G&I Genomics & Informatics

eISSN 2234-0742
Genomics Inform 2014;12(3):127-133
http://dx.doi.org/10.5808/GI.2014.12.3.127

ORIGINAL ARTICLE

Epidemiological and Genome-Wide Association Study of Gastritis or Gastric Ulcer in Korean Populations

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Gastritis is a major disease that has the potential to grow as gastric cancer. Gastric cancer is a very common cancer, and it is related to a very high mortality rate in Korea. This disease is known to have various reasons, including infection with *Helicobacter pylori*, dietary habits, tobacco, and alcohol. The incidence rate of gastritis has reported to differ between age, population, and gender. However, unlike other factors, there has been no analysis based on gender. So, we examined the high risk factors of gastritis in each gender in the Korean population by focusing on sex. We performed an analysis of 120 clinical characteristics and genome-wide association studies (GWAS) using 349,184 single-nucleotide polymorphisms from the results of Anseong and Ansan cohort study in the Korea Association Resource (KARE) project. As the result, we could not prove a strong relation with these factors and gastritis or gastric ulcer in the GWAS. However, we confirmed several already-known risk factors and also found some differences of clinical characteristics in each gender using logistic regression. As a result of the logistic regression, a relation with hyperlipidemia, coronary artery disease, myocardial infarction, hyperlipidemia therapy, hypotensive or antihypotensive drug, diastolic blood pressure, and gastritis was seen in males; the results of this study suggest that vascular disease has a potential association with gastritis in males.

Keywords: coronary artery disease, gastric ulcer, GWAS, hyperlipidemia, myocardial infarction, vascular disease

Introduction

Gastric cancer is a common cancer type. In the world, this cancer type has the second highest incidence among males and third highest among females [1]. In Korea, the incidence rate of gastric cancer was second highest, and the mortality rate of gastric cancer was third highest among all cancer types in a 2010 Korean cancer statistics study [2].

The incidence rate of gastric cancer differs between patient age, location, and even sex [3], because gastric cancer has various subtypes [3, 4] and a lot of risk factors [5]. *Helicobacter pylori* is known for having a relation with gastric cancer [6]. Almost all gastric cancer patients are infected with *H. pylori* [3]. As known before, dietary habits also have the potential to affect gastric cancer [1]. The incidence risk factors have differences in gastric cancer or peptic ulcers by blood type [7] and sex [8]. Gastric cancer type also depends on patient populations or race [5]. So, an analysis is needed to find known and unknown risk factors in diverse phenotypes [3]. Gastritis is related with gastric cancer. Chronic gastric inflammation has the potential to grow into gastric cancer [9].

Many risk factors are related with gastritis, as already reported. However, even though gender is known to be associated with gastritis infraction, there is not much information about the effects on gastritis depending on gender. So, we examined Korean risk factors of gastritis and gastric ulcer using genotypes and clinical characteristics of patients who were diagnosed with gastritis or gastric ulcer in each gender. For revealing the correlation with gastritis and known and unknown risk factors, we analyzed single-nucleotide polymorphisms (SNPs) and epidemiological data of the Korea Association Resource (KARE) project, which comprised the results of the Anseong and Ansan cohorts study.

Methods

Clinical characteristics and study genotypes

This study analyzed cohort data that comprised the

Received June 30, 2014; Revised August 6, 2014; Accepted August 12, 2014

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Anseong and Ansan population study in the KARE projects. Anseong is a rural area, and Ansan is a city. Both areas are in Gyeonggi-do. Citizen of these two cities have different lifestyles, and they are exposed to different environment. Detailed information of the KARE data was reported [10]. The KARE data included 8,842 individuals, 352,228 SNPs, and 277 phenotypes.

Among 8,842 total individuals, we divided patients and normal subjects for a control and case study using a positive diagnosis experience of gastritis. There were 1,885 patients and 6,957 normal subjects. First, for selecting the case, we eliminated 104 patients who were diagnosed under age 20 or had unknown age. Then, 1,781 patients remained. Of these, 804 patients were men, and 977 patients were women. Of 6,957 normal subjects, no one was aged under 20; 3,335 were men, and 3,622 were women.

