

## 5,10-Methylenetetrahydrofolate Reductase (MTHFR C677T A1298C)

1, 3, 4,  
2  
1\* 2 2 1 3 3  
4 2 1

### Polymorphisms of 5,10-Methylenetetrahydrofolate Reductase (MTHFR C677T and A1298C) Gene in Recurrent Spontaneous Abortion

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**Objective:** Previous studies have suggested that hyperhomocysteinemia and methylenetetrahydrofolate reductase (MTHFR C677T) mutations are associated with increased risk of recurrent spontaneous abortion (RSA). Recently, a second site polymorphism in MTHFR, 1298A→C, which changes a glutamic acid into an alanine residue, was shown to be associated with a decreased enzyme activity. We tested whether the variant alleles of MTHFR C677T and A1298C are risk factor (biomarker) for RSA.

**Materials and Methods:** We analyzed DNA from a case-control study in the Korean DNA was extracted from blood samples of 118 patients with RSA and 123 healthy fertile patients as the controls. MTHFR variant alleles were determined by a PCR-restriction fragment length polymorphism assay.

**Results:** We found no evidence for an association between 677TT genotype and risk of RSA (OR=1.95, 95% CI=0.84~4.50, p=0.12). However, the MTHFR 1298AC (OR=0.36, 95% CI=0.20~0.63, p=0.0004) and 1298AC+CC (OR=0.35, 95% CI=0.20~0.61, p=0.0002) genotypes were lower among 118 RSA cases compared with 123 controls, conferring a 2.8-fold decrease in risk of RSA, respectively. Moreover, the combined genotypes of MTHFR 677CC/1298AC (OR=0.30, 95% CI=0.10~0.88, p=0.029) and 677CT/1298AC (OR=0.77, 95% CI=0.60~0.99, p=0.043) also showed significantly lower risk than those with MTHFR 677CC/1298AA type.

**Conclusion:** MTHFR 1298AC, MTHFR 677CC/1298AC and 677CT/1298AC genotypes may represent genetic markers for the protection of RSA at least in Korean women.

**Key Words:** MTHFR, Polymorphism, Recurrent spontaneous abortion, Korean, Vascular disease, Thrombotic disease

( )  
 1~5% ,  
 40~55% .<sup>1-3</sup>  
 (hyperhomocysteinemia) , ,  
 , (placental abruption),  
 (placental infarction), (preeclampsia)

. 5,10-Methylenetetrahydrofolate reductase (MTHFR) 5,10-methylenetetrahydrofolate 5-methyltetrahydrofolate , 가

alanine  
 (A) valine (V) , glutamate (G)가 alanine (A)  
 , 20~30%

.<sup>4</sup>  
 .<sup>5-7</sup>  
 가

.<sup>8,9</sup>  
 Kang<sup>10</sup> MTHFR 가 37  
 , 46

,  
 Frosst<sup>11</sup> MT-  
 HFR C677T mutation , 1998 van der  
 Put<sup>12</sup> MTHFR A1298C mutation

,  
 10%

,  
 MTHFR A1298C C677T

,  
 가 .<sup>6</sup>

,  
 가 ,  
 .<sup>11,14,15</sup>

MTHFR C677T  
 ,

type  
 가 .<sup>16-20</sup>  
 , MTHFR C677T (pre-  
 clampsia), (placental abruption),

(intrauterine growth retardation; IUGR),  
 (stillbirth) .<sup>21</sup> , Ne-  
 len<sup>22,23</sup> Quere<sup>24</sup>

,  
 , MTHFR A1298C site

MTHFR C677T A1298C  
 MTHFR C677T/A1298C  
 (combined genotype)

1.  
 2

118 1  
 123

33.1  
 (age range, 23~43) 31.2 (age range, 23~43)

2000 11 1 2002 7  
 30

2.  
 DNA DNA (extraction column,  
 QIAmp blood kit, Qiagen)

DNA (primer  
 set) sense primer (5'-TGA AGG AGA AGG TGT  
 CTG CGG GA-3') antisense primer (5'-AGG ACG  
 GTG CGG TGA GAG AGT C3')

