Risk of gastric cancer is associated with the MUC1 568 A/G polymorphism

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Abstract. Identifying the genetic variants that alter MUC1 protein expression may further our understanding of the risk for development of gastric cancer (GC). We used PCR-SSPs to identify the genotype of MUC1 A/G polymorphism at its 568 site of exon 2 and immunohistochemistry to detect MUC1 protein expression in GC patients and non-cancer subjects and analyzed the association between this polymorphism and MUC1 protein expression. We found that the frequency of AA genotype was significantly high in the GC patients and the risk for GC in AA genotype carriers increased 1.81-fold. Moreover, we found a significant underexpression of MUC1 protein in GC as compared to non-cancer subjects, which was negatively correlated to AA genotype of MUC1 (r=-0.1790, P=0.004). Furthermore, this study provides a possible mechanistic insight that the MUC1 A/G polymorphism at its 568 site disrupts the physiological functions of MUC1 which is important to the physiological protection of gastric mucosa. Thus we have provided evidence that may identify the MUC1 A/G polymorphism at 568 site, as a potential genetic factor which leads to an increase in susceptibility for GC through alteration of MUC1 gene and MUC1 expression in the population that carry the A allele.

Introduction

A number of factors, including hereditary, environmental, occupation and social factors are now recognized as potential contributors to the development of gastric cancer (GC). The contributions of bacterial factors to the disease pathogenesis have been illustrated by the results from our previous study and others, in which most evidence suggests that host factors are paramount in determining progression to GC (1). Cancer susceptibility represents a continuum of interactions between the host and environment. The risk of developing GC is increased by up to 3-fold in individuals with an immediate blood relative with gastric cancer and 10% of cases show familial clustering (2). Susceptibility to Helicobacter pylori and to GC appears to be associated to with MUC1 allele length (3,4). Gene polymorphism has been reported to influence or modify individual sensitivity towards micro and macro environmental factors. However, the contribution of genetic factors, such as gene polymorphism, to GC risk is not fully understood.

Secreted mucins are considered the first line of defense for epithelial tissues since they act as physical barriers between the extracellular milieu and the mucosal surface. Tethered transmembrane mucins are the second line of defense, acting as sensors of the different disturbances occurring environmentally and signaling these messages to the inner cytoplasmic milieu (5). MUC1 is a highly polymorphic membrane-associated mucin that is often aberrantly expressed in cancer (6). It possesses a centrally located tandem repeat (TR) domain (7-10) comprised of 20-120 or more repeat units of 60 nucleotides, which encode 20 amino acids. The repeating units include several serine and threonine residues, which carry most of the glycosylation and this glycosylation, as well as the general pattern of expression, is altered in cancerous cells. MUC1 gene is a member of the mucin family and encodes a membrane-bound, glycosylated phosphoprotein. The protein is anchored to the apical surface of many epithelia by a transmembrane domain, with the degree of glycosylation varying with cell type. It also contains a 20 amino acid variable number tandem repeat (VNTR) domain, with the number of repeats varying from 20 to 120 in different individuals. MUC1
also functions in a cell signaling capacity (11,12). Due to its large conformation, MUC1 has an anti-adhesive role (13), which may block cell-cell interactions by destabilizing cell-cell and cell-matrix connections. MUC1 restricts access of *H. pylori* to the epithelial surface, hence reducing exposure of the host to proinflammatory bacterial products (3).