Among 352,228 SNPs, we excluded 3,044 SNPs based on the Hardy-Weinberg equilibrium test for quality control. After frequency and genotyping pruning, 349,184 SNPs remained.

Among 277 total phenotypes, we filtered missing phenotypes and low genotyping rates. Then, 120 clinical characteristics remained. We also eliminated gastritis phenotype variables and unknown drug information variables; 101 clinical characteristics remained.

Statistical analysis

For data filtering and finding significant SNPs, we used PLINK version 1.07, that is a tool made for analyzing whole-genome association using computational methods [11]. We used the default options of PLINK [11], and we analyzed phenotypes by logistic regression test for classifying patients and normal subjects and estimating factors. We also assessed the result factors of the logistic regression by Student's t-test for revealing meaningful differences between patients and normal subjects using R version 3.0.2 for finding gastritis-associated factors. Then, we used the receiver operating characteristic (ROC) curve and area under the curve (AUC) scores to confirm the prediction ability of the factors.

Results

Clinical characteristics

Tables 1 and 2 explain the results of the logistic regression test among total clinical characteristics in each gender. There were differences in gender-specific clinical characteristics. Among 1,781 total patients, 977 patients and 804 patients were male and female, respectively. Patients had several disease-association factors in both genders: area, positive

Table 1. Clinical characteristics of gastritis variables in male

Total	Description	Control (n = 3,379)	Case (n = 804)	t-test
AS1_Age	Age	51.83 ± 8.85	51.58 ± 8.52	4.70E-001
AS1_Area	Area	1,403 (41.5)	406 (50.5)	5.00E-006
AS1_PdCd	Positive diagnosis experience of coronary artery disease	25 (0.7)	4 (0.5)	0.5303
AS1_PdLp	Positive diagnosis experience of hyperlipidemia	84 (2.5)	38 (4.7)	0.003968
AS1_PdPs	Positive diagnosis experience of mental disease	1 (0.03)	4 (0.5)	0.0379
AS1_PdIm	Positive diagnosis experience of erectile dysfunction	21 (0.6)	21 (2.6)	0.0004339
AS1_TrtLp	Hyperlipidemia therapy	17 (0.5)	4 (0.5)	0.09085
AS1_TrtHp	Hepatitis therapy	5 (0.1)	0 (0)	0.09239
AS1_TrtTb	Tuberculosis therapy	6 (0.2)	2 (0.3)	0.07514
AS1_Drug	Continual use of one or more drugs	983 (29.1)	363 (45.1)	2.20E-016
AS1_DrugCp	Oral contraceptive drug-taking experience	3,171 (93.8)	778 (96.8)	9.94E-005
AS1_DrugTbCu	Continual use of tuberculosis drug	6 (0.2)	2 (0.2)	0.3127
AS1_DrugIns	Insulin drug-taking experience	36 (1.1)	3 (0.4)	0.005567
AS1_DrugHt	Hypotensive or antihypotensive drug-taking experience	332 (9.8)	76 (9.5)	0.07174
AS1_DrugHtCu	Continual use of hypotensive of antihypotensive drug	295 (8.7)	72 (9.0)	0.9601
AS1_DrugDm	Diabetes drug taking experience	165 (4.9)	13 (1.6)	0.7207
AS1_Albumin	Degree of albumin	4.34 ± 0.37	4.34 ± 0.36	0.7188
AS1_DBP	Diastolic blood pressure (mm Hg)	82.17 ± 11.0	80.38 ± 10.56	2.06E-005
AS1_Waist	Waist size (cm)	83.89 ± 7.75	82.78 ± 8.19	0.0005079
AS1_Hip	Hip size (cm)	93.62 ± 6.63	93.03 ± 6.54	0.02187
AS1_Height	Height (cm)	166.85 ± 5.84	167.18 ± 5.77	0.1432
AS1_MT	Midshaft tibia T bone density (standard deviation)	0.12 ± 1.22	0.27 ± 1.89	0.001048

Values are presented as mean ± standard deviation or number (%).

