C-type lectin receptors and RIG-I-like receptors: new points on the oncogenomics map

Anton G Kutikhin
Arseniy E Yuzhalin
Department of Epidemiology, Kemerovo State Medical Academy, Kemerovo, Russian Federation

Abstract: The group of pattern recognition receptors includes families of Toll-like receptors, NOD-like receptors, C-type lectin receptors, and RIG-I-like receptors. They are key sensors for a number of infectious agents, some of which are oncogenic, and they launch an immune response against them, normally promoting their eradication. Inherited variations in genes encoding these receptors and proteins and their signaling pathways may affect their function, possibly modulating cancer risk and features of cancer progression. There are numerous studies investigating the association of single nucleotide polymorphisms within or near genes encoding Toll-like receptors and NOD-like receptors, cancer risk, and features of cancer progression. However, there is an almost total absence of articles analyzing the correlation between polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors and cancer risk or progression. Nevertheless, there is some evidence supporting the hypothesis that inherited C-type lectin receptor and RIG-I-like receptor variants can be associated with increased cancer risk. Certain C-type lectin receptors and RIG-I-like receptors recognize pathogen-associated molecular patterns of potentially oncogenic infectious agents, and certain polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors may have functional consequences at the molecular level that can lead to association of such single nucleotide polymorphisms with risk or progression of some diseases that may modulate cancer risk, so these gene polymorphisms may affect cancer risk indirectly. Polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors thereby may be correlated with a risk of lung, oral, esophageal, gastric, colorectal, and liver cancer, as well as nasopharyngeal carcinoma, glioblastoma, multiple myeloma, and lymphoma. The list of the most promising polymorphisms for oncogenic investigations may include rs1926736, rs2478577, rs2437257, rs691005, rs2287886, rs735239, rs4804803, rs16910526, rs36055726, rs11795404, and rs10813831.

Keywords: C-type lectin receptors, RIG-I-like receptors, cancer, single nucleotide polymorphisms, genetic variation, inflammation

Brief description of pattern recognition receptors

Pattern recognition receptors directly recognize common antigen determinants of virtually all classes of pathogens (so-called pathogen-associated molecular patterns, or PAMPs). In addition, they recognize endogenous ligands, usually releasing during cell stress and known as damage-associated molecular patterns. As a result of ligand recognition, pattern recognition receptors initiate an immune response via specific intracellular signaling pathways, and so have a key role in initiation and promotion of septic and aseptic inflammation. Pattern recognition receptors also have a number of other vital functions apart from participation in the immune response, in that they may regulate many aspects of cell proliferation, survival, apoptosis, autophagy, generation
of reactive oxygen species, pyroptosis, angiogenesis, and, consequently, tissue remodeling and repair.1-4 There are four main groups of pattern recognition receptors, ie, Toll-like receptors, NOD-like receptors, C-type lectin receptors, and RIG-I-like receptors, and genes encoding them are broadly expressed, eg, in epithelial cells, endothelial cells, keratinocytes, lymphocytes, granulocytes, fibroblasts, and neurons.1,4 A summary of the most modern conceptual data about members of these groups and about their structure and function can be obtained from recent comprehensive reviews by Kawai and Akira,1 Elinav et al,2 Osorio et al,3 and Loo and Gale.4

The completion of the human genome project and widespread distribution of genotyping technologies have led to an enormous number of studies devoted to associating inherited gene polymorphisms with various diseases. Single nucleotide polymorphisms may result in amino acid substitutions altering protein function or splicing, and they can also change the structure of enhancer sequences during splicing and affect mRNA stability.6 Single nucleotide polymorphisms may alter transcription factor binding motifs, change the efficacy of enhancer or repressor elements,7 and alter the structure of translation initiation codons that may lead to downregulation of wild-type transcripts.8 Gene polymorphisms located in leucine-rich repeats constituting ectodomains of many pattern recognition receptors may affect the ability of these receptors to bind pathogens they normally recognize,9 single nucleotide polymorphisms in transmembrane domains can lead to defects of intracellular receptor transport that prevent receptors localizing to the cell membrane,10 and, finally, polymorphisms in the cytosolic domains may result in altered interactions with adaptor proteins or in disrupted receptor dimerization. Therefore, there are many avenues by which single nucleotide polymorphisms may alter pattern recognition receptor expression and activity. Because pattern recognition receptors recognize a number of oncogenic infectious agents and launch an immune response against them, inherited variation in their structure may modulate cancer risk and, possibly, influence cancer progression. In addition, pattern recognition receptors bind a lot of endogenous ligands,1,4 so polymorphisms of genes encoding them can affect risk and/or progression of some autoimmune disorders and, consequently, cancer risk and/or progression, given that there is a fundamental and epidemiological association between many autoimmune diseases and cancer risk.

The problem
Although there are a lot of studies investigating the association between single nucleotide polymorphisms in genes encoding Toll-like receptors and NOD-like receptors and the risk and features of cancer progression, there is an almost complete absence of articles analyzing the correlation between polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors and cancer risk or progression. This can be explained by the fact that the first wave of studies devoted to the association of polymorphisms of genes encoding Toll-like receptors and NOD-like receptors with cancer risk appeared only in 2004, and the number of such papers was relatively small until 2008. In addition, known hypotheses about the infectious agents causing human cancer and their recognition by pattern recognition receptors suggested that Toll-like receptors and NOD-like receptors should play a major role in the immune response against biological carcinogens. However, more recent findings concerning specific potentially carcinogenic ligands of C-type lectin receptors and RIG-I-like receptors were only obtained in the last few years,3,4 so there has not been enough time as yet to conduct comprehensive investigations between single nucleotide polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors and cancer risk.

However, there is some evidence supporting the hypothesis that inherited features of C-type lectin receptor and RIG-I-like receptor structure can be associated with increased cancer risk.

