Genetic Polymorphisms of PGF and TNFAIP2 Genes Related to Cervical Cancer Risk Among Uygur Females from China

Zumurelaiti Ainiwaer
People's Hospital of Xinjiang Uygur Autonomous
Reyilanmu Maisaidi
People's Hospital of Xinjiang Uygur Autonomous
Jing Liu
People's Hospital of Xinjiang Uygur Autonomous
Lili Han (hanlili19941226@163.com)
People's Hospital of Xinjiang Uygur Autonomous Region https://orcid.org/0000-0002-8664-0820
Sulaiya Husaiyin
People's Hospital of Xinjiang Uygur Autonomous
Jing Lu
People's Hospital of Xinjiang Uygur Autonomous
Mayinuer Niyazi
People's Hospital of Xinjiang Uygur Autonomous

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Abstract

Background: *PGF* and *TNFAIP2* are important angiogenic factors, which were abnormal expression in cervical cancer (CC). However, no report was investigating the associations between the polymorphisms in the *PGF* and *TNFAIP2* genes and CC risk.

Methods: We conducted a case-control study of 342 CC patients and 498 cancer-free controls in Chinese Uygur female population. Three selected SNPs (*PGF* rs8019391, *PGF* rs2268615, and *TNFAIP2* rs710100) were genotyped to investigate the possible association of the polymorphisms in *PGF* and *TNFAIP2* with the risk of CC. The analysis adjusted by age was used to assess associations of these SNPs with CC risk.

Results: *PGF* rs2268615 (OR = 1.39, 95% CI = 1.04-1.86, p = 0.024) and *TNFAIP2* rs710100 (OR = 1.44, 95% CI =1.07-1.95, p = 0.018) polymorphisms were significantly associated with the increased risk of CC. Moreover, *PGF* rs8019391 T allele was highly represented in patients with III–IV tumor stage (OR = 2.17, p = $4.58´10^{-4}$). MDR analysis revealed a positive interaction between the SNPs.

Conclusion: Our data suggested that *PGF* rs2268615, and *TNFAIP2* rs710100 polymorphisms may be risk factors for susceptibility to CC, which contributed to the increased risk of CC, and this finding requires further validation by larger studies.

Trail registration: Not applicable.

Background

Worldwide, cervical cancer (CC) ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 570,000 cases and 311,000 deaths in 2018(1). CC is the most common cancer of female genital system in China and the incidents of CC tend to be younger (2). A wide range of inter-individual genetic variability in CC susceptibility and other pathogeneses might contribute to cervical carcinogenesis, such as the genetic factor. Accumulating evidence suggests that single nucleotide polymorphisms (SNPs) in tumor-associated genes play an important role in the genetic susceptibility to CC (3–5).

PGF (placental growth factor) gene, also named *PLGF*, which encodes a homologous of vascular endothelial growth factor, has been reported as a potent stimulator in cancer invasion through activating angiogenesis(6). In addition to its angiogenic effects, the overexpression of *PGF* is correlated with tumor stage, cancer progression and metastasis(7). *TNFAIP2* (TNF alpha induced protein 2) is a primary response gene of TNFα, and the expression of TNFAIP2 is regulated by multiple transcription factors and signaling pathways, including NF-κB, KLF5 and retinoic acid(8). *TNFAIP2* is an important angiogenic factor, which was significantly associated with intratumoral microvessel density(9). In addition, previous studies have shown that the abnormal expression of *PGF* and *TNFAIP2* in human cancer, including CC(6, 10). However, there is no report on investigating associations between the polymorphisms in *PGF* and *TNFAIP2* and CC risk. We hypothesized that genetic variants in *PGF* and *TNFAIP2* could modulate CC susceptibility.

The aim of our study was to investigate the possible association between the polymorphisms of three SNPs (*PGF* rs8019391, *PGF* rs2268615, and *TNFAIP2* rs710100) and the risk of CC in Chinese Uygur female population. This may reveal a new aspect of CC etiology in the future.