Gene-  
 Amp PCR machine (Perkin Elmer 2400)

. 198 bp 95 60

62 90  
 (annealing) 72 60

35  
 MTHFR 677C T  
*Hinf* I (10 unit/reaction  
 mixture) 37 3~4 . A

**Table 1.** Number of recurrent spontaneous abortion (RSA) cases and controls, adjusted ORs and 95% CIs by MTHFR 677, using 677CC as a reference, and MTHFR1298, using 1298AA as a reference

| Genotype          | Cases (n=118) | Control (n=123) | OR (95% CI)       | P      |
|-------------------|---------------|-----------------|-------------------|--------|
| <b>MTHFR 677</b>  |               |                 |                   |        |
| CC                | 35 (29.7)     | 45 (36.6)       | 1.0               | -      |
| CT                | 61 (51.7)     | 64 (52.0)       | 1.29 (0.72~2.30)  | 0.388  |
| TT                | 22 (18.6)     | 14 (11.4)       | 1.95 (0.84~4.50)  | 0.120  |
| CT+TT             | 83 (70.3)     | 78 (63.4)       | 1.42 (0.82~2.47)  | 0.216  |
| <b>MTHFR 1298</b> |               |                 |                   |        |
| AA                | 86 (72.9)     | 61 (49.6)       | 1.0               | -      |
| AC                | 29 (24.6)     | 56 (45.5)       | 0.36 (0.20~0.63)  | 0.0004 |
| CC                | 3 (2.5)       | 6 (4.9)         | 0.32 (0.076~1.35) | 0.120  |
| AC+CC             | 32 (27.1)     | 62 (50.4)       | 0.35 (0.20~0.61)  | 0.0002 |

**Table 2.** Number of recurrent spontaneous abortion (RSA) cases and controls, adjusted ORs and 95% CIs by MTHFR 677 and MTHFR 1298, using MTHFR 677CC and MTHFR 1298AA as a reference

| MTHFR677 | MTHFR1298 | Case (%)  | Control (%) | OR (95% CI)      | P     |
|----------|-----------|-----------|-------------|------------------|-------|
| CC       | AA        | 19 (16.1) | 14 (11.4)   | 1.0              | -     |
| CC       | AC        | 13 (11.0) | 25 (20.3)   | 0.30 (0.10~0.88) | 0.029 |
| CC       | CC        | 3 (2.5)   | 6 (4.9)     | 0.49 (0.21~1.16) | 0.103 |
| CT       | AA        | 45 (38.1) | 33 (26.8)   | 1.01 (0.76~1.33) | 0.956 |
| CT       | AC        | 16 (13.6) | 31 (25.2)   | 0.77 (0.60~0.99) | 0.043 |
| CT       | CC        | -         | -           | -                | -     |
| TT       | AA        | 22 (18.6) | 14 (11.4)   | 1.03 (0.87~1.20) | 0.953 |
| TT       | AC        | -         | -           | -                | -     |
| TT       | CC        | -         | -           | -                | -     |

(Ala) (allele) 198 bp bp 5 , MTHFR 1298CC 84,  
*Hinf*I V (Val) 31, 30, 18 bp 4 .  
 175 bp 23 bp 3.  
 . *Hinf*I .  
 3.0% agarose gel ethidium bro- X<sup>2</sup>-test , odds  
 mide . MTHFR (odds ratio; OR) 95% (95% confide-  
 1298A->C primer (5'-CTT nce interval; CI) . SAS  
 TGG GGA GCT GAA CGA CTA CTA C-3' and 5'-CAC release 6.12 for Windows .  
 TTT GTG ACC ATT CCG GTT TG-3')  
 163 bp fragment amplify , *Mbo*II  
 . MTHFR 1298AA 56, 31, 30, 28, 18 118 123