Table 2. Clinical characteristics of gastritis variables in female

Total	Description	Control (n = 3,682)	Case (n = 977)	t-test
AS1_Age	Age	51.83 ± 8.85	51.58 ± 8.5	9.79E-007
AS1_Area	Area	1,880 (51.1)	516 (52.8)	0.329
AS1_PdAl	Positive diagnosis experience of allergy	875 (23.8)	102 (10.4)	5.02E-006
AS1_PdLp	Positive diagnosis experience of hyperlipidemia	63 (1.7)	31 (3.2)	0.009013
AS1_PdCl	Positive diagnosis experience of chronic obstructive pulmonary disease	15 (0.4)	2 (0.2)	0.4173
AS1_PdKd	Positive diagnosis experience of renal disease	108 (2.9)	55 (5.6)	0.0005104
AS1_PdHp	Positive diagnosis experience of hepatitis	87 (2.4)	46 (4.7)	0.0009411
AS1_PdTb	Positive diagnosis experience of tuberculosis	123 (3.3)	49 (5.0)	0.02303
AS1_PdPs	Positive diagnosis experience of mental disease	27 (0.7)	9 (0.9)	0.4748
AS1_PdDem	Positive diagnosis experience of dementia	0 (0)	1 (0.1)	0.9094
AS1_PdUt	Positive diagnosis experience of urinary tract infection	10 (0.3)	9 (0.9)	0.03397
AS1_TrtPs	Mental disease therapy	1 (0.03)	2 (0.2)	0.0003288
AS1_TrtDem	Dementia therapy	0 (0)	1 (0.1)	0.0003688
AS1_Drug	Continual use of one or more drugs	1,476 (40.1)	546 (55.9)	2.20E-016
AS1_DrugSp	Anticonvulsant-taking experience	1 (0.03)	0 (0)	9.16E-013
AS1_DrugSpCu	Continual use of anticonvulsants	1 (0.03)	0 (0)	0.3174
AS1_DrugSl	Anticoagulant-taking experience	1 (0.03)	0 (0)	9.16E-013
AS1_DrugTb	Tuberculosis drug-taking experience	63 (1.7)	18 (1.8)	7.11E-009
AS1_DrugOs	Osteoporosis drug-taking experience	104 (2.8)	46 (4.7)	8.56E-011
AS1_DrugOsCu	Continual use of osteoporosis drug	81 (2.2)	28 (2.9)	0.06314
AS1_DrugDi	Diuretic-taking experience	2 (0.05)	3 (0.3)	3.43E-013
AS1_HDL_C	High-density lipoprotein (HDL)-cholesterol (mg/dL)	45.34 ± 10.0	46.52 ± 10.3	0.001425
AS1_SBP	Systolic blood pressure (mm Hg)	121.72 ± 20.0	118.86 ± 18.1	1.92E-005
AS1_Waist	Waist size (cm)	81.96 ± 10.1	80.47 ± 9.5	2.07E-005
AS1_Height	Height (cm)	153.6 ± 5.6	154.5 ± 5.4	2.92E-006
AS1_DT	Distal radius T bone density (standard deviation)	−0.05 ± 1.6	0.23 ± 1.5	3.74E-007

Values are presented as mean ± standard deviation or number (%).

diagnosis of hyperlipidemia, positive diagnosis of mental disease, continual use of one or more drugs, waist, and height.

Through previous studies, how these factors are related with gastritis was verified.

The incidence of gastritis is affected by population, geographic variation, or lifestyle [1, 5]. In this study, we used cohort data that comprised country and city populations. As shown Tables 1 and 2, in both genders, the population of local A had a higher gastritis incidence rate. This means that differences in patient lifestyle and environment affect the disease incidence rate.