Subjects And Methods

Study participants

This study protocol was approved by the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region and under the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

This study involving 342 cervical cancer patients (cases, 43.27 ± 11.78) and 498 age-matched cancer-free individuals (controls, 43.46 ± 13.03) were enrolled from the People's Hospital of Xinjiang Uygur Autonomous Region, as shown in Table 1. All the patients were women newly diagnosed and histopathologically confirmed primary cervical cancer according to the clinical staging standards of the International Federation of Gynecology and Obstetrics (FIGO). 132 cases were stage I–II, 80 cases were stage III–IV and 130 cases were missing. Patients with any history of other cancers, having undergone radiotherapy, chemotherapy, or surgery and inflammatory diseases were excluded. Controls were health women without any history of cancers and diseases of the liver, kidneys, heart, brain, and vascular system, as well as gynecological inflammatory diseases from the health checkup in the same hospital during the same period. All recruited subjects were unrelated ethnic Han Chinese. Demographic characteristics and clinical information were collected from the standardized questionnaires.

Table 1
Characteristics of patients with cervical cancer and controls

Characteristics		Cases (n = 342)	Controls (n = 498)	*p*
Age	Mean ± SD (years)	43.27 ± 11.78	43.46 ± 13.03	0.832
	> 43	176 (51.5%)	263 (52.8%)	
	≤ 43	166 (48.5%)	235 (47.2%)	
HPV status	Negative	51 (14.9%)		
	Positive	195 (57.0%)		
	Missing	96 (28.1%)		
Stage	□-□	132 (38.6%)		
	□-□	80 (23.4%)		
	Missing	130 (38.0%)		

Snp Selection And Genotyping

Peripheral venous blood samples (5 mL) were obtained from patients and healthy subjects and were stored in EDTA-coated tubes. Genomic DNA extraction was carried out using the GoldMag DNA Purification Kit (GoldMag Co. Ltd, Xi'an City, China) according to the manufacturer's protocol, then quantified by NanoDrop 2000 (Thermo Scientifc, Waltham, MA, USA), and stored at -20 ° C for further experiments. The SNPs were selected from the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP) and the 1000 Genomes Project data (http://www.internationalgenome.org/), based on minor allele frequency (MAF) of at least 5% in Chinese populations and with a pairwise $r^2 > 0.80$. *PGF* rs8019391 and rs2268615, and *TNFAIP2* rs710100 were selected as candidate SNPs. miRNASNP_v2 database (http://bioinfo.life.hust.edu.cn/ miRNASNP2/index.php) and HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/ haploreg.php) were used to predict the potential function of these

polymorphisms (Supplementary Table 1). These candidate SNPs were genotyped with Agena MassARRAY system (Agena, San Diego, CA, U.S.A.) as described previously(11, 12), and conducted by two laboratory technicians double-blinded. The primers for PCR amplification and single base extension were designed using the Assay Design 3.0 software (Supplementary Table 2). For quality control, approximately 10% of the samples were randomly chosen and repeated genotyping, and a 100% concordance rate was observed.

Data analysis

SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and PLINK software were used for all statistical analyses. Student's t-test was performed to analyze the differences in the age distribution between the cervical cancer patients and the healthy controls. Hardy–Weinberg equilibrium (HWE) was tested by a goodness-of-fit χ^2 test for each SNP among the control subjects. The genotype and allele frequencies between cases and controls were compared using the χ^2 test or Fisher's exact test. The association of candidate SNPs with cervical cancer risk was assessed by odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analysis, for both combined and respective genotype(13). The association was also evaluated in subgroup analyses stratified by demographic and clinic variables. Multifactor dimensionality reduction (MDR) (version 3.0.2) was performed to evaluate the SNP–SNP interactions in the risk of cervical cancer (14). A two-tailed p-value < 0.05 was considered to be statistically significant for all the analyses.

