Rheumatol Int (2016) 36:1657–1662
DOI 10.1007/s00296-016-3570-8

Rheumatology INTERNATIONAL

GENES AND DISEASE

Gene–gene interaction between CD40 and CD226 gene on systemic lupus erythematosus in the Chinese Han population

Daqing Nie[1] · Hongbo Li[1] · Guixiu Yan[2] · Zhengyi Wang[3] · Zhaomin He[4] · Wenyu Zhou[5]

Received: 22 June 2016 / Accepted: 24 September 2016 / Published online: 8 October 2016

Abstract The aim of the study is to investigate the impact of CD40 and CD226 gene single-nucleotide polymorphism (SNP) and additional gene–gene interaction on systemic lupus erythematosus (SLE) risk in Chinese Han populations. Three SNPs were selected for genotyping in the case–control study: rs4810485, rs763361, and rs3765456. Logistic regression was performed to investigate association between SNP within CD40 and CD226 and SLE. Generalized multifactor dimensionality reduction (GMDR) was used to analyze the interaction among three SNPs. Logistic regression analysis showed that SLE risk was significantly higher in carriers of T allele of rs4810485 in CD40 gene than those with GG genotype (GT+ TT vs GG), adjusted OR (95 % CI) 1.84 (1.40–2.29). In addition, we also found SLE risk was also significantly higher in carriers of rs763361 T allele within CD226 gene than those with CC genotype (CT+ TT vs CC), adjusted OR (95 % CI) 1.89 (1.38–2.13). GMDR analysis suggested a potential gene–gene interaction between rs4810485 and rs763361. Overall, cross-validation consistency of the two-locus model was 10/10, and the testing accuracy was 62.17 %. We also found that subjects with GT or TT of rs4810485 and CT or TT of rs763361 genotype have the highest SLE risk, compared with subjects with GG of rs4810485 and CC of rs763361 genotype, and OR (95 % CI) was 2.14 (1.67–3.08), after covariates adjustment. Our results support an important association of rs4810485 in CD40 gene and rs763361 in CD226 gene polymorphism, combined effect of rs4810485 and rs763361 with increased risk of SLE.

Keywords SLE · CD40 · CD226 · Polymorphism · Interaction

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease and is characterized by production of pathogenic autoantibodies and deposits of immune complexes. The cause of SLE is unknown, but strong genetic and environmental components are involved [1]. SLE is estimated to affect about one in 2000 people in some populations, and the clinical presentation is diverse and can sometimes be fatal [2]. Despite the fact that SLE has been intensively studied, the underlying cause of this autoimmune disease remains elusive [3]. Epidemiological evidence, together with recent linkage and association studies, suggested that susceptibility to SLE in humans is strongly influenced by genetic factors [4]. The major histocompatibility complex (MHC) and the human leukocyte antigen (HLA) system have been confirmed as important genetic risk factors associated with SLE. However, the HLA system constitutes 40 % of the overall estimated genetic risk for SLE, and it has been suggested that a substantial proportion of

✉ Wenyu Zhou
zhouwywy667@163.com

1 Department of Rheumatism in the Affiliated Hospital, Changchun University of Chinese Medicine, Changchun 130000, Jilin, China

2 Department of Nursing, College of Humanities and Sciences, Northeast Normal University, Changchun 130000, China

3 College of Nursing and Health Science, Nanfang College, Sun Yat-Sen University, Guangzhou, China

4 College of Nursing and Health Science, The University of Texas at Tylar, 3900 University Blvd, Tyler, TX, USA

5 Department of Urology and Rheumatism, The Central Hospital of Wuhan, No. 26 Shengli Street, Wuhan 430014, Hubei, China

SLE genetic susceptibility is encoded by non-HLA genes [5]. The rs763361 single-nucleotide polymorphism (SNP) within the CD226 gene has recently been reported as a novel susceptibility locus for multiple autoimmune diseases [6]. It has also been reported that CD226 expression deficiency causes high sensitivity to apoptosis in NK T cells obtained from patients with SLE, providing supporting evidence for the role of CD226 in autoimmune diseases [7].

