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Letter to the editor:

NON-RANDOM DISTRIBUTION OF GASTRIC CANCER SUSCEPTIBLE LOCI ON HUMAN CHROMOSOMES

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Dear Editor,

It has been well established that many molecular alterations are involved in the etiology of cancers. Genetic studies indicated that gastric cancer (GC) has significant heritability in human populations (Graham et al., 1994; Drăghicescu et al., 1998; Gao et al., 2011) through different molecular and genetics features (Gigek et al., 2017). In order to find the genetic elements involved, many studies investigated the association of genetic variations of a wide range of candidate genes. Meta-analyses studies have shown significant associations of many polymorphisms of candidate loci with the risk of GC at least in a specific ethnic group.

Numerous data revealed the non-randomness distribution of genes 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). Previously our study group has reported that polymorphic loci which were associated with the risk of breast cancer (Saify and Saadat, 2012), Alzheimer's disease (Saadat, 2016), schizophrenia (Saadat, 2013), Parkinson's disease and multiple sclerosis (Saadat, 2014) are non-randomly dispersed on human chromosomes. Based on our knowledge, there is no published data about randomness of distribution of the GC susceptible loci on human chromosomes. Therefore the present study was carried out.

A literature database (PubMed) was searched for relevant studies (the last search was updated in February 2018). The following search terms were used: Gastric cancer, meta-analysis, and genetic polymorphism. The search was limited to articles published in English. There were significant associations between genetic polymorphisms of 64 genes and the risk of GC in at least one human ethnic groups. Table 1 summarized these studies.

To evaluate the randomness/non-randomness distribution of GC susceptible loci on chromosomes, the statistical method of Tai and his colleagues (1993) was used. The relative width of human chromosomal band was determined using the diagram of the International System for Chromosome Nomenclature (ISCN, 1981). P-values less than 0.05 were considered as significant differences.

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Table 1: List of polymorphic loci associated with susceptibility to gastric cancer

Symbol	OMIM	Location	Reference	Symbol	OMIM	Location	Reference
GSTM1	138350	1p13.3	Ribeiro et al., 2017	***TLR4***	603030	9q33.1	Zhou et al., 2014
LEPR	601007	1p31.3	Shi et al., 2014	***Fas***	134637	10q23.31	Tian et al., 2012
MTHFR	607093	1p36.22	Chen et al., 2015	***Cyp2C19***	124020	10q23.33	Wang et al., 2013
MTX1	600605	1q22	Mocellin et al., 2015	***PLCE1***	608414	10q23.33	Liu et al., 2014b
MUCIN-1	158340	1q22	Ye et al., 2017	***CYP2E1***	124040	10q26.3	Zhang et al., 2016a
FASLG	134638	1q24.3	Xu et al., 2014b	***GSTP1***	134660	11q13.2	Ma et al., 2013b
PTGS2	600262	1q31.1	Wang et al., 2015b	***CCND1***	168461	11q13.3	Zhang et al., 2016b
IL-10	124092	1q32.1	Namazi et al., 2018	***MMP7***	178990	11q22.2	Yang et al., 2014
PARP1	173870	1q42.12	Hua et al., 2014	***MMP1***	120353	11q22.2	Peng and Xu, 2015
DNMT3A	602769	2p23.3	Li et al., 2017	***HOTAIR***	611400	12q13.13	Qi et al., 2016
IL-1β	147720	2q14.1	Ma et al., 2017	***miR-196a2***	609687	12q13.13	Ma et al., 2013a
IL-1RN	147679	2q14.1	Zhang et al., 2012	***MDM2***	164785	12q15	Shen et al., 2014
CTLA-4	123890	2q33.2	Yan et al., 2013	***ALDH2***	100650	12q24.12	Wang et al., 2014
miR 149	615209	2q37.3	Xu et al., 2015	***XPG***	133530	13q33.1	Liang et al., 2018
hMLH1	120436	3p22.2	He et al., 2013	***APEX1***	107748	14q11.2	Dai et al., 2015
PPARG	601487	3p25.2	Wang et al., 2015a	***XRCC3***	600675	14q32.33	Cheng et al., 2015
ZBTB20	606025	3q13.31	Shi et al., 2017	***CYP1A1***	108330	15q24.1	Han et al., 2012
CXCL8	146930	4q13.3	Zhang et al., 2015	***NOD2***	605956	16q12.1	Liu et al., 2014a
ADH1	103700	4q23	Wang et al., 2014	***NQO1***	125860	16q22.1	Yadav et al., 2018
EGF	131530	4q25	Wu et al., 2015	***CDH1***	192090	16q22.1	Deng et al., 2014
CD14	158120	5q31.3	Gong et al., 2016	***TP53***	191170	17p13.1	Zhang et al., 2013
IL4	147780	5q31.1	Jia et al., 2017	***BRCA1***	113705	17q21.31	Xu et al., 2018
miR-146a	610566	5q33.3	Xie et al., 2017	***NME1***	156490	17q21.33	Shi et al., 2018
IL-17A	603149	6p12.2	Li et al., 2015	***ACE***	106180	17q23.3	Pabalan et al., 2015
IL-17F	606496	6p12.2	Li et al., 2015	***TIMP-2***	188825	17q25.3	Yang et al., 2016
VEGFA	192240	6p21.1	Liu et al., 2011b	***BIRC5***	603352	17q25.3	Xu et al., 2014a
CDKN1A	116899	6p21.2	Liu et al., 2011a	***TYMS***	188350	18p11.32	Mo et al., 2016