First premise: specific ligands
Certain C-type lectin receptors and RIG-I-like receptors recognize PAMPs of oncogenic infectious agents.3,4,11,12 C-type lectin receptors:
- MRC1 (CD206, CLEC13D, mannose receptor) and PAMPs of Mycobacterium tuberculosis, Klebsiella pneumoniae, Streptococcus pneumoniae, Candida albicans, human immunodeficiency virus type-1 (HIV-1)
- CD207 (CLEC4K, langerin) and PAMPs of Candida spp, HIV-1
- LY75 (CD205, CLEC13B, DEC-205) and PAMPs of HIV-1
- CD209 (CLEC4L, DC-SIGN) and PAMPs of Mycobacterium spp, Schistosoma mansoni, C. albicans, HCV, HIV-1, cytomegalovirus
- CLEC7A (Dectin-1) and PAMPs of Mycobacterium spp
- CLEC1B (CLEC-2) and PAMPs of HIV-1
- CLEC6A (CLEC4N, Dectin-2) and PAMPs of Mycobacterium tuberculosis, C. albicans, Paracoccidioides brasiliensis, Histoplasma capsulatum
- CLEC4E (Mincle) and PAMPs of Mycobacterium tuberculosis and C. albicans
- CLEC4A (DCIR) and PAMPs of HIV-1
RIG-I-like receptors:

- RIG-I and PAMPs of Epstein–Barr virus and hepatitis C virus

On the basis of known associations between inherited structural variations in Toll-like receptors and NOD-like receptors and cancer risk,1,2 and according to data about cancer types caused by carcinogenic infectious agents,3,11,12 it is possible to suggest that risk of lung cancer may be modulated by polymorphisms of the MRC1, CD209, CLEC7A, CLEC6A, and CLEC4E genes, oral cancer risk by single nucleotide polymorphisms of the MRC1, CD207, CD209, CLEC6A, and CLEC4E genes, risk of glioblastoma and colorectal cancer by polymorphisms of the CD209 gene, hepatocellular carcinoma risk by polymorphisms of the CD209 and RIG-I genes, and risk of lymphoma, multiple myeloma, nasopharyngeal carcinoma, and esophageal and gastric cancer by single nucleotide polymorphisms of the RIG-I gene. In addition, single nucleotide polymorphisms of MRC1, CD207, LY75, CD209, CLEC1B, and CLEC4A genes may correlate with cancer types associated with HIV-1 infection.

Second premise: polymorphisms affecting function

Certain polymorphisms of genes indicated above may have functional consequences on the molecular level that can lead to association of such single nucleotide polymorphisms with risk or progression of some diseases that may modulate cancer risk, so these gene polymorphisms may affect cancer risk indirectly. In addition, polymorphisms of these genes correlating with diseases that are not related to cancer risk may also be useful in oncogenomics because they may have functional consequences at the molecular level as well, although they have not been investigated in relation to association with cancer risk or progression.

For instance, it was suggested that variant alleles of MRC1 rs2477637, rs2253120, rs2477664, rs692527, rs1926736, and rs691005 gene polymorphisms are associated with development of asthma13 (eg, variant A allele of rs1926736 was connected with decreased asthma risk). In addition, Alter et al14 found that the variant A allele (S396) of rs1926736, and rs691005 gene polymorphisms are associated with a lower leprosy risk and, conversely, G allele (G396) correlates with increased risk of this disease. Interestingly, G396 did not influence leprosy risk in combination with T399 and L407 (amino acids resulting from variant alleles of rs2478577 and rs2437257, respectively).14 The authors noted that all three of these MRC1 gene single nucleotide polymorphisms map to the second C-type lectin domain (CTLD2) of the MRC1 protein, with their in vitro results suggesting that a direct interaction between CTLD2 and an accessory receptor molecule is necessary in order for microbial ligand recognition to occur.14 It is logical to propose that such interaction would be sensitive to G396 only in the context of the A399-F407 haplotype, and not in the context of the T399-L407 haplotype.14 Thus, rs1926736 may have substantial functional consequences at the molecular level, but this depends on its relationship with other single nucleotide polymorphisms in the same exon. Finally, Hattori et al15 showed that a variant allele of rs691005 polymorphism, located within the 3′ untranslated region of the MRC1 gene, is associated with a higher risk of sarcoidosis. Because of its location, it is feasible that this single nucleotide polymorphism may alter the regulatory binding sequence and influence mRNA expression.15

The only study investigating the association of polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors with cancer risk is a study by Xu et al.16 They investigated single nucleotide polymorphisms of the CD209 gene and found that the GG genotype of the rs2287886, AA genotype of the −939 promoter polymorphism, and the G allele of the rs735239 single nucleotide polymorphism were connected with higher nasopharyngeal carcinoma risk.16 Polymorphisms in the promoter of the CD209 gene and in the CD209 gene were also associated with hemorrhage in patients with dengue fever (G allele of rs4804803),17,18 modulated tuberculosis risk (G allele of rs4804803, A allele of rs735239),19–21 higher celiac disease risk in HLA-DQ2-negative cases (G allele of rs4804803),22 increased ulcerative colitis risk in HLA-DR3-positive patients (G allele of rs4804803),23 higher susceptibility to cytomegalovirus infection (G allele of rs735240 and C allele of rs2287886),24 protection from lung cavitation20 and fever during tuberculosis25 (GG genotype and G allele of rs4804803), decreased HIV-1 infection risk (GG genotype of rs4804803),21 accelerated progression to acquired immune deficiency syndrome in HIV-1-infected hemophiliacs (C allele of rs2287886),26 decreased human T-lymphotropic virus type I infection risk (G allele of rs4804803, A allele of rs2287886),27 increased severity of liver disease during hepatitis C virus infection (G allele of rs4804803),28 and better prognosis following severe acute respiratory syndrome (G allele of rs4804803).29,30

It was shown that the A allele of the rs4804803 single nucleotide polymorphism may increase gene expression in vitro,17 and, consequently, decreased CD209 gene
Table 1 Results of case-control studies investigating the association of polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of their signaling pathways with various diseases, and conditions or features

| Reference, population          | SNP number, variant allele frequency in cases and controls | Disease or condition | Sample size | OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results) |
|-------------------------------|----------------------------------------------------------|---------------------|-------------|-------------------------------------------------------------------------------------------------|
| Hattori et al13                | rs2477637 (Japanese 0.605–0.645, Afro-American 0.686–0.667) | Japanese, Asthma    | Japanese, 446 cases, 424 controls; Afro-American, 86 cases, 90 controls | Japanese, dominant model 1.38 (1.02–1.87) Afro-American, no association |
|                               | rs2253120 (Japanese 0.698–0.752, Afro-American 0.663–0.667) |                     |             | Japanese, additive model 1.34 (1.07–1.68); dominant model 1.55 (1.16–2.09); Afro-American, no association; Japanese, no association; Afro-American, no association |
|                               | rs2477631 (Japanese 0.484–0.522, Afro-American 0.238–0.267) |                     |             | Japanese, additive model 1.25 (1.01–1.55), dominant model 1.39 (1.00–1.94); Afro-American, additive model 2.17 (1.40–3.37), dominant model 2.87 (1.43–5.80) recessive model 2.76 (1.34–5.70) |
|                               | rs692527 (Japanese 0.521–0.559, Afro-American 0.581–0.389) |                     |             | Japanese, additive model 0.76 (0.61–0.95), recessive model 0.61 (0.41–0.89) 0.61; Afro-American, no association; Japanese, no association; Afro-American, additive model 1.81 (1.16–2.81), dominant model 2.43 (1.32–4.46) |
| Alter et al14                  | rs1926736 (in Vietnamese controls 0.35, in Brazilian controls 0.32) | Leprosy Vietnamese, 704 cases, 396 controls; Brazilian, 384 cases, 399 controls | Vietnamese, dominant model 0.76 (0.60–0.96), in the case with multibacillary leprosy, 0.71 (0.51–0.99); Brazilian, additive model, for carriers of wild-type G allele 1.34 (1.06–1.70), in the case with multibacillary leprosy, 1.42 (1.05–1.93) No association |
|                               | rs2437256 (in Vietnamese and Brazilian controls 0.21) |                     |             | No association |
|                               | rs2478577 (in Vietnamese controls 0, in Brazilian controls 0.21) |                     |             | For carriers of wild-type G allele, dominant model 0.75 (0.54–1.05); in the case with multibacillary leprosy 0.63 (0.41–0.97) |