However, it was reported that overexpression, aberrant intracellular localization, and changes in glycosylation of this protein were associated with carcinomas (14). MUC1 was significantly overexpressed in prostate cancer with poor clinical outcomes after radical surgery. Strawbridge reported that genetic variation in *MUC1* altered prostate cancer risk and progression (15) with identifying five haplotype-tagging single nucleotide polymorphisms (SNP) that describe inherited genetic variation in and around MUC1. The fact that susceptibility to GC appears to be associated with *MUC1* allele length has also been reported (16-18). Clinically, the protective function of mucosa varies between individuals. The observations that MUC1 plays a role in the progression to GC highlight the importance of understanding all the aspects of the normal variation of this gene. It has been reported that MUC1 possesses two variations of the length and structure resulting from *MUC1* A/G SNP at +568 site (10,19). Association between MUC1 and gastrointestinal disease has been attracting the attention of more researchers recently. However, whether the incidence of GC is related to the protective functional variation of MUC1 or the protective functional variation of MUC1 is a consequence of the variation of *MUC1* in length and structure remains unknown. The identification of thousands of single nucleotide polymorphisms (SNPs) in the human genome has prompted a rise in population-based research studies designed to link gene-specific SNPs to complex disease states, pharmacogenetic applications, and individual predisposition and susceptibility to diseases (20). We previously found that the distribution frequency of AA genotype was statistically higher in the GC group than AG, GG genotypes in a population from North-Eastern China (1). In the present study, we hypothesized that the association between +568 site A/G polymorphism in *MUC1* and the function of MUC1 protein was influenced by *MUC1* +568 A/G SNP, which may be responsible for individuals’ susceptibility to GC. If such an effect could be demonstrated, it would provide useful information for better understanding the role of *MUC1* polymorphism and MUC1 protein in the modification of individuals’ (or a population’s) potential risk towards GC and provide support for the design of a MUC1-based tumor vaccine and pharmaceuticals. In this study, we investigated the distribution of *MUC1* A/G polymorphism at +568 site and the association between the A/G polymorphism and susceptibility to GC from the North-Eastern Chinese population. We analyzed the effect of the A/G polymorphism on MUC1 protein expression with the aim of discovering the potential genetic risk factors of GC.

Materials and methods

**Patients.** This research project was approved by the Ethics Committee of the China Medical University. Gastric tissue specimens and venous blood samples were prospectively collected from patients who underwent gastroscopy in hospitals located in the North-Eastern area of China between 2002 and 2005. All of the samples were collected with letters of consent from the patients and medical histories were taken by questionnaire and the record was computerized. A total of 379 patients from the Shenyang city and Zhuang River region where there was a high incidence of GC were included in this study. Blood samples were taken from 138 patients with GC with an average age of 57.6±11.5 years ranging from 30 to 84 years old. The male/female ratio of the GC patients was 2:1. One hundred and thirty-one patients with superficial gastritis (GS) and 110 patients with atrophic gastritis (GA) were used as control groups. The control population groups had a similar male/female ratio to the GC group and had an average age of 56.6±12.0 years ranging from 30 to 80 years old. The GC group and control group had no statistical difference in terms of gender and age composition (P<0.75 and P<0.43, respectively). Whole blood from individuals was collected and blood clots were allowed to form to incubate clot-activating tubes at room temperature for 60 min. Serum was separated from the clots by centrifugation. Each clot was transferred to a 2 ml centrifuge tube and stored at -80°C until DNA extraction. Both blood samples and gastric biopsies were analyzed in all cases. The biopsy specimens from the gastroscopies were paraffin-embedded and stained by H&E staining for histological diagnosis. Samples that had an unclear or mixed histology and samples from patients that had received immunoregulatory therapy were excluded from further immunohistochemical analysis. Thus, we prioritized samples from 262 (of 379) patients, including 71 patients with GC (47 male and 24 female, male: female ratio 2:1) at an average age of 59.6±10.6, ranging from 34 to 80 years old; 105 patients with GS; and 86 patients with GA, which served as control groups. The control groups had a similar male/female ratio to the GC group and were at an average age of 55.7±12.4 years, ranging from 30 to 80 years old. The GC group and control groups showed no statistical difference in terms of gender composition (P<0.97); but a slight difference in age composition (P<0.028). Therefore we performed an age correction and gender OR value when analyzing the statistical results.

Genomic DNA from clotted blood for *MUC1* single nucleotide polymorphism genotyping. Genomic DNA was purified using a method described (21,22) with some modifications. Briefly, each frozen clot (500 μl) was thawed rapidly at room temperature and placed on ice. The thawed clots were transferred to a centrifuge tube with 800 μl of TE buffer (triethanolamide), mixed well and centrifuged at 10,000 x g for 5 min to disperse the clots. Following clot disruption, 5 sec to mix and placed on a rotator for 15 min to extract DNA. After rotation, the tube was vortexed for 5 sec to mix and placed on a rotator for 15 min to extract DNA. Following centrifugation, the supernatant was poured off and the third extraction was performed with the addition of an equal volume of phenol and chloroform (1:1) to the tube to further extract DNA. Following centrifugation, the supernatant was poured off and the third extraction was performed with the addition of an equal volume of chloroform.