It is well known that stress has an influence on carcinogenesis. A study reported that gastritis is closely connected with mental illness [12] and differs in degree according to drug use—taking medicine affects the stomach. Nonsteroidal anti-inflammatory drugs can cause gastrointestinal damage [13].

Losing appetite is the one of phenotypes of gastritis that are connected with waist size or hip size as gastritis-associated factors. However, definite evidence is lacking [14]. As shown in Tables 1 and 2, we can explain the associative relation that waist size or hip size is smaller despite patients being taller than normal. Also, height is considered to be a gastritis risk factor. As shown in a previous study, higher height tends to increase the gastric cancer incidence rate [15].

In males and females, hyperlipidemia and gastritis are related with gastritis. Only male cases are associated with vascular disease. Coronary artery has the potential to grow into myocardial infarction [16], and myocardial infarction is related with blood pressure [17]. As previously reported, approximately 30% of patients with coronary heart disease suffer from hyperlipidemia at the same time [18]. So, hyperlipidemia, coronary artery, and myocardial infarction are all related to each other. As shown in Table 1, in males, by logistic regression, there is a relation with hyperlipidemia, coronary artery, myocardial infarction, hyperlipidemia therapy, hypotensive or antihypotensive drug use, and diastolic blood pressure. This relation is more remarkable in males than in females. Repeatedly, it can be considered that vascular disease is connected with gastritis. In fact, in this study,

including males and females, 16 patients had gastritis and myocardial infarction (20%), 77 patients had gastritis and hyperlipidemia (36%), and 13 patients had gastritis and coronary artery (25.5%).

Female patients with gastritis have 4 more gastritis-associated factors by logistic regression test compared with males. In the case of taking osteoporosis medicine, the incidence rate is 1.7 times higher compared with normal. Taking anticonvulsants is a meaningful factor by logistic regression test, but few patients were taking this medicine

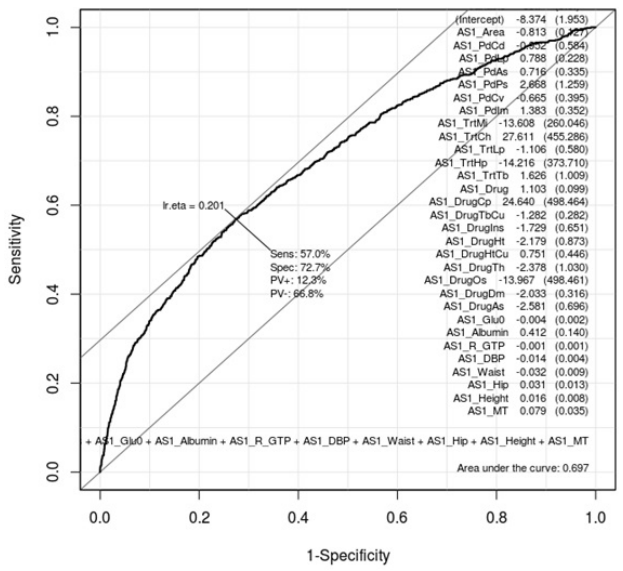

Fig. 1. Receiver operating characteristic (ROC) curve of gastritis-associated factors in males. This shows how well the 22 gastritis-associated clinical characteristic factors (Table 1) classify patients and normal subjects in males. As much as the ROC curve, these factors can classify gastritis patients and normal subjects in males.

