

Association of gene polymorphisms in ABO blood group chromosomal regions and menstrual disorders

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Abstract. This study aimed to investigate whether single nucleotide polymorphisms (SNPs) located near the gene of the ABO blood group play an important role in the genetic aetiology of menstrual disorders (MDs). Polymerase chain reaction-ligase detection reaction technology was used to detect eight SNPs near the ABO gene location on the chromosomes in 250 cases of MD and 250 cases of normal menstruation. The differences in the distribution of each genotype, as well as the allele frequency in the normal and control groups, were analysed using Pearson's χ^2 test to search for disease-associated loci. SHEsis software was used to analyse the linkage disequilibrium and haplotype frequencies and to inspect the correlation between haplotypes and the disease. Compared with the control group, the experimental group exhibited statistically significant differences in the genotype distribution frequencies of the rs657152 locus of the ABO blood group gene and the rs17250673 locus of the tumour necrosis factor cofactor 2 (TRAF2) gene, which is located downstream of the ABO gene. The allele distribution frequencies of rs657152 and rs495828 loci in the ABO blood group gene exhibited significant differences between the groups. Dominant and recessive genetic model analysis of each locus revealed that the experimental group exhibited statistically significant differences from the control group in the genotype distribution frequencies of rs657152 and rs495828 loci, respectively. These results indicate that the ABO blood group gene and TRAF2 gene may be a cause of MDs.

Introduction

Menstruation is the periodic endometrial shedding and bleeding that accompanies ovarian cyclical ovulation. Regular menstruation is one of the signs of mature female reproductive function. Menstrual disorders (MDs) are common gynaecological diseases that not only affect the health and quality of life of females but also increase the potential risks of certain gynaecological diseases (1-4). In recent years, research has increasingly focused on the genetic factors that cause MDs. Taylor *et al* (5) found that polymorphisms in the progesterone receptor gene were associated with young menarche ages and excessively short menstrual cycles. The probability of premenstrual syndrome (PMS) has been found to be higher in identical twins than in fraternal twins (6), and mutation of the follicle-stimulating hormone receptor (FSH-R) gene may lead to amenorrhoea, infertility or premature ovarian failure (7). These findings indicate that genetic susceptibility is significant in the occurrence of MDs. Furthermore, a predisposing gene of polycystic ovary syndrome, which is normally accompanied by MDs (8), is located in 9q33.3 (9). The ABO gene is located on chromosome 9q34.2; thus, the association of the blood type system with MDs may involve the ABO gene. Previous studies have described the correlation of the ABO blood group with ovarian reserve functions and infertility. It has been reported that antigen A may be a protective factor of ovarian reserve capacity and that type O blood decreases the risk of ovarian reserve capacity more than blood types A and AB (10-12). It has been proposed that type O blood is associated with infertility (13). In certain studies, pregnant females with type A blood were discovered to be more prone to ovarian hyperstimulation than females with type O blood (14,15). These studies indicate that the ABO blood system is closely associated with diseases of the female reproductive system. As MDs are common gynaecological diseases that reflect the ovarian state, the occurrence of MDs may be associated with the ABO blood group system.

To verify these hypotheses and evaluate whether single nucleotide polymorphisms (SNPs) are associated with MDs, the ABO blood group gene and eight related gene loci, which are located at upstream and downstream sites of the ABO gene, were examined in the present study.

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Materials and methods

Subjects. A total of 1,035 females of childbearing age were enrolled by the Reproductive Health Research Institute of Henan Provincial People's Hospital (Jinshui, China). Among the subjects, 532 cases had regular menstruation and 503 cases had MDs. All patients were not biological relations of any other patient. The females with regular menstruation were set as the control group, whereas females with MDs were set as the experimental group. Random sampling was performed to select 250 cases from each group. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Henan Provincial People's Hospital. Written informed consent was obtained from all participants.

Judgment criteria. Menstrual cycles <21 days and >35 days were defined as polymenorrhoea and oligomenorrhoea, respectively. Regarding menstrual blood volume, daily usages of <2 and >5 sanitary towel pieces, each fully soaked by menstrual blood, were defined as hypomenorrhoea and hypermenorrhoea, respectively. Menstruation durations that were not between three and seven days were considered abnormal. The presence of dysmenorrhoea was defined as the occurrence before, during or after menstruation of lower abdominal pain and a feeling of fullness and bloating accompanied by backache or other symptoms that seriously affected the quality of life.