Results

In Supplementary table 3, the minor allele frequency (MAF) of the *PGF* rs8019391 and rs2268615, and *TNFAIP2* rs710100 polymorphisms among the case and control groups were listed. The genotype distribution of these SNPs in controls were in accordance with the Hardy-Weinberg equilibrium ($p > 0.05$). The MAF distribution of *PGF* rs2268615-A allele and *TNFAIP2* rs710100-A allele, were found to be higher in the case group, which have increased risk of cervical cancer (rs2268615, A vs C, OR = 1.27, 95% CI = 1.03–1.58, $p = 0.029$; and rs710100, A vs G, OR = 1.23, 95% CI = 1.01–1.50, $p = 0.043$).

Multiple genetic model results adjusted by age were also revealed *PGF* rs2268615 and *TNFAIP2* rs710100 polymorphisms conferred to the increased risk of cervical cancer (Table 2). *PGF* rs2268615 polymorphism was associated with a significantly increased risk of cervical cancer under heterozygote (OR = 1.39, 95% CI = 1.04–1.86, $p = 0.024$), dominant (OR = 1.40, 95% CI = 1.06–1.84, $p = 0.018$) and log-additive (OR = 1.29, 95% CI = 1.03–1.61, $p = 0.027$) models. For rs710100 in *TNFAIP2*, GA genotype (OR = 1.44, 95% CI = 1.07–1.95, $p = 0.018$) and GA + AA genotype (OR = 1.42, 95% CI = 1.07–1.89, $p = 0.016$) compared with GG genotype increased 1.44-fold and1.42-fold the susceptibility of cervical cancer, respectively. Moreover, the result of additive model also showed an increased risk of cervical cancer (rs710100, OR = 1.23, 95% CI = 1.00-1.50, $p = 0.046$). However, there were no significant association of cervical cancer susceptibility with *PGF* rs8019391 variants.

Table 2
Relationships between the candidate SNPs and cervical cancer risk

Gene SNP ID	Model	Genotype	Case	Control	Adjusted by age and gender	
					OR (95%CI)	p
PGF	Genotype	CC	208	327	1.00	
		CT	119	145	1.29 (0.96–1.74)	0.093
		TT	15	26	0.91 (0.47–1.76)	0.777
	Dominant	CC	208	327	1.00	0.150
rs8019391		CT-TT	134	171	1.23 (0.93–1.64)	
	Recessive	CC-CT	327	472	1.00	0.585
		TT	15	26	0.83 (0.43–1.6)	
	Log-additive	—	—	—	1.13 (0.89–1.42)	0.324
PGF	Genotype	CC	160	273	1.00	
rs2268615		CA	156	191	**1.39 (1.04–1.86)**	**0.024**
		AA	26	31	1.43 (0.82–2.49)	0.209
	Dominant	CC	160	273	1.00	**0.018**
		CA-AA	182	222	**1.40 (1.06–1.84)**	
	Recessive	CC-CA	316	464	1.00	0.453
		AA	26	31	1.23 (0.72–2.11)	
	Log-additive	—	—	—	**1.29 (1.03–1.61)**	**0.027**
TNFAIP2	Genotype	GG	118	210	1.00	
rs710100		GA	171	211	**1.44 (1.07–1.95)**	**0.018**
		AA	53	69	1.37 (0.89–2.08)	0.150
	Dominant	GG	118	210	1.00	**0.016**
		GA-AA	224	280	**1.42 (1.07–1.89)**	
	Recessive	GG-GA	289	421	1.00	0.576
		AA	53	69	1.12 (0.76–1.65)	
	Log-additive	—	—	—	**1.23 (1.00-1.50)**	**0.046**

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

p values were calculated by logistic regression analysis with adjustments for age and gender.

$p < 0.05$ means the data is statistically significant.

Age stratification displayed *PGF* rs2268615 and *TNFAIP2* rs710100 polymorphisms increased the risk of cervical cancer among women at age ≤ 43 years (Table 3). After calculating the ORs for the allele (OR = 1.38, $p = 0.041$ and OR = 1.42, $p = 0.018$, respectively), the genotype (CA vs CC, OR = 1.55, $p = 0.039$; and AA vs GG, OR = 1.97, $p = 0.031$,

respectively), the dominant (OR = 1.56, $p = 0.030$; and OR = 1.57, 95%, $p = 0.034$, respectively), and the log-additive (OR = 1.40, $p = 0.042$; and OR = 1.42, $p = 0.020$) genetic models, they all concluded that there were significant association of *PGF* rs2268615 and *TNFAIP2* rs710100 polymorphisms with susceptibility to cervical cancer.