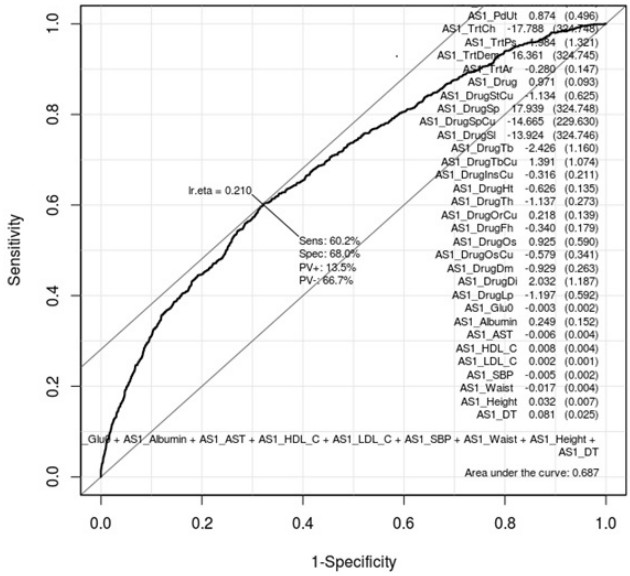

Fig. 2. Receiver operating characteristic (ROC) curve of gastritis-associated factors in females. This shows how well the 26 gastritis-associated clinical characteristic factors (Table 2) classify patients and normal subjects in females. As much as the ROC curve, these factors can classify gastritis patients and normal subjects in females.

Table 3. Top 20 ranked SNPs of genomewide association analysis in males

	RefSNP cluster ID (rs#)	Gene	CHR	SNP	BP	Minor allele	CHISQ	p-value	OR
1	rs8112449	-	19	SNP_A-2030176	10,381,064	T	22.69	0.000001901	1.304
2	rs11088226	-	21	SNP_A-1815523	32,847,402	G	21.38	0.00000376	1.3
3	rs2833889	-	21	SNP_A-2018178	32,849,639	G	20.99	0.000004623	1.297
4	rs2833890	-	21	SNP_A-2018180	32,849,757	A	20.42	0.000006206	1.293
5	rs2605883	-	8	SNP_A-2123956	74,349,808	A	19.44	0.00001039	1.299
6	rs4349972	-	8	SNP_A-2244783	74,357,797	T	19.22	0.00001167	1.296
7	rs12035141	-	1	SNP_A-4283116	207,145,759	C	18.79	0.00001461	0.7551
8	rs4274061	-	1	SNP_A-1786324	114,356,860	T	18.75	0.0000149	1.434
9	rs11088486	*B3GALT5*	21	SNP_A-1788320	39,868,999	T	18.69	0.00001538	0.7094
10	rs10483756	*KCNH5*	14	SNP_A-2224691	62,357,755	A	18.6	0.00001616	1.373
11	rs12682469	-	8	SNP_A-2293684	74,412,067	C	18.38	0.00001809	1.291
12	rs3785579	*CACNG1*	17	SNP_A-1912783	62,472,963	G	18	0.0000221	1.344
13	rs6845935	*CCSER1*	4	SNP_A-2009981	91,700,294	G	17.69	0.00002603	2.007
14	rs6960838	-	7	SNP_A-2070043	149,754,931	A	17.6	0.00002722	1.265
15	rs6978639	-	7	SNP_A-4259144	149,754,864	C	17.53	0.00002828	1.265
16	rs2029087	*PRKCE*	2	SNP_A-2121197	46,023,866	T	17.51	0.00002861	1.262
17	rs1365665	-	18	SNP_A-4296712	33,476,022	T	17.18	0.000034	1.295
18	rs1863645	-	18	SNP_A-4204442	33,478,276	G	17.11	0.00003523	1.294
19	rs10758596	*GLIS3*	9	SNP_A-2245408	4,291,601	C	16.85	0.00004047	1.689
20	rs2250538	*SOX13*	1	SNP_A-1960774	202,348,515	C	16.7	0.00004369	0.7963

SNP, single-nucleotide polymorphism; CHR, chromosome; BP, base pair; OR, odds ratio.

[4]; so, it is hard to prove that taking anticonvulsants has a positive relation with gastritis. Patients who were diagnosed with tuberculosis and patients who have taken tuberculosis drugs suffer gastritis more than normal subjects. This gives information on the relation between gastritis and tuberculosis in females.

ROC curves can show how gastritis-associated factors of Tables 1 and 2 affect gastritis patients and normal subjects. Whether these factors are conclusive should be confirmed by AUC values. Figs. 1 and 2 are ROC curves using the result of the logistic regression test of Tables 1 and 2, respectively. Each AUC value is 0.697 and 0.687. This result means that these factors are not useful as gastric-specific markers.

