World Journal of Gastrointestinal Oncology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4251/wjgo.v7.i11.328

*World J Gastrointest Oncol* 2015 November 15; 7(11): 328-337
ISSN 1948-5204 (online)


TOPIC HIGHLIGHT

2015 Advances in Gastric Cancer

# Polymorphisms in mucin genes in the development of gastric cancer

Rong Wen, Fang Gao, Cheng-Jiang Zhou, Yan-Bin Jia

Rong Wen, Fang Gao, Cheng-Jiang Zhou, Yan-Bin Jia, School of Basic Medicine, Baotou Medical College, Baotou 014060, Inner Mongolia Autonomous Region, China

Yan-Bin Jia, Inner Mongolia Institute of Digestive Diseases, the Second Affiliated Hospital of Baotou Medical College, Baotou 014030, Inner Mongolia Autonomous Region, China

Author contributions: All authors contributed to this work.

Supported by National Natural Science Foundation of China, No. 30960169 and No. 81250024; Natural Science Foundation of Inner Mongolia, No. 2011MS1103; and Inner Mongolian Committee of Science and Technology, China, No. 20110501.

Conflict-of-interest statement: The authors declare that there is no conflict of interest related to this paper.



Correspondence to: Yan-Bin Jia, Professor, School of Basic Medicine, Baotou Medical College, 31 Jianshe Road, Donghe District, Baotou 014060, Inner Mongolia Autonomous Region, China. jyb690318@hotmail.com
Telephone: +86-472-7167832
Fax: +86-472-7167739

Received: April 25, 2015
Peer-review started: April 26, 2015
First decision: June 2, 2015
Revised: July 1, 2015
Accepted: August 30, 2015
Article in press: September 7, 2015
Published online: November 15, 2015

## Abstract

Gastric cancer (GC) is the third leading cause of cancer-related death worldwide. In areas of high prevalence, such as Japan, South Korea and China, most cases of GC are related to *Helicobacter pylori* (*H. pylori*), which involves well-characterized sequential stages, including infection, atrophic gastritis, intestinal metaplasia, dysplasia, and GC. Mucins are the most abundant high-molecular-weight glycoproteins in mucus, which is the first line of defense and plays a major role in blocking pathogenic factors. Normal gastric mucosa shows expression of MUC1, MUC5AC and MUC6 that is specific to cell type. However, the specific pattern of MUC1, MUC5AC and MUC6 expression is changed in gastric carcinogenesis, accompanied by *de novo* expression of secreted MUC2. Recent studies have provided evidence that variations in these mucin genes affect many steps of GC development, such as *H. pylori* infection, and gastric precancerous lesions. In this review, we focus on studies of the association between polymorphisms in mucin genes and development of GC. This information should be helpful for the early detection, surveillance, and treatment of GC.

**Key words:** Gastric cancer; *Helicobacter pylori*; Genetic polymorphism; Mucin; Risk; Association study; Atrophic gastritis



**Core tip:** *Helicobacter pylori* (*H. pylori*) infection is the single most important risk factor in the development of gastric cancer (GC), however the etiology of GC involves host and other environmental factors. Genetic and biological evidence highlights the important roles of variations in mucin genes in the development and progression of GC. In this review, we summarize studies

of the association between polymorphisms in *MUC1*, *MUC5AC*, *MUC6* and *MUC2* and development of GC, which should be helpful for the early detection, surveillance, and treatment of GC.

Wen R, Gao F, Zhou CJ, Jia YB. Polymorphisms in mucin genes in the development of gastric cancer. *World J Gastrointest Oncol* 2015; 7(11): 328-337 Available from: URL: http://www.wjgnet.com/1948-5204/full/v7/i11/328.htm DOI: http://dx.doi.org/10.4251/wjgo.v7.i11.328

## INTRODUCTION

Although gastric cancer (GC) incidence and mortality rates are declining in most countries, it is still the fifth most common cancer and the third leading cause of cancer-related death worldwide[1]. Epidemiological studies have shown that a high intake of salt, tobacco smoking, and *Helicobacter pylori (H. pylori)* infection increase the risk of GC[2-4]. In areas of high prevalence of GC, such as Japan, Korea and China, most cases of GC are related to *H. pylori*. GC is the result of a long complex multifactorial and multistep process that involves well-characterized sequential stages. The initial lesion is inflammatory and is usually caused by *H. pylori* infection, which results in chronic superficial gastritis. The following pathological model of GC progression includes atrophic gastritis, intestinal metaplasia, dysplasia and GC[5,6]. *H. pylori* infection is the most important risk factor for GC and it was classified as a class Ⅰ carcinogen by the World Health Organization in 1994, nevertheless, the etiology of GC also involves host and other environmental factors. This is demonstrated by the fact that only 1%-3% of patients with *H. pylori* infection develop GC[7,8]. The hypothesis that genetic susceptibility or predisposition plays an important etiological role in GC is supported by many case-control studies and genome-wide association studies (GWASs)[9-14].

*H. pylori* initiates colonization of the gastric mucosa by crossing the gastric mucus layer and adhering to the gastric epithelium[15]. Mucus is the first line of defense and plays a major role in blocking pathogenic factors, and mucins are the major components in mucus and are responsible for its biochemical and biophysical properties[16]. The mucin family comprises 21 members. The mucins are high-molecular-weight glycoproteins characterized by a heavily O-glycosylated tandem repeat region rich in proline, threonine and serine, which is encoded by a variable number of tandem repeats (VNTRs)[17-20]. Mucins are categorized into two subgroups according to their physiological and structural characteristics: membrane-bound, such as MUC1, and secreted, including MUC2, MUC5AC and MUC6[17]. *In situ* hybridization and immunohistochemistry have demonstrated the cell-type-specific expression of mucins in epithelial tissues[21,22]. Normal gastric mucosa shows cell-type-specific expression of MUC1, MUC5AC and MUC6[21-23]. Apical MUC1 is expressed in the gastric mucosa in the superficial and foveolar epithelium and mucous neck zone cells[24]. Secreted mucin MUC5AC is detected in the superficial epithelium, whereas MUC6 is found in the deep glands[25,26]. This specific pattern of MUC1, MUC5AC and MUC6 expression is changed in gastric carcinogenesis, accompanied by *de novo* expression of secreted MUC2[26-30]. Recent genetic and biological evidence highlights the important roles of variations in these mucin genes in the development and progression of GC. In this review, we focus on studies of the association between polymorphisms in *MUC1*, *MUC5AC*, *MUC6* and *MUC2* genes and development of GC (Table 1). Details of the studied single nucleotide polymorphisms (SNPs) in mucin genes are described in Table 2.

## POLYMORPHISMS IN *MUC1* IN THE DEVELOPMENT OF GC

MUC1 is a highly polymorphic membrane-associated mucin that is often aberrantly expressed in cancer[31]. *MUC1* gene is located on chromosome 1q21 and contains a highly conserved VNTR of 20 amino acids, varying from 25 to 125 repeats, depending on the allele[32]. In recent decades, some studies were performed to investigate the potential roles of genetic variations in *MUC1* in gastric carcinogenesis, but most of them were focused on the VNTRs, with inconsistent results. Costa *et al*[33] observed that polymorphism in the *MUC1* VNTRs influenced the binding of *H. pylori* to gastric cells. Vinall *et al*[28] reported that small *MUC1* VNTR alleles were correlated with *H. pylori*-associated gastritis in European populations. Two studies from Portugal (which has the higher risk of GC in Europe) showed that small *MUC1* VNTR alleles were significantly associated with gastric carcinoma[34], as well as chronic atrophic gastritis and incomplete intestinal metaplasia, which are two well-established precursor lesions of GC[35]. However, another study from Denmark indicated that small *MUC1* VNTR alleles are more frequent in the Danish population (which has the lower risk of GC in Europe) than in Portugal[36].