Materials and methods
Following centrifugation, the supernatant was absorbed and two volumes of protein precipitation solution (two volumes of absolute ethanol containing 10% 3 M sodium acetate) were added and incubated for 1 h at -20°C. Each sample was vortexed at high speed for 20 sec and then centrifuged at 10,000 x g for 10 min. After centrifugation, the resulting DNA pellet was rinsed with 75% ethanol and centrifuged at 10,000 x g for 5 min. The 75% ethanol was decanted and the tube inverted on clean absorbent paper for 10 sec. The resulting DNA was reconstituted in a TE buffer and stored at -20°C until use.

PCR-SSPs for MUC1 568 A/G SNP polymorphism determination. Genomic DNA was amplified using sequence-specific primers - polymerase chain reaction (PCR-SSPs). The primers and reagents were purchased from Takara Inc., Japan. The forward primer 5’-CTA TGG GCA GAG AGA AGG AG-3’ (primer 1), the reverse SSPs 5’-AGC TTG CAT GAC CAG AAC CC-3’ (primer 2) and 5’-AGC TTG CAT GAC CAG AAC CT-3’ (primer 3) were used in combination with the consensus forward primer, i.e. primer 1, leading to expected PCR product sizes of 233 bp (23). The total PCR reaction volume was 26 μl containing 2.6 μl of 10X PCR buffer, 1.024 μl of 2.5 mM dNTP mixture, 0.6 U of rTaq DNA polymerase, 10 ng of the template DNA and an appropriate amount of dH2O. PCR reaction was performed by pre-denaturing at 95°C for 1 min, 5 cycles with 95°C for 25 sec, 70°C for 25 sec, 72°C for 30 sec, then 21 cycles with 95°C for 35 sec, 65°C for 30 sec, 72°C for 30 sec, and then, 4 cycles 95°C for 30 sec, 55°C for 60 sec, 72°C for 90 sec (23,24). Twelve μl of PCR product in 2% agarose gel was electrophoresized at 150 V for 30 min separation, then stained by ethidium bromide for 5 min and observed. PCR products on the two different alleles (A allele and G allele) of MUC1 were commercially sequenced using an ABI377 DNA Sequencer (ABI, USA).

Tissue array-based immunohistochemical staining for detection of MUC1 protein expression in situ. Immunohistochemical analysis was performed in 5-μm-thick sections from sequentially sliced samples of formalin-fixed and paraffin-embedded specimens according to the method described (25) with slight modification. Briefly, tissue sections were deparaffinized and rehydrated. Endogenous peroxidase was blocked using 3% hydrogen peroxide in methanol and an appropriate amount of dH2O. PCR reaction was performed by pre-denaturing at 95°C for 1 min, 5 cycles with 95°C for 25 sec, 70°C for 25 sec, 72°C for 30 sec, then 21 cycles with 95°C for 35 sec, 65°C for 30 sec, 72°C for 30 sec, and then, 4 cycles 95°C for 30 sec, 55°C for 60 sec, 72°C for 90 sec (23,24). Twelve μl of PCR product in 2% agarose gel was electrophoresized at 150 V for 30 min separation, then stained by ethidium bromide for 5 min and observed. PCR products on the two different alleles (A allele and G allele) of MUC1 were commercially sequenced using an ABI377 DNA Sequencer (ABI, USA).

The fragments type of MUC1 gene A/G polymorphism at 568 site. Previously, we demonstrated an obviously increased risk of developing GC for those who carried both AG+GG genotype and H. pylori-IgG-positive, both AA genotype and H. pylori-IgG-negative, and both AA genotype and H. pylori-IgG-positive, when compared with both AG+GG genotype and H. pylori-IgG-negative, in a population from the North-Eastern region of China (1). This finding prompted us to examine MUC1 A/G polymorphism at 568 site in a population from the same region. As indicated in Fig. 1A, we found that the amplified size of MUC1 was 233 bp. According to the presence of 233 bp band, the test samples were divided into AA, AG, and GG genotypes. We further sequenced genomic DNA of two alleles to confirm the PCR products (Fig. 1B and C). To test whether this population was a representative group for the frequencies of MUC1 A/G genotype, a Hardy-Weinberg genetic equilibrium law was performed for the genotype frequencies of the GC and the control groups. The results showed there was no significant difference between the actual number and the theoretical number using χ² test (P=0.27, P=0.26, respectively). Since the distribution frequencies of the three genotypes were consistent with the Hardy-Weinberg genetic equilibrium law, it demonstrated that this study population was a representative group.