(Continued)
Table 1 (Continued)

| Reference, population, SNP number, variant allele frequency in cases and controls | Disease or condition | Sample size | OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results) |
|---|---|---|---|
| Hattori et al15 Japanese population | rs2477637 (0.412–0.355, AG genotype 0.37–0.441, GG genotype 0.227–0.134) | Sarcoidosis | 181 cases, 424 controls | No association |
| | rs2253120 (0.301–0.248, AG genotype 0.448–0.325, GG genotype 0.077–0.085) | | No association |
| | rs2477631 (0.472–0.478, AC genotype 0.547–0.479, CC genotype 0.199–0.238) | | No association |
| | rs2477664 (0.472–0.463, AT genotype 0.514–0.455, TT genotype 0.215–0.236) | | No association |
| | rs692527 (0.492–0.441, AG genotype 0.464–0.505, GG genotype 0.26–0.189) | | No association |
| | rs1926736 (0.453–0.478, AG genotype 0.475–0.521, AA genotype 0.215–0.217) | | No association |
| | rs544995 (0.298–0.295, AG genotype 0.431–0.467, AA genotype 0.083–0.061) | | No association |
| | rs554313 (0.34–0.396, AG genotype 0.492–0.462, AA genotype 0.094–0.153) | | No association |
| Xu et al16 Cantonese population | rs2287886 (0.275 in controls) | NPC | 444 cases, 464 controls | No association |
| | rs554313 (0.34–0.396, AG genotype 0.492–0.462, AA genotype 0.094–0.153) | | 1.42 (1.15–1.74); for carriers of AG genotype, 1.41 (1.05–1.88), for carriers of GG genotype, 2.10 (1.23–3.59) |
| | rs690005 (0.376–0.321, TC genotype 0.376–0.458, CC genotype 0.188–0.092) | Recessive model, 2.53 (1.47–4.37) | | |
| Sakuntabhai et al17 Thai population | rs4804803 (0.093 in dengue disease patients, 0.023 in dengue fever patients, 0.116 in dengue hemorrhagic fever patients, 0.104 in controls) | Dengue disease, dengue fever, dengue hemorrhagic fever | 606 cases, 696 controls | Risk of hemorrhage during dengue fever, 5.84 (2.77–12.31); risk of dengue fever, 0.204; decreased CD209 gene expression |

(Continued)
| Reference, population | SNP number, variant allele frequency in cases and controls | Disease or condition | Sample size | OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results) |
|-----------------------|----------------------------------------------------------|---------------------|-------------|---------------------------------------------------------------------------------------------------|
|                       | rs2287886 (0.292 in dengue disease patients, 0.266 in dengue fever patients, 0.301 in dengue hemorrhagic fever patients, 0.312 in controls) | DCSIGN1.in2+11      | (0.066 in dengue patients, 0.019 in dengue fever patients, 0.081 in dengue hemorrhagic fever patients, 0.083 in controls) | No association                                                                                     |
|                       | DCSIGN1.in5-178 (0.064 in dengue disease patients, 0.017 in dengue fever patients, 0.079 in dengue hemorrhagic fever patients, 0.079 in controls) | DCSIGN1.ex4SF       | (0.007 in dengue patients, 0.003 in dengue fever patients, 0.009 in dengue hemorrhagic fever patients, 0.003 in controls) | No association                                                                                     |
|                       | DCSIGN1.ex6TI (0.005 in dengue disease patients, 0.003 in dengue fever patients, 0.006 in dengue hemorrhagic fever patients, 0.005 in controls) | DCSIGN1.in6-37     | (0.049 in dengue disease patients, 0.023 in dengue fever patients, 0.057 in dengue hemorrhagic fever patients, 0.064 in controls) | No association                                                                                     |
|                       | DCSIGN1.2281 (0.391 in dengue disease patients, 0.42 in dengue fever patients, 0.38 in dengue hemorrhagic fever patients, 0.344 in controls) | DCSIGN1.3197       | (0.112 in dengue disease patients, 0.09 in dengue fever patients, 0.119 in dengue hemorrhagic fever patients, 0.122 in controls) | No association                                                                                     |

(Continued)
Table 1 (Continued)