Table 3
Relationships between the candidate SNPs and cervical cancer risk according to the stratification by age

SNP ID	Model	Genotype	> 43 years				≤ 43 years			
			Case	Control	OR (95%CI)	*p*	Case	Control	OR (95%CI)	*p*
PGF	Allele	C	253	393	1.00	0.303	223	344	1.00	**0.041**
rs2268615		A	99	131	1.17 (0.87–1.59)		109	122	**1.38 (1.01–1.88)**	
	Genotype	CC	89	147	1.00		71	126	1.00	
		CA	75	99	1.25 (0.84–1.86)	0.282	81	92	**1.55 (1.02–2.36)**	**0.039**
		AA	12	16	1.22 (0.55–2.70)	0.626	14	15	1.62 (0.74–3.56)	0.228
	Dominant	CC	89	147	1.00	0.269	71	126	1.00	**0.030**
		CA-AA	87	115	1.24 (0.85–1.82)		95	107	**1.56 (1.05–2.33)**	
	Recessive	CC-CA	164	246	1.00	0.795	152	218	1.00	0.481
		AA	12	16	1.11 (0.51–2.41)		14	15	1.31 (0.61–2.81)	
	Log-additive	—	—	—	1.17 (0.86–1.60)	0.317	—	—	**1.40 (1.01–1.92)**	**0.042**
TNFAIP2	Allele	G	217	331	1.00	0.597	190	300	1.00	**0.018**
rs710100		A	135	191	1.08 (0.82–1.43)		142	158	**1.42 (1.06–1.90)**	
	Genotype	GG	64	111	1.00		54	99	1.00	
		GA	89	109	1.41 (0.93–2.14)	0.105	82	102	1.46 (0.94–2.27)	0.092
		AA	23	41	0.96 (0.53–1.74)	0.890	30	28	**1.97 (1.07–3.63)**	**0.031**
	Dominant	GG	64	111	1.00	0.208	54	99	1.00	**0.034**

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

p values were calculated by logistic regression analysis with adjustments for age.

$p < 0.05$ indicates statistical significance.

	GA-AA	112	150	1.29 (0.87–1.91)		112	130	**1.57 (1.03–2.38)**	
Recessive	GG-GA	153	220	1.00	0.418	136	201	1.00	0.103
	AA	23	41	0.80 (0.46–1.38)		30	28	1.59 (0.91–2.79)	
Log-additive	—	—	—	1.07 (0.81–1.41)	0.635	—	—	**1.42 (1.06–1.90)**	**0.020**

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

p values were calculated by logistic regression analysis with adjustments for age.

$p < 0.05$ indicates statistical significance.

Subsequently, stratified analyses by tumor stage showed that the risk effect for *PGF* rs8019391 polymorphism appeared to be more prominent in the subset of patients with stage III + IV (Table 4). Compared with the C allele, rs8019391 T allele was highly represented in patients with III–IV tumor stage as compared to patients with I–II tumor stage under the allele (OR = 2.17, $p = 4.58 \cdot 10^{-4}$), heterozygote (OR = 2.34, $p = 0.005$), homozygote (OR = 5.76, $p = 0.015$), dominant (OR = 2.59, $p = 0.001$), recessive (OR = 4.13, $p = 0.045$), and log-additive models (OR = 2.36, $p < 0.001$).