The distribution of MUC1 A/G polymorphism is associated with the risk of GC. We next sought to identify a potential
correlation between MUC1 A/G polymorphism at 568 site and the risk of GC. We compared the distribution frequencies of AA, AG, and GG genotypes in the MUC1 gene between GC subjects and control subjects. The distribution frequencies of AA, AG, GG genotypes in the control groups were 74.7% (180/241), 21.2% (51/241) and 4.1% (10/241) respectively. The frequency of allele A was 85.3% (205.5/241) and allele G was 14.7% (35.5/241), which was in agreement with the frequencies of the Human Genome Project (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4072037). In the GC groups, we found that the distribution frequencies of AA, AG, GG genotype were 84.1% (116/138), 13.0% (18/138) and 2.9% (4/138). Interestingly, we noted that the frequency of A allele was 90.6% (125/138) and the frequency of G allele was 9.4% (13/138) in GC subjects. The results suggested that the distribution frequency of AA genotype in the GC group was significantly higher than in the control group (84.1 vs. 74.7%, P=0.031). For the statistical analysis, we combined AG and GG genotypes into one group (AG+GG) because of the scarcity of GG genotype in the subjects. We hypothesized that MUC1 A/G polymorphism at 568 site might be the factor that increases the susceptibility of this population to GC. To test this hypothesis, we used logistic regression adjusted by age and gender (95% CI: 1.06-3.12, Table I) to analyze our data and confirmed that the risk of GC was increased 1.81-fold in AA genotype compared to AG+GG genotype in the subjects studies.

**MUC1 protein expression in situ in subclassification of GC.**

We next asked whether this MUC1 A/G polymorphism at 568 site has an influence on the expression and function of MUC1 protein that consequently may be associated with the susceptibility of this population to GC. To address this question, we first detected the protein expression of MUC1 from the samples using an immunohistochemical analysis in situ. Fig. 2 shows representative immunohistochemistry staining for the MUC1 protein expression in the GC, subclassifications of GC and control samples. The MUC1 protein was extensively expressed in the gastric mucosa of the control tissue from superficial gastritis (Fig. 2A) and atrophic gastritis (Fig. 2B). The expression of MUC1 protein were mainly detected in the membrane (thick black arrow). We also observed that MUC1 protein was located in cytoplasm (thin black arrow). We assessed the potential association between MUC1 protein expression and subclassifications of GC diagnosed according to Lauren classification (27). The expression of MUC1 protein in the intestinal adenocarcinoma was highly positive as demonstrated in Fig. 2D, while it was not clearly seen in the cell of well-differentiated tubular adenocarcinoma (Fig. 2C). However, we observed a negative or weak expression of MUC1 protein in diffuse carcinoma (Fig. 2E and F). We examined the association between MUC1 protein expression and GC including subclassifications of GC, and control samples. The MUC1 HSCORE and MUC1 positive rates of these samples are summarized in Table II. Association between MUC1 protein expression and GC is confirmed by a comparison of GC and subclassifications of GC with non-cancer samples. The percentage of positive and highly positive MUC1 expression in GC was significantly lower than that in control samples (P=0.000 and P=0.039 respectively). Comparison between two subclasses of GC showed that the positive rate of diffuse carcinoma (80.0%) was significantly lower than that of intestinal adenocarcinoma (100.0%, P=0.022, Fisher's exact probabilities). While the difference between highly positive rate of diffuse carcinoma and intestinal adenocarcinoma was not statistically significant (P=0.06), the results showed a trend for an association between MUC1 protein expression and subclassifications of GC.