MTHFR 677 nucleotide가 cyto-  
sine thymine , 1298 nucleotide가  
adenine cytosine

PCR/RFLP . Table 1

MTHFR 677CC, CT, TT type  
35 (29.7%), 61 (51.7%), 22 (18.6%)  
, 45 (36.6%), 64 (52.0%),  
14 (11.4%) (Table 1). MTH-  
FR C677T site

, MTHFR 1298AA,  
AC, CC type , 86 (72.9%),  
29 (24.6%), 3 (2.5%) , 61  
(49.6%), 56 (45.5%), 6 (4.9%) (Table  
1). , MTHFR C677T site MTH-  
FR A1298C site MTHFR 1298AC type  
가 (OR=  
0.36, 95% CI=0.20~0.63; p=0.0004).  
type 가 가  
2.8 . ,  
MTHFR 1298AC 1298CC type  
1298AA type 가  
(OR=0.35, 95% CI=0.20~0.61; p=0.0002).  
MTHFR C677T A1298C  
, 677CC/1298AA, 677CC/1298AC, 677CC/  
1298CC, 677CT/1298AA, 677CT/1298AC, 677TT/1298  
AA 19 (16.1%), 13 (11.0%), 3 (2.5%),  
45 (38.1%), 16 (13.6%), 22 (18.6%) ,  
14 (11.4%), 25 (20.3%), 6 (4.9%), 33  
(26.8%), 31 (25.2%), 14 (11.4%) (Ta-  
ble 2). 677CC/1298AC (OR=0.23; 95% CI=  
0.10~0.88; p=0.029), 677CT/1298AC (OR=0.77; 95%  
CI=0.60~0.99; p=0.043)  
가  
(Table 2).  
, 가 3  
677CT/1298CC, 677TT/1298AC, 677TT/1298CC  
3가  
(embryonic lethal)  
.25 , MT-  
HFR 677TT 1298AA ,  
1298CC 677CC .

tight linked haplotype  
.26

1997 Nelen 22  
MTHFR C677T  
, 2000  
, , , ,  
5 가 data  
.22-24  
, , MTHFR  
C677T site 가  
.2,3,27-32 , Kuttch 33 Brenner 34  
MTHFR 677TT 가  
가 ,  
MTHFR  
C677T  
가 ,  
가 .  
11,35 , MTHFR C677T  
(preeclampsia), (placental abrup-  
tion), (neural tube defect)  
.21,36 ,  
, MTHFR , activated  
Protein C resistance, Protein C thrombotic risk fac-  
tor 2 odd 3.40 (95% CI=  
1.80~6.42), 3 가 6.83 (95% CI=1.52~  
30.7)  
가  
.37  
, MTHFR A1298C  
MTHFR C677T/A1298C  
,  
.12,38 ,  
MTHFR 1298AC  
(Table  
1; p=0.0004). , MTHFR 1298AC 1298CC  
MTHFR 1298AA  
2.9

(Table 1; p=0.0002).

(lymphoma),<sup>9,39</sup>

folate MT-  
HFR folate deficiency  
가

<sup>40-42</sup>  
MTHFR  
, MTHFR  
, MTHFR  
vitamin B<sub>12</sub> (folic acid)  
MTHFR  
<sup>18,43</sup>, folic acid  
( )  
가<sup>44</sup>  
MTHFR methyl  
THF ,  
promoter CpG island  
, tumor suppressor  
gene proto-oncogene  
dUMP가 dTMP  
methyl (5,10-methylene THF)  
"dTMP stress"  
, (colorectal cancer) (ac-  
ute lymphocytic leukemia) C677T A1298C  
<sup>39,41,45</sup>  
, MTHFR A1298C C677T/A1298C  
compound heterozygosity  
가  
, MTHFR C677T A1298C  
3  
677CT/1298CC, 677TT/  
1298AC, 677TT/1298CC ,  
MTHFR C677T A1298C

(Tables 1 and 2).

MTHFR , folate , homocys-  
teine 가 ,  
folic acid  
가 MTHFR  
, MTHFR  
가 ,  
MTHFR 677TT  
가 , A1298C  
가 .

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