| Reference, population          | SNP number, variant allele frequency in cases and controls | Disease or condition | Sample size | OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results) |
|--------------------------------|-----------------------------------------------------------|----------------------|-------------|------------------------------------------------------------------------------------------------------|
| Wang et al18 Taiwanese population | DCSIGN1.3852 (0.243 in dengue disease patients, 0.24 in dengue fever patients, 0.244 in dengue hemorrhagic fever patients, 0.267 in controls) | Dengue disease, dengue fever, dengue hemorrhagic fever | 176 dengue fever cases, 135 dengue hemorrhagic fever cases, 143 patients with other non-dengue febrile illnesses, 120 controls | Risk of dengue infection, 2.34 (1.14–4.83); risk of dengue hemorrhagic fever, 3.57 (1.67–7.63); risk of hemorrhage during dengue fever, 2.44 (1.36–4.40); increased levels of TNF-α, IL-12p40, IP-10 |
| Wang et al19 South African population | rs2048022 (0.434–0.483) | Tuberculosis | 351 cases, 360 controls | No association |
| Barreiro et al19 South African population | rs1380229 (0.361–0.384) | | | No association |
| | rs650389 (0.152–0.195) | | | No association |
| | rs870384 (0.483–0.468) | | | No association |
| | rs695982 (0.321–0.277) | | | No association |
| | rs706862 (0.119–0.123) | | | No association |
| | rs715774 (0.143–0.161) | | | No association |
| | rs1433456 (0.199–0.197) | | | No association |
| | rs807131 (0.355–0.339) | | | No association |
| | rs1672183 (0.12–0.117) | | | No association |
| | rs2024628 (0.422–0.465) | | | No association |
| | rs1028184 (0.342–0.39) | | | No association |
| | rs2056773 (0.395–0.371) | | | No association |
| | rs1479067 (0.259–0.284) | | | No association |
| | rs327747 (0.258–0.292) | | | No association |
| | rs12665321 (0.142–0.129) | | | No association |
| | rs1566838 (0.465–0.458) | | | No association |
| | rs12785524 (0.39–0.424) | | | No association |
| | rs975423 (0.351–0.378) | | | No association |
| | rs914904 (0.292–0.282) | | | No association |
| | rs876287 (0.413–0.409) | | | No association |
| | rs1582598 (0.275–0.265) | | | No association |
| | rs1364198 (0.252–0.227) | | | No association |
| | rs739259 (0.361–0.39) | | | No association |
| | rs169479 (0.133–0.115) | | | No association |
| | rs4804803 (0.454–0.402) | | | No association |
| | rs735239 (0.089–0.141) | | | No association |
| | rs735240 (0.283–0.313) | | | No association |
| | rs2287886 (0.271–0.288) | | | No association |
| Vannberg et al20 Gambian, Guinean, Guinea-Bissauan, Malawian populations | rs4804803 (in Gambian population 0.48–0.54, in Guinean population 0.489–0.47, in Guinea-Bissauan population 0.475–0.504, in Malawian population 0.352–0.364) | Tuberculosis | Gambian: 678 cases, 327 controls Guinean: 151 cases, 180 controls Guinea-Bissauan: 162 cases, 141 controls Malawian: 244 cases, 295 controls | For Gambian population, 0.75 (0.61–0.94); overall, 0.86 (0.77–0.96); for cavitating tuberculosis, 0.42 (0.27–0.65) |
**Table 1** (Continued)

| Reference, population | SNP number, variant allele frequency in cases and controls | Disease or condition | Sample size | OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results) |
|-----------------------|----------------------------------------------------------|---------------------|-------------|------------------------------------------------------------------------------------------------------------------|
| Selvaraj et al21 South Indian population | rs4804803 (0.181–0.223) | Tuberculosis, HIV | 238 HIV cases, 107 HIV+ and tuberculosis cases, 157 controls | For carriers of GG genotype, risk of tuberculosis among HIV-infected patients, 9.8 (2.2–44.3) |
| | rs2287886 (0.471–0.468) | | | No association |
| | rs7252229 (0.105–0.101) | | | No association |
| | rs1544767 (0.105–0.108) | | | No association |
| | rs4804803 (0.23–0.21) | | For carriers of GG genotype; for HLA-DQ2(−) individuals compared with HLA-DQ2(+), 1.95 (1.03–3.67) |
| Nunez et al22 Spanish population | rs4804803 (0.25 in Crohn’s disease patients, 0.22 in ulcerative colitis patients, 0.22 in controls) | Crohn’s disease, ulcerative colitis | 515 Crohn’s disease cases, 497 ulcerative colitis cases, 731 controls | Risk of ulcerative colitis in HLA-DR3-positive patients 1.77 (1.04–3.02) |
| | rs4804803 (0.23–0.21) | Celiac disease | 103 cases, 312 controls | For carriers of GG genotype; no association |
| | rs735240 | Human CMV reactivation and disease after allogeneic stem cell transplantation | 70 patients with human CMV reactivation, 59 patients with human CMV disease, 65 controls | Risk of human CMV disease, 1.88 (0.91–3.87) |
| | | | | Risk of human CMV reactivation, 2.41 (1.22–4.75); risk of human CMV disease, 2.01 (1.05–3.86) |
| | | | | 0.209 (0.058–0.758) |
| | rs735239 (0.207–0.234) | Tuberculosis | 237 cases, 244 controls | No association |
| | rs2287886 | AIDS progression | 104 HIV-1-positive Japanese hemophiliacs | Risk of accelerated AIDS progression: 1.95 (1.03–3.67) |
| | rs4804803 | HTLV-1 infection | 66 cases, 33 controls | For carriers of A allele: Risk of HTLV-1-infection: 0.3758 (0.1954–0.7229) |
| | rs2287886 (0.594–0.795) | | | For carriers of AA genotype: Risk of HTLV-1-infection: 0.1116 (0.02168–0.5745) |
| | –201 promoter polymorphism (0.038–0.016) | | | No association |
| | –332 promoter polymorphism (0.03–0) | | | No association |
| | rs4804803 (0.144–0.297) | | | No association |
| | rs4804803 (0.25–0.19) | HCV infection | 131 cases, 79 controls | Increased risk of advanced liver disease |
| Ryan et al28 Irish population | | SARS | 585 cases with lower LDH level, 96 cases with higher LDH level | Risk of higher LDH level during SARS, 0.41 (0.20–0.86); decreased expression of CD209 gene; Sp1 and AP2 proteins bind more effectively to G allele of rs4804803 |

(Continued)
| Reference, population | SNP number, variant allele frequency in cases and controls | Disease or condition | Sample size | OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results) |
|-----------------------|----------------------------------------------------------|---------------------|-------------|--------------------------------------------------------------------------------------------------|
| Chan et al30 Hong Kong population CLEC7A (Dectin-1) | rs4804803 | SARS | 824 cases, 471 controls | Risk of higher LDH level during SARS, 0.41 (0.20–0.86) |
| Plantinga et al31 Dutch population | rs16910526 (0.078–0.076) | Rheumatoid arthritis | 262 cases, 284 controls | Diminished TNF-α and IL-1β production in cells from homozygous and heterozygous individuals; the TLR2/Dectin-1 synergism was reduced in cells isolated from heterozygous and homozygous subjects |
| Cunha et al32 Italian population | rs16910526 | Invasive aspergillosis | 205 cases with hematopoietic stem cell transplantation | Risk of invasive aspergillosis after hematopoietic stem cell transplantation, polymorphic donor + wild-type recipient, 2.50 (1.00–6.53) Polymorphic donor + polymorphic recipient: 3.89 (1.51–9.99) Unstimulated CD14-positive monocytes from polymorphic persons display a decreased surface expression of Dectin 1 in response to β-glucan or A conidia, PBMCs from heterozygous persons showed decreased production of IL-1β, IL-6, IL-10, IL-17A, and IFN-γ |
| Chai et al33 Dutch and Flemish population | rs16910526 (0.19 in patients without hematopoietic transplantation with invasive aspergillosis, 0.077 in controls, 0.07 in patients with transplantation [with and without invasive aspergillosis]) | Invasive aspergillosis | 71 cases with invasive aspergillosis after hematopoietic stem cell transplantation, 21 cases with invasive aspergillosis without transplantation, 108 controls with transplantation | Increased risk of invasive aspergillosis in patients without hematopoietic transplantation PBMCs from variant homozygous persons had reduced proinflammatory TNF-α and IL-6 production in response to heat-killed Aspergillus fumigatus hyphae, Candida albicans blastoconidia, and live A. fumigatus conidia; monocyte-derived macrophages from polymorphic individuals had deficient expression of the Dectin 1 receptor; stimulation using β-glucan failed to generate a TNF-α response in the Dectin 1-deficient monocyte-derived macrophages from variant homozygotes |