**MUC1 gene polymorphism affected MUC1 protein expression in stomach.**

We next addressed the question of whether the SNP affects MUC1 expression in GC patients by analyzing

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**Table I. Distribution frequencies of SNP genotype at MUC1 gene 568 site.**

<table>
<thead>
<tr>
<th>Groups</th>
<th>AG+GG (%)</th>
<th>AA (%)</th>
<th>χ²</th>
<th>P</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>61 (25.3)</td>
<td>180 (74.7)</td>
<td>1.00</td>
<td>0.031</td>
<td>1.81 (1.06-3.12)</td>
</tr>
<tr>
<td>GC</td>
<td>22 (15.9)</td>
<td>116 (84.1)</td>
<td>4.19</td>
<td>0.000</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*OR value was adjusted by age and gender.
logistic regression. bOR value was adjusted by age and gender. Non-cancer 191 140/141 (99.3) 56/141 (39.7) 50/50 (100.0) 36/50 (72.0) 0.000 3.76 (1.87-1.53)
GC 71 51/58 (87.9) 19/58 (32.8) 11/13 (84.6) 4/13 (30.8) 3.13 (1.28-7.69) 0.000 5.88 (1.75-20.00)
Intestinal adenocarcinoma 26 0 6 8 12 100.0 46.2
Diffuse carcinoma 45 9 16 9 11 80.0 24.4

Comparison was performed using \( \chi^2 \) test. \(^{a}P=0.000\), GC group vs. non-cancer group; \(^{b}P=0.039\), GC group verses non-cancer group; \(^{c}\)Comparison was performed between GC and diffuse carcinoma using Fisher's extract probabilities, \( P=0.022 \).

### Table III. Expression of MUC1 protein in different gastric diseases.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Positive (%)</th>
<th>Highly positive (%)</th>
<th>Positive (%)</th>
<th>Highly positive (%)</th>
<th>P-value(^{a})</th>
<th>OR(^{b}) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>71</td>
<td>51/58 (87.9)</td>
<td>19/58 (32.8)</td>
<td>11/13 (84.6)</td>
<td>4/13 (30.8)</td>
<td>0.00</td>
<td>3.76 (1.87-1.53)</td>
</tr>
<tr>
<td>Non-cancer</td>
<td>191</td>
<td>140/141 (99.3)</td>
<td>56/141 (39.7)</td>
<td>50/50 (100.0)</td>
<td>36/50 (72.0)</td>
<td>0.00</td>
<td>3.13 (1.28-7.69)</td>
</tr>
<tr>
<td>Superficial gastritis</td>
<td>105</td>
<td>76/77 (98.7)</td>
<td>28/77 (36.4)</td>
<td>28/28 (100.0)</td>
<td>18/28 (64.3)</td>
<td>0.011</td>
<td>3.13 (1.28-7.69)</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>86</td>
<td>64/64 (100.0)</td>
<td>28/64 (43.8)</td>
<td>22/22 (100.0)</td>
<td>18/22 (81.8)</td>
<td>0.002</td>
<td>5.88 (1.75-20.00)</td>
</tr>
</tbody>
</table>

\(^{a}\)Comparison was performed using \( \chi^2 \) test. \(^{b}\)Comparison was performed using Fischer's extract probabilities, \( P=0.022 \).

The identification of genetic factors capable of modulating cancer development has the potential to unravel disease heterogeneity and aid diagnostic and prevention strategies. We report, for the first time, the distribution frequencies of AA, AG, and GG genotypes in the North-East region of China. The results presented here demonstrate that the frequency of AA genotype in patients with GC is significantly higher than that of the non-cancer group. This is the first study that shows a clear association of the MUC1 A/G polymorphism at 568 site with an increased risk of GC. The result of a significantly reduced frequency in blood DNA of
MUC1 568G allele (G to A) provides the evidence that MUC1 A/G polymorphism at 568 site might be the factor which leads to an increase in the susceptibility of the population in the North-East region of China to GC. Our result confirms our initial hypothesis that the MUC1 A/G polymorphism at 568 site influences the expression and/or functions of MUC1 protein that consequently may be associated with the susceptibility of a population that carries the A allele to GC.