Table 4
Relationship of clinical stage with PGF **rs8019391 polymorphism in cervical cancer patients adjusted by age**

SNP ID	Model	Genotype	I-II	III-IV	OR (95%CI)	*p*
rs8019391	Allele	C	110	220	1.00	**$4.58 \cdot 10^{-4}$**
		T	50	44	**2.27 (1.43–3.62)**	
	Codominant	CC	37	91	1.00	
		CT	36	38	**2.34 (1.29–4.25)**	**0.005**
		TT	7	3	**5.76 (1.41–23.52)**	**0.015**
	Dominant	CC	37	91	1.00	**0.001**
		CT-TT	43	41	**2.59 (1.46–4.60)**	
	Recessive	CC-CT	73	129	1.00	**0.045**
		TT	7	3	**4.13 (1.04–16.45)**	
	Log-additive	—	—	—	**2.36 (1.45–3.86)**	**< 0.001**

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

p values were calculated by logistic regression analysis with adjustments for age.

$p < 0.05$ indicates statistical significance.

Subsequently, MDR analysis was implemented to assess the impact of the SNP-SNP interactions. Association of higher order interactions with cervical cancer risk was analyzed by MDR analysis as summarized in Fig. 1. The interaction information analysis revealed additive effect between *TNFAIP2* rs710100-GA, *PGF* rs2268615-CA, and *PGF* rs8019391-

CT on conferring risk towards the progression of the cervical cancer. The dendrogram and the Fruchterman-Reingold interaction analysis of our data showed that *PGF* rs2268615, *TNFAIP2* rs710100, *PGF* rs8019391 exhibited a strong synergy effect on the risk of cervical cancer development as shown in Fig. 2. Table 5 showed that *TNFAIP2* rs710100 was the best single-locus model to predict the risk of cervical cancer (testing accuracy = 0.508, CVC = 6/10, $p = 0.014$). The best two-locus model was the combination of *PGF* rs2268615 and *TNFAIP2* rs710100 (testing accuracy = 0.536, CVC = 9/10, $p < 0.0001$. The three-locus model included *TNFAIP2* rs710100, *PGF* rs2268615, and *PGF* rs8019391 (testing accuracy = 0.550, CVC = 10/10, $p < 0.0001$).

Table 5
SNP–SNP interaction models of the *PGF* and *TNFAIP2* genes analyzed by the MDR method

Model	Training Bal. Acc.	Testing Bal. Acc.	CVC	OR (95% CI)	*p*
TNFAIP2 rs710100	0.544	0.508	6/10	1.46 (1.08–1.97)	**0.014**
PGF rs2268615, *TNFAIP2* rs710100	0.564	0.536	9/10	1.91 (1.41–2.59)	**< 0.0001**
PGF rs2268615, *TNFAIP2* rs710100, *PGF* rs8019391	0.587	0.550	10/10	2.11 (1.56–2.84)	**< 0.0001**
MDR, multifactor dimensionality reduction; Bal. Acc., balanced accuracy; CVC, cross–validation consistency; OR, odds ratio; CI, confidence interval.					
p values were calculated using χ^2 tests.					
$p < 0.05$ indicates statistical significance.					

Discussion

In this case–control study, we assessed the association between three SNPs (*PGF* rs8019391, *PGF* rs2268615, and *TNFAIP2* rs710100) and the susceptibility to CC in Chinese Uygur female population. We found that *PGF* rs2268615, and *TNFAIP2* rs710100 polymorphisms were significantly associated with the increased risk of CC. Our findings also suggest some possible interactions between *PGF* rs2268615, and *TNFAIP2* rs710100 genetic variations and age. Moreover, the risk effect for *PGF* rs8019391 polymorphism appeared to be more prominent in the subset of patients with stage III + IV. To the best of our knowledge, this is the first report to describe the possible role of *PGF* and *TNFAIP2* polymorphisms as a risk factor for CC.