GWASs have recently been important in identifying potential genetic variations related to cancer susceptibility. In 2010, Abnet *et al*[37] conducted a GWAS in 1625 patients with GC and 2100 controls. They identified a significant SNP of rs4072037 A/G in the *MUC1* gene for GC. The A allele was correlated with increased susceptibility to GC in Chinese patients during initial scanning, however, this association was not maintained in the second phase, or when the results of the two phases were combined. A GWAS on GC in Japan revealed the top 10 SNPs that were significantly related to the diffuse type of GC, which included two located in chromosome 1q22[38]. Subsequently, Saeki *et al*[39] performed high-density mapping to explore the

**Table 1 List of association studies between polymorphisms in mucin genes and development of gastric cancer**

| Gene | Ref. | Population | Disease | Study design | Sample (case/control) | Polymorphism | Association |
|---|---|---|---|---|---|---|---|
| *MUC1* | Vinall *et al*[28] | European | *H. pylori* related gastritis | Case–control study | 57 gastritis patients | VNTR | Yes |
| | Carvalho *et al*[34] | Portuguese | GC | Case–control study | 159/324 | VNTR | Yes |
| | Silva *et al*[35] | Portuguese | CAG, IM | Case–control study | 174 patients | VNTR | Yes |
| | Abnet *et al*[37] | Chinese | GC | GWAS | 1625/2100 | rs4072037 | Yes |
| | | | | | Replication: 615/1202 | | No |
| | | | | | Combined: 2240/3302 | | No |
| | Saeki *et al*[39] | Japanese | DGC | Case–control study | 606/1264/ | rs4072037, rs2070803 | Yes |
| | | Japanese | | | 304/1465 | rs4072037, rs2070803 | Yes |
| | | South Korean | | | 452/372 | rs4072037, rs2070803 | Yes |
| | Xu *et al*[40] | Chinese | GC | Case–control study | 138/241 | rs4072037 | Yes |
| | Jia *et al*[43] | Polish | GC | Case–control study | 273/377 | rs6427184 | Yes |
| | | | | (tag SNP approach) | | rs4971052 | Yes |
| | | | | | | rs4276913 | Yes |
| | | | | | | rs4971088 | Yes |
| | | | | | | rs4971092 | Yes |
| | | | | | | rs4072037 | Yes |
| | Jia *et al*[43] | Polish | *H. pylori* infection | Case–control study | 320/57 | rs6427184 | No |
| | | | | (tag SNP approach) | | rs4971052 | No |
| | | | | | | rs4276913 | No |
| | | | | | | rs4971088 | No |
| | | | | | | rs4971092 | No |
| | | | | | | rs4072037 | No |
| | Zhang *et al*[44] | Chinese | GC | Case–control study | 1681/1858 | rs4072037 | Yes |
| | Palmer *et al*[45] | Caucasian | GC | Case–control study | 596/587 | rs4072037 | Yes |
| | Li *et al*[46] | Chinese | GC | Case–control study | 300/300 | rs2070803 | Yes |
| | Zhang *et al*[47] | Chinese | Non-cardia GC | Case–control study | 288/281 | rs4072037 | No |
| | | | | (tag SNP approach) | | rs2990245 | No |
| | | | | | | rs9628662 | No |
| | | | | | | rs9426886 | No |
| | Zhang *et al*[47] | Chinese | *H. pylori* infection | Case–control study | 122/159 | rs4072037 | No |
| | | | | (tag SNP approach) | | rs2990245 | No |
| | | | | | | rs9628662 | No |
| | | | | | | rs9426886 | No |
| | Frank *et al*[48] | German | CAG | Case–control study | 533/1054 | rs4072037 | No |
| | Marín *et al*[49] | Spanish | GCPLs | Case–control study | 387 patients | rs3814316 | No |
| | | | | (tag SNP approach) | | rs9426886 | No |
| | | | | | | rs1045253 | No |
| | Sun *et al*[50] | Hispanic American | GC | Case–control study | 132/125 | rs4072037 | No |
| | Duan *et al*[51] | - | GC | Meta-analysis | 4220/6384 | rs4072037 | Yes |
| | Zheng *et al*[52] | - | GC | Meta-analysis | 6580/10324 | rs4072037 | Yes |
| | Mocellin *et al*[42] | Asian | DGC | Meta-analysis | 7279 subjects | rs2070803 | Yes |
| *MUC5AC* | Jia *et al*[43] | Polish | GC | Case–control study | 273/377 | rs1541314 | No |
| | | | | (tag SNP approach) | | rs2014486 | Yes |
| | | | | | | rs2075859 | No |
| | | | | | | rs2672785 | No |
| | | | | | | rs2735733 | Yes |
| | | | | | | rs7118568 | No |
| | | | | | | rs868903 | Yes |
| | | | | | | rs4963049 | No |
| | Jia *et al*[43] | Polish | *H. pylori* infection | Case–control study | 320/57 | rs1541314 | No |
| | | | | (tag SNP approach) | | rs2014486 | No |
| | | | | | | rs2075859 | No |
| | | | | | | rs2672785 | No |
| | | | | | | rs2735733 | No |
| | | | | | | rs7118568 | No |
| | | | | | | rs868903 | No |
| | | | | | | rs4963049 | No |
| | Zhou *et al*[61] | Chinese | Non-cardia GC | Case–control study | 288/281 | rs3793966 | No |
| | | | | (tag SNP approach) | | rs7118568 | No |
| | | | | | | rs868903 | No |
| | | | | | | rs3793964 | Yes |
| | | | | | | rs3750919 | No |
| | | | | | | rs5743942 | No |
| | | | | | | rs4963062 | No |
| | | | | | | rs885454 | Yes |
| | | | | | | rs6578810 | No |
| | | | | | | rs11040869 | Yes |
| | | | | | | rs7118481 | No |
| | | | | | | rs7105198 | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Zhou *et al*[62] | Chinese | *H. pylori* infection | Case–control study (tag SNP approach) | 122/159 | rs3793966 | No |
| | | | | | | rs7118568 | No |
| | | | | | | rs868903 | No |
| | | | | | | rs3793964 | No |
| | | | | | | rs3750919 | No |
| | | | | | | rs5743942 | No |
| | | | | | | rs4963062 | No |
| | | | | | | rs885454 | No |
| | | | | | | rs6578810 | No |
| | | | | | | rs11040869 | No |
| | | | | | | rs7118481 | No |
| | | | | | | rs7105198 | No |
| | Wang *et al*[63] | Chinese | GC | Case–control study | 230/328 | VNTR | Yes |
| *MUC6* | Nguyen *et al*[68] | - | *H. pylori* infection | Case–control study | 92/68 | VNTR | Yes |
| | Garcia *et al*[69] | Portuguese | GC | Case–control study | 157/376 | VNTR | Yes |
| | Kwon *et al*[70] | South Korean | GC | Case–control study | 470/1103 | VNTR | Yes |
| | Jia *et al*[43] | Polish | GC | Case–control study (tag SNP approach) | 273/377 | rs1128413 | No |
| | | | | | | rs4077293 | No |
| | | | | | | rs7483870 | No |
| | | | | | | rs7943115 | No |
| | | | | | | rs11602663 | No |
| | | | | | | rs11605303 | No |
| | | | | | | rs10902076 | No |
| | | | | | | rs2071174 | No |
| | | | | | | rs11245936 | No |
| | | | | | | rs10794359 | No |
| | | | | | | rs7112267 | No |
| | | | | | | rs12574439 | No |
| | | | | | | rs7119740 | No |
| | | | | | | rs11601642 | No |
| | Jia *et al*[43] | Polish | *H. pylori* infection | Case–control study (tag SNP approach) | 320/57 | rs1128413 | No |
| | | | | | | rs4077293 | No |
| | | | | | | rs7483870 | No |
| | | | | | | rs7943115 | No |
| | | | | | | rs11602663 | No |
| | | | | | | rs11605303 | No |
| | | | | | | rs10902076 | No |
| | | | | | | rs2071174 | No |
| | | | | | | rs11245936 | No |
| | | | | | | rs10794359 | No |
| | | | | | | rs7112267 | No |
| | | | | | | rs12574439 | No |
| | | | | | | rs7119740 | No |
| | | | | | | rs11601642 | No |
| | Marín *et al*[49] | Spanish | GCPLs | Case–control study (tag SNP approach) | 387 patients | rs4076950 | No |
| | | | | | | rs7481521 | No |
| | | | | | | rs11246384 | No |
| | | | | | | rs6597947 | No |
| | | | | | | rs9794921 | No |
| | Frank *et al*[48] | German | CAG | Case–control study | 533/1054 | rs7481521 | No |
| *MUC2* | Jeong *et al*[72] | South Korean | GC | Case–control study | 455/457 | VNTR | Yes |
| | Marín *et al*[49] | Spanish | GCPLs | Case–control study (tag SNP approach) | 387 patients | rs10902073 | Yes |
| | | | | | | rs10794281 | Yes |
| | | | | | | rs2856082 | No |
| | | | | | | rs2071174 | Yes |
| | | | | | | rs7396030 | No |
| | | | | | | rs11245936 | No |
| | | | | | | rs7944723 | Yes |
| | | | | | | rs6421972 | No |
| | | | | | | rs10794293 | Yes |
| | | | | | | rs11245954 | No |
| | | | | | | rs7480563 | No |
| | | | | | | rs7126405 | No |
| | | | | | | rs3924453 | Yes |
| | | | | | | rs4077759 | Yes |
| | Frank *et al*[48] | German | CAG | Case–control study | 533/1054 | rs2856111 | No |
| | | | | | | rs11825977 | No |