CD40 is a member of the tumor necrosis superfamily, and its gene is located on chromosome 20q12-13.2 [8]. It has nine exons of between 29 and 412 bp in length [9]. CD40 is expressed on B cells, monocytes, dendritic cells, and endothelial cells [10]. CD40 plays an important role in T cell-dependent B cell humoral responses, regulation of cytokines, growth factor production in monocytes, and modulation of adhesion molecule density on the endothelial cell surface [11]. CD40 may be involved in the pathogenesis and exacerbation of different human autoimmune diseases, including SLE [12]. Therefore, the single-nucleotide polymorphisms (SNPs) modulating CD40 gene expression may increase the risk of autoimmune disease. Also several studies have focused on the association between CD40 and CD226 gene polymorphism and SLE risk in different populations; however, no study focused on the impact of gene–gene interaction between CD40 and CD226 gene polymorphism on SLE risk was conducted in Chinese populations. So, the aim of this study was to investigate the impact of CD40 and CD226 gene SNP and additional gene–gene interaction on SLE risk in Chinese Han populations.

Materials and methods

Subjects

This was a case–control study. Participants were consecutively recruited between July 2008 and June 2014 from the Affiliated Hospital to Changchun University of Chinese Medicine. Consecutive, unrelated patients diagnosed with SLE according to classification criteria by the American College of Rheumatology (ACR) [13, 14] were included from the in- and outpatient clinics of a tertiary referral rheumatology center with special interest in SLE. Prevalent in- or outpatients aged more than 18 years were eligible for inclusion. The control group had neither family history nor symptoms related to SLE and was randomly selected from the same regions with nearly 1:1 matched to cases on the basis of age (±3 years) and sex. Blood samples were collected from each participant. At last, a total of 646 subjects (125 males, 521 females), with a mean age of 43.1 ± 11.1 years old, were selected, including 326 SLE patients and 320 normal subjects. Blood samples were collected for genotyping of polymorphisms from each participant. Written informed consent was obtained from each individual prior to participation in the study. This study was approved by the ethics committee of Changchun University of Chinese Medicine.

Data on demographic information, diet style, and family history of SLE for all participants were obtained using a questionnaire administered by trained staffs. Cigarette smokers were those who self-reported smoking cigarettes at least once a day for 1 year or more. Alcohol consumption was expressed as the sum of milliliters of alcohol per week from wine, beer, and spirits. Body weight, height, and waist circumference (WC) were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. WC was measured two times at 1 cm above the umbilicus at minimal respiration by trained observers; the mean of the two WC measurements was utilized in the analysis. Blood samples were collected in the morning after at least 8 h of fasting.

Genomic DNA extraction and genotyping

We selected SNPs within the CD40 and CD226 gene, which has been reported that it associated with SLE and minor allele frequency (MAF) >4 %. Two SNPs of CD40 gene and one SNP of CD226 gene were selected for genotyping in the study: rs4810485, rs763361, and rs3765456. All SNPs were detected by TaqMan fluorescence probe. ABI Prism 7000 software and allelic discrimination procedure were used for genotyping of fore-mentioned three SNPs. Probe sequences of all SNPs are shown in Table 1. Genomic DNA from participants was extracted from EDTA-treated whole blood, using the DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. A 25-μl reaction mixture including 1.25 μl SNP Genotyping Assays (20×), 12.5 μl Genotyping Master Mix (2×), 20 ng DNA, and the conditions was as follows: initial denaturation for 10 min and 95 °C, denaturation for 15 s and 92 °C, annealing and extension for 90 s and 60 °C, 50 cycles.

Statistical analysis

The mean and SD were calculated for normally distributed continuous variables, and percentages were calculated for categorical variables. The categorical data were analyzed using Chi-squared test. Further, continuous variables were analyzed using Student's *t* test. Hardy–Weinberg equilibrium (HWE) was performed by using SNPStats (available online at http://bioinfo.iconcologia.net/SNPstats). Logistic regression was performed to investigate association between SNP and SLE. Generalized multifactor dimensionality reduction (GMDR) [15] was used to analyze the

Table 1 Description and probe sequence for three SNPs used for TaqMan fluorescence probe analysis