PGF, located in 14q24.3, belongs to the vascular endothelial growth factor family, present on various cell types. The expression of *PLGF* in tumors or plasma of cancer patients was upregulated in most human tumor types, including gallbladder, gastric and prostate cancers, which regulates some cell processes such as survival, growth of vascular endothelial cells, invasiveness, and also involves in pathological angiogenesis and metastasis (15–17). Previous researches indicated that *PLGF* is overexpressed in CC tissues compared to adjacent normal tissues and in serum and vaginal lavage compared with normal women group(6, 18). *PGF* promotes migration through regulating epithelial-mesenchymal transition-related protein expression in cervical cancer (6). These lines of evidence have led us to formulate the hypothesis that *PGF* could be of pathogenic importance in CC. In our study, we firstly examined the role of *PGF* genetic polymorphisms (rs8019391 and rs2268615) and the susceptibility to CC, and found that *PGF* SNP rs2268615 conferred increased risks to CC, and *PGF* rs8019391 polymorphism was a significant risk factor for patients with III-IV stage. A retrospective population-based study showed that 5-year relative survival rates of CC were 90.9%, 71.0%, 41.7%, and 7.8% for the stage I, II, III, and IV, respectively(19). Therefore, it is highly speculated that *PGF*

rs8019391 polymorphism may affect the progression of cervical cancer. Further large-scale studies are needed to verify the results of our findings.

The *TNFAIP2* gene, also named B94, which is located on chromosome 14q32, and encodes TNFα-inducible protein 2. *TNFAIP2* were involved in the NFκB and KLF5 signaling pathway to regulate the cell inflammatory, angiogenesis, cell proliferation, migration and invasion (20, 21). Expression of *TNFAIP2* was found to be abnormal in various cancers, including breast cancer, esophageal squamous cell carcinoma, and glioma (20, 22, 23). In cervical cancer, the expression of *TNFAIP2* was significantly increased in CC tissues compared with normal tissues based on the analysis of the TCGA (The Cancer Genome Atlas) database(8). In addition, the disruption of the *TNFAIP2* gene through viral integration contributed to the rapid progression of cervical cancer (10). These lines of evidence suggested that TNFAIP2 might play an important role in the progression of CC. In this study, we found that *TNFAIP2* rs710100 variant was significantly associated with an increased risk of CC. Rs710100 polymorphism in 3'UTR of *TNFAIP2*, located in the predicted miRNAs-binding sites was associated with a significantly increased risk of CC. Specifically, rs1064607 putatively affects the binding sites of miR-155(24), whose abnormal expression in CC was correlated with FIGO stage, lymph nodes metastasis, and vascular invasion(25). Therefore, we propose that rs710100 in 3'UTR of *TNFAIP2* might affect *TNFAIP2* expression in CC by disturbing mRNA stability and miRNA binding activity, thus inducing the higher risk of CC. However, it should be confirmed in further functional studies.

In spite of interesting findings on the association of *PGF* and *TNFAIP2* polymorphisms with cervical cancer risk, several limitations need to be addressed. Firstly, there may be selection and information bias since the retrospective study was designed as a hospital-based case–control study. Secondly, due to insufficient data of HPV screening results and lifestyle data, e.g., smoking, for all cases and controls, we could not evaluate HPV infection and lifestyle as the potential confounder in the risk estimates of CC.

Conclusion

In conclusion, our findings showed a relationship between *PGF* rs2268615, and *TNFAIP2* rs710100 polymorphisms and the increased susceptibility to CC in Chinese Uygur females. Considering this is the first report that *PGF* and *TNFAIP2* polymorphisms contribute to CC risk, well-designed large and prospective studies are required to validate our findings.

Abbreviation

CC, cervical cancer; SNPs, single nucleotide polymorphisms; *PGF*, placental growth factor; *TNFAIP2*, TNF alpha induced protein 2.

Declarations

Ethics approval and consent to participate

This study protocol was approved by the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region and under the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests

The authors declare that they have no competing interests

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Author's contributions

ZA, RM and LLH designed this study protocol and drafted the manuscript; JL and SH performed the DNA extraction and genotyping; JL and RM performed the data analysis; RM and JL performed the sample collection and information recording. MN and LLH conceived and supervised the study. All authors read and approved the final manuscript.

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26. Legend.