CAG: Chronic atrophic gastritis; DGC: Diffuse gastric cancer; GCPLs: Gastric cancer precursor lesions; *H. pylori*: *Helicobacter pylori*; IM: Intestinal metaplasia; SNP: Single nucleotide polymorphism; GC: Gastric cancer.

**Table 2 Description of the studied single nucleotide polymorphisms in mucin genes**

| Gene | Chromosome | SNPs | Wild alleles | Mutated alleles | Contig position[1] | Location[2] |
|---|---|---|---|---|---|---|
| *MUC1* | 1q21 | rs4072037 | A | G | 12007689 | T22T |
| | | rs2070803 | C | T | 12000652 | 3′ flanking region |
| | | rs6427184 | A | G | 11965720 | 3′ flanking region |
| | | rs4971052 | C | T | 11968955 | 3′ flanking region |
| | | rs4276913 | A | G | 11974610 | 3′ flanking region |
| | | rs4971088 | T | A | 11985820 | 3′ flanking region |
| | | rs4971092 | T | C | 11986883 | 3′ flanking region |
| | | rs2990245 | T | C | 12043084 | 5′ flanking region |
| | | rs9628662 | T | G | 12051963 | 5′ flanking region |
| | | rs9426886 | T | A | 11994691 | 3′ flanking region |
| | | rs3814316 | C | T | 11992655 | 3′ flanking region |
| | | rs1045253 | T | C | 12046857 | 5′ flanking region |
| *MUC5AC* | 11p15.5 | rs1541314 | G | A | 1182293 | 3′ flanking region |
| | | rs2014486 | A | G | 1177573 | 3′ flanking region |
| | | rs2075859 | C | T | 1169258 | 3′ flanking region |
| | | rs2672785 | C | T | 1165711 | 3′ flanking region |
| | | rs2735733 | C | T | 1180410 | 3′ flanking region |
| | | rs7118568 | C | G | 1162850 | 3′ flanking region |
| | | rs868903 | T | C | 1161460 | 3′ flanking region |
| | | rs4963049 | A | G | 1155197 | 3′ flanking region |
| | | rs3793966 | C | T | 1221718 | 3′ flanking region |
| | | rs3793964 | C | T | 1220752 | 3′ flanking region |
| | | rs3750919 | G | A | 1211601 | 3′ flanking region |
| | | rs5743942 | C | T | 1232798 | 3′ flanking region |
| | | rs4963062 | G | A | 1245411 | 3′ flanking region |
| | | rs885454 | C | T | 1162161 | 3′ flanking region |
| | | rs6578810 | T | G | 1209349 | 3′ flanking region |
| | | rs11040869 | G | A | 1203382 | 3′ flanking region |
| | | rs7118481 | G | C | 1267108 | 3′ flanking region |
| | | rs7105198 | G | C | 1086133 | 5′ flanking region |
| *MUC6* | 11p15.5 | rs1128413 | C | T | 950694 | 3′ flanking region |
| | | rs4077293 | C | T | 936522 | 3′ flanking region |
| | | rs7483870 | C | T | 916019 | 3′ flanking region |
| | | rs7943115 | G | A | 913885 | 3′ flanking region |
| | | rs11602663 | C | T | 960778 | Intronic |
| | | rs11605303 | G | A | 978110 | 5′ flanking region |
| | | rs10902076 | G | C | 1006044 | 5′ flanking region |
| | | rs2071174 | C | T | 1013712 | 5′ flanking region |
| | | rs11245936 | G | A | 1026266 | 5′ flanking region |
| | | rs10794359 | C | T | 991715 | 5′ flanking region |
| | | rs7112267 | C | T | 996981 | 5′ flanking region |
| | | rs12574439 | G | C | 997948 | 5′ flanking region |
| | | rs7119740 | C | G | 1000419 | 5′ flanking region |
| | | rs11601642 | C | A | 1002509 | 5′ flanking region |
| | | rs4076950 | C | T | 955021 | Intronic |
| | | rs7481521 | G | A | 967811 | V619M |
| | | rs11246384 | C | T | 970448 | Intronic |
| | | rs6597947 | G | T | 977029 | 5′ flanking region |
| | | rs9794921 | G | T | 979867 | 5′ flanking region |
| *MUC2* | 11p15.5 | rs10902073 | C | A | 1000934 | 5′ flanking region |
| | | rs10794281 | C | T | 1003149 | 5′ flanking region |
| | | rs2856082 | C | G | 1011562 | 5′ flanking region |
| | | rs2071174 | C | T | 1013712 | 5′ flanking region |
| | | rs7396030 | C | T | 1025368 | Intronic |
| | | rs11245936 | G | A | 1026366 | G832S |
| | | rs7944723 | C | G | 1039802 | P1832P |
| | | rs6421972 | G | A | 1042586 | I2154T |
| | | rs10794293 | C | T | 1045031 | Intron |
| | | rs11245954 | A | G | 1047170 | V2459V |
| | | rs7480563 | G | A | 1047741 | T2524P |
| | | rs7126405 | G | A | 1049388 | Q2653P |
| | | rs3924453 | G | A | 1051898 | 3′ flanking region |
| | | rs4077759 | C | T | 1052068 | 3′ flanking region |
| | | rs2856111 | T | C | 1015747 | L58P |
| | | rs11825977 | A | G | 1015920 | V116M |