SNP ID	Position	Exon/intron	Nucleotide substitution	Probe sequence
CD40				
rs4810485	20:46119308	Intron variant	G>T	5′-CCTACTTTAGAGGGCTGTAGATTCC[G/T] GCCTGAAGCCTGGGCAGGAATGACC-3′
rs3765456	20:46128252	Intron variant	G>A	5′-GAGTCCTCAGGTGGGGAGGTGTTGG[A/G] GGAGGGAGGGGAGACCACCTGTTTC-3′
CD226				
rs763361	18:69864406	Missense	C>T	5′-TCCATGGATTGATTGGTAGGTTGAC[C/T] GGTAGAGATGGGACTTCTATAGTTA-3′

Table 2 General characteristics of study participants in case and control group

Variables	SLE cases ($n = 326$)	Controls ($n = 320$)	p values
Age (years)	43.8 ± 10.8	42.6 ± 11.4	0.170
Males *N* (%)	60 (18.4)	65 (20.3)	0.539
Smoke *N* (%)	37 (11.4)	40 (12.5)	0.652
Alcohol consumption *N* (%)	31 (9.5)	35 (10.9)	0.549
High-fat diet *N* (%)	47 (14.4)	38 (11.9)	0.339
Low-fiber diet *N* (%)	56 (17.2)	71 (22.2)	0.109
WC (cm)	83.9 ± 12.8	85.1 ± 13.3	0.243
BMI (kg/m^2)	23.7 ± 6.6	24.3 ± 6.3	0.238
Marriage			0.054
Unmarried	26 (8.0)	32 (10.0)	
Married	260 (79.7)	266 (83.1)	
Divorced/widowed	40 (12.3)	22 (6.9)	

Mean ± standard deviation for age, WC, BMI

WC waist circumference, *BMI* body mass index

interaction among three SNPs, and cross-validation consistency, the testing balanced accuracy, and the sign test, to assess each selected interaction, were calculated.

Results

A total of 646 subjects (125 males, 521 females), with a mean age of 43.1 ± 11.1 years old, were selected, including 326 SLE patients and 320 normal subjects. Participants' characteristics stratified by cases and controls are shown in Table 2. There is no significant difference between case group and control group in age, gender, smoking and drinking status, high-fat and low-fiber diet, BMI, WC, and marriage.

All genotypes were distributed according to Hardy–Weinberg equilibrium in controls ($p > 0.05$). The frequencies for T allele of **rs4810485** in CD40 gene were significantly higher in SLE cases (28.8 vs 19.5 %) than that in controls, and T allele of **rs763361** in CD226 gene was also significantly higher in SLE cases (30.1 vs 20.3 %) than that in controls (Table 3). Logistic regression analysis showed that SLE risk was significantly higher in carriers of T allele of **rs4810485** in CD40 gene than those with GG genotype (GT+ TT vs GG), adjusted OR (95 % CI) **1.84 (1.40–2.29)**. In addition, we also found SLE risk was also significantly higher in carriers of T allele of **rs763361** in CD226 gene than those with CC genotype (CT+ TT versus CC), adjusted OR (95 % CI) **1.89 (1.38–2.13)**. However, we did not find any significant association between rs3765456 and SLE risk after covariates adjustment.

We employed the GMDR analysis to investigate the impact of the interaction among three SNPs after adjustment for covariates. Table 4 summarizes the results obtained from GMDR analysis, and we found that there was a significant two-locus model ($p = 0.0100$) involving rs4810485 and rs763361, indicating a potential gene–gene interaction between rs4810485 and rs763361. Overall, the cross-validation consistency of this two-locus model was 10/10, and the testing accuracy was 62.17 %. In order to obtain the odds ratios and 95 % CI for the joint effects of the two SNPs on SLE risk, we conducted interaction analysis between two SNPs by using logistic regression. We found that subjects with GT or TT of rs4810485 and CT or TT of rs763361 genotype have the highest SLE risk, compared with subjects with GG of rs4810485 and CC of rs763361 genotype, and OR (95 % CI) was 2.14 (1.67–3.08), after covariates adjustment (Table 5).