Females with normal menstrual cycles, blood volume and no dysmenorrhoea were considered normal, whereas females with any of the above symptoms were considered MD patients (16).

Samples. The questionnaire was co-designed with epidemiological, statistical and endocrinological experts. The questionnaire included general situations, menstrual characteristics and relevant family history. The questionnaire was completed by the respondents. Thereafter, a specialist individually asked the patients for verification and supplemental information.

The medical staff of Henan Provincial People's Hospital conducted ABO blood group detection by the slide method. Anti-A and -B antibodies were purchased from the Biomedical Engineering Center of Hebei Medical University (Shijiazhuang, China). A total of 2 ml venous blood was drawn from each participant and was placed into a 2-ml disposable dipotassium ethylenediamine-N,N,N',N'-tetraacetic acid-containing human blood vial, followed by covering and mixing. The vial was placed into a freezer at -80°C for future extraction of DNA.

DNA extraction and detection. A 1 ml blood genomic DNA extraction kit based on a centrifugation-column method (Shanghai Lifefeng Biotechnology Co. Ltd., Shanghai, China) was used to extract DNA from the blood samples, and a NanoDrop-1000 UV/VIS spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) was used to ensure that the concentrations of each DNA sample were ≥ 50 ng/ μ l, the purity at optical density (OD) 260/280 was 1.7-2.0 and at OD 260/230 was >1.5. Polymerase chain reaction-ligase detection (PCR-LDR) technology was used to genotype the loci. The PCR-LDR was completed by Shanghai Generay Biotech Co. Ltd. (Shanghai, China) with an accuracy rate of up to 98%.

Choice of SNP loci. The ABO gene is located on chromosome 9q34.2 (NM_020469), and the bases are located at positions 136130563 to 136150630. Eight loci near the ABO gene were chosen. rs657152 is inside one of the ABO gene introns, and rs495828 is located upstream of the ABO gene. Downstream of the ABO gene, four loci of the tumour necrosis factor receptor cofactor 2 (TRAF2) gene, namely, rs7852970, rs4448378, rs10781522 and rs17250673, and two loci of the patatin-like phospholipase domain containing 7 (PNPLA7) gene, namely, rs61754920 and rs11137410, were selected. SNP information was downloaded from the website of the International HapMap for the Han Chinese in Beijing, China (CHB) population (17). The SNP information met the minimum allele frequency (MAF) standard of >0.05.

Data analysis. Counting data are expressed as percentages, and measurement data are expressed as mean \pm standard deviation. The Hardy-Weinberg genetic equilibrium law was performed to test the genotype distribution of the experimental and control groups. Pearson's χ^2 test was used to test the differences of genotype frequencies and allele frequency distributions between the two groups. The linkage disequilibrium and haplotype frequency of each locus was analysed by SHEsis software (18) to investigate the relevance of haplotypes composed of these loci and MDs. SPSS version 13.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used for statistical data processing, with $P < 0.05$ considered to indicate a statistically significant difference.

Ethical and clinical test specification. The stages of the research program were evaluated by the Ethics Committee of Henan Provincial People's Hospital, and all participants in the study provided signed informed consent prior to the survey.

Results

Genotype frequencies and allele frequencies of the eight SNP loci near the ABO gene. The tests revealed that the genotype distributions of the eight loci between the two groups met the Hardy-Weinberg genetic equilibrium law. Thus, the eight loci exhibited good population representation.

The results showed that among females of childbearing age in the Han population of Henan province, the frequency of the GG genotype and allele G in the rs657152 locus in the ABO blood group of the experimental group was higher than that in the control group. The frequency of the TT genotype of the experimental group was lower than that of the control group with a statistically significant difference ($P < 0.01$). Relative risk analysis showed that the females who carried allele G exhibited an increased risk of MD [odds ratio (OR)=0.602; 95% confidence interval (CI), 0.468-0.773]. The difference in the distribution frequency of allele T of the rs495828 locus upstream of the ABO blood group gene between the experimental and control groups was statistically significant ($P < 0.05$); females with allele T had a reduced risk of MDs (OR=1.372; 95% CI, 1.026-1.835). The AA genotype frequency of the TRAF2 rs17250673 locus, downstream of the ABO blood group gene was higher in the experimental group than in the control group; the difference was statistically significant ($P < 0.05$); pairwise comparison revealed that only

Table I. Genotype and allele frequency distributions of eight SNP loci in the experimental and control groups.