[1]Based on contig NT_004487.20 for *MUC1* gene, and contig NT_009237.19 for *MUC5AC*, *MUC6* and *MUC2* genes; [2]SNP location relative to each gene in the region. SNPs: Single nucleotide polymorphisms.

susceptibility locus of GC at chromosome 1q22 and reported that two SNPs of rs2070803 and rs4072037 were significantly related to susceptibility to diffuse GC in Japan, and the results were validated in other Japanese and Korean studies. SNP rs4072037 is located in exon 2 of the *MUC1* gene and controls alternative splicing at the boundary between exons 1 and 2[39-41]. This SNP affects promoter activity and disrupts the physiological function of MUC1[41,42]. The rs4072037 G allele is correlated with higher VNTRs and the A allele with lower VNTRs[41]. However, the VNTRs are unlikely to be the causal polymorphism for GC susceptibility because the TRs are not translated in normal or malignant gastric epithelial cells[39]. This suggests that the VNTRs are a tagging polymorphism for other genetic variations, such as rs4072037, related to risk of gastric carcinogenesis. It is particularly interesting that rs4072037 A is a major allele in Chinese, Japanese and Korean populations, which have a high incidence of GC, but a minor allele in Caucasians, who have a low incidence of GC. SNP rs2070803 G/A is downstream of the *MUC1* and *TRIM46* genes and its functional effects are unknown. *MUC1* is located downstream of the *TRIM46* gene. These two genes are part of a cluster, which also includes *KRTCAP2*, *THBS3*, *MTX1*, *PKLR* and *HCN3*, located in a region of strong linkage disequilibrium (LD) and are transcribed in opposite directions[42]. *TRIM46* is not expressed in gastric mucosa[39], therefore, SNP rs2070803 might also be a tag for variants in other genes located in this LD region, such as *MUC1*, which are involved in gastric carcinogenesis.

In addition to GWASs, the association of *MUC1* SNPs with GC has been investigated in many case-control studies using a candidate gene approach. An association study in China showed that patients with rs4072037 AA genotype had a significantly increased risk of GC[40]. Jia *et al*[43] conducted a population-based, case-control study in the Polish population. Each of the tested tag SNPs (including rs6427184, rs4971052, rs4276913, rs4971088, rs4971092 and rs4072037) across the *MUC1* region had significant associations with increased risk of GC. This association remained significant after adjusting for multiple tests, which also demonstrated that rs4072037 AA genotype was related to increased risk of GC. However, the study showed that *MUC1* tag SNPs were not associated with *H. pylori* infection, suggesting that the effects of *MUC1* polymorphisms on risk of GC are not mediated by *H. pylori* infection. The association between rs4072037 A allele and increased GC risk was further replicated in Chinese and Caucasian populations[44,45]. Another study demonstrated that rs2070803 GA/AA genotypes were protective against GC, with > 50% risk reduction in Chinese individuals[46]. However, other studies have shown conflicting results. A case-control study conducted by our group showed that four tag SNPs (including rs4072037) in *MUC1* were not associated with the risk of non-cardia GC, or *H. pylori* infection in the Han population in Northwest China[47]. Another study showed no association between rs4072037 and risk of chronic atrophic gastritis, a well-defined precursor of GC in the German population[48]. Marín *et al*[49] reported that three tag SNPs (rs3814316, rs9426886 and rs1045253) in *MUC1* were not associated with precursor lesions of GC in a high-risk area of Spain. Another study demonstrated that rs4072037 was not associated with GC risk in Hispanic Americans[50]. To clarify the current limited and conflicting evidence, and to establish the true impact of *MUC1* variations on gastric carcinogenesis, several meta-analyses have been performed. Duan *et al*[51] conducted an analysis of 10 case-control studies comprising 4220 cases and 6384 controls. They found that rs4072037 G allele was associated with a decreased risk of GC progression, especially in Asians. This result is consistent with the study of Zheng *et al*[52] of 6580 cases and 10324 controls, which suggested the involvement of *MUC1* rs4072037 polymorphism in gastric carcinogenesis among Asian individuals. A further meta-analysis showed that the rare rs2070803 A allele was associated with reduced risk of diffuse-type GC[42]. All the evidence suggests that *MUC1* polymorphisms, such as rs4072037, are promising biological markers for predicting GC risk, especially in Asian populations.

## POLYMORPHISMS IN *MUC5AC* IN THE DEVELOPMENT OF GC

MUC5AC is a major secreted mucin in healthy gastric mucosa and is the major receptor for *H. pylori* in the human stomach. BabA and SabA adhesins on *H. pylori* bind to Lewis B blood group antigens on MUC5AC, facilitating colonization[53-55]. In chronic *H. pylori* infection, normally expressed MUC5AC and MUC5AC-producing cells may gradually decrease[56,57]. *MUC5AC* is located on chromosome 11p15.5[58], which often has loss of heterozygosity in patients with GC[59,60]. Studies on the association between *MUC5AC* polymorphisms and GC development are limited at present. Jia *et al*[43] investigated the relationship between eight tag SNPs of *MUC5AC* and GC in a Polish study. The three tag SNPs rs868903, rs2014486 and rs2735733 in the 3' flanking region of *MUC5AC* were related to the risk of GC. Their minor allele homozygotes were significantly associated with increased risk of GC. However, none of the eight tested tag SNPs were associated with risk of *H. pylori* infection. Our group also performed a case-control study to evaluate the association of 12 tag SNPs of *MUC5AC* with risk of non-cardia GC in the Han population in Northwest China. We observed that three tag SNPs, rs3793964, rs11040869 and rs885454, were significantly associated with the risk of non-cardia GC. The minor allele homozygotes of rs3793964 and rs11040869, as well as the heterozygote of rs885454 had a protective effect on risk of non-cardia GC[61]. These three tag SNPs are all located in the 3' flanking region of *MUC5AC*. The discrepancies between the

two studies may have been due to racial differences in variant frequencies. However, few biological studies on genetic variations in *MUC5AC* have been reported. Similarly, our results also suggested that polymorphisms of *MUC5AC* gene were not associated with the risk of *H. pylori* infection, suggesting *MUC5AC* polymorphisms are involved in other processes besides bacterial binding in developing GC[62]. Wang *et al*[63] conducted a case-control study in the Chinese population, which reported that some variations in an upstream repetitive region of *MUC5AC* were associated with GC susceptibility and progression. Their findings highlight the importance of *MUC5AC* polymorphisms in risk of GC.