Figures

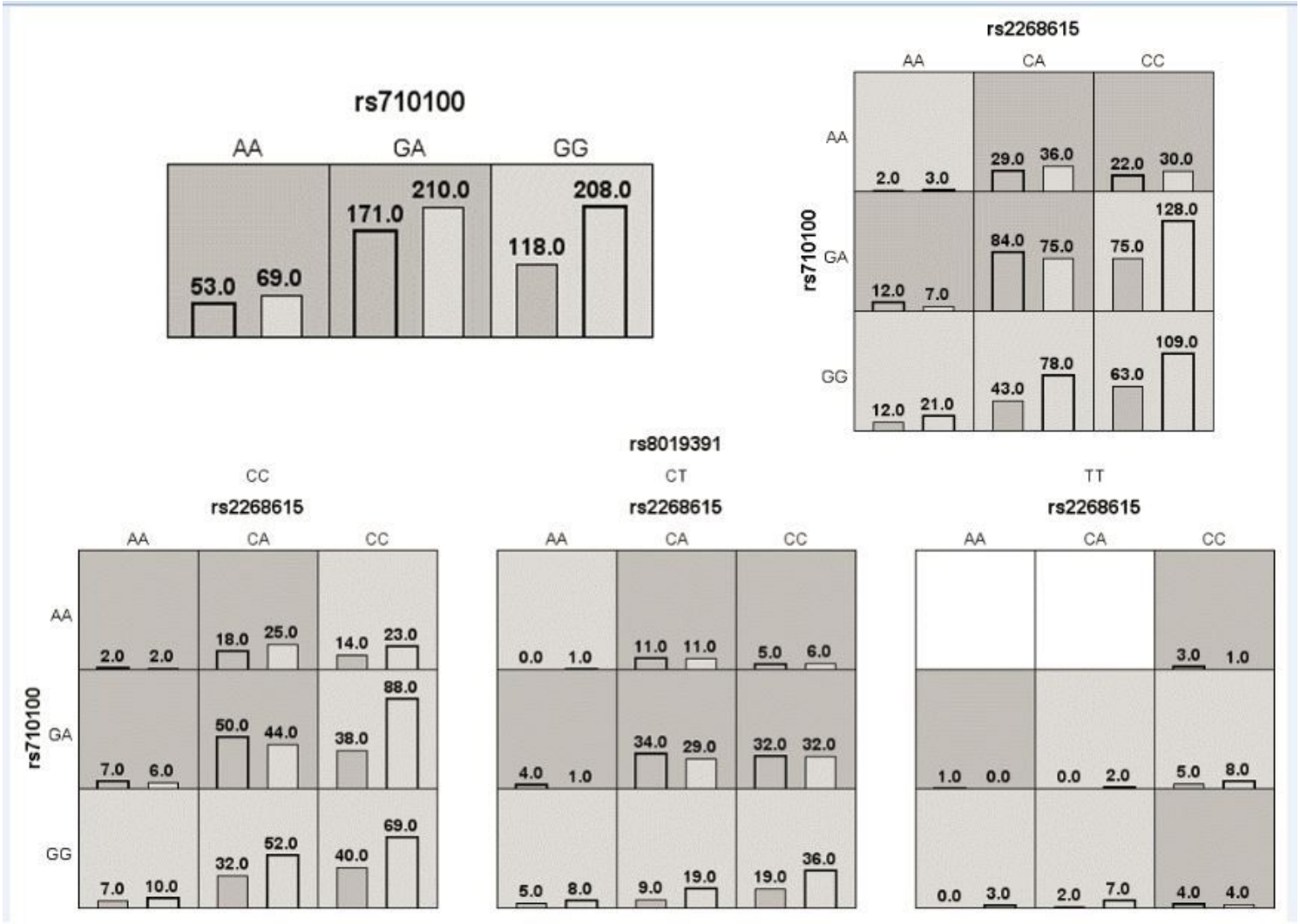

Figure 1

Summary of MDR gene-gene interaction. Each cell shows counts of “case” on left and “control” on right.

Figure 2

SNP-SNP interaction dendrogram and Fruchterman-Reingold.

Supplementary Files

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- SupplementaryTable.docx