(Continued)
Table 1 (Continued)

| Reference, population | SNP number, variant allele frequency in cases and controls | Disease or condition | Sample size | OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results) |
|-----------------------|----------------------------------------------------------|---------------------|-------------|---------------------------------------------------------------------------------------------------|
| Plantinga et al\(^34\) Dutch population | rs16910526 (0.106–0.138) | Colonization with Candida spp | 142 cases with hematopoietic stem cell transplantation, 138 controls | Risk of Candida spp colonization, 12.0 (2.5–57.1); risk of Candida spp colonization after transplantation, 15.5 (1.9–123.6); monocytes from the variant homozygous individuals exhibited no Dectin 1 expression on the cell surface, whereas cells from heterozygous individuals had intermediate cell surface expression; IL-1β induction by C. albicans was lower in cells from individuals bearing the polymorphism; no possibility to amplify TLR2 signaling by Dectin 1 in cells isolated from variant homozygous individuals |
| Plantinga et al\(^35\) East African population | I223S | Oropharyngeal candidiasis | 225 cases with HIV | IFN-γ production capacity and ability to bind zymosan was markedly lower in cells from subjects bearing the polymorphism |
| Ovsyannikova et al\(^38\) | rs10813821 | Cytokine immune response in healthy children following rubella vaccination | 738 cases | Increased level of IFN-γ |
| | rs9650702 | | | Increased level of IFN-γ and decreased level of GM-CSF |
| | rs626214 | | | Increased level of IFN-γ |
| | rs592515 | | | Increased level of IFN-γ and TNF-α |
| | rs6476363 | | | Decreased level of TNF-α |
| | rs3739674 | | | Decreased level of TNF-α |
| | rs10813829 | | | Decreased level of TNF-α |
| | rs4633144 | | | Increased level of TNF-α |
| | rs3824456 | | | Decreased level of GM-CSF and IL-6 |
| | rs10813831 | | | |
| Ovsyannikova et al\(^39\) | rs10813831 | Cytokine immune response in healthy children following rubella vaccination | 738 cases | Decreased rubella-specific antibody response (median antibody level) |
| | rs669260 | | | Increased rubella-specific antibody response |
| Hu et al\(^40\) US population | rs10813831 | Cytokine immune response to Newcastle disease | 130 cases | Increased gene expression in Newcastle disease virus-infected cells |
| | rs12006123 | | | No association |

(Continued)
| Reference, population | SNP number, variant allele frequency in cases and controls | Disease or condition | Sample size | OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results) |
|-----------------------|----------------------------------------------------------|---------------------|-------------|--------------------------------------------------------------------------------------------------|
| **MAVS/VISA/IPS-1**   |                                                          |                     |             |                                                                                                  |
| Pothlichet et al      | rs1905552 (0.126–0.102 in Afro-American population, 0.013–0 in European-American population) | SLE                 | 520 cases, 510 controls | For Afro-American population, probability of absence of anti-RNA-binding protein autoantibodies 2.6 (1.5–4.6); decreased level of NF-kB, IL-8, IFN-β and RANTES; significantly reduced interaction of MAVS with TRAF3 No association |
| Liu et al             | Q198K (0.187–0.2 in African-American population, 0.128–0.155 in European-American population) | SLE                 | 123 cases, 95 controls | Risk of SLE-related renal nephritis, 0.58 [0.34–0.97] Risk of SLE-related arthritis, 0.27 (0.09–0.80) No association Association with patients positive for SLE-related arthritis, 0.45 (0.21–0.94); association with patients positive for SLE-related renal nephritis, 0.42 (0.18–0.98); association with patients negative for SLE-related oral ulcer, 0.40 (0.18–0.89); association with patients negative for SLE-related photosensitivity, 0.38 (0.17–0.89) |
| **Abbreviations**: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MRC, mannose receptor C; CD, cluster of differentiation; NPC, nasopharyngeal carcinoma; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon-gamma inducible protein 10; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus; HCV, hepatitis C virus; SARS, severe acute respiratory syndrome; LDH, lactate dehydrogenase; Sp, specificity protein; AP, activator protein; CLEC, C-type lectin domain, the next number is the family number 7, the next letter is the letter of family member; TLR, toll-like receptor; PBMC, peripheral blood mononuclear cell; IFN, interferon; RIG-I, retinoic acid-inducible gene I; GM-CSF, granulocyte-macrophage colony-stimulating factor; MAVS/VISA/IPS-1, mitochondrial antiviral signaling protein/virus-induced signaling adapter/induced by phosphate starvation-1; NF-kB, nesris factor kappa B; RANTES, regulated on activation, normal T-cell expressed and secreted; TRAF, TNF receptor-associated factor; SLE, systemic lupus erythematosus. |

expression in subjects with the G allele may result in an impaired immune response against hepatitis C virus,28 *M. tuberculosis*,19,21 and bacteria potentially causing celiac disease22 and ulcerative colitis,23 that elevates the risk of diseases caused by these infectious agents. Such a decreased immune response may protect from hemorrhage during dengue fever,27 from lung cavitation,20 from fever during tuberculosis,25 and from lung injury during severe acute respiratory syndrome29,30 as a result of less cytokine production and diminished activation of immune cells. However, from the point of view of Vannberg et al,20 conversely, lower CD209 gene expression as a consequence of G allele of rs4804803 polymorphism may protect against tuberculosis because of decreased production of proinflammatory cytokines such as interleukin-4. Further fundamental, translational, and clinical studies are necessary to clarify these discrepancies. Nevertheless, although there are a number of reasons for the discrepancies between studies devoted to the association between CD209 single nucleotide polymorphisms and development of tuberculosis, but confounding host, bacterial, and...
environmental factors between different study populations should be taken into account. In addition, Mezger et al. demonstrated that alleles of rs735240 and rs2287886 polymorphisms may also influence CD209 gene expression and thus affect transcription factor binding.

In relation to the CLEC7A (Dectin-1) gene, it was also found that a variant allele of rs16910526 polymorphism is associated with impaired cytokine production by macrophages and with a defective response to Aspergillus and Candida invasion. The variant S form of I223S polymorphism was characterized by a lower capacity of the receptor to bind zymosan.