## POLYMORPHISMS IN *MUC6* IN THE DEVELOPMENT OF GC

The secreted mucin, MUC6, is highly expressed in normal gastric mucosa. One study has shown that MUC6 has antimicrobial properties against *H. pylori*. Unique glycan residues on MUC6 inhibit biosynthesis of major cell wall component cholesteryl-α-D-glucopyranoside[64]. MUC6 is aberrantly expressed in response to *H. pylori* infection[65], and MUC6 expression is lower in GC compared with normal mucus[66]. *MUC6* is also located on chromosome 11p15.5, which is a region rich in recombination[59]. *MUC1* and *MUC6* have a large number of VNTRs[67]. Several studies have focused on the relationship between VNTR polymorphisms of *MUC6* and GC development. In one of these, small VNTR alleles of *MUC6* gene were associated with increased risk of *H. pylori* infection[68]. Others showed that small *MUC6* VNTR alleles were more frequent in patients with GC than in healthy blood donors[69], and short rare *MUC6* minisatellite 5 alleles had an effect on susceptibility to GC by regulating gene expression[70]. However, Jia *et al*[43] investigated the relationship between *MUC6* polymorphisms and GC, using a tag SNP approach. Fourteen of the tag SNPs tested across the *MUC6* region were not associated with risk of GC or *H. pylori* infection. The authors inferred that VNTR polymorphisms had many alleles, which might have divided the study population into several classes, thus making statistical analysis difficult. Similarly, Marín *et al*[49] observed that five tag SNPs in *MUC6* were not associated with GC precursor lesions. Furthermore, Frank *et al*[48] investigated the association between polymorphism in *MUC6* and the risk of chronic atrophic gastritis, using a candidate SNP approach. However, there was no association between the putative functional SNP rs7481521 (*MUC6* V619M) and chronic atrophic gastritis. Further studies are needed to elucidate the roles of *MUC6* polymorphisms in the gastric carcinogenesis pathway.

## POLYMORPHISMS IN *MUC2* IN THE DEVELOPMENT OF GC

Normal gastric mucosa shows little or no expression of MUC2. However, in intestinal metaplasia and GC, the level of MUC2 is increased[27,29,30]. MUC2 might be activated by proinflammatory cytokines expressed after *H. pylori* infection, leading to its overexpression[71]. *MUC2* gene is clustered on chromosome 11p15.5 with *MUC5AC*, *MUC5B* and *MUC6*[58]. Only three studies have evaluated the relationship between *MUC2* polymorphisms and development of GC. Jeong *et al*[72] reported that the short rare minisatellite 6 alleles of *MUC2* gene are associated with GC. Marín *et al*[49] have investigated the association of 14 tag SNPs in *MUC2* with evolution of GC precursor lesions in 387 patients with 12.8 years follow-up. According to the diagnosis at recruitment and after follow-up, the patients were divided into three groups, that is, those with no change in lesions, progression of lesions, and regression of lesions. The results indicated that three SNPs (rs10794293, rs3924453 and rs4077759) at the 3′ moiety in *MUC2* were associated with a decreased risk of lesion progression. In contrast, another four SNPs (rs10902073, rs10794281, rs2071174 and rs7944723) at the 5′ moiety were significantly associated with lesion regression. The association of SNPs with GC precursor lesions was stronger in patients with *H. pylori* infection. However, it was also shown that functional SNP rs11825977 (V116M) in *MUC2*, which might influence *MUC2* mRNA expression[73], as well as the potentially functional SNP rs2856111 (L58P), were not associated with the risk of chronic atrophic gastritis[48].

## CONCLUSION

GC is the third leading cause of cancer mortality and a serious global problem. Many studies have tried to identify the factors responsible for GC, but the exact sequence of molecular events involved in the development of GC remains unclear. In areas of high GC prevalence, most cases are related to *H. pylori* infection, and GC develops through several stages, including infection, gastric atrophy, intestinal metaplasia and dysplasia. There is a lot of evidence to support the key role of mucins in development of GC. This review focused on studies of the association between polymorphisms in mucin genes and development of GC. The strength of such an association varied among the studies. The diversity in study populations and lifestyle, as well as sample size may account for this inconsistency. For example, functional SNP rs4072037 in *MUC1* gene may affect the development of GC, but the effects seem to be stronger in Asian populations. Future association studies need global collaboration to expand sample size and identify more susceptibility polymorphisms. However, lifestyle factors should be taken into account to ensure accurate and significant results. Such studies will identify useful biomarkers for early detection of GC, with the potential for better disease prevention through selective treatment and surveillance of individuals harboring high-risk genetic profiles.

## REFERENCES


1 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

2 **Lee SA**, Kang D, Shim KN, Choe JW, Hong WS, Choi H. Effect of diet and Helicobacter pylori infection to the risk of early gastric cancer. *J Epidemiol* 2003; **13**: 162-168 [PMID: 12749604]

3 **Shikata K**, Doi Y, Yonemoto K, Arima H, Ninomiya T, Kubo M, Tanizaki Y, Matsumoto T, Iida M, Kiyohara Y. Population-based prospective study of the combined influence of cigarette smoking and Helicobacter pylori infection on gastric cancer incidence: the Hisayama Study. *Am J Epidemiol* 2008; **168**: 1409-1415 [PMID: 18945691 DOI: 10.1093/aje/kwn276]

4 **Helicobacter and Cancer Collaborative Group**. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**: 347-353 [PMID: 11511555]

5 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]

6 **Yuasa Y**. Control of gut differentiation and intestinal-type gastric carcinogenesis. *Nat Rev Cancer* 2003; **3**: 592-600 [PMID: 12894247]

7 **Wang F**, Meng W, Wang B, Qiao L. Helicobacter pylori-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014; **345**: 196-202 [PMID: 23981572 DOI: 10.1016/j.canlet.2013.08.016]

8 **Wroblewski LE**, Peek RM, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. *Clin Microbiol Rev* 2010; **23**: 713-739 [PMID: 20930071 DOI: 10.1128/CMR.00011-10]

9 **Xie Y**, Wang Y, Zhao Y, Guo Z. Single-nucleotide polymorphisms of microRNA processing machinery genes are associated with risk for gastric cancer. *Onco Targets Ther* 2015; **8**: 567-571 [PMID: 25784816 DOI: 10.2147/OTT.S79150]

10 **Ismaili A**, Yari K, Moradi MT, Sohrabi M, Kahrizi D, Kazemi E, Souri Z. IL-1B (C+3954T) gene polymorphism and susceptibility to gastric cancer in the Iranian population. *Asian Pac J Cancer Prev* 2015; **16**: 841-844 [PMID: 25684535 DOI: 10.7314/APJCP.2015.16.2.841]

11 **Shao A**, Zheng L, Chen S, Gu H, Jing H. p21, p53, TP53BP1 and p73 polymorphisms and the risk of gastric cardia adenocarcinoma in a Chinese population. *Biomarkers* 2015; **20**: 109-115 [PMID: 25532599]

12 **Ferrer-Ferrer M**, Malespín-Bendaña W, Ramírez V, González MI, Carvajal A, Une C. Polymorphisms in genes coding for HSP-70 are associated with gastric cancer and duodenal ulcer in a population at high risk of gastric cancer in Costa Rica. *Arch Med Res* 2013; **44**: 467-474 [PMID: 24051039 DOI: 10.1016/j.arcmed.2013.08.008]

13 **Shi Y**, Hu Z, Wu C, Dai J, Li H, Dong J, Wang M, Miao X, Zhou Y, Lu F, Zhang H, Hu L, Jiang Y, Li Z, Chu M, Ma H, Chen J, Jin G, Tan W, Wu T, Zhang Z, Lin D, Shen H. A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. *Nat Genet* 2011; **43**: 1215-1218 [PMID: 22037551 DOI: 10.1038/ng.978]