SNP	Gene	Genotype/ allele	Experimental group		Control group		χ^2	P-value	OR	95% CI
			Absolute frequency	Frequency (%)	Absolute frequency	Frequency (%)				
rs657152	ABO	TT	46	0.184	58	0.232	26.979	<0.001 ^a		
		TG	113	0.452	152	0.608				
		GG	91	0.364	40	0.160	15.158	<0.001 ^a	0.349	0.204-0.596
		G	295	0.590	232	0.464	15.922	<0.001 ^a	0.602	0.468-0.773
		T	205	0.410	268	0.536				
rs495828	Upstream of ABO	GG	152	0.608	130	0.520	4.942	0.089		
		GT	89	0.356	104	0.416				
		TT	9	0.036	16	0.064				
		T	107	0.214	136	0.272	4.572	0.033 ^a	1.372	1.026-1.835
		G	393	0.786	364	0.728				
rs7852970	TRAF2	TT	22	0.088	22	0.088	0.406	0.804		
		CT	104	0.416	97	0.388				
		CC	124	0.496	131	0.524				
		C	352	0.704	359	0.718	0.238	0.625	1.071	0.814-1.407
		T	148	0.296	141	0.282				
rs4448378	TRAF2	GG	5	0.020	5	0.020	0.041	0.979		
		CG	67	0.268	65	0.260				
		CC	178	0.712	180	0.720				
		C	423	0.846	425	0.850	0.031	0.860	1.032	0.730-1.457
		G	77	0.154	75	0.150				
rs10781522	TRAF2	AA	21	0.084	22	0.088	1.914	0.384		
		AG	107	0.428	92	0.368				
		GG	122	0.488	136	0.544				
		G	315	0.702	364	0.728	2.789	0.095	1.266	0.960-1.670
		A	149	0.298	136	0.272				
rs17250673	TRAF2	AA	10	0.040	5	0.020	7.312	0.026 ^a		
		AG	50	0.200	74	0.294				
		GG	190	0.760	171	0.684				
		G	430	0.860	416	0.832	1.504	0.220	0.806	0.571-1.138
		A	70	0.140	84	0.168				
rs61754920	PNPLA7	GG	150	0.600	149	0.596	2.939	0.230		
		AG	89	0.356	80	0.320				
		AA	11	0.044	21	0.084				
		A	111	0.222	122	0.244	0.677	0.411	1.131	0.843-1.517
		G	389	0.778	378	0.756				
rs11137410	PNPLA7	CC	158	0.632	155	0.620	2.231	0.313		
		CT	81	0.324	76	0.304				
		TT	11	0.044	19	0.076				
		T	103	0.206	114	0.228	0.712	0.399	1.138	0.842-1.538
		C	397	0.794	386	0.772				

^aP<0.05 was considered statistically significant. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; TRAF2, tumour necrosis factor cofactor 2; PNPLA7, patatin-like phospholipase domain containing 7.

the differences between the AG and GG genotypes were statistically significant (P<0.05). The differences of the intergroup

allele distribution frequencies of rs17250673 were statistically insignificant (Table I).

Table II. Genotype and allele frequency distributions of eight SNP loci in the experimental and control groups in the dominant and recessive models.

SNP	Gene	Dominant model				Recessive model			
		χ^2	P-value	OR	95% CI	χ^2	P-value	OR	95% CI
rs657152	ABO	26.904	<0.001 ^a	3.005	1.964-4.596	0.868	2.086	1.340	0.868-2.068
rs495828	ABO upstream	2.063	0.151	1.831	0.793-4.255	3.936	0.047 ^a	0.698	0.490-0.996
rs7852970	TRAF2	0.392	0.531	1.119	0.788-1.589	0.000	1.000	1.000	0.539-1.857
rs4448378	TRAF2	0.039	0.843	1.040	0.705-1.534	0.000	1.000	1.000	0.286-3.498
rs10781522	TRAF2	1.570	0.210	1.252	0.881-1.779	0.025	0.873	1.052	0.563-1.967
rs17250673	TRAF2	3.597	0.058	0.684	0.461-1.014	1.718	0.190	0.490	0.165-1.454
rs61754920	PNPLA7	3.339	0.068	1.992	0.940-4.225	0.008	0.927	0.983	0.688-1.406
rs11137410	PNPLA7	2.270	0.132	1.787	0.832-3.838	0.077	0.782	0.950	0.661-1.365

^aP<0.05 was considered statistically significant. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; TRAF2, tumour necrosis factor cofactor 2; PNPLA7, patatin-like phospholipase domain containing 7.