Table 1 (cont.): List of polymorphic loci associated with susceptibility to gastric cancer

Symbol	OMIM	Location	Reference		Symbol	OMIM	Location	Reference
TNF-α	191160	6p21.33	Wang et al., 2016		***MIR27A***	612153	19p13.12	Xu et al., 2015
LTA	153440	6p21.33	Lu et al., 2012		***DNMT1***	126375	19p13.2	Li et al., 2017
HspA1B	603012	6p21.33	Kuang et al., 2014		***TGFβ1***	190180	19q13.2	Chang et al., 2014
NAT2	612182	8p22	Yu et al., 2014		***XRCC1***	194360	19q13.31	Zhao et al., 2014
PSCA	602470	8q24.3	Qin et al., 2017		***DNMT3B***	602900	20q11.21	Li et al., 2016

Analysis revealed that the 64 susceptible loci were distributed non-randomly on chromosome segments. The 1q22 (P<0.001), 2q14.1 (P<0.001), 5q31-q33 (P<0.001), 6p12-p21 (P<0.001), 10q23 (P<0.001), 11q13-q22 (P=0.025), 12q13.13 (P<0.001), 16q22.1 (P<0.001), 17q21-q25 (P<0.001), 19p13 (P=0.025) and 19q13 (P=0.025) were bearing higher numbers of GC susceptible loci. The human chromosome segments 6p12-p21, 17q21-q25, and 11q13-q22 were bearing seven (*IL-17A*, *IL-17F*, *VEGFA*, *CDKN1A*, *TNF-α*, *LTA*, and *HspA1B*), five (*TP53*, *BRCA1*, *NME1*, *ACE*, *TIMP-2*, and *BIRC5*) and four (*GSTP1*, *CCND1*, *MMP7*, and *MMP1*) GC susceptible genes, respectively.

The current findings have two significant aspects:

1) Distribution of the susceptible genes is not random throughout the human chromosomes.

2) The present findings help investigators to design a mass screening test tool for finding high risk persons to GC using the genetic polymorphisms in above-mentioned segments.

Previously it has been reported that human chromosome segments 10q23.3-q24.3, 16q13-q22.1, 17q12-q23, 19q13.1-q13.4, 22q11.2-q13.2 were significantly bearing breast cancer susceptible loci (Saify and Saadat, 2012). Comparing with the present findings, the segments 10q23, 16q22.1, 17q12-q23, and 19q13 revealed significant associations with both gastric and breast cancers.

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Conflict of interest

None.

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