Discussion

In current study, we investigated the impact of CD40 and CD226 gene polymorphism on SLE risk. We found that SLE risk was significantly higher in carriers of **rs4810485** T allele in CD40 gene than those with GG and was also significantly higher in carriers of **rs763361** T allele in CD226 gene than those with CC. However, we did not find any significant association between rs3765456 and SLE risk

Table 3 Genotype and allele frequencies of three SNPs between case and control group

SNP	Genotypes and alleles	Frequencies *N* (%)		OR (95 % CI)*	HW test for controls
		Control ($n = 320$)	Case ($n = 326$)		
rs3765456					
	GG	188 (58.8)	173 (53.1)	1.00	0.288
	GA	110 (34.4)	121 (37.1)	1.27 (0.94–1.68)	
	AA	22 (6.8)	32 (9.8)	1.43 (0.91–1.87)	
	GA + AA	132 (41.2)	153 (46.9)	1.31 (0.93–1.71)	
	G	486 (75.9)	467 (71.6)		
	A	154 (24.1)	185 (28.4)		
rs4810485					
	GG	209 (65.3)	168 (51.5)	1.00	0.524
	GT	97 (30.3)	128 (39.3)	**1.72 (1.32–2.15)**	
	TT	14 (4.4)	30 (9.2)	**2.18 (1.63–2.84)**	
	GT + TT	111 (34.7)	158 (48.5)	**1.84 (1.40–2.29)**	
	G	515 (80.5)	164 (71.2)		
	T	125 (19.5)	188 (28.8)		
rs763361					
	CC	208 (65.0)	166 (50.9)	1.00	0.098
	CT	94 (29.4)	124 (38.1)	**1.58 (1.23–1.90)**	
	TT	18 (5.6)	36 (11.0)	**2.09 (1.65–2.93)**	
	CT + TT	112 (35.0)	160 (49.1)	**1.89 (1.38–2.13)**	
	C	510 (79.7)	456 (69.9)		
	T	130 (20.3)	196 (30.1)		

Bold values indicate $p < 0.05$

* Adjusted for gender, age, smoking, high-fat diet, low-fiber diet, alcohol status, BMI, and WC

Table 4 Best gene–gene interaction models in GMDR model

Locus no.	Best combination	Cross-validation consistency	Testing accuracy	*p* values*
2	rs4810485 rs763361	**10/10**	**0.6217**	**0.0100**
3	rs4810485 rs763361 rs3765456	9/10	0.5399	0.0547

Bold values indicate $p < 0.05$

* Adjusted for gender, age, smoking, high-fat diet, low-fiber diet, alcohol status, BMI, and WC

Table 5 Interaction analysis for rs4810485 and rs763361 by using logistic regression

rs4810485	rs763361	OR (95 % CI)*	*p* values
GG	CC	1.00	–
GT or TT	CC	1.20 (1.08–1.67)	0.030
GG	CT or TT	1.53 (1.28–1.91)	<0.001
GT or TT	CT or TT	2.14 (1.67–3.08)	<0.001

* Adjusted for gender, age, smoking, high-fat diet, low-fiber diet, alcohol status, BMI, and WC

after covariates adjustment. Till now, just two studies have focused on the association between CD40 SNP and SLE risk, and the results on association between CD40 gene and SLE were inconsistent [16, 17]. Piotrowski et al. [16] indicated that the CD40 T variant might be negatively associated with some clinical disease manifestations in patients with SLE. CD40 has been identified as a new susceptibility locus with SLE in Greek and Turkish populations. However, Vazgiourakis et al. [17] indicated that the rs4810485 minor allele T is underrepresented in SLE and correlates with reduced CD40 expression in peripheral blood monocytes and B cells, with potential implications for the regulation of aberrant immune responses in the disease. This result was inconsistent with that in current study. The rs3765456 was another SNP in CD40 which was reported in the previous study. Joo et al. [18] conducted a study in Korean population and indicated that CD40 gene polymorphisms are possible risk factors for SLE development,

especially rs3765456 in the dominant model. CD40 polymorphisms are also associated with SLE clinical manifestation, mainly nephritis and arthritis. However, in this study, we found that the rs3765456 was not associated with SLE risk, although the frequencies for the A allele of rs3765456 in CD40 gene were higher in SLE cases than that in control; however, there was no significance.