Table III. Genotype and allele frequency distribution of the rs17250673 locus in the ultra-dominant model.

SNP	Gene	Ultra-dominant model			
		χ^2	P-value	OR	95% CI
rs657152	TRAF2	6.177	0.013 ^a	0.595	0.394-0.898

^aP<0.05 was considered statistically significant. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; TRAF2, tumour necrosis factor cofactor 2.

Allele frequencies of the eight SNP loci in the recessive and dominant models. To expand the sample size further and increase the differences among the genotypes, each locus was analysed under the dominant and recessive models. The results demonstrated that the difference in the genotype distribution frequency of the rs657152 locus of the ABO blood group gene between the two groups exhibited statistical significance in the dominant model; the TT or TG genotype-carrying population had a lower risk of MDs than the GG population (OR=3.005; 95% CI, 1.964-4.596). The difference in the rs495828 locus genotype distribution frequency was statistically significant in the recessive model, with the TT or TG genotype-carrying population having higher risk of MDs than the GG population (OR=0.698; 95% CI, 0.490-0.996). The other loci exhibited no statistically significant differences (Table II).

The three genotypes of the TRAF2 gene rs17250673 locus between the two groups had statistically significant differences in distribution frequency, whereas the dominant and recessive models had statistically insignificant differences. However, given the difference in AG and GG genotype frequencies, the difference was analysed in the ultra-dominant model and found to be significant (Table III), indicating that the pathogenic effect of the heterozygous genotype AG at this locus was greater than that of any homogeneous genotype. This result may be attributed to the increased interaction between genes

due to the heterozygous state and that heterozygosity itself is the fundamental reason for hybrid advantages.

Haplotype analysis. SHEsis software was used to analyse the linkage disequilibrium and haplotype frequency of all loci. Out of the eight loci, only S3 and S52 loci were in a region of linkage disequilibrium ($D'=0.090$) and could be used to build haplotypes AA and GG. The P-values of the two loci in the experimental and control groups were both 0.539, thus indicating statistical insignificance.

Discussion

MDs are a common gynaecological diseases that not only affect the health and quality of life of females but also increase the potential risks of certain gynaecological diseases. For example, menarche at an earlier age increases the risk of breast cancer (1) and endometrial cancer (2), and late menarche increases the risk of Alzheimer's disease (3) and osteoporosis (4). The occurrence of MDs is affected by various factors. Taylor *et al* (5) studied the progesterone receptor gene and 37 SNP loci in upstream and downstream regions and found that the polymorphisms of the progesterone receptor gene were associated with a young menarche age and excessively short menstrual cycle. Furthermore, the risk for PMS has been found to be higher in identical twins than in fraternal twins (6), and mutation of the FSH-R gene may lead to amenorrhoea, infertility or premature ovarian failure (7). These results indicate that genetic susceptibility is significant to MD occurrence.

Previous reports have described the associations of ABO blood group with ovarian reserve functions and infertility (10-12). In 2010, experts from Yale University and Albert Einstein Medical College proposed at the 66th ASRM Annual Meeting (13) that type O blood was associated with infertility. Binder *et al* (14,15) found that pregnant females with type A blood were more prone to suffer from symptoms of ovarian hyperstimulation than females with type O blood. Nejat *et al* (10) found that antigen A may be a protective factor

of ovarian reserve capacity and that type O blood decreased the risk of ovarian reserve capacity more than blood of types A and AB. Chen *et al* (9) performed a genome-wide association study, identified a predisposing gene for the polycystic ovary syndrome located in 9q33.3 and found that polycystic ovary syndrome was normally accompanied by MDs. The ABO gene is located on chromosome 9q34.2; thus, the association of the blood group system with MDs may be related to the ABO gene. Specific genes that are associated with MDs may be linked with the ABO gene and located near the chromosome 9q34.2. An unknown mutation close to the ABO gene might be associated with MDs, thus explaining the correlation of the ABO blood group system with the abnormalities of menstrual and reproductive systems from a theoretical basis. Thus, the ABO blood group gene and eight loci located in upstream and downstream related genes were examined. Whether these SNPs are correlated with MDs was evaluated in this study.