14 **Sala N**, Muñoz X, Travier N, Agudo A, Duell EJ, Moreno V, Overvad K, Tjonneland A, Boutron-Ruault MC, Clavel-Chapelon F, Canzian F, Kaaks R, Boeing H, Meidtner K, Trichopoulos A, Tsiotas K, Zylis D, Vineis P, Panico S, Palli D, Krogh V, Tumino R, Lund E, Bueno-de-Mesquita HB, Numans ME, Peeters PH, Quirós JR, Sánchez MJ, Navarro C, Ardanaz E, Dorronsoro M, Hallmans G, Stenling R, Manjer J, Allen NE, Travis RC, Khaw KT, Jenab M, Offerhaus GJ, Riboli E, González CA. Prostate stem-cell antigen gene is associated with diffuse and intestinal gastric cancer in Caucasians: results from the EPIC-EURGAST study. *Int J Cancer* 2012; **130**: 2417-2427 [PMID: 21681742 DOI: 10.1002/ijc.26243]

15 **Ruggiero P**. Helicobacter pylori and inflammation. *Curr Pharm Des* 2010; **16**: 4225-4236 [PMID: 21184659 DOI: 10.2174/138161210794519075]

16 **Rachagani S**, Torres MP, Moniaux N, Batra SK. Current status of mucins in the diagnosis and therapy of cancer. *Biofactors* 2009; **35**: 509-527 [PMID: 19904814 DOI: 10.1002/biof.64]

17 **Hollingsworth MA**, Swanson BJ. Mucins in cancer: protection and control of the cell surface. *Nat Rev Cancer* 2004; **4**: 45-60 [PMID: 14681689 DOI: 10.1038/nrc1251]

18 **Moniaux N**, Escande F, Porchet N, Aubert JP, Batra SK. Structural organization and classification of the human mucin genes. *Front Biosci* 2001; **6**: D1192-D1206 [PMID: 11578969]

19 **Hanisch FG**. O-glycosylation of the mucin type. *Biol Chem* 2001; **382**: 143-149 [PMID: 11308013 DOI: 10.1515/BC.2001.022]

20 **Carraway KL**, Hull SR. O-glycosylation pathway for mucin-type glycoproteins. *Bioessays* 1989; **10**: 117-121 [PMID: 2658987 DOI: 10.1002/bies.950100406]

21 **Audie JP**, Janin A, Porchet N, Copin MC, Gosselin B, Aubert JP. Expression of human mucin genes in respiratory, digestive, and reproductive tracts ascertained by in situ hybridization. *J Histochem Cytochem* 1993; **41**: 1479-1485 [PMID: 8245407 DOI: 10.1177/41.10.8245407]

22 **Gendler SJ**, Spicer AP. Epithelial mucin genes. *Annu Rev Physiol* 1995; **57**: 607-634 [PMID: 7778880 DOI: 10.1146/annurev.ph.57.030195.003135]

23 **Perez-Vilar J**, Hill RL. The structure and assembly of secreted mucins. *J Biol Chem* 1999; **274**: 31751-31754 [PMID: 10542193 DOI: 10.1074/jbc.274.45.31751]

24 **Jass JR**. Mucin core proteins as differentiation markers in the gastrointestinal tract. *Histopathology* 2000; **37**: 561-564 [PMID: 11122439]

25 **De Bolós C**, Garrido M, Real FX. MUC6 apomucin shows a distinct normal tissue distribution that correlates with Lewis antigen expression in the human stomach. *Gastroenterology* 1995; **109**: 723-734 [PMID: 7657100]

26 **Reis CA**, David L, Nielsen PA, Clausen H, Mirgorodskaya K, Roepstorff P, Sobrinho-Simões M. Immunohistochemical study of MUC5AC expression in human gastric carcinomas using a novel monoclonal antibody. *Int J Cancer* 1997; **74**: 112-121 [PMID: 9036879]

27 **Babu SD**, Jayanthi V, Devaraj N, Reis CA, Devaraj H. Expression profile of mucins (MUC2, MUC5AC and MUC6) in Helicobacter pylori infected pre-neoplastic and neoplastic human gastric epithelium. *Mol Cancer* 2006; **5**: 10 [PMID: 16545139 DOI: 10.1186/1476-4598-5-10]

28 **Vinall LE**, King M, Novelli M, Green CA, Daniels G, Hilkens J, Sarner M, Swallow DM. Altered expression and allelic association of the hypervariable membrane mucin MUC1 in Helicobacter pylori gastritis. *Gastroenterology* 2002; **123**: 41-49 [PMID: 12105832 DOI: 10.1053/gast.2002.34157]

29 **Reis CA**, David L, Carvalho F, Mandel U, de Bolós C, Mirgorodskaya E, Clausen H, Sobrinho-Simões M. Immunohistochemical study of the expression of MUC6 mucin and co-expression of other secreted mucins (MUC5AC and MUC2) in human gastric carcinomas. *J Histochem Cytochem* 2000; **48**: 377-388 [PMID: 10681391]

30 **Ho SB**, Shekels LL, Toribara NW, Kim YS, Lyftogt C, Cherwitz DL, Niehans GA. Mucin gene expression in normal, preneoplastic, and neoplastic human gastric epithelium. *Cancer Res* 1995; **55**: 2681-2690 [PMID: 7780985]

31 **Nath S**, Mukherjee P. MUC1: a multifaceted oncoprotein with a key role in cancer progression. *Trends Mol Med* 2014; **20**: 332-342 [PMID: 24667139 DOI: 10.1016/j.molmed.2014.02.007]

32 **Fowler J**, Vinall L, Swallow D. Polymorphism of the human muc genes. *Front Biosci* 2001; **6**: D1207-D1215 [PMID: 11578959 DOI: 10.2741/Fowler]

33 **Costa NR**, Mendes N, Marcos NT, Reis CA, Caffrey T, Hollingsworth MA, Santos-Silva F. Relevance of MUC1 mucin variable number of tandem repeats polymorphism in H pylori adhesion to gastric epithelial cells. *World J Gastroenterol* 2008; **14**: 1411-1414 [PMID: 18322957 DOI: 10.3748/wjg.14.1411]

34 **Carvalho F**, Seruca R, David L, Amorim A, Seixas M, Bennett E,

Clausen H, Sobrinho-Simões M. MUC1 gene polymorphism and gastric cancer--an epidemiological study. *Glycoconj J* 1997; **14**: 107-111 [PMID: 9076520]

35 **Silva F**, Carvalho F, Peixoto A, Seixas M, Almeida R, Carneiro F, Mesquita P, Figueiredo C, Nogueira C, Swallow DM, Amorim A, David L. MUC1 gene polymorphism in the gastric carcinogenesis pathway. *Eur J Hum Genet* 2001; **9**: 548-552 [PMID: 11464247 DOI: 10.1038/sj.ejhg.5200677]

36 **Carvalho F**, Peixoto A, Steffensen R, Amorim A, David L, Sobrinho-Simões M. MUC1 gene polymorphism does not explain the different incidence of gastric cancer in Portugal and Denmark. *Ann Hum Genet* 1999; **63**: 187-191 [PMID: 10738530 DOI: 10.1046/j.1469-1809.1999.6330187.x]