Genome-wide association studies

We selected the top 20 ranked SNPs by association test using chi-square test and p-values among 349,184 SNPs in males and in females, respectively. The results of SNPs association analysis described in Tables 3 and 4. Tables 3 and 4 are top 20 ranked SNPs of genomewide association analysis in males and females, respectively. They are sorted by P-value. But there was no considerable SNP associated with gastritis. Astonishingly, there was no common SNP between males and females. This means that associated-SNPs are different, depending on the patient's gender.

Table 5 describes the important SNPs associated with gastritis by logistic regression analysis among the top 20 ranked SNPs. The p-values of these SNPs were all <0.001. Figs. 3 and 4 show the ROC curve by using these SNPs in males and in females, respectively. The AUC scores are 0.675 and 0.658 in males and in females, respectively. The AUC score was too low to use as a specific factor for diagnosis.

Discussion

In this study, we confirmed that vascular disease and gastritis have considerable association in Korean males. We also verified that gastritis is affected by other various drugs. However, we could not find gastritis-specific biomarkers for diagnosis.

Gastritis has numerous causes and is distributed as

Table 5. Gastritis-associated single-nucleotide polymorphisms

	Male	Female
1	rs8112449	rs6561072
2	rs12035141	rs1503059
3	rs4274061	rs17755119
4	rs11088486	rs16963496
5	rs10483756	rs945144
6	rs3785579	rs1465093
7	rs6845935	rs2414539
8	rs2029087	rs17834472
9	rs10758596	rs12707453
10	rs2250538	rs2665904
11	-	rs7766133
12	-	rs6437416

Table 4. Top 20 ranked SNPs of genomewide association analysis in females

	RefSNP cluster ID (rs#)	Gene	CHR	SNP	BP	Minor allele	CHISQ	p-value	OR
1	rs6445797	-	3	SNP_A-4260597	56,538,380	C	22.72	0.000001879	1.402
2	rs1503059	*CA10*	17	SNP_A-1859357	47,559,455	G	22.23	0.000002425	0.7834
3	rs10955971	*COL14A1*	8	SNP_A-2256799	121,445,527	T	22.18	0.000002484	1.319
4	rs7826906	-	8	SNP_A-1910277	121,570,904	G	21.92	0.00000285	1.316
5	rs978979	-	3	SNP_A-1911674	56,508,056	G	21.78	0.000003064	1.391
6	rs7835363	*COL14A1*	8	SNP_A-2240251	121,449,563	G	21.32	0.000003895	1.312
7	rs13263962	*MRPL13*	8	SNP_A-2198485	121,499,780	C	21.08	0.000004397	1.319
8	rs7835198	*COL14A1*	8	SNP_A-2021181	121,449,386	T	20.63	0.000005573	1.307
9	rs945144	*LY86-AS1*	6	SNP_A-1984941	6,421,277	A	19.81	0.000008575	0.7919
10	rs7766133	*MBOAT1*	6	SNP_A-4259064	20,301,726	T	18.29	0.00001897	1.244
11	rs16963496	*HDC*	15	SNP_A-1937381	48,323,730	G	17.75	0.00002521	1.519
12	rs6437416	*AC090505.6*	3	SNP_A-4269427	195,981,661	G	17.59	0.00002737	1.485
13	rs2665904	-	5	SNP_A-2301041	123,666,386	C	17.51	0.00002852	1.786
14	rs6561072	-	13	SNP_A-1808093	42,173,146	G	17.51	0.00002862	1.24
15	rs2238294	*HDC*	15	SNP_A-1887051	48,324,474	T	17.33	0.00003148	1.511
16	rs2414539	*AQP9*	15	SNP_A-2124556	56,240,798	T	17.26	0.00003258	1.316
17	rs17834472	-	14	SNP_A-2138553	60,684,493	G	17.17	0.00003418	1.369
18	rs17755119	-	10	SNP_A-1870834	29,299,456	T	16.81	0.00004131	1.468
19	rs1465093	*MGAM*	7	SNP_A-1991521	141,355,094	T	16.57	0.00004678	0.7989
20	rs12707453	*HGF*	7	SNP_A-2288799	81,207,355	G	16.49	0.0000489	1.237

SNP, single-nucleotide polymorphism; CHR, chromosome; BP, base pair; OR, odds ratio.