Among polymorphisms of genes encoding RIG-I-like receptors, RIG-I single nucleotide polymorphisms are the most investigated. Pothlichet et al. conducted a comprehensive study investigating the functional consequences of rs36055726 (P229fs) and rs11795404 (S183I) polymorphisms. They found that the variant allele of rs36055726 results in a truncated constitutively active RIG-I (that leads to permanent production of proinflammatory mediators, particularly antiviral), and, conversely, the variant allele of rs11795404 induces an abortive conformation of RIG-I, causing formation of unintended stable complexes between CARD modules of RIG-I and between RIG-I and its downstream adapter protein, MAVS, rendering RIG-I incapable of downstream signaling and further cytokine synthesis. Moreover, Shigemoto et al identified a variant of rs11795404 as a loss-of-function allele. Ovsyannikova et al. showed that a minor allele of rs10813831 polymorphism is associated with a decrease in the rubella virus-specific granulocyte-macrophage colony-stimulating factor/interleukin-6/IgG response, whilst a variant allele of rs3824456 is connected with an increase in the rubella virus-specific tumor necrosis factor alpha response, and a variant allele of rs669260 correlates with an increase in the rubella-specific antibody level. Hu et al. discovered that a variant allele of rs10813831 polymorphism leads to increased gene expression and, consequently, cytokine production due to an amino acid substitution in the CARD domain of RIG-I that results in functional alteration of this RIG-I-like receptor.

There are also a lot of studies investigating the role of IFIH1/MDA5 (the gene encoding MDA5 protein that is also a RIG-I-like receptor) single nucleotide polymorphisms in the etiology of autoimmune diseases, but almost all of them are devoted to type 1 diabetes and multiple sclerosis, and data about the association of these diseases with cancer risk are conflicting, in that some studies showed an increased risk in patients with type 1 diabetes and multiple sclerosis, and in other investigations no connection or decreased risk of cancer has been observed. Taking into account that there are no carcinogenic infectious agents recognizing MDA5, it does not seem to be prudent to investigate IFIH1/MDA5 gene polymorphisms from the oncogenic point of view.

### Table 2 Polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of their specific signaling pathways that have known functional consequences and may be relevant to oncogenomics

| Gene | Single nucleotide polymorphism |
|------|-------------------------------|
| MRC1 | rs11905552                     |
| CD209| rs11795404                     |
| CLEC7A| rs16910526                   |
| MAVS/VISA/IPS-1 | rs10813831* |
| MAVS/VISA/IPS-1 | rs11905552* |
| MAVS/VISA/IPS-1 | rs11795404* |
| MAVS/VISA/IPS-1 | rs10813831* |
| MAVS/VISA/IPS-1 | rs36055726* |
| MAVS/VISA/IPS-1 | rs11795404* |
| MAVS/VISA/IPS-1 | rs10813831* |
| MAVS/VISA/IPS-1 | rs36055726* |

**Note:** Single nucleotide polymorphisms that can be valued as the most promising for further oncogenomic investigation.

**Abbreviations:** PRRs, pattern recognition receptors; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLRs, Toll-like receptors; NLRs, NOD-like receptors; CLRs, C-type lectin receptors; RLRs, RIG-I-like receptors; SNPs, single nucleotide polymorphisms; MRC, mannose receptor C; CD, cluster of differentiation; CLEC, C-type lectin domain, the next number is the family number 7, the next letter is the letter of family member; HIV, human immunodeficiency virus; LV, lymphocyte antigen; DEC-205, dendritic and epithelial cells 205 kDa; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; HCV, hepatitis C virus; CMV, cytomegalovirus; DCIR, dendritic cell immunoreceptor; RIG-I, retinoic acid-inducible gene I; EBV, Epstein-Barr virus; CAR, caspase recruitment domain; MAVS, mitochondrial antiviral signaling protein; IFN, interferon induced with helicase C domain; MDA, melanoma differentiation-associated gene; VISA, virus-induced signaling adapter; IPS-1, induced by phosphate starvation-1.
In addition, polymorphisms of genes coding for components of the Toll-like receptor signaling pathway may modulate cancer risk as single nucleotide polymorphisms of the TLR gene family. The same statement can be true for C-type lectin receptor and RIG-I-like receptor signaling pathways. For instance, a variant allele of rs11905552, encoding MAVS/VISA/IPS-1, a key downstream signaling molecule of RIG-I and MDA5, was associated with a particular systemic lupus erythematosus phenotype. It was found that this single nucleotide polymorphism leads to reduced production of type I interferon and other proinflammatory mediators, and also to the absence of anti-RNA-binding protein autoantibodies. It is associated with nephritis and arthritis in patients suffering from systemic lupus erythematosus. A variant allele of another single nucleotide polymorphism of this gene, rs7269320, showed associations with different clinical characteristics of this autoimmune disease. All the population case-control studies mentioned above are summarized in Table 1.

**Conclusion and future directions**

All polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of their specific signaling pathways that have known functional consequences and may be relevant to oncogenomics are summarized in Table 2. The fundamental basis for the association of the inherited coding variation in genes encoding C-type lectin receptors and RIG-I-like receptors with cancer is represented by the defects in the immune response (that are caused by various single nucleotide polymorphisms) against specific carcinogenic infectious agents. Some polymorphisms may be valued as the most promising for further oncogenomic investigations on the basis of their association with cancer risk or because of their substantial functional consequences on the molecular level according to the following concept:

Gene polymorphism may be included on the short list for further oncogenomic studies if:

- The single nucleotide polymorphism leads to substantial functional consequences at the molecular level (for instance, it strongly affects transcription, splicing, translation, stability and transport of pre-mRNA, mRNA, noncoding RNA, or protein encoding by the gene, or it noticeably influences signaling of synthesized protein)
- It is associated with risk of cancer in population studies
- It has functional consequences at the molecular level and it is strongly associated with a condition that significantly increases the risk of cancer (threshold may vary for each cancer type)

The gene polymorphism can be also included on the extended list if:

- It is characterized by more subtle functional alterations in a gene that, nonetheless, result in qualitative or quantitative alterations of the encoding protein (or noncoding RNA)
- It is associated with a condition that substantially increases the risk of cancer but has not specifically been identified to increase the risk of cancer.