37 **Abnet CC**, Freedman ND, Hu N, Wang Z, Yu K, Shu XO, Yuan JM, Zheng W, Dawsey SM, Dong LM, Lee MP, Ding T, Qiao YL, Gao YT, Koh WP, Xiang YB, Tang ZZ, Fan JH, Wang C, Wheeler W, Gail MH, Yeager M, Yuenger J, Hutchinson A, Jacobs KB, Giffen CA, Burdett L, Fraumeni JF, Tucker MA, Chow WH, Goldstein AM, Chanock SJ, Taylor PR. A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. *Nat Genet* 2010; **42**: 764-767 [PMID: 20729852 DOI: 10.1038/ng.649]

38 **Study Group of Millennium Genome Project for Cancer**, Sakamoto H, Yoshimura K, Saeki N, Katai H, Shimoda T, Matsuno Y, Saito D, Sugimura H, Tanioka F, Kato S, Matsukura N, Matsuda N, Nakamura T, Hyodo I, Nishina T, Yasui W, Hirose H, Hayashi M, Toshiro E, Ohnami S, Sekine A, Sato Y, Totsuka H, Ando M, Takemura R, Takahashi Y, Ohdaira M, Aoki K, Honmyo I, Chiku S, Aoyagi K, Sasaki H, Ohnami S, Yanagihara K, Yoon KA, Kook MC, Lee YS, Park SR, Kim CG, Choi IJ, Yoshida T, Nakamura Y, Hirohashi S. Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer. *Nat Genet* 2008; **40**: 730-740 [PMID: 18488030 DOI: 10.1038/ng.152]

39 **Saeki N**, Saito A, Choi IJ, Matsuo K, Ohnami S, Totsuka H, Chiku S, Kuchiba A, Lee YS, Yoon KA, Kook MC, Park SR, Kim YW, Tanaka H, Tajima K, Hirose H, Tanioka F, Matsuno Y, Sugimura H, Kato S, Nakamura T, Nishina T, Yasui W, Aoyagi K, Sasaki H, Yanagihara K, Katai H, Shimoda T, Yoshida T, Nakamura Y, Hirohashi S, Sakamoto H. A functional single nucleotide polymorphism in mucin 1, at chromosome 1q22, determines susceptibility to diffuse-type gastric cancer. *Gastroenterology* 2011; **140**: 892-902 [PMID: 21070779 DOI: 10.1053/j.gastro.2010.10.058]

40 **Xu Q**, Yuan Y, Sun LP, Gong YH, Xu Y, Yu XW, Dong NN, Lin GD, Smith PN, Li RW. Risk of gastric cancer is associated with the MUC1 568 A/G polymorphism. *Int J Oncol* 2009; **35**: 1313-1320 [PMID: 19885554]

41 **Ng W**, Loh AX, Teixeira AS, Pereira SP, Swallow DM. Genetic regulation of MUC1 alternative splicing in human tissues. *Br J Cancer* 2008; **99**: 978-985 [PMID: 19238635 DOI: 10.1038/sj.bjc.6604617]

42 **Mocellin S**, Verdi D, Pooley KA, Nitti D. Genetic variation and gastric cancer risk: a field synopsis and meta-analysis. *Gut* 2015; **64**: 1209-1219 [PMID: 25731870 DOI: 10.1136/gutjnl-2015-309168]

43 **Jia Y**, Persson C, Hou L, Zheng Z, Yeager M, Lissowska J, Chanock SJ, Chow WH, Ye W. A comprehensive analysis of common genetic variation in MUC1, MUC5AC, MUC6 genes and risk of stomach cancer. *Cancer Causes Control* 2010; **21**: 313-321 [PMID: 19924550 DOI: 10.1007/s10552-009-9463-3]

44 **Zhang H**, Jin G, Li H, Ren C, Ding Y, Zhang Q, Deng B, Wang J, Hu Z, Xu Y, Shen H. Genetic variants at 1q22 and 10q23 reproducibly associated with gastric cancer susceptibility in a Chinese population. *Carcinogenesis* 2011; **32**: 848-852 [PMID: 21427165 DOI: 10.1093/carcin/bgr051]

45 **Palmer AJ**, Lochhead P, Hold GL, Rabkin CS, Chow WH, Lissowska J, Vaughan TL, Berry S, Gammon M, Risch H, El-Omar EM. Genetic variation in C20orf54, PLCE1 and MUC1 and the risk of upper gastrointestinal cancers in Caucasian populations. *Eur J Cancer Prev* 2012; **21**: 541-544 [PMID: 22805490 DOI: 10.1097/CEJ.0b013e3283529b79]

46 **Li F**, Zhong MZ, Li JH, Liu W, Li B. Case-control study of single nucleotide polymorphisms of PSCA and MUC1 genes with gastric cancer in a Chinese. *Asian Pac J Cancer Prev* 2012; **13**: 2593-2596 [PMID: 22938426]

47 **Zhang B**, Hao GY, Gao F, Zhang JZ, Zhou CJ, Zhou LS, Wang Y, Jia YB. Lack of association of common polymorphisms in MUC1 gene with H. pylori infection and non-cardia gastric cancer risk in a Chinese population. *Asian Pac J Cancer Prev* 2013; **14**: 7355-7358 [PMID: 24460302 DOI: 10.7314/APJCP.2013.14.12.7355]

48 **Frank B**, Weck MN, Müller H, Klopp N, Illig T, Raum E, Brenner H. Polymorphisms in MUC1, MUC2, MUC5B and MUC6 genes are not associated with the risk of chronic atrophic gastritis. *Eur J Cancer* 2012; **48**: 114-120 [PMID: 21596555 DOI: 10.1016/j.ejca.2011.04.016]

49 **Marín F**, Bonet C, Muñoz X, García N, Pardo ML, Ruiz-Liso JM, Alonso P, Capellà G, Sanz-Anquela JM, González CA, Sala N. Genetic variation in MUC1, MUC2 and MUC6 genes and evolution of gastric cancer precursor lesions in a long-term follow-up in a high-risk area in Spain. *Carcinogenesis* 2012; **33**: 1072-1080 [PMID: 22402132 DOI: 10.1093/carcin/bgs119]

50 **Sun Y**, Gu J, Ajani JA, Chang DW, Wu X, Stroehlein JR. Genetic and intermediate phenotypic susceptibility markers of gastric cancer in Hispanic Americans: a case-control study. *Cancer* 2014; **120**: 3040-3048 [PMID: 24962126 DOI: 10.1002/cncr.28792]

51 **Duan F**, Song C, Dai L, Cui S, Zhang X, Zhao X. The effect of MUC1 rs4072037 functional polymorphism on cancer susceptibility: evidence from published studies. *PLoS One* 2014; **9**: e95651 [PMID: 24755768 DOI: 10.1371/journal.pone.0095651]

52 **Zheng L**, Zhu C, Gu J, Xi P, Du J, Jin G. Functional polymorphism rs4072037 in MUC1 gene contributes to the susceptibility to gastric cancer: evidence from pooled 6,580 cases and 10,324 controls. *Mol Biol Rep* 2013; **40**: 5791-5796 [PMID: 24072653 DOI: 10.1007/s11033-013-2682-4]

53 **Van de Bovenkamp JH**, Mahdavi J, Korteland-Van Male AM, Büller HA, Einerhand AW, Borén T, Dekker J. The MUC5AC glycoprotein is the primary receptor for Helicobacter pylori in the human stomach. *Helicobacter* 2003; **8**: 521-532 [PMID: 14535999 DOI: 10.1046/j.1523-5378.2003.00173.x]