CD226 (also known as the DNAX accessory molecule-1; DNAM-1) plays a role as a costimulatory molecule and is expressed in cells of haematopoietic origin, including T lymphocytes, natural. Several SNPs in CD226 have been reported, and investigation on association between CD226 SNPs and SLE and other autoimmune diseases was conducted in different populations. In the SNPs within CD226, rs763361 was a SNP which was most studied previously. Song [19] and Qiu et al. [20] conducted a meta-study and indicated that the CD226 rs763361 polymorphism confers susceptibility to autoimmune disease in Europeans, South Americans, and Asians, and in particular, shows that the CD226 rs763361 polymorphism is associated with SLE and other autoimmune diseases. These results support the existence of an association between the CD226 gene and a subgroup of autoimmune diseases. Du et al. [21] conducted a study in Chinese population and suggested that polymorphism of Gly307Ser (rs763361) in exon 7 of the CD226 gene may be associated with the development of SLE. Maiti et al. [22] also demonstrate that the coding variant rs763361 in CD226 gene is associated with multiple ADs in non-European populations.

SLE risk was influenced by many genetic factors and both CD40 and CD226 were associated with increased SLE risk, so it was necessary to investigate the impact of gene–gene interaction between CD40 and CD226 gene on SLE risk. In current study, we found a significant gene–gene interaction between rs4810485 and rs763361, and subjects with GT or TT of rs4810485 and CT or TT of rs763361 genotype have the highest SLE risk, compared with subjects with GG of rs4810485 and CC of rs763361 genotype. To our knowledge, this was the first study for investigating interaction between CD40 and CD226 gene on SLE risk in Chinese population. To date, just one study [23] focused on the gene–gene interaction on another autoimmune diseases risk (rheumatoid arthritis), which was conducted for Colombian population and provided evidence for gene–gene interaction between SNP in MMEL1 (rs3890745) and C80rf13-BLK gene.

Several limitations of this study should be considered. Firstly, limited number of SNP in CD40 and CD226 gene was chosen in this study. More SNPs, not only in CD40 and CD226, but also in others SLE-related gene, should be included in the further studies. Secondly, environmental factors should be included in the study, and gene–environment interaction should be investigated.

In conclusion, the results of current study indicated an important association of rs4810485 in CD40 gene and rs763361 in CD226 gene polymorphism, combined effect of rs4810485 and rs763361 with increased risk of SLE.

Acknowledgments The writing of this paper was supported by the Affiliated Hospital to Changchun University of Chinese Medicine. We thank all the partners and staffs who help us in the process of this study.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Zhao J, Wu H, Khosravi M, Cui H, Qian X, Kelly JA, Kaufman KM, Langefeld CD, Williams AH, Comeau ME, Ziegler JT, Marion MC, Adler A, Glenn SB, Alarcón-Riquelme ME, BIOLUPUS Network; GENLES Network, Pons-Estel BA, Harley JB, Bae SC, Bang SY, Cho SK, Jacob CO, Vyse TJ, Niewold TB, Gaffney PM, Moser KL, Kimberly RP, Edberg JC, Brown EE, Alarcon GS, Petri MA, Ramsey-Goldman R, Vilá LM, Reveille JD, James JA, Gilkeson GS, Kamen DL, Freedman BI, Anaya JM, Merrill JT, Criswell LA, Scofield RH, Stevens AM, Guthridge JM, Chang DM, Song YW, Park JA, Lee EY, Boackle SA, Grossman JM, Hahn BH, Goodship TH, Cantor RM, Yu CY, Shen N, Tsao BP (2011) Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. PLoS Genet 7:e1002079
2. Kotzin BL (1996) Systemic lupus erythematosus. Cell 85:303–306
3. Sekigawa I, Naito T, Hira K, Mitsuishi K, Ogasawara H, Hashimoto H, Ogawa H (2004) Possible mechanisms of gender bias in SLE: a new hypothesis involving a comparison of SLE with atopy. Lupus 13:217–222
4. Wakeland EK, Liu K, Graham RR, Behrens TW (2001) Delineating the genetic basis of systemic lupus erythematosus. Immunity 15:397–408
5. Wandstrat A, Wakeland E (2001) The genetics of complex autoimmune diseases: non-MHC susceptibility genes. Nat Immunol 2:802–809
6. Hafler JP, Maier LM, Cooper JD, Plagnol V, Hinks A, Simmonds MJ, Stevens HE, Walker NM, Healy B, Howson JM, Maisuria M, Duley S, Coleman G, Gough SC, International Multiple Sclerosis Genetics Consortium (IMSGC), Worthington J, Kuchroo VK, Wicker LS, Todd JA (2009) CD226 Gly307Ser association with multiple autoimmune disease. Genes Immun 10:5–10
7. Tao D, Shangwu L, Qun W, Yan L, Wei J, Junyan L, Feili G, Boquan J, Jinquan T (2005) CD226 expression deficiency causes high sensitivity to apoptosis in NK T cells from patients with systemic lupus erythematosus. J Immunol 174:1281–1290

