	17q12	182281
STAT3	17q21.2	102582
CD226	18q22.2	605397
VAV1	19p13.3	164875
TYK2	19p13.2	176941
IFI30	19p13.11	604664
TGFB1	19q13.2	190180
APOE	19q13.32	107741
LILRA3	19q13.42	604818
CD40	20q12-q13.2	109535

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CONFLICT OF INTEREST

No conflicts of interest exist.

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