54 **Kocer B**, Ulas M, Ustundag Y, Erdogan S, Karabeyoglu M, Yldrm O, Unal B, Cengiz O, Soran A. A confirmatory report for the close interaction of Helicobacter pylori with gastric epithelial MUC5AC expression. *J Clin Gastroenterol* 2004; **38**: 496-502 [PMID: 15220684]

55 **Kobayashi M**, Lee H, Nakayama J, Fukuda M. Roles of gastric mucin-type O-glycans in the pathogenesis of Helicobacter pylori infection. *Glycobiology* 2009; **19**: 453-461 [PMID: 19150806 DOI: 10.1093/glycob/cwp004]

56 **Van De Bovenkamp JH**, Korteland-Van Male AM, Büller HA, Einerhand AW, Dekker J. Infection with Helicobacter pylori affects all major secretory cell populations in the human antrum. *Dig Dis Sci* 2005; **50**: 1078-1086 [PMID: 15986858]

57 **de Bolos C**, Real FX, Lopez-Ferrer A. Regulation of mucin and glycoconjugate expression: from normal epithelium to gastric tumors. *Front Biosci* 2001; **6**: D1256-D1263 [PMID: 11578953]

58 **Pigny P**, Guyonnet-Duperat V, Hill AS, Pratt WS, Galiegue-Zouitina S, d'Hooge MC, Laine A, Van-Seuningen I, Degand P, Gum JR, Kim YS, Swallow DM, Aubert JP, Porchet N. Human mucin genes assigned to 11p15.5: identification and organization of a cluster of genes. *Genomics* 1996; **38**: 340-352 [PMID: 8975711 DOI: 10.1006/geno.1996.0637]

59 **Baffa R**, Negrini M, Mandes B, Rugge M, Ranzani GN, Hirohashi S, Croce CM. Loss of heterozygosity for chromosome 11 in adenocarcinoma of the stomach. *Cancer Res* 1996; **56**: 268-272 [PMID: 8542579]

60 **Moskaluk CA**, Rumpel CA. Allelic deletion in 11p15 is a common occurrence in esophageal and gastric adenocarcinoma. *Cancer* 1998; **83**: 232-239 [PMID: 9669804 DOI: 10.1002/(SICI)1097-0142(19980715)83: 2<232: : AID-CNCR5>3.0.CO; 2-S]

61 **Zhou CJ**, Zhang LW, Gao F, Zhang B, Wang Y, Chen DF, Jia YB. Association analysis of common genetic variations in MUC5AC gene with the risk of non-cardia gastric cancer in a Chinese

population. *Asian Pac J Cancer Prev* 2014; **15**: 4207-4210 [PMID: 24935372 DOI: 10.7314/APJCP.2014.15.9.4207]
62 **Zhou CJ**, Zhang LW, Gao F, Zhang B, Wang Y, Chen DF, Jia YB. Common genetic variations in the MUC5AC gene are not related to helicobacter pylori serologic status. *Asian Pac J Cancer Prev* 2014; **15**: 10719-10722 [PMID: 25605164 DOI: 10.7314/APJCP.2014.15.24.10719]
63 **Wang C**, Wang J, Liu Y, Guo X, Zhang C. MUC5AC upstream complex repetitive region length polymorphisms are associated with susceptibility and clinical stage of gastric cancer. *PLoS One* 2014; **9**: e98327 [PMID: 24887023 DOI: 10.1371/journal.pone.0098327]
64 **Kawakubo M**, Ito Y, Okimura Y, Kobayashi M, Sakura K, Kasama S, Fukuda MN, Fukuda M, Katsuyama T, Nakayama J. Natural antibiotic function of a human gastric mucin against Helicobacter pylori infection. *Science* 2004; **305**: 1003-1006 [PMID: 15310903 DOI: 10.1126/science.1099250]
65 **Byrd JC**, Yan P, Sternberg L, Yunker CK, Scheiman JM, Bresalier RS. Aberrant expression of gland-type gastric mucin in the surface epithelium of Helicobacter pylori-infected patients. *Gastroenterology* 1997; **113**: 455-464 [PMID: 9247464]
66 **Zheng H**, Takahashi H, Nakajima T, Murai Y, Cui Z, Nomoto K, Tsuneyama K, Takano Y. MUC6 down-regulation correlates with gastric carcinoma progression and a poor prognosis: an immunohistochemical study with tissue microarrays. *J Cancer Res Clin Oncol* 2006; **132**: 817-823 [PMID: 16807756 DOI: 10.1007/s00432-006-0135-3]
67 **Lancaster CA**, Peat N, Duhig T, Wilson D, Taylor-Papadimitriou J, Gendler SJ. Structure and expression of the human polymorphic epithelial mucin gene: an expressed VNTR unit. *Biochem Biophys Res Commun* 1990; **173**: 1019-1029 [PMID: 2268309 DOI: 10.1016/S0006-291X(05)80888-5]
68 **Nguyen TV**, Janssen M, Gritters P, te Morsche RH, Drenth JP, van Asten H, Laheij RJ, Jansen JB. Short mucin 6 alleles are associated with H pylori infection. *World J Gastroenterol* 2006; **12**: 6021-6025 [PMID: 17009402]
69 **Garcia E**, Carvalho F, Amorim A, David L. MUC6 gene polymorphism in healthy individuals and in gastric cancer patients from northern Portugal. *Cancer Epidemiol Biomarkers Prev* 1997; **6**: 1071-1074 [PMID: 9419405]
70 **Kwon JA**, Lee SY, Ahn EK, Seol SY, Kim MC, Kim SJ, Kim SI, Chu IS, Leem SH. Short rare MUC6 minisatellites-5 alleles influence susceptibility to gastric carcinoma by regulating gene. *Hum Mutat* 2010; **31**: 942-949 [PMID: 20506113 DOI: 10.1002/humu.21289]
71 **Mejías-Luque R**, Lindén SK, Garrido M, Tye H, Najdovska M, Jenkins BJ, Iglesias M, Ernst M, de Bolós C. Inflammation modulates the expression of the intestinal mucins MUC2 and MUC4 in gastric tumors. *Oncogene* 2010; **29**: 1753-1762 [PMID: 20062084 DOI: 10.1038/onc.2009.467]
72 **Jeong YH**, Kim MC, Ahn EK, Seol SY, Do EJ, Choi HJ, Chu IS, Kim WJ, Kim WJ, Sunwoo Y, Leem SH. Rare exonic minisatellite alleles in MUC2 influence susceptibility to gastric carcinoma. *PLoS One* 2007; **2**: e1163 [PMID: 18000536 DOI: 10.1371/journal.pone.0001163]
73 **Moehle C**, Ackermann N, Langmann T, Aslanidis C, Kel A, Kel-Margoulis O, Schmitz-Madry A, Zahn A, Stremmel W, Schmitz G. Aberrant intestinal expression and allelic variants of mucin genes associated with inflammatory bowel disease. *J Mol Med* (Berl) 2006; **84**: 1055-1066 [PMID: 17058067 DOI: 10.1007/s00109-006-0100-2]

**P- Reviewer**: Chiurillo MA
**S- Editor**: Ma YJ **L- Editor**: A **E- Editor**: Jiao XK

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com