8. Shuang C, Dalin L, Weiguang Y, Zhenkun F, Fengyan X, Da P, Li D (2011) Association of CD40 gene polymorphisms with sporadic breast cancer in Chinese Han women of Northeast China. PLoS One 6:e23762
9. Park JH, Chang HS, Park CS, Jang AS, Park BL, Rhim TY, Uh ST, Kim YH, Chung IY, Shin HD (2007) Association analysis of CD40 polymorphisms with asthma and the level of serum total IgE. Am J Respir Crit Care Med 175:775–782
10. Foy TM, Aruffo A, Bajorath J, Buhlmann JE, Noelle RJ (1996) Immune regulation by CD40 and its ligand GP39. Annu Rev Immunol 14:591–617
11. Schonbeck U, Libby P (2001) The CD40/CD154 receptor/ligand dyad. Cell Mol Life Sci 58:4–43
12. Peters AL, Stunz LL, Bishop GA (2009) CD40 and autoimmunity: the dark side of a great activator. Semin Immunol 21:293–300
13. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–1277
14. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725
15. Lou XY, Chen GB, Yan L, Ma JZ, Zhu J, Elston RC, Li MD (2007) A generalized combinatorial approach for detecting gene-by gene and gene-by-environment interactions with application to nicotine dependence. Am J Hum Genet 80(6):1125–1137
16. Piotrowski P, Lianeri M, Wudarski M, Olesinska M, Jagodzinski PP (2013) Single nucleotide polymorphism of CD40 region and the risk of systemic lupus erythematosus. Lupus 22(3):233–237
17. Vazgiourakis VM, Zervou MI, Choulaki C, Bertsias G, Melissourgaki M, Yilmaz N, Sidiropoulos P, Plant D, Trouw LA, Toes RE, Kardassis D, Yavuz S, Boumpas DT, Goulielmos GN (2011) A common SNP in the CD40 region is associated with systemic lupus erythematosus and correlates with altered CD40 expression: implications for the pathogenesis. Ann Rheum Dis 70(12):2184–2190
18. Joo YB, Park BL, Shin HD, Park SY, Kim I, Bae SC (2013) Association of genetic polymorphisms in CD40 with susceptibility to SLE in the Korean population. Rheumatology (Oxford) 52(4):623–630
19. Song G, Bae SC, Choi S, Ji J, Lee Y (2012) Association between the CD226 rs763361 polymorphism and susceptibility to autoimmune diseases: a meta-analysis. Lupus 21(14):1522–1530
20. Qiu ZX, Zhang K, Qiu XS, Zhou M, Li WM (2013) CD226 Gly307Ser association with multiple autoimmune diseases: a meta-analysis. Hum Immunol 74(2):249–255
21. Du Y, Tian L, Shen LX, Wang F, Yu LK, Song Y, Zhu JF, Du R (2011) Association of the CD226 single nucleotide polymorphism with systemic lupus erythematosus in the Chinese Han population. Tissue Antigens 77(1):65–67
22. Maiti AK, Kim-Howard X, Viswanathan P, Guillén L, Qian X, Rojas-Villarraga A, Sun C, Cañas C, Tobón GJ, Matsuda K, Shen N, Cherñavsky AC, Anaya JM, Nath SK (2010) Non-synonymous variant (Gly307Ser) in CD226 is associated with susceptibility to multiple autoimmune diseases. Rheumatology (Oxford) 49(7):1239–1244
23. Deshmukh HA, Maiti AK, Kim-Howard XR, Rojas-Villarraga A, Guthridge JM, Anaya JM, Nath SK (2011) Evaluation of 19 autoimmune disease-associated loci with rheumatoid arthritis in a Colombian population: evidence for replication and gene–gene interaction. J Rheumatol 38(9):1866–1870