MUC1 is a large molecular weight (2000 kDa) glycoprotein, its space structure is composed of the core chain region and some glycosylated side chains. MUC1 is a transmembrane molecule with a large extracellular domain which contains a variable number of tandem repeats (VNTR) sequences of 20 amino acids. The MUC1 gene in 1q21-24 which encodes the MUC1 protein, is now known to have two exon polymorphisms, which have been reported as a VNTR polymorphism in exon 2 and its upstream as an A/G single nucleotide polymorphism (SNP) within exon 2 at 568 site (10,23,28). The Human Genome Project has reported (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4072037) the distribution frequencies from the people of representative countries and regions in MUC1 A/G polymorphism at 568 site. The study showed that the distribution frequencies of AA, AG, and GG genotypes in 45 Han Chinese in Beijing were 64.4, 31.1 and 4.4%, that of allele A was 80% and allele G was 20%. The allele frequencies of Japanese people were similar to the observation of the Chinese people, while Europeans and Africans were different from the Chinese and Japanese (allele frequencies were 57.9 and 42.1% in American and 49.2 and 50.8% in African populations, respectively). Less specific information is available on the association between MUC1 A/G single nucleotide polymorphism and the risk of gastric cancer (GC). Several cancer-related studies have reported an association between the MUC1 A/G polymorphism at 568 site and alterations in DNA and its encoding proteins have recently been linked with diseases. Janssen and colleagues reported this polymorphism had association with the KL-6 expression in the serum, which was MUC1 antibody in the lung and was an indicator of pulmonary fibrosis (23). Imbret and colleagues found that this polymorphism was associated with the dry eye syndrome, and MUC1 secreted by allele A carriers in the cornea and conjunctiva functioned in an inferior manner when compared to allele G carriers, which were more susceptible to dry eye syndrome (29,30). Silva (17) predicted that MUC1 polymorphism might define different susceptibility backgrounds for the development of conditions that precede gastric carcinoma: chronic atrophic gastritis and intestinal metaplasia. The results of these and other studies provide increasing evidence for the pathological and clinical significance that the MUC1 A/G polymorphism at 568 site may have. This study provides useful information for a better understanding of a population’s susceptibility to GC in the North-East region of China where a high incidence rate of GC has been observed. Whether this polymorphism can serve as a potential predictor of GC among other Asian populations who share the same color of skin requires additional studies, likely with large sample sizes and multiple-centers.

Analysis of the association between the MUC1 A/G polymorphism at 568 site and the increase of risk to GC,
demonstrating an increased risk to GC, implicates the underlying mechanisms. This polymorphism may be attributed to the decrease of the MUC1 expression in individuals with AA genotype and the further decrease of the physiologically protective functions to the gastric mucosa. MUC1 protein possesses multiple functions. Its participation in the ‘mucusc bicarbonate barriers’ could enable the pepsin on the surface epithelial cells to lose their function of decomposing protein, thereby preventing digestive enzymes (pepsin) from destroying themselves (31-33). When external factors stimulate gastric mucosa, the mucin could prevent mucosa from stomach acid and digestive enzymes (pepsin), which is beneficial to epithelial repair (31,34). MUC1 protein is also viscous and gluey, so it formed a certain thick mucous layer on the stomach surface, with the function of lubricating and protecting (35). It has been reported that the weaker protective function of AA genotype as compared to that of AG+GG genotype was caused either by the impact on the physiology, or by the length extending out of the cell membrane (29,36). In short, the increase of the genetic susceptibility to GC in AA genotype carriers could be a result of the alteration of MUC1 protein expression and function encoded from an altered MUC1 gene by this MUC1 A/G polymorphism at 568 site. We hypothesized that this SNP might play a role in the regulation of MUC1 and its MUC1 protein expression. We here provide an experimental basis for the association between MUC1 gene polymorphism and GC. The detection of this polymorphism may have the clinical significance of its use as a screening indicator for GC.

Ligtenberg and colleagues noted the possible importance and potential prognostic value of this polymorphism and suggested a genetic basis for the variable splicing event (10). The secondary structure of the pre-mRNA was also predicted to be different, where only the G allele forms a physiologically stable stem loop structure as demonstrated by Ligtenberg and colleagues who noted the possible importance of this difference. In the putative effect of secondary structure predicted by Ligtenberg, if a G was present at +8, it could form a stem-loop structure of the region surrounding the splice acceptor site. We speculate that the secondary structure of the region surrounding the splice acceptor site. We speculate that the secondary structure of the pre-mRNA can make the variant B splice acceptor site

References