According to this concept, the indicated short list of polymorphisms includes rs1926736, rs2478577, rs2437257, rs691005 (all located in the MRC1 gene), rs2287886, -939 promoter polymorphism, rs735239, rs735240, rs4804803 (all located in the CD209 gene), rs16910526 (CLEC7A gene), and rs36055726, rs11795404, rs10813831 (all located in the RIG-I gene). Other polymorphisms mentioned in this article may be added to the extended list for further investigations. Polymorphisms with known functional effects (rs1926736, rs2437257, rs691005, rs2287886, rs735240, rs4804803, rs16910526) were associated with relatively significant modulation of risk of diseases (as shown in Table 1) which is logical and demonstrates the correctness of the studies in which functional consequences of such single nucleotide polymorphisms were analyzed. There are still no comprehensive functional investigations for other single nucleotide polymorphisms correlated with risk of disease, so it is difficult to conclude which of them have independent significance, and which of them are just in linkage disequilibrium with truly functional variants.

In addition, PAMPs of specific infectious agents recognized by each C-type lectin receptor or RIG-I-like receptor define cancer types which can be primarily associated with inherited structural variation in the receptors discussed earlier. Furthermore, if a single nucleotide polymorphism of a gene encoding a specific C-type lectin receptor or RIG-I-like receptor is associated with risk or progression features of certain malignancies, polymorphisms in genes encoding specific signaling molecules constituting pathways of these receptors should correlate with similar neoplasms, if they have substantial functional consequences at the molecular level. The issue of an association of single nucleotide polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of pattern recognition receptor pathways with various features of cancer progression is open, and only further population studies would be likely to give a definite answer.
Reasons for discrepancies in different investigations analyzing the association of polymorphisms in genes encoding C-type lectin receptors, RIG-I-like receptors, and the proteins of their signaling pathways with various aspects of cancer development may include confounding host, bacterial, or environmental factors in different ethnicities modulating penetrance of variant alleles and affecting the risk of conditions increasing cancer risk (such as autoimmune diseases, precancerous gastric lesions, tuberculosis, recurrent pneumonia), different bacterial impact on the etiology of such conditions in different populations (that will be reflected in different features of C-type lectin receptor/RIG-I-like receptor-mediated immune response because of specific C-type lectin receptor/RIG-I-like receptor-ligand interaction), differences in sample size, in clinicopathological characteristics between study samples, in prevalence of infectious agents in case and control groups, diagnostics, stratification, genotyping methods, and chance.

Another interesting issue is that associations between single nucleotide polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors and cancer risk can be skewed by differences between cohorts in various immune responses and infections that may not influence cancer development. The problem is that the design in an epidemiological study having a large sample is very seldom ideal. Stratification by status of chronic infection is rather difficult because of their extreme diversity and because of the very high cost of such testing. Stratification by an immune response is even more complex because of innumerable peculiarities in functioning of the immune system. Therefore, if the study has a perfect funding source, stratification by infection status can be possible, but stratification by immune response status will be far from ideal.

Unfortunately, to the best of the authors’ knowledge, no genome-wide association studies of the connection between polymorphisms of genes encoding the C-type lectin receptor and RIG-I-like receptors and cancer risk or progression have been performed, and this can be explained by the relative newness of the problem or perhaps by another unknown reason.

Summing up, polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of their signaling pathways may be promising targets for oncogenomics and possibly could be used in programs of cancer prevention and early cancer diagnostics in the future. Population and further fundamental studies devoted to their association with cancer risk of progression should shed light on this issue.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

1. Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity*. 2011;34(5):637–650.

2. Elinav E, Strowig T, Henao-Mejia J, Flavell RA. Regulation of the antimicrobial response by NLR proteins. *Immunity*. 2011;34(5):665–679.

3. Osorio F, Reis E, Sousa C. Myeloid C-type lectin receptors in pathogen recognition and host defense. *Immunity*. 2011;34(5):651–664.

4. Loo YM, Gale M Jr. Immune signaling by RIG-I-like receptors. *Immunity*. 2011;34(5):680–692.

5. Lamba V, Lamba J, Yasuda K, et al. Hepatic CYP2B6 expression: gender and ethnic differences and relationship to CYP2B6 genotype and CAR (constitutive androstane receptor) expression. *J Pharmacol Exp Ther*. 2003;307(3):906–922.

6. Tierney MJ, Medcalf RL. Plasminogen activator inhibitor type 2 contains mRNA instability elements within exon 4 of the coding region. Sequence homology to coding region instability determinants in other mRNAs. *J Biol Chem*. 2001;276(17):13675–13684.

7. Thomas KH, Meyn P, Suttrop N. Single nucleotide polymorphism in 5′-flanking region reduces transcription of surfactant protein B gene in H441 cells. *Am J Physiol Lung Cell Mol Physiol*. 2006;291(3):L386–L390.

8. Zysow BR, Lindahl GE, Wade DP, Knight BL, Lawn RM. C/T polymorphism in the 5′ untranslated region of the apolipoprotein(a) gene introduces an upstream ATG and reduces in vitro translation. *Arterioscler Thromb Vasc Biol*. 1995;15(1):58–64.

9. Bell JK, Mullen GE, Leifer CA, Mazzoni A, Davies DR, Segal DM. Leucine-rich repeats and pathogen recognition in toll-like receptors. *Trends Immunol*. 2003;24(10):528–533.

10. Johnson CM, Lyle EA, Omueti KO, et al. Cutting edge: a common polymorphism impairs cell surface trafficking and functional responses of TLR1 but protects against leprosy. *J Immunol*. 2007;178(12):7520–7524.

11. Chang AH, Parsonnet J. Role of bacteria in oncogenesis. *Clin Microbiol Rev*. 2010;23(4):837–857.

12. de Martel C, Franceschi S. Infections and cancer: established associations and new hypotheses. *Crit Rev Oncol Hematol*. 2009;70(3):183–194.

13. Hattori T, Konno S, Hizawa N, et al. Genetic variants in the mannose receptor gene (MRC1) are associated with asthma in two independent populations. *Immunogenetics*. 2009;61(11–12):731–738.

14. Alter A, de Léséleuc L, Van Thuc N, et al. Genetic and functional analysis of common MRC1 exon 7 polymorphisms in leprosy susceptibility. *Hum Genet*. 2010;127(3):337–348.

15. Hattori T, Konno S, Takahashi A, et al. Genetic variants in mannose receptor gene (MRC1) confer susceptibility to increased risk of sarcoidosis. *BMC Med Genet*. 2010;11:151.

16. Xu YF, Liu WL, Dong QJ, et al. Sequencing of DC-SIGN promoter indicates an association between promoter variation and risk of nasopharyngeal carcinoma in cantonese. *BMC Med Genet*. 2010;11:161.

17. Sakuntabhai A, Turbauboon C, Casadémont I, et al. A variant in the MRC1 gene introduces an upstream ATG and reduces in vitro translation. *Exp Ther Med*. 2006;3(2):e20.

18. Wang L, Chen RF, Liu JW, et al. DC-SIGN (CD209) Promoter -336 A/G polymorphism is associated with dengue hemorrhagic fever and correlated to DC-SIGN expression and immune augmentation. *PLoS Negl Trop Dis*. 2011;5(1):e934.