The ABO blood group gene is located on chromosome 9q34.1-q34.2 (19), which contains seven exons with lengths of ~18 kb and six introns with lengths of ~19,514 bp. The product of the ABO gene is glycosyltransferase, which controls the biosynthesis of ABO blood group antigens. The chemical structure of the ABO antigens comprises glycoproteins. The product of the A gene is N-acetyl galactosyltransferase, which links α -N-acetylgalactosamine with antigen H, an ABO antigen precursor, thus producing the A antigenic determinant. The product of the B gene is galactosyltransferase, which links acetyl- α -D-galactose with antigen H, thus generating the B antigenic determinant. In type O blood, several inactive genes that potentially encode non-active transferase were found. Type O blood is the unaltered precursor of A or B, and the OO gene does not generate a specific antigen (20).

It has been assumed that a definite link exists between the ABO blood group and disease. Henry and Samuelsson (21) made the following summary of the correlation of ABO polymorphisms and diseases: 'the bacterial infection tended to infringe the A type, the viral infection was usually associated with O type, the tumour was most associated with A type, and the autoimmunity was associated with type O blood'. In the present study, the correlation analysis of the ABO-gene chromosomal-regional allele distribution frequencies and genotypes showed that the three genotypes of the rs657152 locus of the ABO gene exhibited statistically significant differences between the experimental and control groups. The frequency of the GG genotype was higher in the experimental group than in the control group, and people carrying allele G suffered from an increased risk of MD. A previous study reported the association of this locus with a variety of diseases, and an increased risk of pancreatic cancer and gastric ulcers in populations with allele G at this locus (22). The levels of inflammatory cytokines, intercellular adhesion molecules and E-selectin are increased in patients with pancreatic cancer carried on the G allele, indicating that allele G is the marker gene in Caucasians with type O blood; the G allele at this locus is a risk allele (22). Several key proteins associated with follicle development and menstruation, such as the FSH-R and luteinizing hormone receptor, are glycosyltransferase proteins. This explains the association of the ABO blood group with female reproductive endocrinology and the association between

the O blood type and infertility. Glycosyltransferase blood type antigens, which exist in females without type O blood, might have an important role in the development of ovarian endocrine cells. Williams and Stanley (23) found that mice with lower ovulation rates lacked a certain oocyte-specific glycosyltransferase.

The rs495828 locus, which is located upstream of the ABO gene, exhibited statistical insignificance among the three genotypes but exhibited a statistical significance between alleles T and G. Carriers of T alleles exhibited a reduced risk of MD occurrence. It has been reported that this locus is associated with the activity of angiotensin-converting enzyme (ACE) (24). ACE is the key enzyme of the renin-angiotensin system, which converts angiotensin I into angiotensin II; the latter could lead to follicular atresia at various stages, thus resulting in anovulation. This locus may cause MDs by influencing ACE activities.

Tumour necrosis factor (TNF)- α is a pleiotropic cytokine that is involved in cell proliferation and apoptosis and plays an important regulatory role during follicle development, ovulation, corpus luteum formation and steroid hormone generation. The TRAF family is a class of plasmalemma adapter proteins that directly binds to the intracellular region of cell surface receptors. TRAFs interact with the members of the TNF receptor superfamily, thus causing a series of downstream signalling cascades, activating downstream signalling molecules, such as I κ B kinase and mitogen-activated protein kinase, and ultimately affecting the activities of transcription factors NF- κ B and AP-1 (25). In TNFR and IL-1R/Toll receptor-mediated signalling pathways, TRAF2, TRAF5 and TRAF6 play key roles in the activation of the I κ B kinase complex and JNK (26).

The rs17250673 locus of the TRAF2 gene exhibits statistical significance in the genotype frequency distributions and statistically significant differences in the ultra-dominant model. TRAF2 locus mutation may affect the expression level or functions of TRAF2, thus influencing the biological effects of various factors during the expression of TRAF2 regulatory genes and TNF signalling pathways, causing anabolism disorder of ovarian steroid hormones and affecting follicular development and ovulation. This indicates that females with the heterozygous genotype of TRAF2 rs17250673 suffer from increased MD susceptibility.

In summary, the ABO blood group gene and TRAF2 gene may be predisposing genes of MDs since the chromosome region at which the ABO blood group gene is located is associated with genetic causes of MDs. However, a large-sample, multi-regional study of other related loci in this region is required to elucidate the pathogenesis of MDs and obtain results with theoretical significance and application values.

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