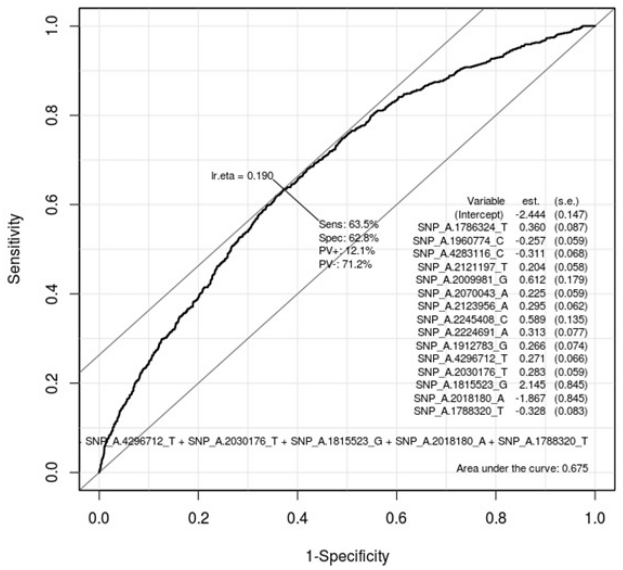

Fig. 3. Receiver operating characteristic (ROC) curve of gastritis-associated single-nucleotide polymorphisms (SNPs) in males. This shows how well 20 ranked gastritis-associated SNPs (Table 3) classify patients and normal subjects in males. As much as the ROC curve, these factors can classify gastritis patients and normal subjects in males.

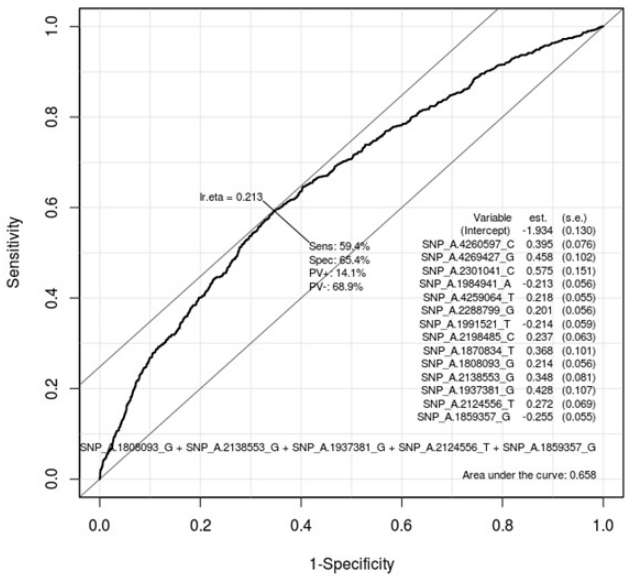

Fig. 4. Receiver operating characteristic (ROC) curve of gastritis-associated single-nucleotide polymorphisms (SNPs) in females. This shows how well 20 ranked gastritis-associated SNPs (Table 4) classify patients and normal subjects in females. As much as the ROC curve, these factors can classify gastritis patients and normal subjects in females.

variable subtypes by phenotype. So, correctly diagnosing it is very important for therapy. Gastritis has non-specific phenotypes that can obscure finding the disease causes. So, more information is also needed to analyze the complex factors associated with disease rather than each factor associated with the disease. For example, confirmation of *H. pylori* infection, tobacco, smoking period, and alcohol intake are considered. This needs further study.

Acknowledgments

This work was supported by grants from the Korea Centers for Disease Control and Prevention, Republic of Korea (4845-301, 4851-302, 4851-307).

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