19. Barreiro LB, Neyrolles O, Babb CL, et al. Promoter variation in the DC-SIGN-encoding gene CD209 is associated with tuberculosis. *PLoS Med*. 2006;3(2):e20.

20. Vannberg FO, Chapman SJ, Khor CC, et al. CD209 genetic polymorphism and tuberculosis disease. *PLoS One*. 2008;3(1):e1388.
21. Selvaraj P, Alagarasu K, Swaminathan S, Harishankar M, Narendran G. CD209 gene polymorphisms in South Indian HIV and HIV-TB patients. Infect Genet Evol. 2009;9(2):256–262.

22. Núñez C, Rueda B, Martínez A, et al. A functional variant in the CD209 promoter is associated with DQ2-negative celiac disease in the Spanish population. World J Gastroenterol. 2006;12(27):4397–4400.

23. Núñez C, Oliver J, Mendoza JL, et al. CD209 in inflammatory bowel disease: a case-control study in the Spanish population. BMC Med Genet. 2007;8:75.

24. Mezger M, Steffens M, Semmler C, et al. Investigation of promoter variations in dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN) (CD209) and their relevance for human cytomegalovirus reactivation and disease after allogeneic stem-cell transplantation. Clin Microbiol Infect. 2008;14(3):228–234.

25. Zheng R, Zhou Y, Qin L, et al. Relationship between polymorphism of DC-SIGN (CD209) gene and the susceptibility to pulmonary tuberculosis in an eastern Chinese population. Hum Immunol. 2011;72(2):183–186.

26. Koizumi Y, Kageyama S, Fujimura Y, et al. RANTES -28G delays and DC-SIGN – 139C enhances AIDS progression in HIV type 1 infected Japanese hemophiliacs. AIDS Res Hum Retroviruses. 2007;23(5):713–719.

27. Kashima S, Rodrigues ES, Azevedo R, et al. DC-SIGN (CD209) gene promoter polymorphisms in a Brazilian population and their association with human T-cell lymphotropic virus type 1 infection. J Gen Virol. 2009;90(Pt 4):927–934.

28. Ryan EJ, Dring M, Ryan CM, et al. Variant in CD209 promoter is associated with severity of liver disease in chronic hepatitis C virus infection. Hum Immunol. 2010;71(8):829–832.

29. Chan KY, Xu MS, Ching JC, et al. CD209 (DC-SIGN) -336 A > G promoter polymorphism and severe acute respiratory syndrome in Hong Kong Chinese. Hum Immunol. 2010;71(7):702–707.

30. Chan KY, Xu MS, Ching JC, et al. Association of a single nucleotide polymorphism in the CD209 (DC-SIGN) promoter with SARS severity. Hong Kong Med J. 2010;16(5 Suppl 4):37–42.

31. Plantinga TS, Fransen J, Takahashi N, et al. Functional consequences of DECTIN-1 early stop codon polymorphism Y238X in rheumatoid arthritis. Arthritis Res Ther. 2010;12(1):R26.

32. Cunha C, Di Ianni M, Bozza S, et al. Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. Blood. 2010;116(24):5394–5402.

33. Chai LY, de Boer MG, van der Velden WJ, et al. The Y238X stop codon polymorphism in the human β-glucan receptor Dectin-1 and susceptibility to invasive aspergillosis. J Infect Dis. 2011;203(5):736–743.

34. Plantinga TS, van der Velden WJ, Ferwerda B, et al. Early stop polymorphism in human Dectin-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2009;49(5):724–732.

35. Plantinga TS, Hamza OJ, Willment JA, et al. Genetic variation of innate immune genes in HIV-infected African patients with or without oropharyngeal candidiasis. J Acquir Immune Defic Syndr. 2010;55(1):87–94.

36. Potthichet J, Burtey A, Kubarenko AV, et al. Study of human RIG-I polymorphisms identifies two variants with an opposite impact on the antiviral immune response. PLoS One. 2009;4(10):e7582.

37. Shigemoto T, Kageyama M, Hirai R, Zheng J, Yoneyama M, Fujita T. Identification of loss of function mutations in human genes encoding RIG-I and MDAX: implications for resistance to type I diabetes. J Biol Chem. 2009;284(20):13348–13354.

38. Osvyannikova IG, Dinham N, Haralambieva IH, et al. Rubella vaccine-induced cellular immunity: evidence of associations with polymorphisms in the Toll-like, vitamin A and D receptors, and innate immune response genes. Hum Genet. 2010;127(2):207–212.

39. Osvyannikova IG, Haralambieva IH, Dinham N, et al. Polymorphisms in the vitamin A receptor and innate immunity genes influence the antibody response to rubella vaccination. J Infect Dis. 2010;201(2):207–213.

40. Hu J, Nistal-Villán E, Vóho A, et al. A common polymorphism in the caspase recruitment domain of RIG-I modifies the innate immune response of human dendritic cells. J Immunol. 2010;185(1):424–432.

41. Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K. Cancer risk among patients hospitalized for Type 1 diabetes mellitus: a population-based cohort study in Sweden. Diabet Med. 2010;27(7):791–797.

42. Zendelesh K, Nyrén O, Ostenson CG, Adami HO, Ekham A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. J Natl Cancer Inst. 2003;95(23):1797–1800.

43. Swedlow AJ, Laing SP, Qiao Z, et al. Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study. Br J Cancer. 2005;92(11):2070–2075.

44. Hjalgrim H, Frisch M, Ekham A, Kypik KO, Mellbye M, Green A. Cancer and diabetes – a follow-up study of population-based cohorts of diabetic patients. J Intern Med. 1997;241(6):471–475.

45. Bahmanyar S, Montgomery SM, Hillert J, Ekham A, Olsson T. Cancer risk among patients with multiple sclerosis and their parents. Neurology. 2009;72(13):1170–1177.

46. Nielsen NM, Rostgaard K, Rasmussen S, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. Int J Cancer. 2006;118(4):979–984.

47. Svenelauth ML, Pukkala E, Hakama M. Cancer incidence in multiple sclerosis: a 35-year follow-up. J Intern Med. 2004;255(5):224–227.

48. Mistry R, Glatt E, Gromming M, Riise T, Edland A, Nyland H. Multiple sclerosis and cancer in Norway. Acta Neurol Scand. 1996;93(6):411–415.

49. Fois AF, Wotton CJ, Yeates D, Turner MR, Goldacre MJ. Cancer in patients with insulin-treated diabetes: a population-based cohort study. J Neurol. 2006;253(1):119–123.

50. Knowledge of the oncogenomics map

New receptors on the oncogenomics map

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